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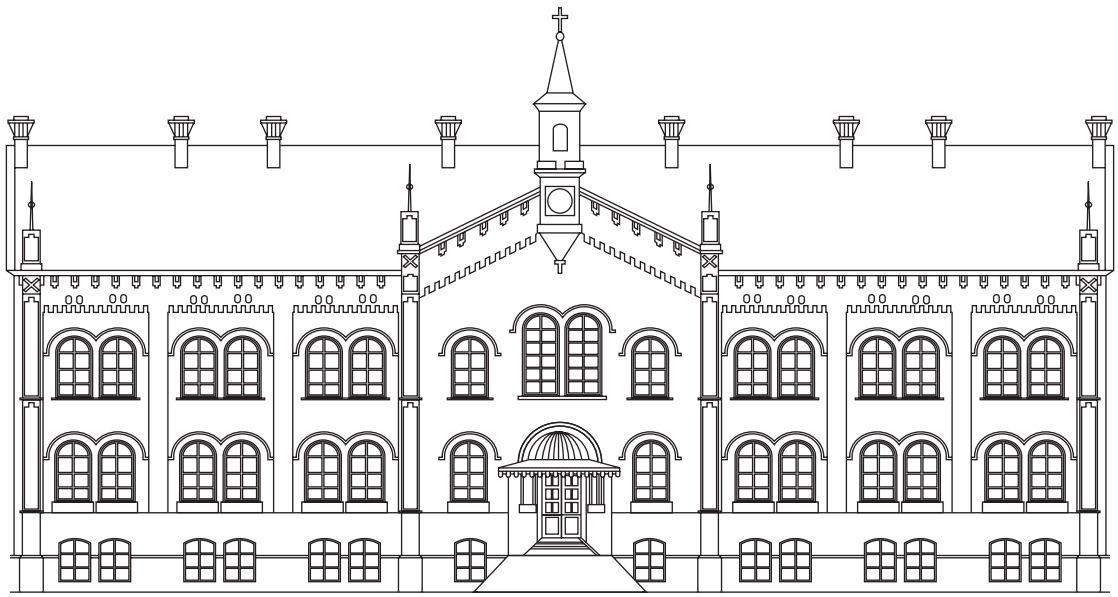

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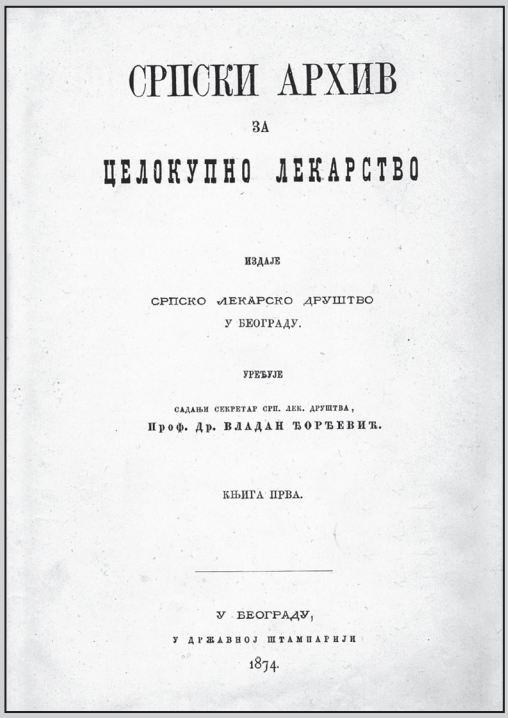

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

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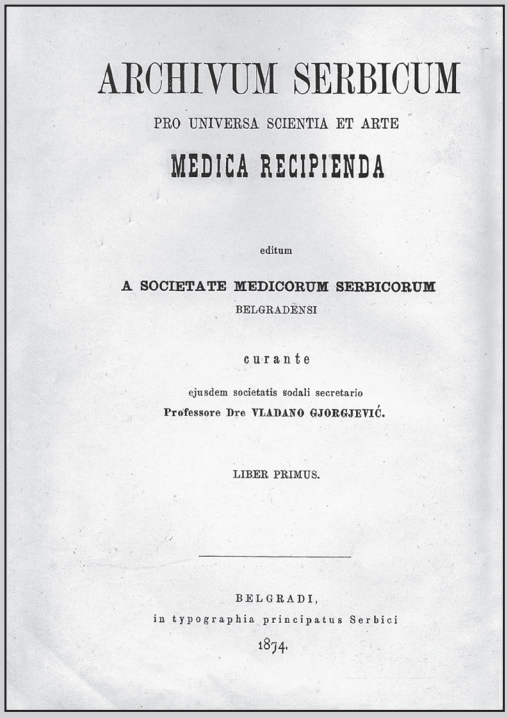
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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1874.

The title page of the first journal volume in Latin

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Colorimetric (CIEDE2000) comparison between two shade guides used for visual evaluation of tooth whitening efficacy

Rade D. Paravina[1,2], Natalie A. Pereira Sanchez[1,2], Razvan Ghinea[2,3], John M. Powers[4]

[1]University of Texas, School of Dentistry, Department of Restorative Dentistry and Prosthodontics, Houston, Texas, USA;
[2]Houston Center for Biomaterials and Biomimetics (HCBB), Houston, Texas, USA;
[3]University of Granada, Faculty of Sciences, Department of Optics, Granada, Spain;
[4]Dental Consultants, Inc., Ann Arbor, Michigan, USA

SUMMARY

Introduction/Objective The objective of this study was to perform colorimetric comparison between two shade guides used for visual tooth whitening monitoring.

Methods VITA Bleachedguide 3D-Master (BG) and value scale of VITA classical A1–D4 (VC) were evaluated (n = 3) using a non-contact spectroradiometer. Ranges, distribution, and correlation among color parameters were evaluated using CIEDE2000 color difference formula. In addition, optimized whiteness index for dentistry (WI_D), and Yellowness Index E313 (YI) were analyzed. ANOVA and Fisher's PLSD test at a 0.05 level of significance were used in statistical analysis.

Results The lightness (L'), chroma (C'), and hue (h') ranges for BG were 20.4, 25.9, and 19.1, respectively. The corresponding ranges for VC were 15.3, 10.9, and 20.6. R^2 values for individual color coordinate/tab arrangement were higher for BG than VC. The same is true for R^2 values of pairs of color coordinates for BG/VC: L'C' = 0.89/0.33, L'h' = 0.88/0.53, and C'h' = 0.70/0.51. BG also exhibited better agreement between the manufacturer's tab arrangement with ΔE', WI_D and YI. The ΔE' between the lightest and the darkest BG and VC tab were 20.6 and 13.2, respectively. The average ΔE' among the adjacent tabs were 1.9 (0.5) for BG (corresponding to two shade guide units, SGU) and 3.0 (1.0) for VC (1 SGU).

Conclusion VITA Bleachedguide 3D-Master exhibited wider L', C', ΔE', WI_D, and YI ranges compared to value scale of VITA classical A1–D4 shade guide and better distribution of evaluated color parameters. This, along with the presence of several shades lighter than B1 of VC, recommends the use of BG for visual evaluation of tooth whitening efficacy.

Keywords: tooth whitening; color; dentistry; psychophysics; shade guide

INTRODUCTION

Tooth whitening is probably one of the most popular cosmetic procedures in dentistry. A convincing evidence of the validity of this statement is presented on Medline search, where more than 3,000 papers show up with keywords *tooth* and *whitening* or *bleaching*. Tooth whitening is performed using the one or a combination of the three basic methods: in office (power bleaching), dentist-administered at-home bleaching and bleaching using over-the-counter products.

Tooth whitening efficacy ranges from barely noticeable to very pronounced and it can be monitored and documented using visual and/or instrumental method [1–5]. Visual method is more popular due to limited percentage of practices that have color measuring devices. Visual method implies the usage of dental shade guides, and is expressed in shade guide units (SGU). One SGU means that tooth become one shade tab lighter upon whitening. Consequently, whitening efficacy is calculated and shade tab number before whitening minus shade tab number after whitening.

VITA classical A1–D4 shade guide (VC) (VITA Zahnfabrik, Bad Säckingen, Germany), with the original A1–D4 tab arrangement modified to so-called value scale B1–C4 (Figure 1) is the most frequently used method of visual monitoring of tooth whitening efficacy. Another shade guide, VITA Bleachedguide 3D-Master (BG) (VITA Zahnfabrik) (Figure 1) is the only shade guide developed specifically for tooth whitening monitoring. Previously reported

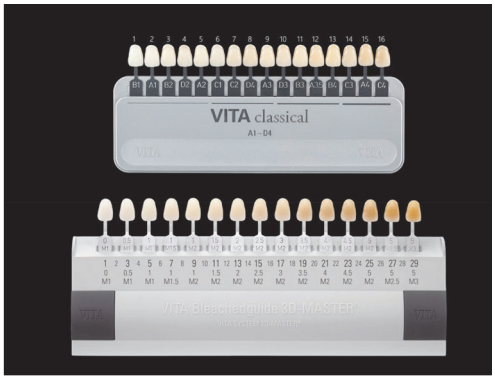

Figure 1. Top: value scale of VITA classical A1–D4 shade guide; bottom: VITA Bleachedguide 3D-Master shade guide

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Correspondence to:
Rade D. PARAVINA
University of Texas
School of Dentistry
7500 Cambridge St.
Houston, TX 77054, USA
rade.paravina@uth.tmc.edu

performance and/or advantages of BG resulted in its recommendation as a shade guide of choice for tooth whitening monitoring by the American Dental Association in 2016 [6–11].

Color is a psychophysical phenomenon that can also be evaluated using instrumental method ("color by numbers") with the ultimate goal of providing objectivity and correlating with visual findings. The CIELAB color difference formula from 1976 has predominantly been used in color research in dentistry. However, new and more advanced formulas have been subsequently introduced, including the most recent CIEDE2000 formula. The agreement with visual finding greater than 95% is the main advantage of CIEDE2000 formula over the CIELAB formula with 75% agreement [12]. Although the advantages of BG compared to VC have been clearly demonstrated in the past, very limited data are available on their comparison utilizing CIEDE2000 color difference formula. The objective of this study was to provide a colorimetric comparison between these two shade guides using the CIEDE2000 formula. The null hypothesis was that there was no difference between BG and VC in any of evaluated color parameters.

METHODS

Colorimetric evaluation of BG and VC shade guides (n = 3) was performed by a non-contact spectroradiometer (SpectraScan PR-670, Photo Research, Syracuse, NY, USA). The instrument setup was as follows: bi-directional 45°/0° optical geometry, D65 illuminant and 2° standard observer, with 0.5° aperture (corresponding to 4 mm diameter at the 40 cm distance). The spectroradiometer was calibrated using white reflectance standard (SRS-3, PhotoResearch) under controlled illumination using Xenon lamp (Newport Corporation, Irvine, CA, USA) mounted inside the lamp housing (Newport Corporation). Shade tab positioning jigs were made using clear bite registration material (Clear Bite Matrix, Lompoc, CA, USA) and placed inside custom made clear acrylic holder to allow proper repositioning of shade tabs, thus enabling measurements with no background. The measured area corresponded to the middle of clinical crown, from incisal to gingival and from mesial to distal. The horizontal, x-positions of the left and right edge of shade tabs were recorded, and the middle x-position was defined as the center x-position, with the zeroed horizontal instrument readout. After determining the vertical, y-positions of shade tabs, the vertical readout was also set to zero. Spectral reflection data (in 2 nm intervals) were obtained for each shade tab five times with repositioning and further processed using the Commission Internationale De l'Eclairage (International Commission on Illumination) (CIE) CEIDE2000 formula as follows:

Computations with the CIEDE2000 (ΔE_{00}) total color difference formula were made according to the following equation [13]:

$$\Delta E_{00} = \left[\left(\frac{\Delta L'}{K_L S_L}\right)^2 + \left(\frac{\Delta C'}{K_C S_C}\right)^2 + \left(\frac{\Delta H'}{K_H S_H}\right)^2 + R_T \left(\frac{\Delta C'}{K_C S_C}\right)\left(\frac{\Delta H'}{K_H S_H}\right)\right]^{1/2} \quad /1/$$

where $\Delta L'$, $\Delta C'$, and $\Delta H'$ are the differences in lightness, chroma, and hue for a pair of samples in CIEDE2000, and R_T is a function (the so-called rotation function) that accounts for the interaction between chroma and hue differences in the blue region. Weighting functions, S_L, S_C, S_H, adjust the total color difference for variation in the location of the color difference pair in L', a', b' coordinates and the parametric factors K_L, K_c, K_H, are correction terms for experimental conditions. For calculation performed in this study, all parametric factors were set to 1. Discontinuities due to mean hue computation and hue-difference computation were taken into account [14].

The Whiteness Index for Dentistry (WI_D) is an optimized, CIELAB-based whiteness index specifically designed for dentistry, which computation is given by the following equation [15]:

$$WI_D = 0.511\ L^* - 2.324\ a^* - 1.10\ b^* \quad /2/$$

The yellowness of the samples can be evaluated from instrumentally measured color coordinates using the YI E313 Yellowness Index [16]:

$$YI\ E313 = \frac{100(C_X X - C_Z Z)}{Y} \quad /3/$$

where X, Y and Z are the tristimulus values of the sample, while C_X and C_Z are illuminant and observer specific constants (in this case, $C_X = 1.2985$ and $C_Z = 1.13335$ as recommended for D65/2° Illuminant/Observer combination)

Means and standard deviations were determined. Anova and Fisher's PLSD test at a 0.05 level of significance were used in statistical analysis.

RESULTS

CIEDE2000 color coordinate values for of BG and VC shade guides are presented in Table 1. The L'C'h' ranges for BG were 20.4, 25.9, and 19.1, respectively. The corresponding ranges for VC were 15.3, 10.9 and 20.6. The L' and C' ranges were wider, while h' range of BG was slightly narrower as compared to VC. Based on R^2 values, all three-color coordinates exhibited more uniform distribution in BG (Figure 2). The R^2 values for pairs of color coordinates for BG were as follows: L'C' = 0.89, L'h' = 0.88, and C'h' = 0.70. Corresponding values for VC were 0.33, 0.53, and 0.51, respectively. Fisher's PLSD intervals ($p < 0.0001$) for comparisons among L'C'h' values for BG were 0.26, 0.28, and 0.49, respectively. Corresponding values for VC were 0.35, 0.29, and 0.59.

Color differences (ΔE') from the lightest to the darkest BG and VC tab (according to manufacturer's tab arrangement/order) and corresponding color distribution are shown in Figure 3. The ΔE' ranges for BG and VC were 20.6 and 13.2 respectively. The recorded R^2 values clearly demonstrate more uniform color distribution of BG. When the average ΔE' values (s.d.) from two to 14 (BG) and 15 (VC) tabs apart were compared (Table 2), the

Table 1. CIEDE2000 color coordinate values (s.d.) for of VITA Bleachedguide 3D-Master and value scale of VITA classical A1–D4 shade guides: lightness (L'), chroma (C'), and hue (h')

VITA Bleachedguide 3D-Master				VITA classical A1–D4, Value scale			
Tab	L'	C'	h'	Tab	L'	C'	h'
1	81.5 (0.5)	5.6 (0.1)	87.1 (1.2)	1	75.6 (0.6)	12.8 (0.2)	99.3 (0.6)
3	79.3 (0.5)	8.4 (0.3)	92.9 (1)	2	76.4 (0.5)	14.0 (0.2)	91.4 (0.6)
5	76.4 (0.3)	10.8 (0.1)	91.6 (0.6)	3	74.1 (0.3)	17.7 (0.2)	92.7 (0.9)
7	76.3 (0.2)	13.7 (0.1)	92.5 (0.7)	4	70.1 (0.6)	13.7 (0.6)	87.0 (1.3)
9	76.9 (0.4)	16.7 (0.3)	93.4 (0.4)	5	74.1 (0.2)	18.4 (0.3)	86.3 (1.2)
11	74.8 (0.2)	16.7 (0.3)	89.8 (0.7)	6	70.9 (0.6)	13.7 (0.6)	91.7 (1.4)
13	73.3 (0.4)	17.0 (0.3)	87.6 (0.6)	7	68.3 (0.2)	19.0 (0.2)	88.4 (0.7)
15	71.6 (0.2)	18.2 (0.5)	85.6 (0.8)	8	68.2 (0.5)	21.0 (0.3)	90.6 (0.2)
17	69.4 (0.3)	19.6 (0.4)	83.0 (0.2)	9	71.4 (0.7)	20.5 (0.6)	84.7 (1)
19	66.8 (0.3)	21.2 (0.6)	80.6 (0.9)	10	68.6 (0.5)	17.5 (0.5)	83.7 (0.7)
21	64.8 (0.3)	21.9 (0.3)	78.4 (0.5)	11	70.2 (0.3)	23.3 (0.3)	86.3 (0.7)
23	62.3 (0.2)	23.9 (0.3)	75.8 (0.3)	12	68.2 (0.6)	24.1 (0.3)	82.4 (0.4)
25	61.3 (0.5)	24.9 (0.4)	73.8 (0.8)	13	69.5 (0.1)	25.7 (0.6)	85.1 (0.7)
27	61.1 (0.5)	29.2 (0.7)	74.8 (0.2)	14	65.8 (0.2)	19.0 (0.2)	87.2 (0.3)
29	61.8 (0.2)	31.5 (0.6)	75.8 (0.1)	15	64.5 (0.6)	23.8 (0.5)	78.7 (0.8)
				16	61.2 (0.5)	21.9 (0.4)	80.3 (0.5)

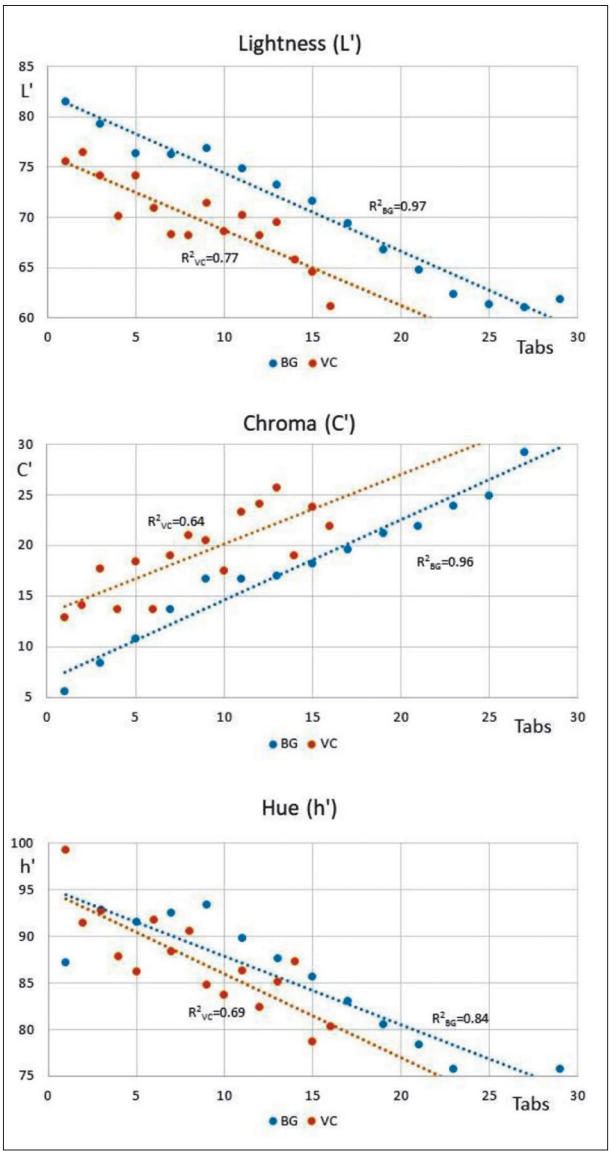

Figure 2. Color coordinate ranges and distribution of VITA Bleachedguide 3D-Master and value scale of VITA classical A1–D4 shade guide; top: lightness (L'); middle: chroma (C'); bottom: hue (h')

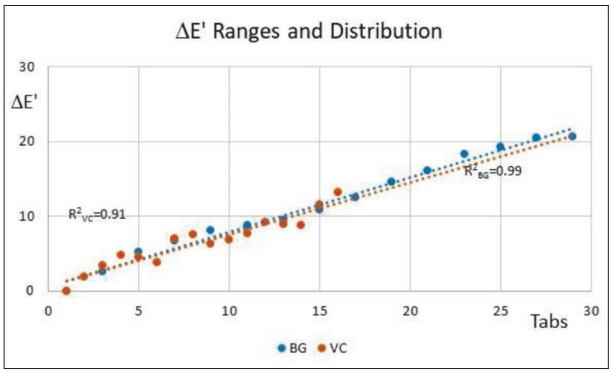

Figure 3. Color differences (ΔE') from the lightest to the darkest tab of VITA Bleachedguide 3D-Master (BG) and value scale of VITA classical A1–D4 (VC) shade guide (according to manufacturer's tab arrangement/order) and corresponding color distribution

Table 2. Average ΔE' values (s.d.) from adjacent tab pairs to 14 tabs apart for VITA Bleachedguide 3D-Master (BG), and from adjacent tab pairs to 15 tabs apart for value scale of VITA classical A1–D4 (VC)

Tab pairs	ΔE' (BG)	ΔE' (VC)
Adjacent tabs	1.9 (0.5)	3.0 (1)
2 tabs apart	3.5 (0.8)	3.2 (1.3)
3 tabs apart	5.0 (1.2)	3.8 (1.4)
4 tabs apart	6.5 (1.4)	3.8 (1.1)
5 tabs apart	8.0 (1.4)	4.8 (1.4)
6 tabs apart	9.5 (1.3)	5.0 (1.9)
7 tabs apart	11.1 (1.1)	5.7 (1.9)
8 tabs apart	12.6 (0.8)	5.6 (0.8)
9 tabs apart	14.0 (0.6)	6.8 (0.6)
10 tabs apart	15.3 (0.8)	7.5 (1.9)
11 tabs apart	16.6 (1.5)	8.5 (1.7)
12 tabs apart	17.9 (1.7)	8.8 (0.1)
13 tabs apart	19.5 (1.5)	10.3 (1.3)
14 tabs apart	20.6	12.3 (1)
15 tabs apart		13.2

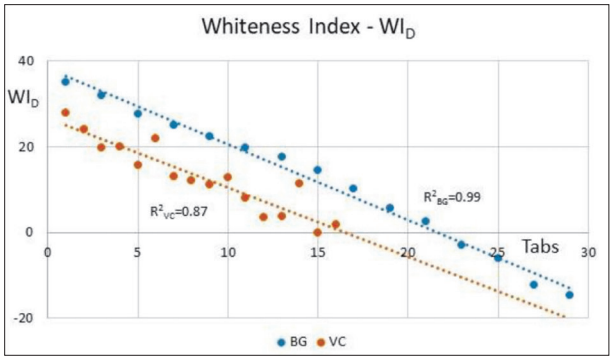

Figure 4. Ranges and distribution of whiteness index for dentistry (WID) for VITA Bleachedguide 3D-Master (BG) and value scale of VITA classical A1–D4 shade guide (VC)

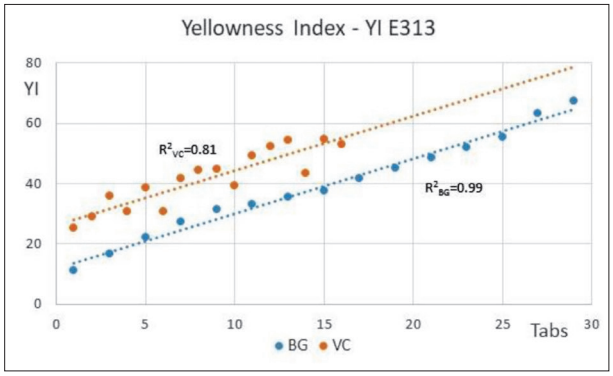

Figure 5. Ranges and distribution of yellowness index E313 (YI) for VITA Bleachedguide 3D-Master (BG) and value scale of VITA classical A1–D4 shade guide (VC)

BG exhibited almost perfect distribution of color differences $R^2 = 0.99$, while corresponding for VC was $R^2 = 0.91$.

WI_D ranges for BG and VC were 49.8 ($R^2 = 0.99$) and 28.0 ($R^2 = 0.87$), respectively, with much more consistent distribution in BG (Figure 4). Corresponding YI ranges were 56.4 ($R^2 = 0.99$) and 29.6 ($R^2 = 0.81$), respectively (Figure 5). Shadowed cells designate shade tabs that are not positioned in accordance with manufacturer order (1–29 tab arrangement for BG and B1–C4 for VC value scale).

The BG and VC comparison of the manufacturer's order (MO, tab arrangement from the lightest to the darkest: 1–29 for BG and 1–16 from B1 to C 4 for VC) and evaluated parameters are presented in Table 3 and Table 4.

Table 3. VITA Bleachedguide 3D-Master shade guide: comparison of the manufacturer's order: MO – tab arrangement from the lightest to the darkest, from 1–29; L' – lightness; C' – chroma; h' – hue; ΔE' – color difference compared to 0M1; WID – whiteness index for dentistry; YI – yellowness index E313

VITA Bleachedguide 3D-Master (1–29)						
MO	L'	C'	h'	ΔE' (1–15)	WID	YI
1	1	1	9	1	1	1
3	3	3	7	3	3	3
5	9	5	3	5	5	5
7	5	7	5	7	7	7
9	7	9	11	9	9	9
11	11	11	1	11	11	11
13	13	13	13	13	13	13
15	15	15	15	15	15	15
17	17	17	17	17	17	17
19	19	19	19	19	19	19
21	21	21	21	21	21	21
23	23	23	23	23	23	23
25	29	25	29	25	25	25
27	27	27	27	27	27	27
29	25	29	25	29	29	29

Table 4. Value scale of VITA classical A1–D4 shade guide: comparison of the manufacturer's order: MO – tab arrangement from the lightest to the darkest, from 1–16; L' – lightness; C' – chroma; h' – hue; ΔE' – color difference compared to 0M1; WID – whiteness index for dentistry; YI – yellowness index E313 (YI)

VITA classical A1–D4, Value scale (1–16)						
MO	L'	C'	h'	ΔE' (1–16)	WID	YI
1	2	1	1	1	1	1
2	1	4	3	2	2	2
3	3	6	2	3	6	4
4	5	2	6	6	3	6
5	9	8	7	5	4	3
6	11	10	4	4	5	5
7	6	3	14	9	10	10
8	4	5	11	10	7	7
9	13	7	13	7	8	14
10	10	14	5	8	14	8
11	8	9	9	11	9	9
12	12	16	10	14	11	11
13	7	11	12	13	13	12
14	14	15	16	12	12	16
15	15	12	15	15	16	13
16	16	13	8	16	15	15

DISCUSSION

The null hypothesis was rejected as difference between BG and VC were recorded in each of evaluated color parameters. L' and C' coordinate ranges were much wider than the corresponding VC ranges, while the h' range was slightly narrower. Differences among R^2 values for individual color coordinates vs. manufacturer-suggested tab order (from lightest to darkest), however, clearly demonstrated both the advantages of BG in terms of uniformity of shade distribution and inconsistencies of VC value scale tab arrangement. The same is true for R^2 values among pairs of color coordinates (L'/C', L'/h' and C'/h'). This is not very surprising given that VC, introduced in 1956, has not originally been developed for tooth whitening monitoring. The modern-day whitening practically started in 1989 [17]. It is also important to mention that color coordinates of BG consistently mimic the behavior of natural teeth upon whitening: from far right (tab #29 or 5M3) to far left (tab #1 or 0M1) the tabs become lighter (L'↑), less chromatic (C'↓) and less red (h'↓).

When it comes to color differences (ΔE') from the lightest to the darkest and tab of the two shade guides, the BG ΔE' range was 56% wider and more uniform ($R^2 = 0.99$) than the corresponding VC range. The average ΔE' among pair of adjacent tabs was 1.9 for BG and 3.0 for VC, with the former one representing 2 SGU as BG tabs are marked

with odd numbers 1–29 (with maximal shade change of 28 SGU), and the later one corresponds to 1 SGU (with maximal shade change of 15 SGU). Hence, 1 SGU of BG corresponded to ΔE' = 1.0.

Another important consideration involves the overlapping of shades that reduces the quality of color distribution, i.e., color uniformity. Given the mean color difference between the adjacent tabs, the color difference for 14 tabs apart of BG would ideally be 1.9 × 14 = 26.6; corresponding calculation for 15 tabs apart of VC would be 3 × 15 = 45. This means that the shade overlapping for BG is 23% (BG range of ΔE' = 20.6 is 77% of the ideal range of ΔE' = 26.6), and 71% for VC (VC range of ΔE' = 13.2 is 29% of the ideal range of ΔE' = 45). Consequently, 1 SGU for BG would correspond to ΔE' = 0.7 (ΔE' = 1 was reported), while VC shade change of 1 SGU would correspond to ΔE' = 0.88 (ΔE' = 3 was reported). This result provides additional evidence of uniformity and lack of it for BG and VC, respectively.

Another concern with BG is that B1 is the lightest shade in value scale. If patient's teeth are very light before bleaching (close to B1 shade), visual monitoring for these patients becomes a problem, as the value scale has no tabs that would correspond to shade after whitening. The B1 shade, being the lightest shade in VC, has frequently resulted in recruitment exclusion of teeth that are lighter than A3 (#9 on a value scale) before bleaching. In this fashion, approximately 50% of patients would be excluded from the study [18], and these studies would, essentially, report on "tooth whitening efficacy for darker teeth." Using the parameter that is to be evaluated as inclusion/exclusion criterion does not contribute to objectivity of findings. The problem of the lack of very light shades has been resolved in BG as the closest match to B1 is 1M1.5 (ΔE' = 1.9), which is #7 in BG. This enables the inclusion of all patients into whitening studies, given that there are practically no patients with teeth lighter than 0M1, before or after bleaching. Adding of tabs from group "0" from Linearguide 3D Master to VC value scale can partly resolve the "B1 issue," but one should keep in mind that there is a huge gap (ΔE'≈ 5.0) between 0M3 and B1.

The first whiteness index optimized for dentistry (WIO) has been reported in 2009 and validated in subsequent publication [19]. However, the WI_D has been the first CIELAB-based whiteness index specifically designed for dental application as it was developed based on correlations with visual perception of tooth shaped shade tabs and dental materials [15]. In a recent study, the performance of existing equations that measure perceptual whiteness of teeth was assessed concluding that indexes that have been optimized for use with tooth whiteness (WIO and WI_D) performed better than the more general CIE whiteness index (WIC) [20]. Similarly to other results, the BG WI_D exhibited a wider range and more consistent color distribution as compared to VC. The same is true for the yellowness index YI E313. The BG is therefore expected to provide a better coverage for color of bleached teeth or for those teeth that present uncommon colorimetric coordinates.

It was reported that the visually determined order of BG tabs from 1–29 was identical with the manufacturer's tab arrangement, which was not the case with the VC value scale [7]. Shadowed cells in Table 3 and Table 4, designating tabs that are not positioned in accordance with manufacturer order, provide further evidence on the advantages of BG over VC. Here are some examples of VC inconsistencies and explanations from respective columns in Table 4:

- L': tabs #4, 6, 7, and 8 are darker than tabs #11 and 14; the tabs with lower number should be lighter (should have higher L' value);
- C': tab #9 is more chromatic (higher C' values) than tabs #11, 13, and 14; the tabs with lower number should be less chromatic (should have lower C' value);
- h': tab #9 has lower hue angle (redder) than tabs #11, 13, and 14; the tabs with lower number should be less red (should have greater h' value);
- ΔE' compared to B1: ΔE' between tabs 1 and 8 is greater than 1 to 9 and 1 to 10; the tabs with lower number should exhibit lower color difference to B1 (tab #1).
- WI_D: tab #9 have lower WI_D than tabs #10 and 14; the tabs with lower number should be "whiter" (should exhibit greater WI_D);
- YI: tab #14 has lower YI than tabs 8, 9, 11, 12, and 13; the tabs with lower number should be less "yellow" (should exhibit lower YI).

In addition to aforementioned, the overall color analysis revealed that VC was darker (L'), more chromatic (C'), redder (h'), whiter (WI_D), and less yellow (YI) than BG. Consequently, the BG was lighter, less chromatic, less red, less white, and more yellow.

CONCLUSION

VITA Bleachedguide 3D-Master exhibited wider L', C', ΔE', WI_D, and YI ranges compared to value scale of VITA classical A1–D4 shade guide and better distribution of evaluated color parameters. This, together with the presence of several shades lighter than B1 of VC, recommends the usage of BG for visual evaluation of tooth whitening efficacy.

CONFLICT OF INTEREST STATEMENT

VITA Bleachedguide 3D-Master shade guide was jointly developed by Dr. Rade D. Paravina and VITA Zahnfabrik. The University of Texas HSC at Houston has executed licensing agreements with VITA dealing with commercialization of these shade guides. Dr. Paravina is a paid consultant for VITA Zahnfabrik.

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Колориметријско (*CIEDE2000*) поређење два кључа за одређивање боје који се користе за визуелно процењивање ефикасности избељивања зуба

Раде Д. Паравина[1,2], Натали А. Переира Санчез[1,2], Разван Гинеа[2,3], Џон М. Пауерс[4]

[1]Универзитет Тексаса, Стоматолошки факултет у Хјустону, Одељење за ресторативну стоматологију и протетику, Хјустон, Тексас, САД;
[2]Хјустонски центар за биоматеријале и биомиметике, Хјустон, Тексас, САД;
[3]Универзитет у Гранади, Природно-математички факултет, Одсек за оптику, Гранада, Шпанија;
[4]*Dental Consultants*, *Inc*., Ен Арбор, Мичиген, САД

САЖЕТАК

Увод/Циљ Циљ истраживања је био да се изврши колориметријско поређење два кључа за боју који се користе за визуелно процењивање ефикасности избељивања зуба.

Методе Кључеви за одређивање боје зуба *VITA Bleachedguide 3D-Master* (*BG*) и *VITA classical A1–D4, value scale* (*VC*) ($n = 3$) испитивани су помоћу неконтактног спектрорадиометра. Опсези, дистрибуција и однос између параметара боје су испитивани коришћењем једначине *CIEDE2000* за разлику у боји. Оптимизовани *whiteness index* за стоматологију (*WID*) и *yellowness index E313* (*YI*) такође су анализирани. При статистичкој обради података коришћени су *ANOVA* и Фишеров *PLSD* тест ($\alpha = 0,05$).

Резултати Светлина – *lightness* (*L'*), засићеност – *chroma* (*C'*) и основна боја – *hue* (*h'*), односно *L'C'h'* опсези од 20,4, 25,9 и 19,1 забележени су код *BG*. Одговарајући опсези за *VC* су били 15,3, 10,9 и 20,6. R^2 вредности за индивидуалне колор координате у односу на распоред узорака су биле више за *BG* него за *VC*. Исто важи и за R^2 вредности парова колор координата за *BG*/*VC*: *L'C'* = 0,89/0,33, *L'h'* = 0,88/0,53 и *C'h'* = 0,70/0,51. *BG* је имао бољи однос између оригиналног распореда узорака и разлике у боји ($\Delta E'$), WI_D и *YI* вредности. $\Delta E'$ између најсветлијег и најтамнијег узорка је био 20,6 за *BG* и 13,2 за *VC*. Просечна разлика у боји између суседних узорака је била 1,9 (0,5) за *BG* (2 *SGU*, *shade guide units*) и 3,0 (1,0) за *VC* (1 *SGU*).

Закључак Утврђено је да *BG* има шире *L'*, *C'*, $\Delta E'$, WI_D и *YI* опсеге и бољу дистрибуцију анализираних параметара боје у поређењу са *VC* кључем. Ово, као и присуство неколико нијанси светлијих од *B1* нијансе у *VC*, препоручује коришћење *BG* за визуелно процењивање ефикасности избељивања зуба.

Кључне речи: избељивање зуба; боја; стоматологија; психофизика; кључ боја

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The first dental visit – comparative analysis of two successive five-year periods

Duška Blagojević[1,2], Ljubica Pavlović-Trifunović[3], Milica Šipovac[1], Isidora Nešković[1,2], Sanja Vujkov[1,2], Bojan Petrović[1,2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Dentistry Clinic of Vojvodina, Department of Preventive and Pediatric Dentistry, Novi Sad, Serbia;
[3]Public Health Care Center, Novi Sad, Serbia

SUMMARY

Introduction/Objective An important moment in oral health care and preventive dentistry is the first dental visit, recommended to be undertaken between the child's sixth and 12th month of life. Worldwide evidence shows a considerable delay. This study evaluates characteristics of the first dental visit in a public health care center in Novi Sad, Serbia, during 2006–2015 period, and changes in occurrence driven by the healthcare reform.

Methods The study design was retrospective, evaluating available data on age and the main reason for the first dental visit of 270 children, who come to the same dentist and pediatrician in a public health care center during the 2006–2015 period.

Results Collected data determined the third and the fourth year of life as the dominant age (45.8% of children) for the first dental visit in 2006–2010, initiated mostly by a dental check-up (53.8%). During the second period (2011–2015), most of the first visits (31.1%) were done by the age of one, while the main reason for 80.1% of the visits was dental check-up.

Conclusion Considerable progress regarding the first dental visit was made in the observed period, which is, at least partially, due to the health care reform and emphasized preventive versus curative measures, by means of advanced communication between parents and chosen medical staff in prenatal and pediatric clinics.

Keywords: caries; dental visit; oral health promotion

INTRODUCTION

One of the essential components of general health is certainly oral health, since it concerns all age groups – from newborns to elders. Even though the most common public belief is that oral care begins at the time of the eruption of the first tooth, it is actually initiated far earlier: good oral hygiene practices are formed as soon as the child is born, with the oral cavity regularly cleaned. Later, when the children's teeth first erupt, parents should begin cleaning with damp face towels, wash cloth wrapped around a finger, or a very soft toothbrush, as the American Academy of Pediatric Dentistry recommends, and continuing with toothbrushing with fluoride toothpaste [1–4]. However, the cleaning is not the only issue that can influence future oral health condition, and parents should be aware of feeding and dietary habits related to oral health, the use of pacifiers, digit sucking, age-appropriate injury prevention, frequency of dental visits, etc. [5, 6]. Overall, they must be enlightened that most oral diseases are preventable. Thus, an important moment in the lifelong program of oral health care and preventive dentistry is certainly the first dental visit, when the appropriate, most significant data regarding oral health care and the preventive measures should be presented to parents [7]. According to recommendations of the American Academy of Pediatric Dentistry, but also other relevant associations, such as the European Academy of Paediatric Dentistry, the American Dental Association, the American Academy of Pediatrics, the American Association of Public Health Dentistry, the Academy of General Dentistry, dental visits begin with the appearance of a child's first tooth, typically around six months of life but no later than the age of one year [2]. Still, there are many reports which demonstrate that the first dental visit is prolonged and that it was commonly initiated after a decay noticed by a parent, caries-related pain and other lesions, followed by a routine check-up [7–11].

Concerning the initiation of the first dental visit, it is expected that pediatricians advise parents [12]. Additionally, another approach to timely education of parents, especially expectant mothers, was revealed [13, 14, 15]. Namely, it is considered that mothers are a primary source of early education in children; they care about good hygiene and healthy nutritional practices of their children, and, consequently, the children's oral condition depends of their knowledge about positive attitudes towards oral habits. Moreover, expectant mothers systematically go to the healthcare facilities, generally are willing to follow counsel during pregnancy, and

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Correspondence to:
Duška BLAGOJEVIĆ
Department of Preventive and Pediatric Dentistry
Dentistry Clinic of Vojvodina
Faculty of Medicine
University of Novi Sad
Hajduk Veljkova 12
21000 Novi Sad, Serbia
duska.blagojevic@mf.uns.ac.rs

are more open to health-related information [16]. Thus, they could be targeted by health education programs. For instance, a gynecologist can present the importance of a mother's state of oral cavity for the child's development, early childhood caries development, transmission of the oral infection, etc., but can also point out the importance of the first dental visit. Furthermore, the presence of the dental staff at prenatal classes is necessary to introduce the concept of the early dental visit and to increase the awareness of the overall importance of oral and dental health as part of general health [17].

Considering the above-explained importance of the first dental visit, the main aim of this study was to evaluate the characteristics of the first dental visit in a public health care center (PHCC) in Novi Sad, Serbia, during the 2006–2015 period, and changes in occurrence driven by the healthcare reform.

Table 1. Overview of the children's age at the first dental visit during the two observed periods: 2006–2010 and 2011–2016

Year of children's life at first dental visit	Percentage of patients	
	Period I: 2006–2010	Period II: 2011–2015
First	12.1%	31.1%
Second	11.7%	25.5%
Third	23.5%	24.4%
Fourth	22.3%	11.1%
Fifth	17.8%	7.7%
Sixth	12.5%	0%

Table 2. Overview of the main reasons for the first dental visit during the two observed periods: 2006–2010 and 2011–2016

Main reasons for the first dental visit	Percentage of patients	
	Period I: 2006–2010	Period II: 2011–2015
Dental check-up	53.8%	80.1%
Dental trauma	14.6%	2.2%
Pain	31.6%	17.7%

METHODS

Subjects

The research target group were children attending public dental clinics belonging to the Jovan Jovanović Zmaj PHCC in Novi Sad, Serbia. The presented study includes data on 270 children, of both sexes, who come to the same dentist and pediatrician in primary healthcare clinics of the same PHCC. The consent for this research was given by the Ethics Committee of the Jovan Jovanović Zmaj PHCC.

Data collection

The data was collected retrospectively from dental records. Information about each child's age and the main reason for the first dental visit was recorded. A data set for two periods was formed: the first observed period was from year 2006 to 2010, and the second one was from 2011 to 2015.

Ethical considerations

The study was conducted without shared consent from the families involved. We handled all the material with confidentiality. The data was collected after the Ethics Committee approval (No. 21/29-2) and the research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki.

RESULTS

The data on the children's age and main reasons for their first dental visit during the two periods was collected retrospectively from dental records. According to the results, presented in Table 1, in the first observed period, the initial dental visit was made by almost the same number of children during the first and the second year of life (12.1% and 11.7%, respectively), as well as the fifth and sixth (17.8% and 12.5%, respectively). Similarly, almost analogous number of two- to three-year-olds (58, 23.5%) and three- to four-year-old children (55, 22.3%) visited the dentist for the first time, which determined the third and the fourth year of life as the dominant age for the first dental visit in the 2006–2010 period. At the same time, the main reason (Table 2) for the first dental visit was predominantly a dental check-up (53.8%), followed by pain (31.6%), and dental trauma (14.6%). During the second period, from 2011 to 2016, our data showed different situation: most of the first visits (31.1%) were done by the age of one, while the main reason for 80.1% of the first dental visit was a dental check-up. In the second period, first visits during the second year were also intensified (up to 25.5%), and there was no child over five and under six years old who had not visited the dentist yet.

DISCUSSION

Despite a clear recommendation that the first dental visit should be undertaken around six months of life but no later than the age of one year, worldwide evidence shows that there is a considerable time delay [1]. For example, a report from the Wroclaw Medical University, Poland, showed that 9.5% of the children had their first dental visit by the age of one, 21.5% of the children had their first dental visit between the ages of one and two years, 22.5% of the children visited the dentist for the first time when they were between the ages of two and three years, 38.7% of the children first visited the dentist when they were older than three, and 5.8% of 6–7-year-olds had not visited the dentist yet [7]. Leroy et al. [8] demonstrated that 62% of three-year-old children and 21% of five-year-old children in Belgium had not visited the dentist yet. According to data from Riyadh, Saudi Arabia, 32.2% of children had their first dental visit between the ages of one and three, but 52.9% of the group had their first dental visit between the third and fifth, and 14% between the fifth and eighth year of life. One percent of children had their first dental visit when they were older than eight years [10]. Also, a Bulgarian study reported that the majority of

children making their first dental visit were 3–6 year-olds (51.9%) and the least attendance was in the children younger than one year (1.73%) [9]. According to another study from Iowa, USA, of 340 parents who completed questioners, 2% reported having taken their child for a dental visit by one year of age, 11% by two years of age, and 31% by three years of age [11]. In contrast, a study in four communities within Manitoba, Canada, reported that 74.7% of caregivers (guardians and majority being mothers) favored a dental visit by the age of one year [17]. In general, apart from the latter study, all of the listed studies are in accordance with findings concerning the first period of our research: about 10% or even less children visited the dentist in the first year of their life. However, during the second period of our research, a significant increase in the early visits could be noticed: over 30% of children went to the dentist before the first birthday. One of the major factors of this change could be the result of the health care reform in Serbia, conducted between 2004 and 2012. Namely, in Serbia, the Ministry of Health is the owner of public health facilities and provides funding, monitoring, and control of public healthcare activities in public health institutes. On the other hand, the National Health Insurance Fund provides compulsory social insurance and ensures that insured persons may exercise their healthcare rights governed by the Law on Health Insurance [18]. One of the rights under compulsory health insurance is right to health care, which involves, among other things, examination and treatment of mouth and teeth diseases. These essential healthcare rights were the same in both observed periods. However, the healthcare reform aimed to modify the existing system and to put the focus on primary healthcare service. In addition, it emphasized preventive measures versus curative ones in order to decrease the rate of preventable diseases and to reduce health expenditures. Among other things, patients can choose their general practitioner, pediatrician, occupational health specialist, dentist, gynecologist, etc., who can then continuously monitor their health. In regard to the first dental visit, this had an immediate impact by advancing the communication between the chosen general practitioners (pediatricians), dentists, and even gynecologist and medical staff at prenatal classes. At the health care center where this study was conducted, the flow of information and good practice on advising about the importance of the first dental visit was constantly performed by a listed medical staff, as it was implicated by the health reform instructions. This enhanced communication, as it was conducted in appropriate primary healthcare clinics, where data for this research was collected and where children and their parents, particularly mothers, were receiving health care, obviously resulted in an increased awareness about the importance of the first dental visit before the child's first birthday.

Furthermore, the main reasons for the first dental visit were quite diverse. Dental check-up stands as the main reason in a report by Leroy et al. [8] for over half the subjects (54.3%); the reason for one third of the subjects was decay noticed by a parent, and for the remaining subjects the reasons were caries-related pain (9.1%) and other lesions (2.5%). According to a study by Murshid [10], pain was the dominant factor (71.5%) which brought children to their first dental visit, while a check-up was the main reason for 27.3% of children. A study from Nigeria reported that toothache was the reason for a child's first visit to the dentist in 47.4% of the cases, while a routine dental check-up accounted for 42.7% [19]. Even in this case, the results from the two observed periods in our research can support positive influence of advanced communication between all subjects involved in a child's oral care. Namely, a dental check-up become a pronouncedly dominant reason for the first dental visit in the second period, reflecting the positive influence of the healthcare reform, while dental trauma and pain were diminished.

Regarding the limitation of this study, the method of collecting the data on the first dental visit was convenient for the authors due to their direct access to patient records, but some impedance that may have affected the study results should be noted. For example, the PHCC where this study was conducted is one of the biggest regional PHCCs and it accommodates clinics of general practitioners (pediatricians), dentists, and gynecologist and prenatal classes. Furthermore, patients regularly choose one PHCC for the primary health care and prevention. Therefore, although authors did not access records of parents (mothers), it was considered that the parents' (mothers') health was regularly monitored, and that expectant mothers attended prenatal classes at the same PHCC. Also, this PHCC is situated in an urban area and future studies including different clinics in different cities or rural areas are strongly recommended.

CONCLUSION

An important moment in the lifelong program of oral health care and preventive dentistry is certainly the first dental visit, recommended to be undertaken around the child's sixth month of life but no later than its first birthday. However, worldwide evidence shows that there is considerable time delay, which was also noticed in the presented study. Nonetheless, the healthcare reform, conducted in Serbia from 2005, focused on primary healthcare service and emphasizing preventive measures versus curative ones, contributed, at least partially, to some notable changes: the time for the first dental visit was changed from the third and the forth (dominant in the 2006–2010 period) to the first year of life (2011–2016), followed by a significant increase of the dental check-up as the main reason for the first dental visit (from 53.8% to 80.1%). However, even though considerable progress has been made, further strengthening of the partnership between medical and dental professionals through more organized prevention, promotion, and education programs are needed in Serbia in order to introduce early dental visits as a common, routine medical appointment.

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Прва посета стоматологу – компаративна анализа два узастопна петогодишња периода

Душка Благојевић[1,2], Љубица Павловић-Трифуновић[3], Милица Шиповац[1], Исидора Нешковић[1,2], Сања Вујков[1,2], Бојан Петровић[1,2]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Клиника за стоматологију Војводине, Одељење дечје и превентивне стоматологије, Нови Сад, Србија;
[3]Дом здравља Нови Сад, Нови Сад, Србија

САЖЕТАК

Увод/Циљ У циљу очувања оралног здравља веома је важна прва посета стоматологу, која је препоручена да се обави између шестог и дванаестог месеца живота детета. Подаци из целог света указују да се прва посета дешава касније. Циљ овог рада је био да анализира карактеристике прве посете стоматологу и промене после реформи у здравству.
Методе Ретроспективно су анализирани подаци о узрасту и разлогу прве посете стоматологу 270 деце која су посећивала истог стоматолога и педијатра у Дому здравља Нови Сад од 2006. до 2015. године.
Резултати У периоду од 2006. до 2010. године доминантан узраст у коме су деца први пут прегледана је био између три и четири године (45,8%), а разлог је био рутински стоматолошки преглед (53,8%). У периоду од 2011. до 2015. године већина посета је обављена у првој години живота (31,1%), а разлог је такође био стоматолошки преглед (80,1%).
Закључак У посматраним периодима је приметан знатан напредак у узрасту у коме су деца дошла у прву посету стоматологу, који се догодио захваљујући здравственим реформама и побољшаним превентивним мерама, као и бољој комуникацији између родитеља, педијатара и изабраних стоматолога.

Кључне речи: каријес; посета стоматологу; промоција оралног здравља

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Vertical facial disproportions in children with Class III malocclusion

Zdenka Stojanović[1], Jasmina Milić[2], Verica Pavlić[3,4]

[1]Military Medical Academy, Department of Orthodontics, Belgrade, Serbia;
[2]Faculty of Dentistry, Pančevo, Serbia;
[3]University of Banja Luka, Medical Faculty, Department of Periodontology and Oral Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[4]Institute of Dentistry, Department of Periodontology and Oral Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Class III malocclusion is a sagittal intermaxillary disproportion with dominant presence of mandible. Apart from primary sagittal, anomalies in vertical face dimension can also be present. The aim of this study is to evaluate vertical facial disproportions in the skeletal Class III malocclusion in stage of mixed dentition, in order to better plan its early therapy.

Methods In total 100 children were randomly selected and divided according to cephalometric analyzes in the two equal groups: Group 1 (experimental group) – skeletal Class III malocclusion (n = 50) and Group 2 (control group) – skeletal Class I (n = 50). The groups were further divided into three subgroups according to the age and gender of the children. Vertical craniofacial proportions were measured by anterior (upper, lower and total) and posterior facial height and their proportion. The values were statistically analyzed ($p \leq 0.05$).

Results Upper anterior, lower anterior, total anterior and posterior facial height, proportion between lower and total anterior facial height, and proportion of posterior to total anterior facial height did not have a significant difference among children with Class I and Class III malocclusions. Upper anterior facial height proportional to total anterior facial height was statistically significant greater in experimental group when compared to control. Significant gender dimorphism was noted among the same subgroups.

Conclusion Vertical craniofacial proportions in children with Class III malocclusion in stage of mixed dentition was not significantly changed. This finding leaves room for the successful application of early, individually planned orthodontic therapy.

Keywords: Class III malocclusion; mixed dentition; facial height; gender dimorphism

INTRODUCTION

Class III malocclusion is defined as a heterogenous group of skeletal and dental anomalies of intermaxillary relationships, mainly in sagittal dimension. Combination of these anomalies in facial morphology is resulting in dominant presence of the mandible. Beside primary sagittal intermaxillary disharmony, anomalies in vertical dimension could also be present, causing the specific "long face" or "short face" morphology. Vertical facial type, defined by viscerocranium type and direction of rotation to cranial base, is the most responsible (apart from genetic) for Class III malocclusion. Vertical facial height is directly depending on mutual relations of jaws' bones to cranial structures. Therefore, malocclusions are considered developmental anomalies that are the result of a specific development. That is the reason why they are having a full clinical appearance only when craniofacial growth is over.

Linear parameters for facial analysis varied according to age, gender, ethnic race and other characteristics. That is the reason why proportions among linear parameters are having greater importance in practice.

The cephalometric analysis proposed by Johnson, which represents an addition to Wylie's analysis, suggested that the relationships in anterior facial height can be considered normal if upper segment of anterior facial height is 45% of total anterior height, and if lower is 55%.

Jarabak's, which is based on the Björk's cephalometric analysis, suggested that the relationship between anterior and posterior facial height should be 62–65% of anterior facial height. If that relationship is bigger than 65%, facial growth is determined by anterior rotation-convergent type of growth, which will probably lead to the development of the "short face" or deep bite. If the relationship is lower than 62%, it will cause a backward rotation-divergent type, leading to "long face" and open bite [1].

Estimation of the facial height in Class III malocclusion is having a huge practical importance in early prediction of the therapy success. Hyperdivergent growth type, determined by lower values of this proportion ("long face") is, according to many authors, considered to be a bad prognostic sign in the therapy outcome [2]. This fact is very important when therapy plan for Class III malocclusion is made, and should be considered mandatory (keeping in mind a

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Correspondence to:
Zdenka STOJANOVIĆ
Department of Orthodontic, Military Medical Academy
Crnotravska 17, 11000 Belgrade, Serbia
zdebra@sezampro.rs

Table 1. The measurements of this study and the result of subgroup comparison

The measurements parameters	Group	Subgroup years	X ± SD		p
			Male	Female	
Upper anterior facial height **NSna**	1	**a/** 6–7.11	51.50 ± 4.28	49.17 ± 1.60	0.29 NS
		b/ 8–9.11	49.17 ± 3.57	52.17 ± 4.63	1.00 NS
		c/ 10–12	53.22 ± 3.42	53.29 ± 1.98	0.79 NS
	2	**a/** 6–7.11	49.67 ± 0.58	48.75 ± 1.50	0.27 NS
		b/ 8–9.11	52.46 ± 2.54	51.08 ± 2.63	0.37 NS
		c/ 10–12	53.64 ± 2.11	53.25 ± 3.28	0.59 NS
Lower anterior facial height **SnaMe**	1	**a/** 6–7.11	65.00 ± 5.57	62.00 ± 3.41	0.94 NS
		b/ 8–9.11	65.50 ± 2.80	63.33 ± 4.85	0.32 NS
		c/ 10–12	67.56 ± 4.56	66.14 ± 3.76	0.56 NS
	2	**a/** 6–7.11	65.00 ± 5.57	66.25 ± 4.35	0.86 NS
		b/ 8–9.11	66.00 ± 3.07	62.39 ± 3.10	0.01**
		c/ 10–12	67.64 ± 3.44	63.13 ± 4.64	0.02*
Total anterior facial height **NMe**	1	**a/** 6–7.11	113.33 ± 8.12	111.60 ± 5.32	0.78 NS
		b/ 8–9.11	117.10 ± 4.84	115.50 ± 8.13	0.32 NS
		c/ 10–12	120.78 ± 6.26	119.43 ± 4.24	0.75 NS
	2	**a/** 6–7.11	114.67 ± 5.69	115.00 ± 4.97	1.00 NS
		b/ 8–9.11	118.46 ± 4.16	113.46 ± 4.70	0.02*
		c/ 10–12	121.27 ± 4.54	116.38 ± 4.31	0.05*
Posterior facial height **SGo**	1	**a/** 6–7.11	69.50 ± 5.54	67.00 ± 3.52	0.47 NS
		b/ 8–9.11	75.30 ± 4.64	73.00 ± 6.81	0.32 NS
		c/ 10–12	77.67 ± 8.22	75.86 ± 5.05	0.83 NS
	2	**a/** 6–7.11	74.33 ± 5.69	71.75 ± 4.92	0.48 NS
		b/ 8–9.11	76.36 ± 7.06	69.39 ± 6.25	0.02*
		c/ 10–12	74.82 ± 4.12	72.38 ± 5.98	0.51 NS

NS – p > 0.05 – not significant;
*p < 0.05 – significant;
**p < 0.01 – highly significant, Mann–Whitney, Wilcoxon test

complex combination of genetic and environmental factors). Early therapy should be considered as "the focus" of orthodontic therapy. This can be the ideal time to eliminate bad habits, such as thumb sucking, mouth breathing, enlarged adenoid vegetation, just to name a few. The benefit of orthodontic prevention is wide, having in mind a potential to self-correct an open bite, malocclusion Class III, incisal overbite [3, 4]. Later, intrusion of the molars with mini implants showed satisfying results in the therapy of closing the open bite (better results obtained in adolescents than in adults, which is in accordance with previously published studies [5, 6].

METHODS

This study included children with skeletal Class I and III, in stage of mixed dentition, aged 6–12 years, both sexes, that have never undergone any orthodontic treatment before. This study did not include children with congenital anomalies, clefts and hypodontia. To all participants, gnathometric analyses of the dental casts were done. Further, panoramic radiographs and lateral cephalometric radiograms (natural position of the head with lateral teeth in maximal intercuspation) were analyzed. According to the cephalometric and gnathometric analyses, participants (n = 100) were divided into two groups: first (experimental) group (n = 50) included children with Class III malocclusion with negative overjet (OJ) and angle of sagittal intermaxillary relationship ANB ≤ 0° (Figure 1). Second (control) group (n = 50) included children with Class I with normal OJ and normal values of sella–nasion–point angles SNA = 80–82°, SNB = 78–80° and point–nasion–B point angle ANB = 2–4° (Figure 1). On lateral cephalometric radiograms face length was determined by linear parameters such as upper anterior, lower anterior, total anterior and posterior facial height (NSna, SnaMe, NMe

Figure 1. Angular cephalometric measurements for selection into groups used in the study: SNA – angle of sagittal maxillary position in relation to the cranial base anterior; SNB – angle of sagittal mandibular position in relation to the cranial base anterior; ANB – angle of sagittal intermaxillary relationship

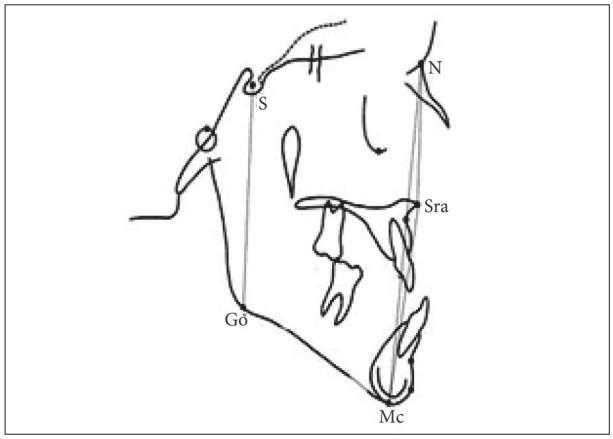

Figure 2. Cephalometric landmarks and linear measurements for assessment facial height: S – sella – the center of sella turcica; N – nasion – the most anterior limit of suture nasofrontalis; Me – menton – the lowermost point on the shadow of the mandibular symphysis; Go – gonion – the most outward point on the angle formed by the junction of the ramus and body of the mandible on its posterior, inferior aspect; Sna – spina nasalis anterior – the apex of the anterior nasal spine; NSna – upper anterior facial height; SnaMe – lower anterior facial height; Nme – total anterior facial height; Sgo – posterior facial height

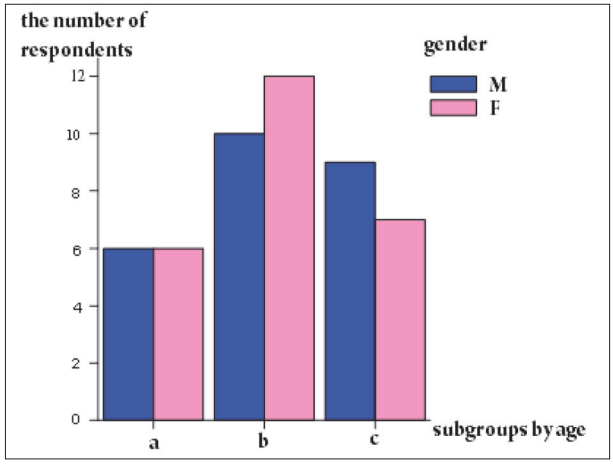

Figure 3. Distribution of respondents in subgroups according to gender and age in Group 1 (experimental group); a – subgroup; age: 6–7 years and 11 months; b – subgroup; age: 8–9 years and 11 months; c – subgroup; age: 10–12 years

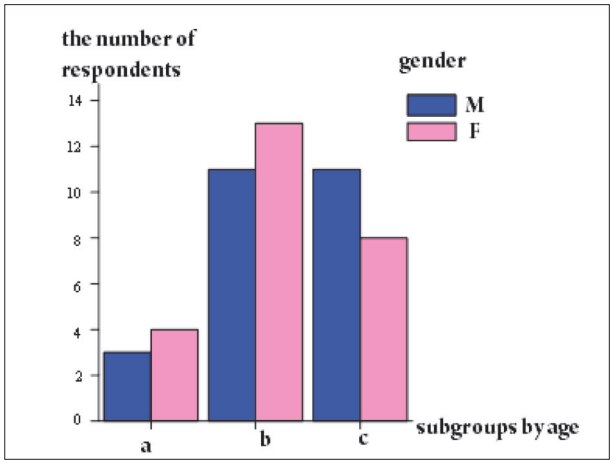

Figure 4. Distribution of respondents in subgroups according to gender and age in Group 2 (control group); a – subgroup; age: 6–7 years and 11 months; b – subgroup; age: 8–9 years and 11 months; c – subgroup; age: 10–12 years

and SGo) and their proportion NSna/NMe, SnaMe/NMe, SGo/NMe (Table 1, Figure 2).

Mean age of the participants in the experimental group was eight years and nine months, and in control group nine years and three months. The participants from both groups were further divided in the subgroups according to the sex (F = 25, M = 25) and age (Figure 3, 4):

a – subgroup; age: 6–7 years and 11 months;

b – subgroup; age: 8–9 years and 11 months;

c – subgroup; age: 10–12 years.

In order to detect significant differences between groups, Multiple comparisons and Brown-Forsythe test were used, and to access significant difference among patients related to gender and age, Mann–Whitney and Wilcoxon's tests were used. A 95% confidence level ($p < 0.05$) was considered statistically significant, while a 99% confidence level was considered highly statistically significant.

This study was done in accord with standards of the Institutional Committee on Ethics.

RESULTS

The upper anterior facial height for the participants from the Group 1 were 46–72 mm (mean height: 51.96 mm). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$). The upper anterior facial height for the participants from the Group 2 were 47–58 mm (mean height: 52.02 mm). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$) and with no significant difference compared to Group 1 ($p > 0.05$).

The lower anterior facial height for the participants from Group 1 were 53–74 mm (mean height: 64.58 mm). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$). Lower anterior facial height for the participants from Group 2 were 56–76 mm (mean height: 64.92 mm). These values were with no significant difference compared to Group 1 ($p > 0.05$). Statistical significance between gender was noted in the middle (b) and the oldest (c) age subgroup ($p \leq 0.01$, $p \leq 0.05$).

Total anterior facial height for the participants from Group 1 were 103–131 mm (mean height: 116.69 mm). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$). Total anterior facial height for the participants from Group 2 were 105–132 mm (mean height: 116.94 mm). Statistical significance between gender was noted in middle (b) and the oldest (c) age subgroup ($p \leq 0.05$) and with no significant difference compared to Group 1 ($p > 0.05$).

The posterior facial height for the participants from Group 1 was 60–94 mm (mean height: 73.56 mm). Even though these values were of huge range; from 67 mm in female participants in the youngest (a) subgroup, to 77.67 mm in male participants in the oldest (c) age subgroup, there was no significant difference between genders in the same age subgroups ($p > 0.05$). Posterior facial height for the participants from Group 2 were 59–92 mm (mean height: 73.08 mm). These values were with no significant

difference compared to Group 1 ($p > 0.05$). Significance among sexes was noted only in the middle (b) age subgroup ($p \leq 0.05$), where lowest value was 69.39 mm and highest value was 76.36 mm for males.

The proportion between upper and total anterior facial height for the participants in Group 1 was in range 40.98 to 48.54 (mean value: 44.9). Significance among sexes was noted only in the youngest (a) age subgroup ($p \leq 0.01$). Proportion between upper and total anterior facial height for the participants in Group 2 were in range 40.68–50.88 (mean value: 44.50). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$), but were highly significant compared to Group 1 ($p \leq 0.05$).

The proportion between lower and total anterior facial height for the participants in Group 1 were in range 51.46–63.93 (mean value: 55.54). Significance among gender was noted only in the youngest (a) age subgroup ($p \leq 0.01$). The proportion between upper and total anterior facial height for the participants in Group 2 were in range 49.12–59.32 (mean value: 55.50). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$), and with no significant difference compared to Group 1 ($p > 0.05$).

Values for the proportion of posterior to anterior facial height in the Group 1 were in range of 50.42–73.73 (mean value: 63.16). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$). Values for the proportion of posterior to anterior facial height in Group 2 were in range of 51.75–74.80 (mean value: 62.51). These values were with no significant difference between genders in the same age subgroups ($p > 0.05$), and with no significant difference compared to group 1 ($p > 0.05$).

DISCUSSION

Etiology of Class III malocclusions is multifactorial, which includes genetic, environmental factors, static and functional muscle factors, as well as individual growth [3, 4]. Many studies investigated sagittal, vertical and transversal changes during growth of the children with Class III malocclusion [7, 8, 9]. The facial growth pattern (anterior or posterior rotation) can lead to vertical craniofacial disproportions, i.e. deep or open bite, but it also affects the sagittal relationship between the jaws and can cause potential disproportions in that plane. Also, there are some studies that have investigated the relationship between the position of the cervical vertebrae and the vertical craniofacial traits [10, 11]. Modern point of view states that the development is related to the presence of dimensional proportions among specific anatomic structures and change of these proportions during growth. The head bones during growth are making a bone mass, rotating and changing in all three dimensions [11]. At imbalanced growth, anterior rotation can dominate causing horizontal growth type with tendency of deep bite growth. Present combination of the facial bones growth types, together with the growth of accompanied surrounding structures, affects type of the whole face, that can encourage or discourage Class III malocclusion and wide morphologic variation of it [12, 13].

Elis et al. [14] compared patients with Class III malocclusion with an open bite and patients with Class III malocclusion without an open bite, while Jacobson et al. [15] defined subclassification of Class III malocclusion of the two big groups according to vertical dimension of the face-divergent and convergent. In order to define the model of vertical growth of the face bones, that will determine their mutual relation to cranial structures, defining a vertical dimension of the face using angular and linear parameters.

The vertical dimension of the face is largely determined by the position of the mandible. Angle of shaft growth (SGnFH), the angle indicating the direction of the mandible growth relative to the cranial base (NSGn) and Y axis of the face (SGn) are parameters that show the mandibular growth model. Their values can be significantly reduced in Class III malocclusions [16].

For the estimation of the vertical facial height, it is very important to determine vertical direction of maxilla to cranial structures [16–19]. Shuster et al. [20] confirmed the importance of this parameter in children with Class III malocclusion in assessing the need for future orthodontic-surgical therapy. Analysis of angle indicator vertical intermaxillary relationships (B angle) in Syrian children with Class III malocclusion demonstrated statistically great value of this angle in comparison with Class I malocclusion [21], while Kerr et al. [22] on Michigan children demonstrated statistically lower value of this angle in children with Class III malocclusion. Contrary, Chang et al. [16] did not find a difference in the value of this angle in Class III malocclusion children with mixed dentition when compared to Class I malocclusion. Results of this study related to values of segmental anterior facial height (upper-NSna, lower-SnaMe and total-NMe) were not significantly different in children with Class I and III malocclusion (Figure 5–8). Chang et al. [16] analyzed these values in children with Class III malocclusion with mixed dentition and demonstrated the presence of significantly lesser lower anterior facial height than in Class I malocclusion, while values of upper and total anterior facial height did not vary significantly.

In participants of different gender in the same age subgroups, statistically significant difference was demonstrated only for values of lower and total anterior facial height in the middle and the oldest control subgroup. This finding demonstrates that male children with normal skeletal relationship, from the age of eight have lower and, consequently, total anterior facial height greater than female children. These results are in accordance with results obtained by Drevensek et al. [23], who demonstrated similar results on Slovenian children in the stage of mixed dentition with good occlusion (estimated by Eismann method). Their study, just like ours, demonstrated greater total anterior facial height in male children, but unlike our results, they did not show a difference among children with early and late mixed dentition.

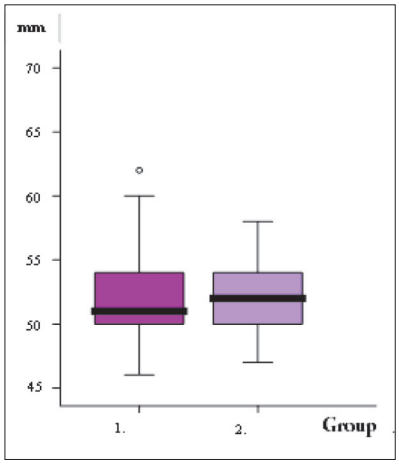

Figure 5 . The parameter values for the upper anterior facial height (NSna); Group 1 – experimental group; Group 2 – control group

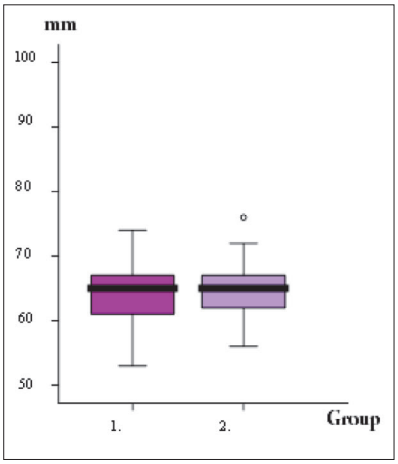

Figure 6. The parameter values for lower anterior facial height (SnaMe); Group 1 – experimental group; Group 2 – control group

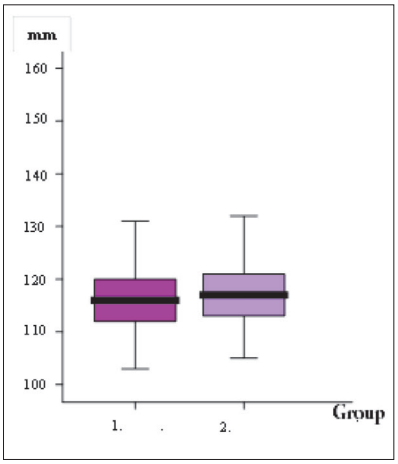

Figure 7. The parameter values for total anterior facial height (Nme); Group 1 – experimental group; Group 2 – control group

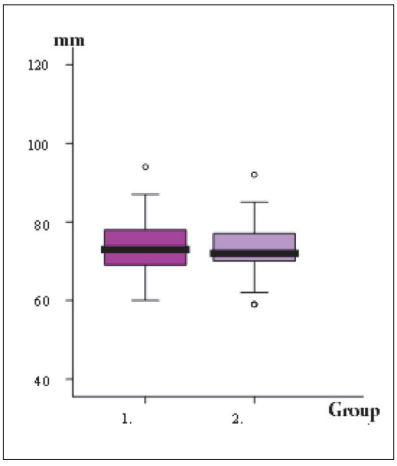

Figure 8. The parameter values for posterior facial height (Sgo); Group 1 – experimental group; Group 2 – control group

Study by Wu et al. [24] on 12-year old Chinese and Caucasian children with normal occlusion (according to McNamara standards) demonstrated a significant sex and ethnical determination of anterior facial height. Further, the results also demonstrated significantly greater lower anterior facial height in male children in both ethnic groups. Longitudinal study on European children with Class I malocclusion, aged 6–18 years demonstrated significantly greater upper anterior facial heights in males after the age of 14, and after the age of 16 lower, as well [25]. Similar study on children aged 10–14 years, that discussed the dynamic of longitudinal and transversal facial growth in that period, also indicated more intensive longitudinal and transversal growth in males than in females, with peak growth at the age of 12–14 years for males and 10–12 years for females. Same study demonstrated greater intensity of longitudinal growth, when compared to transversal, in this period for both sexes [26].

In our study, no statistical significance in anterior facial height had been observed among the children with Class III malocclusion in both sexes in the same age subgroups. Interestingly, the results of Baccetti et al. [19] on the Caucasian children with Class III malocclusion (aged 6–8 years) demonstrated that in eight-year-old males, lower anterior facial height was significantly greater (seen for the first time). This phenomenon will last until the age of 10, until what time the length shall be equalized (at 11 and 12 years), and after the age of 13, significantly greater lower and upper anterior facial height were observed in males [27].

Comparing children with Class I and Class III malocclusions, mean values of the posterior and anterior facial height were with no statistical significance. Difference in the values of the posterior facial height in both sexes was significant just in the middle (b) age subgroup, wherein males had a significantly greater height of this parameter than females. This finding was in accordance with previously published studies, where children with Class III malocclusion were not with significant mean values of the posterior facial height among sexes in the same age subgroups [23].

The upper facial height proportional to the total anterior facial height (NSna/NMe) was statistically significant greater in experimental group when compared to control. Proportion between lower and total anterior facial height (Sna/NMe) and proportion of posterior to anterior facial height (SGo/NMe) did not have a significant difference among children with Class I and Class III malocclusions (Figure 9, 10, 11). The results of the longitudinal study on 8–14-year-old Japanese females with Class III malocclusion demonstrated that 8–10 year old females had no changes in SGo/NMe values compared to Class I values, while 12 and 14 year olds had significantly higher value than in Class I [27].

Results of our study defined that SGo/NMe proportion did not have a significant difference among genders in the same age subgroups, which is an accordance with results of Drevensek et al. [23]. In our study, difference according to the genders was noticed in the youngest (a) age subgroup of the children with Class III malocclusion only. Gender dimorphism in facial height was consider natural and is in accordance with all available studies up to date.

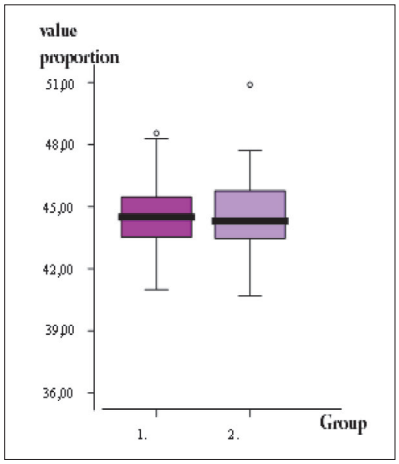

Figure 9. The parameter values NSna/NMe; Group 1 – experimental group; Group 2 – control group

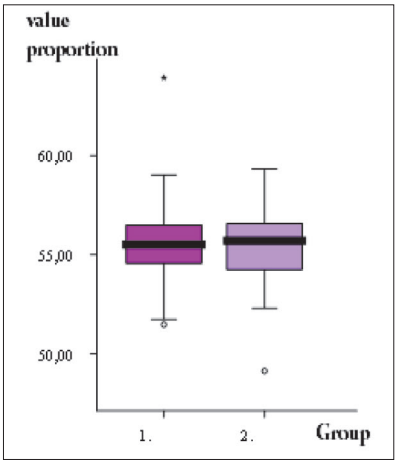

Figure 10. The parameter values SnaMe/Nme; Group 1 – experimental group; Group 2 – control group

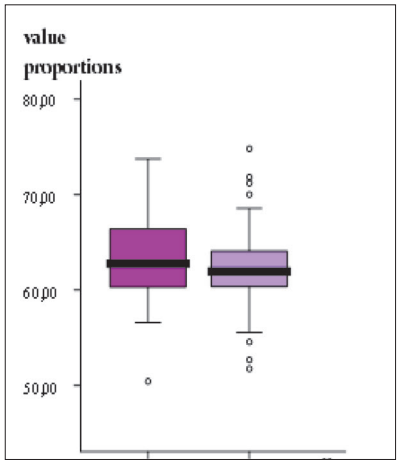

Figure 11. The parameter values SGo/NMe; Group 1 – experimental group; Group 2 – control group

Table 2. The proportions of measurements of this study and the result of subgroup comparison

The measurements parameters	Group	Subgroup years	X ± SD		p
			Male	Female	
Proportional relationship **NSna/NMe**	1	**a/** 6–7.11	45.41 ± 0.76	44.25 ± 0.72	0.01**
		b/ 8–9.11	44.04 ± 1.88	45.16 ± 2.15	0.20 NS
		c/ 10–12	44.08 ± 2.06	44.64 ± 1.68	0.49 NS
	2	**a/** 6–7.11	43.38 ± 2.07	42.43 ± 1.61	0.48 NS
		b/ 8–9.11	44.29 ± 1.57	45.02 ± 1.45	0.24 NS
		c/ 10–12	44.24 ± 1.33	45.79 ± 2.85	0.19 NS
Proportional relationship **SnaMe/NMe**	1	**a/** 6–7.11	54.59 ± 0.76	55.75 ± 0.72	0.01**
		b/ 8–9.11	55.96 ± 1.88	54.84 ± 2.15	0.20 NS
		c/ 10–12	56.65 ± 3.38	55.36 ± 1.68	0.43 NS
	2	**a/** 6–7.11	56.62 ± 2.07	57.57 ± 1.61	0.48 NS
		b/ 8–9.11	55.71 ± 1.57	54.98 ± 1.44	0.24 NS
		c/ 10–12	55.76 ± 1.33	54.21 ± 2.85	0.19 NS
Proportional relationship **SGo/NMe**	1	**a/** 6–7.11	61.39 ± 3.86	60.28 ± 2.24	1.00 NS
		b/ 8–9.11	64.32 ± 3.24	63.36 ± 6.00	0.69 NS
		c/ 10–12	64.41 ± 4.71	63.56 ± 4.48	0.56 NS
	2	**a/** 6–7.11	64.94 ± 6.10	62.36 ± 2.15	0.72 NS
		b/ 8–9.11	64.41 ± 4.60	61.13 ± 4.49	0.12 NS

Drevensek et al. [23] demonstrated interesting finding that gender dimorphism is frequently seen in children with normal intermaxillary relationship, especially in older subgroups, where male participants had greater linear heights of lower and total anterior face, while middle and older age subgroups had even greater posterior heights. In children with Class III malocclusion, gender dimorphism was seen only in youngest age subgroup, where male participants had a significantly greater upper facial height in proportion to total anterior height (Table 2).

Diversity of opinion on parameters values of cephalometric characteristics of skeletal Class III are supposed to be the expression of the ethnic composition of the groups studied. As previously stated, hyperdivergent growth type, determined by lower values of SGo/NMe proportion ("long face") is, according to many authors, considered a bad prognostic sign in the therapy outcome [2]. In our study, we defined the mean values of proportional SGo/NMe relationships that were in normal range for children with class III malocclusion. However, the vertical proportions of the face are to change during growth. These changes depend on the model for the growth of the face. One of the most valid indicators of the growth model is the Björk polygon. In the study by Stojanović [28] on Serbian children with the III skeletal class, the average value of this parameter from 395° ± 7.97 points to a favorable growth model for most respondents. Such findings leave room for the successful application of early orthodontic therapy, which must be individually planned.

CONCLUSION

The face estimation in Class III malocclusion, especially proportional relationship between the anterior and posterior facial height, that defines growth convergention has a great

practical importance in the therapy plan of Class III malocclusion. Since values of proportional relationship SGo/NMe were in normal range for these children, we concluded that there is a great importance of early therapy for the Class III malocclusion. This finding should definitely be used in modern concept of individually planned orthodontic therapy for optimal therapy outcome.

Gender dimorphism is more frequently observed in children with normal sagittal intermaxillary relationship, especially in the older age subgroups, where male participants had a greater linear lower anterior, total anterior and posterior facial height.

Conflict of interest: None declared.

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Вертикалне фацијалне диспропорције код деце са III скелетном класом

Зденка Стојановић[1], Јасмина Милић[2], Верица Павлић[3,4]

[1]Војномедицинска академија, Служба ортопедије вилица, Београд, Србија;
[2]Стоматолошки факултет, Панчево, Србија;
[3]Универзитет у Бањој Луци, Медицински факултет, Катедра за пародонтологију и оралну медицину, Бања Лука, Република Српска, Босна и Херцеговина;
[4]ЈЗУ Завод за стоматологију, Служба за пародontологију и оралну медицину, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Малоклузија III скелетне класе је сагитални међувилични несклад са доминантним изгледом доње вилице. Уз примарне сагиталне, могу постојати и неправилности у вертикалној димензији лица. Циљ ове студије је процена вертикалних диспропорција лица код малоклузије III скелетне класе у доба мешовите дентиције ради успешнијег планирања њене ране терапије.

Методе Случајним избором одабрано је 100 деце, која су подељена према резултатима кефалометријске анализе у две једнаке групе: 1. група (експериментална) – са III скелетном класом ($n = 50$) и 2. група (контролна) – са I скелетном класом ($n = 50$). Групе су даље подељене у по три подгрупе према старости и полу. Вертикалне краниофацијалне пропорције одређиване су мерењем предње (горње, доње и укупне) и задње висине лица и њихових пропорција. Вредности су статистички обрађене ($p \leq 0,05$).

Резултати Горња предња, доња предња, укупна предња и задња висина лица, пропорција између доње и тоталне предње висине лица, као и пропорција између задње и предње укупне висине лица, нису се статистички значајно разликовале код деце са I и III скелетном класом. Горња предња висина лица пропорционално укупној предњој висини лица статистички је значајно већа у експерименталној групи у односу на контролну. Утврђена је значајност родне разлике између истих старосних подгрупа.

Закључак Вертикалне краниофацијалне пропорције код деце са III скелетном класом у доба мешовите дентиције нису битно нарушене. Овакав налаз оставља простора за успешну примену ране, индивидуално планиране ортодонтске терапије.

Кључне речи: малоклузија III скелетне класе; мешовита дентиција; висина лица; родна разлика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The importance of genomic profiling for differential diagnosis of pediatric lung disease patients with suspected ciliopathies

Marina Anđelković[1], Vesna Spasovski[1], Miša Vreća[1], Aleksandar Sovtić[2], Milan Rodić[2], Jovana Komazec[1], Sonja Pavlović[1], Predrag Minić[2,3]

[1]University of Belgrade, Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia;
[2]Dr Vukan Čupić Mother and Child Health Care Institute of Serbia, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Dysfunction of the axonemal structure leads to ciliopathies. Sensory and motile ciliopathies have been associated with numerous pediatric diseases, including respiratory diseases. Primary ciliary dyskinesia (PCD) is ciliopathy linked to the dysfunction of motile cilia. Motile ciliary dysfunction in childhood leads to chronic rhinosinusitis, persistent cough, neonatal respiratory distress, bronchiectasis, and *situs inversus* (*SI*) have 50% of patients. These symptoms are common among pediatric lung diseases, which additionally makes it difficult to establish the accurate diagnosis. The aim of the study was to point out the significance of genomic profiling for patients with suspected ciliopathies and to design a strategy for genomic analysis relevant for differential diagnosis of lung disease patients with suspected ciliopathies.

Methods We conducted a bioinformatic analysis of data generated by New Generation Sequencing (NGS) approach of 21 patients with final or suspected diagnosis of PCD. It was analyzed 93 genes: 29 PCD genes, 45 genes related to individual symptoms of lung diseases, and 19 genes related to sensory ciliopathies.

Results The algorithm we have designed, enabled us to establish the clinical and genetic diagnosis for 17/21 (80.95%) patients, among which 11/21 (52.38%) were PCD patients. In 3/21 (14.28%) patients we detected monoallelic variants in PCD disease-causing genes. In 6/21 (28.57%) patients, variants in genes for other pulmonary diseases were detected, and for one patient, genetic background of disease remained unclear.

Conclusion An improved strategy for easier and faster establishment of final diagnosis of ciliopathies is mandatory and includes both, clinical and genetic confirmation of disease.

Keywords: pediatric lung disease; ciliopathies; PCD; NGS; genomic testing

INTRODUCTION

Aberrant function of the axonemal structure has been related to the class of disorders collectively known as "ciliopathies" which includes primary ciliary dyskinesia (PCD), Alstrom syndrome, Bardet-Biedl syndrome, Joubert syndrome, nephronophthisis polycystic kidney disease, polycystic liver disease, Meckel-Gruber syndrome, hydrocephalus, Jeune syndrome, and laterality defects [1–4]. PCD was the first disease associated with the aberrant function of motile cilia.

Primary ciliary dyskinesia [PCD (MIM 244400)] is a very clinically and genetically diverse group of disorders with aberrant ciliary motility resulting in respiratory tract disease. Iannaccone et al. [5] found that the disease is inherited in autosomal recessive or X-linked manner. Lucas et al. [6] found that aberrant ciliary function in infancy leads to neonatal respiratory distress in term infants, wet cough, chronic rhinosinusitis, hearing impairment, bronchiectasis, and about 50% of patients have *situs inversus* (SI). Noone et al. [7] proposed an explanation for the association between PCD and SI, that the normal function of cilia plays a role in regular organ orientation, whereas orientation of the organs in PCD is a random event due to abnormal function of cilia in early embryonic development. Although the diagnosis of PCD is much easier when abnormal placement of the internal organs is present, SI also can mislead physicians to suppose that patient has PCD, which does not have to be correct since SI is common within ciliopathies, can be isolated (without ciliary dysfunction), or can be an unusual state of cystic fibrosis (CF) [7, 8]. In the recent study, Driscoll et al. [9] described that bronchiectasis was reported in 37% of patients with autosomal-dominant polycystic kidney disease as a consequence of sensory cilia dysfunction. Morini et al. [10] said that, similar to cystic fibrosis, in the early years of life, an infant with ciliopathy may be undernourished, which makes the diagnosis a challenge.

The aim of our study was to point out the significance of genomic profiling for differential diagnosis of patients with comprehensive or partial clinical presentation of PCD, using next-generation sequencing (NGS) approach. This approach allows us to analyze causative

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Correspondence to:
Sonja PAVLOVIĆ
Institute of Molecular Genetics and Genetic Engineering
University of Belgrade
Vojvode Stepe 444a
11010 Belgrade, Serbia
sonya@sezampro.rs

and candidate PCD genes, but also genes involved in other pediatric lung diseases with clinical presentation similar to PCD, and to establish the correct diagnosis. We also wanted to design a strategy for genomic testing relevant for differential diagnosis of pediatric lung disease patients with suspected ciliopathies.

METHODS

Written informed consent was obtained from all participants and the study protocol was approved by the Ethics Committee of the Dr Vukan Čupić Mother and Child Health Care Institute of Serbia in Belgrade, Serbia, and has, therefore, been performed in accordance with the standards lain down in the 1964 Helsinki Declaration and its later amendments. All patients were physically examined and in all of them ciliopathy was detected using optical microscopy. The samples were referred to the Institute of Molecular Genetics and Genetic Engineering for genetic profiling of clinically suspected ciliopathy.

Diagnostic work up

We conducted genetic analysis of 29 (21 previously reported) subjects from 18 unrelated families of Serbian descent. Subjects with two or more clinical symptoms of PCD, as well as their relatives were included in this study. PCD diagnosis was made based on the clinical symptoms such as: chronic sinusitis, neonatal respiratory distress, bronchiectasis, recurrent pneumonia, SI, cilia motility, infertility, and all patients were treated at the Mother and Child Health Care Institute. Nasal cells sampled by nasal brushing procedure were used to examine cilia motility using optical microscope. Absence of CF was verified by analysis of the presence for *Pseudomonas aeruginosa* and sweat chloride test. The control group for candidate disease-causing variants detected using NGS approach, consisted of in-house collection of 69 subjects from general population of Serbia sequenced by NGS methodology.

Genomic analysis

Genomic DNA obtained from 29 subjects (21 patients, two siblings and six parents) was isolated from peripheral blood by QIAampDNA Mini Kit (Qiagen GmbH, Hilden, Germany). Qubit 3.0 fluorimeter (Invitrogen, Carlsbad, CA, USA) was used for measuring the quality and quantity of isolated DNA. Qubit dsDNA HS (Invitrogen) Assay Kit with range of 0.2–100 ng was used. Patients were analyzed by the NGS approach using Clinical-Exome Sequencing TruSight One Gene Panel (Illumina, San Diego, CA, USA). The relatives were analyzed only for detected gene variants in probands by direct Sanger sequencing.

A gene selection strategy and variant filtering

To identify the mutational profile involved in the pathogenesis of PCD, we analyzed disease-associated genes according to the Online Mendelian Inheritance in Man (OMIM). We also searched PubMed for studies describing clinical symptoms and genetic background of PCD patients. The first search implied the following terms: "primary ciliary dyskinesia," "immotile cilia syndrome," "ciliary motility disorders," "Kartagener syndrome," "abnormalities in the ciliary ultrastructure," "abnormalities in the beating pattern," "underlying genetic causes of the ciliary dysfunction," "genes encoding ODA components," "genes related to assembling of dynein arms," "genes encoding radial spokes or CP component," "genes encoding proteins of the N-DRC," "genetic testing in PCD," "novel clinical phenotypes for PCD," "male infertility in PCD," etc. Then, besides the genes described in the literature, we added genes that are coding for proteins that participate in protein-protein interactions with PCD disease-associated proteins in accordance to String Interaction Network (https://string-db.org/), and genes from the same gene family as PCD disease-causing genes. So, the first step of the analysis comprised 29 genes: (*CCDC8, CCDC39, CCDC40, CCDC50, CCDC88, CCDC103, DNAAF1 (LRRC50), DNAAF2 (KTU), DNAAF3, DNAI1, DNAI2, DNAL1, DNAH1, DNAH5, DNAH9, DNAH11, DYNC1H1, HEATR2, HYDIN, LRRC6, NME1, NME8 (TXNDC3), OFD1, RPGR, RSPH4A, RSPH9, SPAG16, SPAG17,* and *TCTE1*).

To identify mutational profile of patients in which we didn't find variants in above listed genes, we analyzed genes related to individual symptoms of the disease. We searched on PubMed for the following terms: "bronchiectasis," "bronchiectasis causes," "chronic cough," "mucus production," "increased mucus secretion," "CF bronchiectasis," "bronchiectasis without CF," "respiratory distress in term neonates," "surfactant metabolism," "highly expressed lung proteins," etc. We selected 45 genes for these symptoms that were present in TruSight One Gene Panel: *ABCA3, ABCA1, ABCB1, ABCC3, ABCA10, ABCB11, ABCC4, ABCA12, ABCB4, ABCC6, ABCA13, ABCB6, ABCC8, ABCA2, ABCB7, ABCC9, ABCC1, ABCD1, ABCA4, ABCC11, ABCD4, ABCA7, ABCC2, ABCG1, ABCG2, ABCG5, ABCG8, CFTR, MUC1, MUC13, MUC2, MUC3A, MUC4, MUC5B, MUC6*, *MUC7*, *SFTPA1, SFTPA2, SFTPB, SFTPC*, *SFTPD*, *SCNN1A, SCNN1B, SCNN1G,* and *SLC26A9*.

The last group of analyzed genes in our genomic analysis was related to sensory ciliopathies, present in TruSight One Gene Panel, 19 genes in total: (*BBS1, BBS2, BBS3, BBS4, BBS5, BBS6, BBS7, BBS8, BBS9, BBIP10, KIF3A, KIF3B, KAP, IFTA, IFTB, IFT43, IFT80, IFT122,* and *TTC21B*). The searching terms were as follows: "diseases associated with ciliary dysfunction", "ciliopathies", "sensory ciliopathies".

Also, all patients were analyzed for presence of homozygous or compound heterozygous variants in CFTR gene to exclude the possibility of CF as final diagnosis.

Overall, we have performed bioinformatic analysis of 93 genes (Table 1).

Table 1. In-house designed list of genes related to pediatric lung diseases associated with ciliopathies; list of 93 genes identified on Illumina Clinical-Exome Sequencing TruSight One Gene Panel

ABCA1	*ABCB1*	*ABCC3*	*ABCG2*	*BBS5*	*CCDC50*	*DNAH5*	*HYDIN*	*KIF3B*	*MUC6*	*SCNN1*	*SFTPB*
ABCA10	*ABCB11*	*ABCC4*	*ABCG5*	*BBS6*	*CCDC8*	*DNAH9*	*IFT122*	*LRRC6*	*MUC7*	*SCNN1B*	*SFTPC*
ABCA12	*ABCB4*	*ABCC6*	*ABCG8*	*BBS7*	*CCDC88*	*DNAH11*	*IFT43*	*MUC1*	*NME1*	*SCNN1G*	*SFTPD*
ABCA13	*ABCB6*	*ABCC8*	*BBIP10*	*BBS8*	*CFTR*	*DNAI1*	*IFT80*	*MUC13*	*NME8*	*SLC26A9*	*TCTE1*
ABCA2	*ABCB7*	*ABCC9*	*BBS1*	*BBS9*	*DNAAF1*	*DNAI2*	*IFTA*	*MUC2*	*OFD1*	*SPAG16*	*TTC21*
ABCA3	*ABCC1*	*ABCD1*	*BBS2*	*CCDC103*	*DNAAF2*	*DNAL1*	*IFTB*	*MUC3A*	*RPGR*	*SPAG17*	
ABCA4	*ABCC11*	*ABCD4*	*BBS3*	*CCDC39*	*DNAAF3*	*DYNC1H1*	*KAP*	*MUC4*	*RSPH4A*	*SFTPA1*	
ABCA7	*ABCC2*	*ABCG1*	*BBS4*	*CCDC40*	*DNAH1*	*HEATR2*	*KIF3A*	*MUC5B*	*RSPH9*	*SFTPA2*	

Bioinformatic analysis

Illumina Clinical-Exome Sequencing TruSight One Gene Panel includes all known disease-associated genes described in the OMIM database until 2013, designed to cover all exons and flanking intronic regions of 4813 genes (~ 62.000 exons). Illumina MiSeq machine was used to generate comprehensive genetic libraries. The software for data analyzing gained using this approach was IlluminaVariant Studio 2.0 and 3.0 (Illumina). After automatically annotation of all samples, we have accessed to variant filtering. Within this Illumina software there are numerous information about the analyzed variant, such as genomic coordinates, classifications, conservation scores, cDNA, CDS, and protein positions, transcripts and consequences, but also information about allele frequencies (1000 Genomes and ExaC) and functional impact of variants (SIFT and PolyPhen2). Only variants that had allele frequencies less than 5%, predicted as damaging, and absent in 69 control samples (TruSight One base), were further analyzed and considered as candidate variants. If the analyzed genetic variant had frequency > 5% in European population, but wasn't detected in our control samples, and was predicted as pathogenic, we took it into account. The databases used to additionally determine candidate variants: VarSome [which includes the databases: ClinVar, classification according to American College of Medical Genetics and Genomics (ACMG)], gnomAD genomes, gnomAD exomes, The Human Gene Mutation Database (HGMD), 1000 Genomes Project, dbSNP, Exome Aggregation Consortium (ExaC), and Ensembl. Tools used for pathogenicity scoring were: MutationTaster, Deleterious Annotation of Genetic Variants Using Neural Networks (DANN), and Functional Analysis through Hidden Markov Models (FATHMM-MKL). The effects on protein level were examined with *in silico tools* Provean, SIFT, and PolyPhen2.

RESULTS

Strategy for differential diagnosis of pediatric lung disease patients with suspected ciliopathies

We have proposed an algorithm for differential diagnosis between PCD and other pediatric lung diseases with similar clinical presentation (Figure 1). Clinical diagnosis of PCD was the criterion for genomic profiling of the patients, and it was established when a patient exhibited two or more symptoms of the clinical presentation of PCD.

Using the NGS for analysis of 4813 genes, we generated large libraries with approximately nine thousand variants per patient. Overall, we have done bioinformatic analysis of 93 genes. First, we prioritized 29 PCD causative genes and candidate genes and established a diagnosis for 11/21 (52.38%) patients from nine unrelated families. Than we expanded our genomic analysis to 45 genes related to individual symptoms such as bronchiectasis, atopic asthma, sinusitis and neonatal respiratory distress, and established the diagnosis for 6/21 (28.57%) patients. Thus, total diagnostic rate in our study reached 80.95%. The last group of analyzed genes were 19 genes related to sensory ciliopathies, but we weren't able to detect homozygous, compound heterozygous or trans allelic pathogenic variants and establish the diagnosis in the remaining 4/21 (19.04%) patients. However, in 3/21 patients we have found mono allelic pathogenic variants within PCD disease-causing genes (14.28%). That resulted in only 1/21 (4.76%) patient, in whom the genetic background of the disease remained unidentified.

Anđelković et al. [11] claimed that genes and variants detected in PCD related genes in 11/21 patients, and mono allelic variants detected in 3/21 patients were previously reported. Among six patients with variants in genes related to individual symptoms of the disease, three (50%) had the same mutation in *SCNN1A* gene (NM_001159576.1, c. 1654T>C, p. Trp552Arg), in two out of three patients, this gene variant was associated with gene variant in *CFTR* gene (NM_000492.3, c. 3485G>A, p.Arg1162Leu), while in the third patient it was present in homozygous state. In the remaining three patients, gene variants were detected in heterozygous state in *ABCA3* (NM_001089.2, c.2125C>T, p.Arg709Trp), in homozygous state in *SLC26A9* (NM_134325.2, c.514G>A, p.Val172Met), and in compound heterozygous state in *MUC2* (NM_002457.2, c.5735G>T, p.Gly1918Val; c.8084T>G, p.Ile2683Ser) genes. All variants were characterized as pathogenic, damaging or deleterious according to various databases and *in silico* prediction scores and tools, and had allele frequency less than 5% in European population. Detected variants in genes related to bronchiectasis, CF, neonatal respiratory distress and asthma are listed in Table 2.

The algorithm we designed provided the mutation detection rate of more than 95%. It also contributed to the improvement of diagnosis rate from 52% (PCD patients) to 81% (all analyzed patients).

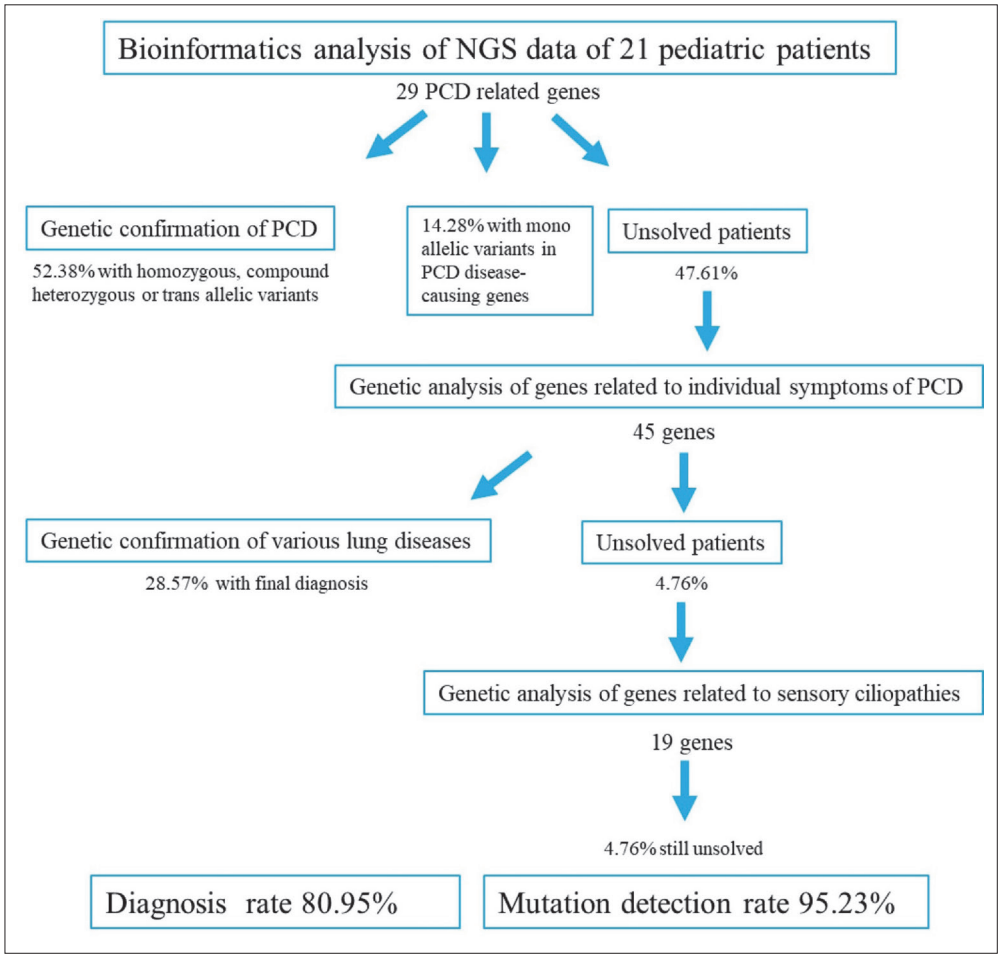

Figure 1. Proposed algorithm for differential diagnosis between PCD and other lung diseases with suspected ciliopathies;
Candidates for genetic testing were patients with situs inversus totalis or other situs abnormalities, with both upper and lower respiratory tract disease, history of unexplained neonatal respiratory distress, infertility in reproductive period, and imotility or abnormal cilia motility. Twenty-one patients had more than two above mentioned symptoms and they were analyzed using TruSightOne panel. We have conducted bioinformatics analysis of NGS data of all patients for presence of homozygous, compound heterozygous or trans allelic variants in 29 known PCD disease-causing and candidate genes. After we had established the diagnosis of PCD for 11/21 52.38% of patients, we extended our analysis on genes related to individual symptoms of the disease (45 genes), and genes related to sensory ciliopathies (19 genes). We reached the mutation detection rate of 95% (20/21), and diagnosis rate of 81% (17/21).

Table 2. Genetic variants detected in Serbian patients with pediatric lung diseases associated with ciliopathies (PCD patients not included); all identified genetic variants were numbered based on cDNA reference sequences and as recommended by the Human Genome Variation Society (http://www.hgvs.org/mutnomen)

GENE	dbSNP	Genetic variants		Type	VarSome allele frequency (%)[a]	ACMG score[b]	DANN[b]	SIFT[c]	Provean[c]	PolyPhen2[c]	HGMD
		Nucleotide change	Amino acid change								
ABCA3	rs148671332	c.2125C>T	p.Arg709Trp	missense	0	PP3	0.9989	Damaging	Damaging	Deleterious	novel
MUC2	rs41359254	c.5735G>T	p.Gly1918Val	missense	0.01	US*	-	Damaging	Damaging	Deleterious	novel
	rs41386948	c.8084T>G	p.Ile2683Ser	missense	0.02	US*	-	Damaging	Damaging	Deleterious	novel
SLC26A9	rs146704092	c.514G>A	p.Val172Met	missense	0	PP3	-	Damaging	Neutral	Deleterious	novel
SCNN1A	rs5742912	c.1654T>C	p.Trp552Arg	missense	2.29	PP3, BP6	0.9961	Damaging	Damaging	Deleterious	novel
CFTR	rs1800120	c.3485G>A	p.Arg1162Leu	missense	0	PP3, BP6	0.9985	Damaging	Damaging	Deleterious	ClinVar RCV000671007.1

[a]According to 1000 Genome Project and ExaC;
[b]ACMG and DANN scores: The detailed explanation of scores was given in the Supporting Information;
[c]SIFT, Provean, and PolyPhen2: *In silico* functional prediction tools

DISCUSSION

In order to reach an exact diagnosis in patients that exhibited the clinical presentation of PCD, which is similar to clinical presentations of other pediatric pulmonary disorders associated with ciliopathy, we have established the strategy for differential diagnosis based on genomic profiling using NGS methodology. In this study, genomic analysis revealed that 52% of patients had PCD. Additionally, we established the diagnosis of other pediatric lung diseases for 29% of patients.

Patients with lung diseases presenting overlapping clinical symptoms with PCD patients

In 6/21 patients without variants in PCD related genes, but with clinical presentation of PCD, extended genomic analysis revealed that this heterogeneous group have genetic background indicating other lung diseases, such as ectopic asthma, NDRS and bronchiectasis without CF. Pathogenic variants in homozygous, compound heterozygous, and trans allelic state were detected in *ABCA3, CFTR, MUC2, SCNN1A*, and *SLC26A9* genes.

Hanukoglu and Hanikoglu [12] reported that the *SCNN1A* gene encodes the alpha subunit of the ENaC (amiloride-sensitive epithelial sodium channel), a channel that allows the movement of sodium ions from the lumen into epithelial cells through the apical cell membrane. Fajac and Viel [13] reported in their previous study that mutations in *SCNN1* gene family might be deleterious for ENaC channel and lead to bronchiectasis, especially in patients that are trans-heterozygotes for ENaC/CFTR mutations. *SCNN1A* gene might be included on the list of potential gene candidates for PCD, since bronchiectasis is one of the well-known PCD clinical manifestations.

Our patient that harbored heterozygous genetic variant in *ABCA3* gene exhibited recurrent bronchiolitis (with hospitalization) and SI. Bronchiolitis affects the tiny airways, and as these airways become inflamed, they swell and fill with mucus, which make breathing difficult. Yamano et al. [14] stated that the *ABCA3* gene encodes a protein that is localized to the limiting membrane of lamellar bodies in alveolar type II cells. Matsumura et al. [15] indicated in their studies in surrogate cell model systems that *ABCA3* pathogenic gene variants impair the metabolism of surfactant by altering intracellular trafficking, the way of folding the *ABCA3* protein or impairing hydrolysis of ATP. Newborns with homozygous or compound heterozygous mutations in *ABCA3* gene develop progressive, lethal, neonatal-onset respiratory distress due to surface tension–lowering function of lung surfactant [16, 17]. Stahlman et al. [18] reported that in newborns with a single gene variant, if combined with developmental immaturity, it could reduce *ABCA3* gene expression below a functional threshold and the consequence is NRDS.

Patient with homozygous pathogenic variants in *MUC2* gene exhibits symptoms of asthma, bronchitis, and sinusitis. The protein encoded by *MUC2* gene is secreted and forms an insoluble barrier composed of mucous (https://www.ncbi.nlm.nih.gov/gene/4583). *MUC2* gene variants may lead to an altered glycoprotein folding or variable glycosylation levels. Clinically, these changes may modify the function of mucin [19, 20, 21]. Kaliner et al. [22] reported that the mucus is overproduced in the respiratory tract during acute conditions of the disease, and in chronic conditions (bronchitis, asthma, CF, and sinusitis), thereby contributing to mucus blockade of the airways.

In one patient, we have found pathogenic genetic variant in *SLC26A9* gene. This genetic variant was not found in our in-house TruSight One base. SLC26A9 functions as a Cl−-HCO3− exchanger, a Cl− channel and a Na+ coupled transporter [23, 24]. Chang et al. [23] reported that the SLC26A9 protein is localized to epithelia of the lung and stomach. CFTR and SLC26A9 have overlapping expression in lung epithelia and gut, making essential protein-protein interactions. Moreover, in a recent GWAS analysis of patients with CF, Sun et al. [25] pointed out that expression of human *SLC26A9* gene is associated with various CF phenotypes. Several studies have indicated that SLC26A9 mutations may impart large (monogenic) or small (polygenic) phenotypic effects in stomach-related diseases, CF, and/or other disorders in humans. Thus, Chen et al. [26] concluded that the functional characterization of *SLC26A9* variants are clinically very important.

Despite a similar clinical presentation in PCD patients and patients affected with other lung diseases, when the diagnosis of PCD was excluded, and the correct diagnosis of bronchiectasis, NRDS and asthma was established, more adequate therapy was used for treatment of the diseases, and the quality of life for those pediatric patients was improved.

In the remaining three patients, monoallelic pathogenic variants were detected in above listed 93 genes. For one patient, we could not associate clinical presentation with alterations in any of the genes included in our algorithm. This suggests that our in-house made list of 93 genes should be increased. New studies and new knowledge will enable the establishment of the genetic background in those patients as well. It is also necessary to emphasize that large chromosomal rearrangements encompassing these 93 genes that could be present in our patients, cannot be detected using NGS methodology.

CONCLUSION

Our study indicates the significance of genomic profiling for differential diagnosis between patients with comprehensive or partial clinical presentation of PCD and patients with other pediatric lung diseases. The strategy we designed includes NGS analysis of 93 genes relevant for symptoms present in ciliopathies. The proposed diagnostic algorithm contributed to the improvement of diagnosis rate from 52% (PCD patients) to 81% (all analyzed patients). Given the heterogeneity of possible symptoms associated with PCD and ciliopathies in general, there is no uniform approach to establish a precise diagnose. Modern high-throughput genetic approaches allow the causative biallelic mutations identification in about 60% of patients.

Although not yet applied for routine diagnostics, NGS turned out to be more efficient and cost-effective in diagnosing PCD and other pediatric lung diseases associated with ciliopathies, compared to traditional sequencing of single genes. An improved strategy for easier and faster establishment of final diagnosis of ciliopathies is mandatory and includes both, clinical and genetic confirmation of the disease. Our study is in accordance with this standpoint.

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Conflict of interest: None declared.

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Значај геномског профилисања за диференцијалну дијагнозу педијатријских болесника са болестима плућа суспектних на цилиопатије

Марина Анђелковић[1], Весна Спасовски[1], Миша Врећа[1], Александар Совтић[2], Милан Родић[2], Јована Комазец[1], Соња Павловић[1], Предраг Минић[2,3]

[1]Универзитет у Београду, Институт за молекуларну генетику и генетичко инжењерство, Београд, Србија;
[2]Институт за здравствену заштиту мајке и детета „Др Вукан Чупић", Београд, Србија;
[3]Универзитет у Београду, Медицински факутет, Београд, Србија

САЖЕТАК

Увод/Циљ Измењена функција аксонемалне структуре доводи до цилиопатија (моторних и сензорних), које су до сада повезане са бројним педијатријским поремећајима, укључујући и респираторне. Примарна цилијарна дискинезија (ПЦД) најчешћа је цилиопатија, која настаје као последица поремећаја у моторним цилијама. Промењена структура и/или функција моторних цилија доводи до неонаталног респираторног дистреса, хроничног влажног кашља, симптома назалне секреције, бронхоектазија, хроничне упале синуса и уха, а 50% болесника има и *situs inversus.* Ови симптоми су прилично уобичајени код мале деце и у другим стањима; стога је успостављање прецизне дијагнозе отежано. Циљ овог истраживања је указивање на значај геномског профилисања болесника и дизајнирање стратегије за генетичку анализу података код болесника суспектних на цилиопатије са клиничком сликом сличном другим болестима плућа.

Методе Спровели смо биоинформатичку анализу података добијених методом секвенцирања нове генерације 21 болесника са потврђеном или суспектном дијагнозом ПЦД-а. Анализирано је 93 гена: 29 ПЦД гена, 45 гена асоцираних са појединачним симптомима плућних болести и 19 гена асоцираних са сензорним цилиопатијама.

Резултати Дизајнирани алгоритам за генетичку анализу нам је омогућио да потврдимо клиничку и успоставимо генетичку дијагнозу код 17/21 (80,95%) болесника, међу којима је 11/21 (52,38%) ПЦД болесника. Код 3/21 (14,28%) болесника детектоване су моноалелске варијанте у ПЦД генима, код 6/21 (28,57%) болесника детектоване су варијанте у генима релевантним за друга плућна обољења, док је код 1/21 (4,76%) болесника генетичка основна болести остала неразјашњена.

Закључак Дизајнирање стратегије за лакше и брже успостављање коначне дијагнозе цилиопатија је обавезно и укључује и клиничку и генетичку потврду болести.

Кључне речи: педијатријске плућне болести; цилиопатије; ПЦД; секвенцирање нове генерације; геномско тестирање

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical characteristic and management of elderly patients with myocardial infarction

Jadranka Dejanović[1,2], Igor Ivanov[1,2], Tanja Popov[1,2], Milenko Čanković[1,2], Aleksandra Vulin[1,2], Dušanka Obradović[2,3], Vladimir Ivanović[1,2], Anastazija Stojšić-Milosavljević[1,2]

[1]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia

SUMMARY

Introduction/Objective Population of elderly people is increasing and modern medicine is faced with the problem of large morbidity and mortality from cardiovascular diseases in this age group. Modern treatment strategies have not been sufficiently investigated in the elderly, therefore these people often receive suboptimal treatment. The aim of the study was to evaluate clinical characteristic, cardiac risk factors, management strategies and early outcome in the elderly patient with ST elevated myocardial infarction (STEMI).

Methods This retrospective study included 217 consecutive patients, aged ≥ 70 years (mean age 77.6 ± 4.9 years, 103 men, 114 women) with STEMI admitted to the Institute of Cardiovascular Diseases of Vojvodina. We have analyzed patients' clinical characteristics, risk factors, left ventricular function and treatment strategies in relation to in-hospital outcome.

Results First clinical symptom was chest pain in 209 (96.3%) of patients. On admission, 35 (16.1%) patients were with severe signs of heart failure (Killip class III–IV). Duration of symptom onset to hospital admission was 14.7 ± 28.6 hours. Out of 217 patients, 168 (77.4%) patients received reperfusion treatment, including primary percutaneous coronary ntervention (PPCI) in 164 (75.6%) patients, and fibrinolytic therapy in 4 (1.8%) patients. Hospital mortality was 26.3% (57 patients). PPCI was univariate predictor of lower in-hospital mortality, whereas multivariate predictors of in-hospital mortality were cardiogenic shock (OR 67.095; 95% CI (6.845–657.646); p < 0.001) and low ejection fraction (OR 0.901; 95% CI (0.853–0.963); p = 0.001).

Conclusion In elederly patients presenting with STEMI, PPCI was asscoiated with lower mortality, whereas cardiogenic shock and lower ejection fraction were independent predictors of worse prognosis after STEMI.

Keywords: ST elevated myocardial infarction; primary percutaneous coronary intervention; fibrinolysis, elderly

INTRODUCTION

Older adults make up an increasingly large proportion of acute coronary syndrome (ACS) [1, 2]. About 60% of hospital admissions for ACS are patients over 65, and approximately 85% deaths occur in this age group. Large registries have shown that about 24–28% of ST-elevation myocardial infarction (STEMI) admissions belong to the patients aged > 75 year [3]. Other studies also confirmed higher in-hospital and long-term mortality from STEMI in patients older than 70 years [2, 4].

In Serbia, as in most developing countries, there is a trend of population aging and the proportion of patients over 65 years has increased from 8.9% in 1971 to 19.2% of population in 2016. In last decades, cardiovascular diseases were the leading cause of mortality in Serbia with 51.7% of all deaths in 2016, and 17.5% due to ischemic heart disease (about 50% from acute coronary syndrome) [5]. According to the latest reports from the population-based Registry of Acute Coronary Syndrome in Serbia [6], out of all newly diagnosed MI in 2016, 44.2% men and 40.3% women were over 70 years old. Incidence rate of MI for the population was 259.7 for men and 157.3 for women, and the highest incidence was in patients > 75 years, for men 963.5 and the women 721.1 per 100,000 population [6]. Mortality rate was also highest in the oldest group: 77.7 for men and 48.6 for women < 75 years, but in patients > 75 years of age significantly increased to 413.9, and 306.8 per 100,000, for men and women respectively [6].

Age is not only a risk factor for cardiovascular disease; it is also an independent risk factor for adverse outcomes after cardiovascular events, including short-term morbidity (stroke, heart failure and shock) and mortality in patients with STEMI treated with percutaneous coronary intervention (PCI) [7]. In study APEX-AMI mortality after 90 days was 13.1% in patients > 75 years and 2.3% at patients < 65 years [8].

Since patients older than 65 years are frequently not well-represented in clinical trials, the effect of treatment is not well documented, particularly for primary PCI (PPCI) and novel

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Correspondence to:
Igor IVANOV
Clinic of Cardiology
Institute of Cardiovascular Diseases of Vojvodina
Put dr Goldmana 4
21204 Sremska Kamenica, Serbia
igor.ivanov@ikvbv.ns.ac.rs
igor.ivanov@mf.uns.ac.rs

medical therapies [3, 4, 8]. However, guidelines have recommended invasive strategy for patients with STEMI irrespective of age, but still there is deficiency of evidence [9, 10, 11].

The aim of this study was to evaluate clinical characteristics, cardiac-risk factors, management strategies and intra-hospital outcome in the elderly (≥ 70 years) patients with STEMI.

METHODS

The retrospective study included 217 consecutive elderly (≥ 70 years) patients with STEMI, 103 (47.5%) men (mean age 77.2 ± 4.6 years), and 114 (52.5%) female (mean age 78.4 ± 5.1 years; p = 0.78) admitted during 2015 at the Institute of Cardiovascular Diseases of Vojvodina.

Acute myocardial infarction was defined according to the ESC Third universal definition of myocardial infarction [12] by significant elevation of cardiac biomarkers in addition to at least one of these criteria: clinical presentation, electrocardiographic abnormalities as persistent ST segment elevation in contiguous leads 1 mm or more; definite T-wave inversion; evolution of pathologic Q-waves; or new onset left bundle branch block (LBBB). STEMI was defined with symptoms of ischaemia, ST-segment elevation in at least two contiguous leads, or new onset LBBB and positive cardiospecific enzymes [9].

In all patients initial clinical, laboratory, and standard 2D echocardiography examination was performed, including evaluation of left ventricle wall motion analysis, and ejection fraction (LVEF) [13].

Reperfusion strategy was defined as: primary reperfusion with PPCI or thrombolysis -when the patient received fibrinolytic agent; no reperfusion therapy when the patient did not receive any reperfusion treatment. PPCI were performend in patients with myocardial icshemia < 12 hours of duration, or regardless of the time from symptoms onset in case of ongoing ischaemia, haemodynamic instability or malignant arrhythmias. PCI in asymptomatic patients > 48 h after onset of symptoms was not performed. Thrombolysis with alteplase was initiate in patients < 12 hours of symptom when PPCI was refused and there was no cotraindications to fibrinolysis.

All patients were given standard therapy according to the ESC guideline for STEMI and according to clinical presentation [9]. Regardless of the type of reperfusion strategy, all patients received a loading dose of aspirin (300 mg) and continued with 100 mg daily, as well as clopidogrel (300–600 mg loading dose followed by 75 mg dose once daily) or ticagrelor (180 mg loading dose, followed by 90 mg maintenance dose twice daily). PPCI was performed according to the standard protocol.

Protocol for fibrinolytic strategy with alteplase was following: 15 mg alteplase i.v. bolus, then continuous infusion of 0.75 mg/kg over 30 minutes and then 0.5 mg/kg over 60 minutes alteplase, followed by unfractionated heparin bolus (60 U/kg i.v.) and continued with enoxaparin 1 mg/kg s.c. twice daily for maximum eight days. For patients ≥ 75 years, loading dose of clopidogrel was omitted, and subcutaneous dose of enoxaparin was reduced to 0.75 mg/kg.

Non-reperfused patients with STEMI received aspirin, clopidogrel, and enoxaparin with same dosages as in patients receiving fibrinolytic therapy.

In patients with chronic kidney disease and eGFR< 30 ml/min/1.73 m^2, dose of enoxaparin was adjusted (0.75 mg/kg s.c. once daily)

ECG, laboratory and clinical follow-up was systematically performed throughout hospital stay, and all adverse events were recorded including mortality, repeated signs of myocardial ischemia, bleeding, heart failure, cardiogenic shock and stroke.

Congestive heart failure at the time of presentation was estimated by Killip's classification [14]. Major bleeding was defined as bleeding requiring transfusion and/or prolonged hospital stay and/or causing a drop-in hemoglobin > 3 g/l [15].

Stroke was defined as the development of new neurologic deficit not present on initial examination, neurologist diagnosis of stroke, or diagnosed by computed tomography imaging [16].

Statistical analysis

Descriptive statistics were generated for all study variables, including means and standard deviations (SD) for continuous variables and relative frequencies for categorical variables. One sample Students t test, Mann-Whitney test and Chi-Square test were performed to evaluate statistically significant differences between groups. Univariate and multivariate logistic regression analyses were used to determine predictors of in-hospital mortality. Statistical significance was defined as p value of 0.05. All statistical analyses were performed using SPSS version 17.0 for Windows.

RESULTS

During the one-year period, 2306 patients were admitted to the Coronary Care Unit, including 1314 (57.0%) patients < 70 years, 715 (31%) patients 70–80 years, and 277 (12%) were > 80 years. One-third of all patients (756) were admitted with STEMI diagnosis, including 217 (28.7%) patients > 70 years of age (114 female vs. 103 male, 52.5% *vs*. 47.5% p = 0.455).

Basic clinical characteristics of examinated patients are presented in Table 1. Initial and dominant clinical symptom was chest pain, presented in 209 (96.3%) patients, whereas dyspnea as a dominant symptom was reported in seven (3.2%) patients, and fatigue in one patient (0.5%). Typical ECG for STEMI had 209 (96.3%) patients, seven (3.2%) had LBBB and one (0.5%) had a pacemaker.

Killip classification on admission was following: 140 patients (64.5%) had no evidence of heart failure or Killip I class; 42 patients (19.4%) had Killip II; 17 patients (7.8%) had pulmonary edema or Killip III; and 18 patients (8.3%) had cardiogenic shock or Killip IV. Mean time from symptom onset to hospital admission was 14.7 ± 28.6 hours.

Table 1. Selected baseline and clinical characteristics at presentation among elderly patients with STEMI

Baseline characteristics	All patients (n = 217)	Survived (n = 160)	Died (n = 57)	p value
Male sex, n (%)	103 (47.5)	82 (51.3)	21 (36.8)	0.061
Age 70–80 years, n (%)	163 (75.1)	126 (78.8)	37 (64.9)	0.038
Age over 80 years, n (%)	54 (24.9)	34 (21.3)	20 (35.1)	0.038
Age (years), mean±SD	77.2 ± 4.6	76.9 ± 4.6	78.2 ± 4.4	0.056
Time from symptom onset to admission (h), (mean, 95% confidence interval for mean)	14.7 (9.98–20.6)	14.8 (10–19.6)	14.3 (8.59–20)	0.907
Systolic blood presure (mmHg), mean ± SD	136.2 ± 38.5	145.9 ± 26.2	108.2 ± 51.5	**< 0.01**
Dyastolic blood pressure (mmHg), mean ± SD	79.1 ± 24.2	85.5 ± 15.5	61 ± 33.6	**< 0.01**
Heart rate (b.p.m.), mean ± SD	80.5 ± 21.1	81 ± 18.5	79 ± 27.3	0.544
Ejection fraction (%), mean ± SD	46.0 ± 1.6	48.1 ± 10.5	34.7 ± 11.1	**< 0.01**
Admission symptoms, n (%)				
Pain	209 (96.3)	155 (96.9)	54 (94.7)	0.436
Dyspnea	7 (3.2)	4 (2.5)	3 (5.3)	0.383
Weakness	1 (0.5)	1 (0.6)	0	1.000
Killip class, n (%)				
I	140 (64.5)	119 (74.4)	21 (36.8)	**< 0.05**
II	42 (19.4)	30 (18.8)	12 (21.1)	0.855
III	17 (7.8)	11 (6.9)	6 (10.5)	0.553
IV	18 (8.3)	0	18 (31.6)	**< 0.05**
Risk factors, n (%)				
Dyslipidaemia	44 (2.3)	37 (23.1)	7 (12.3)	0.080
Current smokers	55 (25.3)	46 (28.8)	9 (15.8)	0.053
Hypertension	184 (84.8)	138 (86.3)	46 (80.7)	0.317
Family history	36 (16.6)	29 (18.1)	7 (12.3)	0.308
Diabetes mellitus, n (%)	62 (28.6)	44 (27.5)	18 (3.6)	0.186
Treatment with oral antidiabetics	46 (21.2)	31 (19.4)	15 (26.3)	0.362
Tretment with insulin	16 (7.4)	13 (8.1)	3 (5.3)	0.570
Glucose intolerance	16 (7.4)	15 (9.4)	1 (1.8)	0.076
Disease history, n (%)				
Previous myocardial infarction	11 (5.1)	6 (3.8)	5 (8.8)	0.138
Previous PCI	2 (0.9)	1 (0.6)	1 (1.8)	0.444
Previous CABG	3 (1.4)	1 (0.6)	2 (3.5)	0.111
Chronic renal failure	12 (5.5)	5 (3.1)	7 (12.3)	**0.009**
Blood test on admission, mean ± SD				
Creatine kinase (mmol/l)	1062.7 ± 1226.7	1042.6 ± 1221.2	2079.0 ± 1303.7	0.148
Creatine kinase myocardial band (mmol/l)	114.6 ± 125.2	113.3 ± 126	180.7 ± 49.2	0.358

Mean LV EF was reduced to 46 ± 11.6%; with 130 (59.9%) patients having EF < 50%.

A total of 168 (77.4%) patients received reperfusion therapy including 164 (75.6%) with PPCI, and only four (1.8%) received fibrinolytic therapy (Table 2). There were 49 (22.6%) patients without primary reperfusion therapy, and not all of the patients underwent coronary angiography (28 patients or 57.1%). Two (0.9%) patients went to urgent surgical revascularization or coronary artery bypass grafting (CABG), whereas nine (4.1%) were referred to cardiac surgery, and 17 (7.8%) for PCI. Out of 164 patients undergoing PPCI, in 82 (50%) infarct-related artery was left anterior descendent coronary artery, in 58 (35.4%) right coronary artery, and in 18 (10.9%) patients was circumflexis artery; in six patients (3.7%) culprit lesion could not be defined.

The most frequently in-hospital complication was heart failure developed in 37 patients (17.1%), and cardiogenic shock in 31 patients (14.3%), followed by reccurent myocardial ischaemia in 16 patients (7.4%), ventricular

Table 2. Treatment and in-hospital outcomes among elderly patients with STEMI

Treatment, n (%)	All patients (n = 217)	Survived (n = 160)	Died (n = 57)	p value
PPCI	164 (75.6)	129 (80.6)	35 (61.4)	**0.005**
Fibrinolysis	4 (1.8)	2 (1.3)	2 (3.5)	0.282
Primary reperfusion	168 (77.4)	131 (81.9)	37 (64.9)	**0.005**
No primary reperfusion	49 (22.6)	29 (18.1)	20 (35.1)	**0.005**
Complications, n (%)				
Reccurent ischaemia	16 (7.4)	8 (5)	8 (14)	0.052
Hematoma	5 (2.3)	3 (1.9)	2 (3.5)	0.608
Cardiac arrest - VT/VF	16 (7.4)	8 (5)	8 (14)	0.052
Atrial fibrillation	17 (7.8)	12 (7.5)	5 (8.8)	0.984
AV block	12 (5.5)	5 (3.1)	7 (12.3)	**0.024**
Shock	31 (14.3)	1 (0.6)	30 (52.6)	**< 0.05**
Heart congestion	37 (17.1)	17(10.6)	20 (35.1)	**0.009**
Stroke	6 (2.8)	2 (1.3)	4 (7)	0.070
Cognitive disturbances	8 (3.7)	7 (4.4)	1 (1.8)	0.684

arrhythmias in 34 patients (15.2%), and AV block in 12 patients (5.5%). Subcutaneous hematoma as complication of femoral arterial punction was recorded in five patients (2.8%), but with no indication for surgical tretment of hemathoma.

Mortality rate during hospitalisation was 26.3% or 57 patients, including 21 men and 36 women. Seven patients (3.2%) were resuscitated in cath lab and died because of cardiac arrest during PPCI. There was borderline difference in mean age between survivors and non-survivors, respectively (76.9 ± 4.6 vs 78.2 ± 4.4 years, p = 0.056), and interestingly no difference in time from symptom onset to admission (14.8 vs 14.3 hours, p = 0.907). Survivors had significantly higher LVEF (48.1 ± 10.5% vs 34.7 ± 11.1%, p < 0.01), higher systolic (145.9 ± 26.2 vs 108.2 ± 51.5 mmHg, p < 0.01), and diastolic blood pressure on admission (85.5 ± 15.5 vs 61 ± 33.6 mmHg, p < 0.01). In-hospital mortality rate for Killip class III–IV was 24/35 (69%) (Table 1).

Table 3. Univariate and multivariate predictors* of in-hospital mortality

Variable	Odds ratio	95% CI	p-value
Killip class III–IV	3.094	2.156–4.439	**< 0.001**
Systolic blood pressure	0.969	0.958–0.981	**< 0.001**
Dyastolic blood pressure	0.953	0.935–0.971	**< 0.001**
Low ejection fraction	0.919	0.877–0.964	**< 0.001**
Renal failure	4.340	1.319–14.281	**0.016**
PPCI	0.364	0.185–0.714	**0.003**
No reperfusion	2.750	1.400–5.402	**0.003**
AV block	4.340	1.319–14.281	**0.016**
Shock	93.564	10.981–797.206	**< 0.05**
Heart congestion	7.421	1.501–34.475	**0.007**
Low ejection fraction *	0.901	0.853–0.963	**0.001**
Shock*	67.095	6.845–657.646	**< 0.001**

By univariate regression analysis (Table 3), predictors of in-hospital mortality were Killip class III–IV (OR 3.094; 95% CI 2.156–4.439; p < 0.001**),** no reperfusion therapy (OR 2.750; 95% CI 1.400–5.402; p = 0.003), heart failure (OR 7.421; 95% CI 1.501–34.475; p = 0.007, cardiogenic shock (OR 93.56; 95% CI 10.981–797.206; p < 0.001), low ejection fraction (OR 0.919: 95% CI 0.877–0.964; p < 0.001). PPCI was a predictor for better survival (OR 0.364; 95% CI 0.185–0.714, p = 0.003. Independent multivariable predictors of in-hospital mortality were cardiogenic shock (OR 67.095; 95% CI (6.845–657.646); p < 0.001) and low ejection fraction (OR 0.901; 95% CI (0.853–0.963); p = 0.001).

DISCUSSION

Our study demonstrated that in elderly patients with STEMI, initial and dominant clinical symptom was chest pain, but still, about 20% was admitted after > 12 hours of symptom onset accompanied by symptoms of heart failure (35.5%). The most commom in-hospital complications of STEMI were heart failure, cardiogenic shock, ventricular arrhythmias and AV blocks. The other disturbing findings of our study is extremely high in-hospital mortality rate of 26.3%, despite reperfusion and PPCI in > 75% of the patients. Thus, the main predictors for the worst outcome were absence of reperfusion therapy, Killip III–IV, heart failure, AV block, whereas low left ventricular EF and cardiogenic shock were independent predictors of in-hospital events. Additionally, patients undergoing PPCI had better in-hospital survival.

In our study, symptoms of myocardial infarction were typical, with chest pain in 96% of patients, which is consistent with previous data [17]. However, atypical symptoms like dyspnea, nausea and syncope [18, 2] may be one of the reason for a delay of elderly patients' arrival to the hospital. It has been shown that the time from onset of symptoms to hospital admission of these patients was prolonged compared to younger patients [2, 18], measured as first medical contact time and total ischemic time (p < 0.001) [16, 19]. Schoenenberger et al. [20] found that the delay from symptom onset to hospital admission of patients ≥ 70 years decreased between 2001 and 2012 in acute myocardial infarction in Switzerland (AMIS) cohort.

In our study, there was no significant difference between the time from symptom onset to admission of surviving and deceased patients, but both groups had very late presentation for STEMI treatment with a mean time delay of 14.7 ± 28.6 hours. The delay to STEMI treatment was very well apprecited medical issue and independent predictor of in-hospital mortality [19].

As shown earlier and confirmed in our study, elderly patients with STEMI were more often female [2, 16], with higher rate of mortality in men [21]. Regarding comorbidities, only chronic renal failure significantly correlated with in-hospital mortality in our patients, also consistent with previous studies [3, 22]. Congestive heart failure is more frequently in older population with IM [16, 20, 23], and appeared to be an important predictor of poor outcome [7, 22] regardless of appropriate therapeutic approach [7], and more elderly patients with STEMI had higher Killip class > 1, including cardiogenic shock, compared to younger patients [16, 21, 24]. Widimsky at al [25] compare importance of Killip class on the outcome after PPCI in relation to the age of patients, and found that in-hospital mortality of Killip IV patients was 69% (elderly group), 54% (65–74 years, p < 0.001) and 27% (< 65 years, p < 0.001). In the same cohort in-hospital mortality of patients with Killip II–III was significantly lower in all age groups: 4% (elderly), 2.7% (65–74 years) and 0.8% (< 65 years).

In patients with STEMI, IMMEDIATE trial [26] has demonstrated that lower LVEF was significantly associated with 1-year mortality or hospitalization for heart failure. For every 5 % LVEF reduction, the hazard ratio [HR] was 1.26 (95% CI 1.15, 1.38, p < 0.001). The presence of LV dysfunction on baseline left ventriculography in patients enrolled in the HORIZONS–AMI trial who underwent PPCI was a powerful predictor of early and late mortality irrespective of the extent of coronary artery disease [27]. In our patients lower EF was also related to higher mortality.

As the clinical presentation of acute MI varies by age and presence of co-morbidities, many physicians use the "first not harm" strategy for elderly population who are at

higher mortality risk, and they are often undergo a more conservative and sub-optimal treatment [11], despite the benefit of more invasive and aggressive approach [2, 8]. Numerous observations and studies proved that these patients could have significant benefit from PPCI in the settings of STEMI [1, 11, 24]. Angeli et al. [28] in the meta-analysis of nine randomised trials found that early revascularisation in elderly patients with MI reduced the risk of rehospitalisation, recurrent myocardial infarction or death to a greater extent compared to younger patients. One of the trials examined the effect of PPCI instead of fibrinolytic therapy in elderly patients with STEMI [24]. The death rates were 7.7%, 15%, and 19.9% with PPCI, fibrinolysis, and no reperfusion ($p < 0.001$), respectively. There was no difference in the rates of hemorrhage stroke and other major bleeding between groups. Authors concluded that early reperfusion, especially PPCI, was safe and effective with absolute reduction of mortality compared with no reperfusion in patients ≥ 75 years old [24]. Our data are consistent with earlier findings, demonstrating PPCI as a favorable predictor of prognosis [1, 8, 14]. In addition, TRIANA study [29] showed advantage of PPCI compared to fibrinolysis concerning mortality, reinfarction and stroke during 30 days. (OR 0.64; 95% IP 0.45–0.91).

Still, STEMI network is less efficient in elderly than younger patients [19], as they received both thrombolytic and invasive procedures less frequently when compared with younger patients [1, 23, 30]. However, recent registries observed trend of increase rate of aggressive treatment of STEMI in elderly, especially PPCI [8, 20, 30].

One of the major concerns in elderly population is bleeding and neurological disorders [1]. However, rates of haemorrhagic stroke (0.3%, 0.6%, and 0.1%) and other major bleeding (3%, 5%, and 3.1%) were similar for primary PCI, fibrinolysis, and no reperfusion group in elder with IM [24]. In our study, neurological complications were observed in small number of patients, stroke in 2.8% and mental disorders in 3.7%.

Mortality in elderly patients with acute MI was higher than in young population [2, 16, 24]. Mortality in this study was 26.3%, similar to 28.4% found by Lovleen et al. [23], in STEMI patients > 65 years, but still unacceptably high.

Study limitations

The major limitation of this study was relatively small number of patients, and quite a long-time interval between symptoms onset and admission to the hospital, which is far beyond recommended time frames for optimal reperfusion. Most probably, the explanation for high in-hospital mortality is long time delay accompanied with all complications of acute MI including low LVEF, heart failure and cardiogenic shock. In addition, not all relevant angiographic and procedure variables were included and analyzed, as TIMI flow grade, SYNTAX score defining angiographic complexity, as well as other procedure characteristics (additional medications, inotropis support, etc).

CONCLUSION

Elderly patients represent a significant and increasing proportion of STEMI patients. In our study population, elderly patients with STEMI presented with typical symptoms of chest pain, but with unacceptably long delay between symptom onset and hospital addmision and a very high in-hospital mortality. Cardiogenic shock and low LVEF were independent predictors of in-hospital mortality, whereas early reperfusion with PPCI significantly reduced in-hospital mortality. Our findings support the need for comprehensive health care STEMI network that will enable efficient care of patients with STEMI, particularly in elderly patient which per se represents most vulnerable subgroup of STEMI patients with worse prognosis.

Conflict of interest: None declared.

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Клиничке карактеристике и збрињавање старијих болесника са инфарктом миокарда

Јадранка Дејановић[1,2], Игор Иванов[1,2], Тања Попов[1,2], Миленко Чанковић[1,2], Александра Вулин[1,2], Душанка Обрадовић[2,3], Владимир Ивановић[1,2], Анастазија Стојшић-Милосављевић[1,2]

[1]Институт за кардиоваскуларне болести Војводине, Сремска Каменица, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Институт за плућне болести Војводине, Сремска Каменица, Србија

САЖЕТАК

Увод/Циљ Популација старијих људи је у порасту и модерна медицина се сусреће са проблемом великог морбидитета и морталитета од кардиоваскуларних болести у овој старосној групи. Модерне стратегије лечења још увек нису довољно испитане код старијих, па су ови људи често субоптимално лечени.

Циљ истраживања је да се испитају клиничке карактеристике, кардиолошки фактори ризика, стратегије збрињавања и рани исход код старијих болесника са инфарктом миокарда са *ST* елевацијом (*STEMI*).

Методе Ретроспективна студија је укључила 217 узастопних болесника животне доби ≥ 70 година (средње животне доби 77,6 ± 4,9 година, 103 мушкараца и 114 жена) са *STEMI*, примљених у Институт за кардиоваскуларне болести Војводине. Анализиране су клиничке карактеристике, фактори ризика, функција леве коморе и стратегије лечења у односу на болнички исход болести.

Резултати Први клинички симптом је био бол у грудима, који је био заступљен код 96,3% болесника. При пријему 35 (16,1%) болесника је имало озбиљне знаке срчане слабости (Килипова класа III–IV). Време од појаве тегоба до пријема у болницу је било 14,7 ± 28,6 сати. Од 217 болесника, 168 (77,4%) добило је реперфузиони третман, укључујући примарну перкутану коронарну интервенцију (ППКИ) код 164 (75,6%) болесника и фибринолизу код четири (1,8%) болесника. Хоспитални морталитет је био 26,3% (57 болесника). ППКИ је био универијантни предиктор ниског интрахоспиталног морталитета, а мултиваријантни предиктори хоспиталног морталитета су кардиогени шок (*OR* 67,095; 95% *CI* (6,845–657,646); $p < 0,001$) и ниска ејекциона фракција леве коморе (*OR* 0,901; 95% *CI* (0,853–0,963); $p = 0,001$).

Закључак Код старијих болесника са *STEMI*, ППКИ је била повезана са мањим болничким морталитетом, док су кардиогени шок и ниска ејекциона фракција леве коморе били независни предиктори лошије прогнозе после *STEMI*.

Кључне речи: инфаркт миокарда са *ST* елевацијом; примарна перкутана коронарна интервенција; фибринолиза, старији

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Chronic inflammation and lipid profile parameters in obese subjects with normal and disturbed glucose metabolism

Radoslav Pejin[1,2], Edita Stokić[1,2], Ilija Tanackov[3], Đorđe Popović[1,2], Artur Bjelica[4,2], Aleksandar Jovanović[5,2]

[1]Clinical Center of Vojvodina, Clinic for Endocrinology, Diabetes and Metabolic Disorders, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]University of Novi Sad, Faculty of Technical Sciences, Novi Sad, Serbia;
[4]Clinical Center of Vojvodina, Clinic for Gynecology and Obstetrics, Novi Sad, Serbia;
[5]Clinical Center of Vojvodina, Clinic for Neurology, Novi Sad, Serbia

SUMMARY

Introduction/Objective In different states of increased chronic inflammation, like obesity and diabetes, early changes in lipid metabolism could represent an adaptive response aimed at diminishing the elevated inflammatory reaction. The aim of study was to investigate the impact of glucose tolerance status on relationship between chronic inflammation and lipid metabolism parameters.

Methods The study consisted of four groups (n = 30 for each group): obese individuals with disturbed glucose metabolism (subjects with newly diagnosed type 2 diabetes (T2DM)) before and after metformin treatment initiation, obese subjects with normal glucose tolerance (NGT) and a control group of healthy normal weight subjects. Appropriate anthropometric measurements and laboratory tests were carried out in all participants.

Results Among the sub-group of obese subjects, the association of highly sensitive C reactive protein (hsCRP) with triglycerides and lipoprotein (a) (Lp(a)) was especially pronounced in the group of T2DM subjects before treatment initiation. In this group, the level of inflammation was the highest and correlation coefficients of triglycerides and Lp(a) with hsCRP were significantly different compared with the group of obese without diabetes (r = 0.21 *vs*. r = -0.36; p = 0.0172) for triglycerides and (r = -0.17 *vs*. r = 0.36, p = 0.0324) for Lp(a). Correlations of hsCRP with triglycerides and Lp(a) in groups of NGT obese subjects and T2DM subjects after treatment initiation did not differ significantly. Treatment with metformin changed the relationship of hsCRP with triglycerides and Lp(a) to the one which is similar to the relationship observed in obese NGT subjects (r = 0.21 *vs*. r = 0.38; p = 0.2449) for triglycerides and (r = -0.17 *vs*. r = -0.27, p = 0.3562) for Lp(a).

Conclusion In subjects with newly diagnosed T2DM, who have the highest level of inflammation, it is probable that the increase in triglycerides is a part of the anti-inflammatory response, whereas Lp(a) is probably produced and used in the reduction of elevated inflammation.

Keywords: C reactive protein; lipoprotein (a); triglycerides; metformin, obesity; type 2 diabetes

INTRODUCTION

Increased inflammation causes changes in the lipid metabolism, which might represent the adaptive response aimed at the reduction of toxicity of different harmful microbiological agents and at a repair of the tissue occurring during the acute inflammatory response. In such conditions, the most frequent changes related to lipid metabolism are a decrease in high density lipoprotein cholesterol (HDL-C) and an increase in triglyceride levels [1].

Chronic inflammation may lead to the development of conditions like atherosclerosis and metabolic syndrome (MetS). It also regulates the gene expression responsible for a scavenger receptor function and foam cell formation. Oxidative stress, by the excess of free radicals' formation, activates the immune system through the redox-sensitive transcription factors such as nuclear factor-kB [2]. Although this chronic stress does not cause reaction such strong as the acute inflammation does, it is still involved in a development of various degenerative diseases including diabetes and cardiovascular diseases (CVD). Lipoprotein (a) [Lp(a)] levels are associated with CVD, as Lp(a) may play a role in atherothrombosis and in activation of acute inflammation [3]. It is also involved in the activation of endothelial reaction, oxidative modification and formation of foam cells, processes involved in atherosclerosis progression [3, 4].

The aim of our study was to investigate the impact of glucose tolerance status on the relationship between chronic inflammation and lipid metabolism parameters. Additionally, we analyzed the influence of metformin therapy on this relationship among newly diagnosed type 2 diabetes (T2DM) patients.

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Correspondence to:
Radoslav PEJIN
Clinic for Endocrinology, Diabetes and Metabolic Disorders
Clinical Center of Vojvodina
Faculty of Medicine
University of Novi Sad
Hajduk Veljkova 1
21000 Novi Sad, Serbia
radoslavpejin@gmail.com

METHODS

The study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center Novi Sad, Serbia. Thirty obese patients with newly diagnosed T2DM before and after the three months metformin treatment (daily dose of 1000 mg), 30 obese individuals with normal glucose tolerance (NGT) and 30 normal weight healthy control subjects were enrolled. All four groups were age- and sex-matched. Subjects suffering from diseases and habits that could influence the oxidative status were not included.

Body mass index (BMI) was calculated as BM (kg)/BH $(m)^2$. Body composition was determined by the bioelectrical impedance method, using Tanita apparatus (TANITA BC-418 Segmental Body Composition Analyzer, Tokyo, Japan), measuring the tissue resistance to an alternating current, thus providing the calculation of body fat mass (BFM, kg), lean body mass (LBM, kg) and total body water (TBW, kg).

Glucose (Architect analyzer C8000, Abbott Laboratories, IL, USA), total cholesterol and triglycerides (Architect ci4100 analyzer, Abbott Laboratories) were assayed by the standard enzymatic procedure, and HDL-C were analyzed with a direct enzymatic colorimetric test (Architect ci4100 analyzer, Abbott Laboratories), while LDL cholesterol was calculated indirectly, using the Friedewald formula. Insulin (Advia Centaur XP Siemens, Erlangen, Germany), apolipoprotein B, apolipoprotein AI, Lp(a) (Architect ci4100 analyzer, Abbott Laboratories), and high sensitivity C reactive protein (hsCRP) (Siemens Healthcare Diagnostic Inc., Camberley, UK) were assayed by the immunoturbidimetric method. The Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) index, an indirect indicator of mainly hepatic IR. HOMA-IR index was calculated from the values of fasting blood glucose (FBG) and fasting insulinemia according the formula:

HOMA-IR = FBG × fasting insulinemia (mIU/l) / 22.5

Lp(a) was analyzed by the immunoturbidimetric method (QUANTIA Lp(a), BIOKIT, S.A., Barcelona, Spain) (Architect ci4100 analyzer, Abbott Laboratories). HgBA1c levels were determined by Abbott Architect analyzer C8000.

Recommendations for specific reference values were: The Guide to Good Clinical Practice recommendations for lipids and lipoproteins by the Ministry of Health of Serbia, ADA recommendations for the value of the glycemic status and the International Federation of Clinical Chemistry, as well as recommendations from producers of reagents. The study was done in accord with standards of the institutional Committee on Ethics.

Statistical analysis

The verification was performed with the statistical probability distribution sets. Statistical tests of parameter sets and corresponding tests of dispersive analysis (ANOVA statistical test) were used. Linear correlations test was performed using the Pearson's product-moment correlation coefficient. For the analytical expression of the relationship between parameters in obese T2DM patients before and after the treatment initiation regression analysis was applied. Linear regression had the highest correlation coefficients. The effect of an onset of diabetes and treatment initiation was expressed by the changes in regression equations, and the value of changes was verified by the Pearson's correlation coefficient test. Duncan's multiple range test (post-hoc ANOVA test) was used to directly highlight statistically significant differences in BMI, triglycerides, Lp(a), HOMA-IR and hsCRP between the groups (control, NGT obese, obese T2DM before and after the metformin treatment). This test was selected due to its tolerance to type I error in the small samples.

RESULTS

Basic characteristics of the study groups are shown in Table 1. As expected, obese subjects with T2DM before and after treatment and NGT obese individuals had a significantly higher BMI compared with the control group, without significant inter-group differences (Table 2). Also, the level of serum triglycerides was the highest in T2DM patients before the treatment, with significant difference compared with the control and NGT obese group (Table 2). Con-

Table 1. Baseline characteristics of the study population among groups

Criteria	Control	Obese	T2DM before treatment	T2DM after treatment
Gender (male/female)	10/20	12/18	14/16	14/16
Age (years)	45.84 ± 14.75	46.57 ± 15.93	53.52 ± 17.24	53.49 ± 17.24
Body weight (kg)	69.17 ± 15.67	109.15 ± 17.73	99.91 ± 19.52	99.16 ± 19.33
Waist circumference (cm)	78.81 ± 11.43	112.03 ± 11.00	113.03 ± 11.10	110.60 ± 11.86
Body fat percentage (%)	25.49 ± 6.81	46.32 ± 12.03	41.55 ± 12.22	41.42 ± 11.03
Glucose fasting (mmol/l)	4.55 ± 0.36	5.07 ± 0.54	9.13 ± 3.62	7.40 ± 2.40
Glucose 2 hours post prandial (mmol/l)	4.95 ± 0.65	5.53 ± 0.97	12.13 ± 5.30	9.31 ± 3.20
Insulin fasting (mIU/l)	6.72 ± 2.92	18.10 ± 9.69	17.61 ± 14.24	15.49 ± 10.29
Hgb A1C (%)	5.20 ± 0.30	5.52 ± 0.33	8.33 ± 2.19	7.42 ± 1.51
Cholesterol (mmol/l)	5.21 ± 0.95	5.39 ± 0.91	6.36 ± 1.32	5.77 ± 1.03
HDL cholesterol (mmol/l)	1.51 ± 0.31	1.14 ± 0.22	1.05 ± 0.23	1.07 ± 0.22
LDL cholesterol (mmol/l)	3.30 ± 0.75	3.62 ± 0.83	4.30 ± 1.18	4.02 ± 0.95
Apolipoprotein B (μg/l)	0.84 ± 0.20	0.93 ± 0.20	1.15 ± 0.23	1.02 ± 0.18

Table 2. Analysis of the relationships of BMI, serum triglycerides, Lp(a), hsCRP, serum creatinine, HOMA-IR index values among studied groups

Parameters and relations	BMI (kg/m^2)	Triglycerides (mmol/l)	Lp(a) (g/l)	HOMA-IR	Hs CRP (mg/l)	Creatinine (μmol/l)
A	23.9 (19.2–24.8)	1.3 (0.4–8.5)	0.27 (0.02–1.17)	1.55 (0.46–3.20)	1.3 (0.1–9.7)	75.22 ± 11.33
B	36.6 (30.1–54.1)	1.4 (0.4–5.6)	0.16 (0.01–0.57)	3.44 (1.69–9.30)	5.2 (0.1–63.1)	78.82 ± 15.19
C	36.6 (30.1–43.7)	3.3 (0.8–9.1)	0.09 (0.01–0.86)	8.57 (1.49–29.08)	7.2 (0.3–28.9)	79.25 ± 16.50
D	35.5 (30.3–42.2)	2.3 (0.6–6.4)	0.13 (0.01–0.98)	5.01 (1.16–13.80)	5.3 (0.3–14.3)	78.42 ± 16.52
A *vs.* B	p = 0.0001	p = 0.80	p = 0.16	p = 0.14	p = 0.02	p = 0.30
A *vs.* C	p = 0.0001	p = 0.004	p = 0.04	p = 0.0005	p = 0.002	p = 0.26
A *vs.* D	p = 0.0001	p = 0.14	p = 0.09	p = 0.01	p = 0.02	p = 0.39
B *vs.* C	p = 0.99	p = 0.007	p = 0.43	p = 0.0002	p = 0.27	p = 0.91
B *vs.* D	p = 0.57	p = 0.19	p = 0.70	p = 0.22	p = 0.92	p = 0.92
C *vs.* D	p = 0.55	p = 0.12	p = 0.65	p = 0.006	p = 0.29	p = 0.85

A – Control; B – NGT obese; C – T2DM before treatment; D – T2DM after treatment

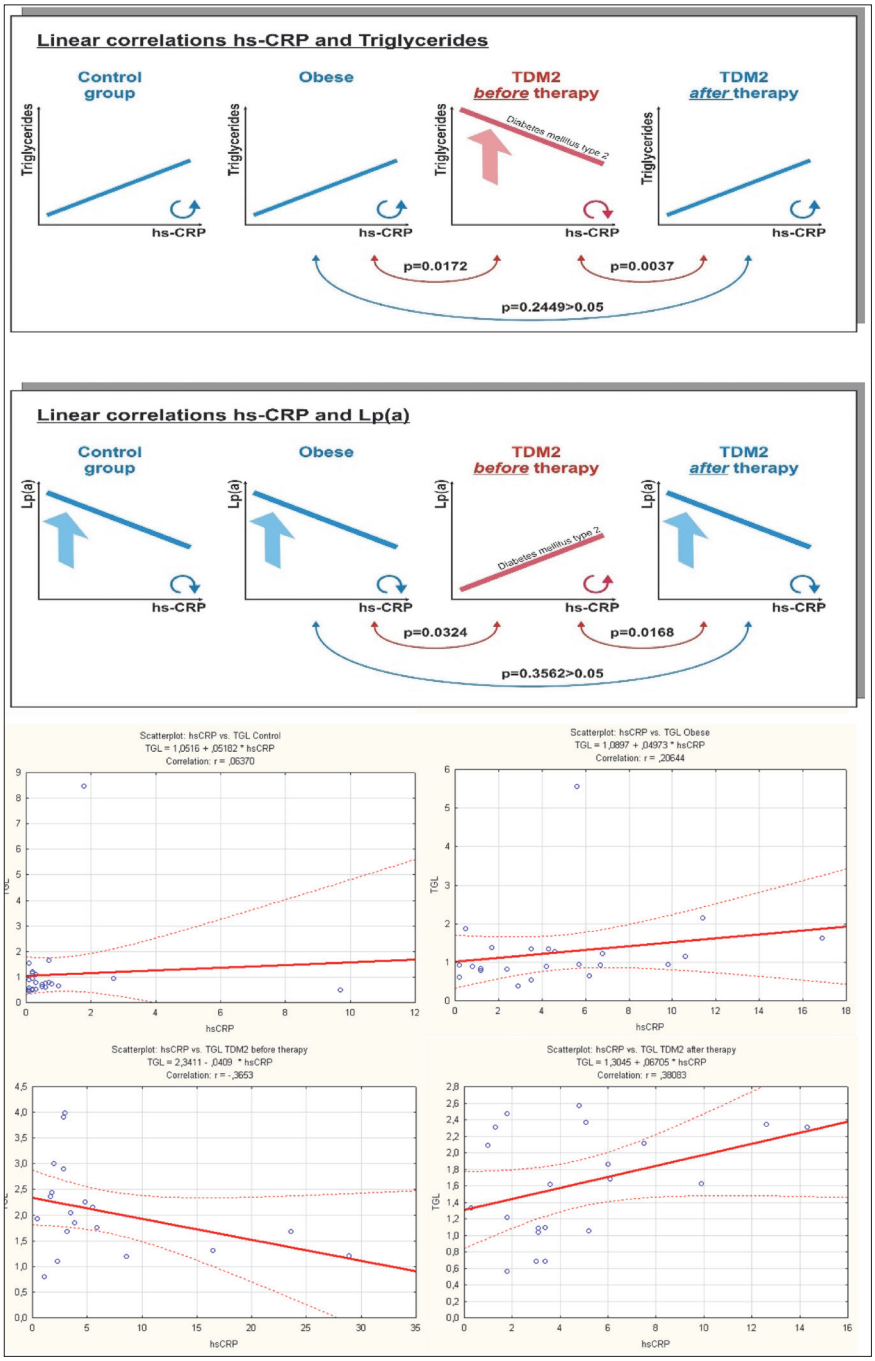

Figure 1. The linear correlations between hsCRP and triglycerides in studied groups; TDM2 – type 2 diabetes mellitus; hsCRP – high sensitive C-reactive protein

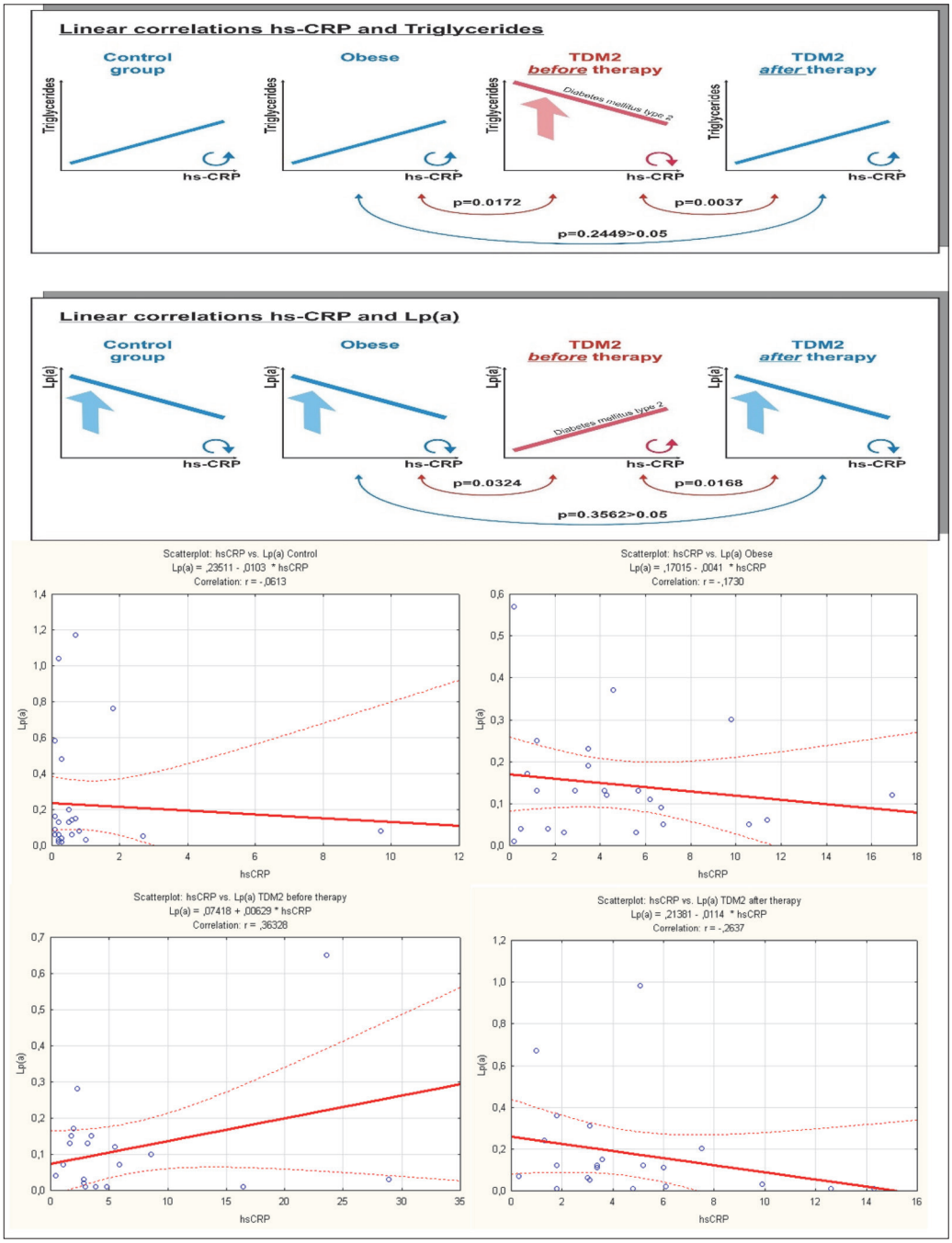

Figure 2. The linear correlations between hsCRP and Lp(a) in studied groups;
TDM2 – type 2 diabetes mellitus; hsCRP – high sensitive C-reactive protein; Lp(a) – lipoprotein (a)

versely, Lp(a) was the highest in control subjects and the difference compared to T2DM patients before the start of metformin treatment reached statistical significance (Table 2). Not surprisingly, those with T2DM were the most insulin resistant before the initiation of metformin treatment. Their HOMA-IR index was significantly higher than in all the other groups, and after the treatment period, their HOMA-IR index was significantly higher only compared with the control group (Table 2). Their hsCRP was also the highest in T2DM patients prior to treatment. Significant differences were observed between the control group and all groups of obese patients, and values in the group of obese subjects were not significantly different from those in patients with newly diagnosed T2DM before and after initiation (Table 2). There were no significant differences in the levels of serum creatinine between the examined groups (Table 2).

We performed a sub-analysis including NGT obese subjects as well as obese T2DM patients before and after metformin treatment. The correlation analysis including hsCRP and triglycerides pointed out that correlations of these two parameters differed significantly between the NGT obese group and the T2DM patients prior to the initiation of metformin treatment ($r = 0.21$ *vs.* $r = -0.36$; $p = 0.0172$) (Figure 1). Therefore, among obese NGT individuals, an increase in triglyceride levels was accompa-

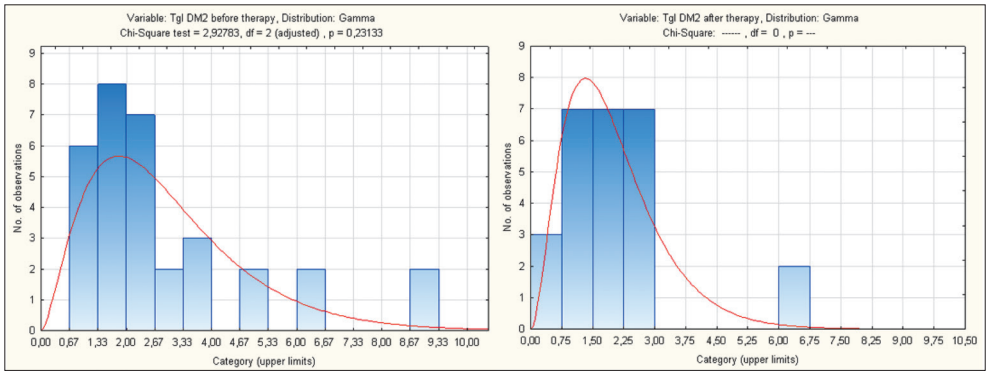

Figure 3. Distribution of serum tryglicerides before and after metformin therapy initiation in T2DM group; Tgl – triglycerides; DM2 – type 2 diabetes mellitus

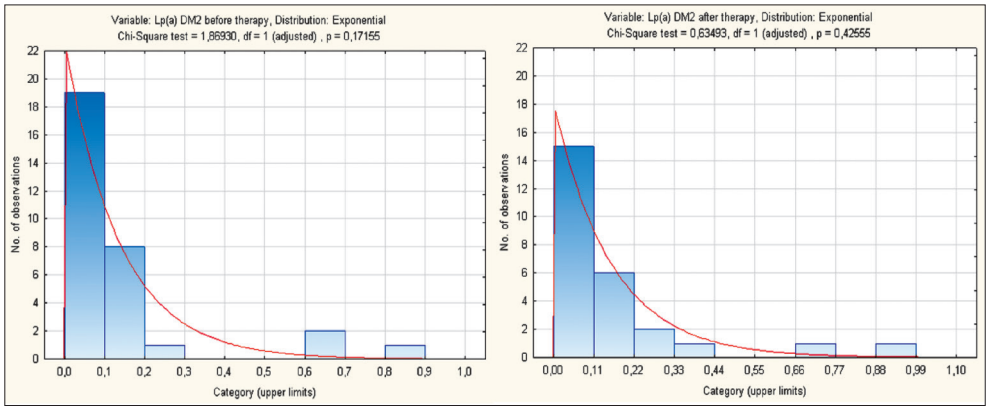

Figure 4. Distribution of Lp(a) before and after metformin therapy initiation in T2DM group; Lp(a) – lipoprotein (a); DM2 – type 2 diabetes mellitus

nied by an increase in hsCRP level, while this relation was completely opposite in T2DM patient before the start of metformin treatment. The similar findings were during the comparison of correlations of these two parameters in T2DM patients before and after the initiation of metformin treatment. (r = -0.36 *vs*. r = 0.38; p = 0.0037) (Figure 1). Finally, the correlation coefficient of these two parameters did not differ significantly between NGT obese subjects and T2DM patients after the treatment initiation (r = 0.21 *vs*. r = 0.38; p = 0.2449) (Figure 1). Namely, after the initiation of metformin therapy, a pattern of relation between hsCRP and triglycerides became similar to the one observed among NGT obese individuals (Figure 1).

The similar results but in the opposite direction were found during the sub-analysis of correlations between hsCRP and Lp(a) in obese subjects. Correlation coefficients between two parameters in NGT obese group and in T2DM patients prior to the metformin treatment differed significantly (r = -0.17 *vs*. p = 0.36, p = 0.0324) (Figure 2). In other words, while the higher levels of hsCRP were followed by a decrease in Lp(a) in NGT obese group, this relation was direct in T2DM patients before they started the metformin treatment. The same was during the comparison of correlation coefficients between hsCRP and Lp(a) in T2DM patients before and after the metformin treatment period (p = 0.36 *vs*. p = -0.27; p = 0.0168) (Figure 2). After the initiation of metformin therapy, the pattern of relation between hsCRP and Lp(a) became similar to the one observed among NGT obese individuals: a decrease in hsCRP level was accompanied by an increase in Lp(a) level. This was also supported by the calculation of probability for the hypothesis on the coincidence of the linear coefficients in two sets which showed that there were no significant differences in correlation coefficient between hsCRP and Lp(a) in groups of NGT obese subjects and T2DM patients after the metformin treatment initiation (r = -0.17 *vs*. p = -0.27, p = 0.3562) (Figure 2).

Although there was no significant change in the level of triglycerides prior and after the metformin therapy initiation, the shift in type of distribution should be emphasized, so albeit the effect of metformin initiation was not quantitatively verified, the qualitative effect of a therapy was apparent (Figure 3).

Likewise, metformin therapy did not significantly change the Lp(a) levels, but it has not caused the qualitative change either, since the distribution remained unchanged (Figure 4).

DISCUSSION

HsCRP is an acute phase reactant which is responsible for quick response in the case of stress, infection, injury or malignancy. Although chronic stress does not cause excessive

reactions, prolonged low-grade inflammation leads to the development of different degenerative diseases [5].

Strong correlation between inflammation and glycemic control in patients with T2DM suggests that inflammation plays an important role in the pathogenesis of diabetes [6].

Recent studies found that that low hs-CRP (< 2 mg/L) appeared to be associated with reduced risk of incident stroke, incident coronary heart disease and coronary heart disease death, whereas low LDL-C (< 70 mg/dL) was not associated with protective effects [7]. These results support those of the recent CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial with respect to the importance of inflammatory processes in the pathogenesis of CVD [8].

Recent trials with targeting both LDL-C and hs-CRP by statin therapy in patients with acute coronary syndrome could further reduce the incidence of MACE and the residual cardiovascular risk [9]. Tang et al. [10] found that elevated serum levels of hs-CRP are associated with high levels of uric acid, low levels of HLD cholesterol and superoxide dismutase (SOD) but not levels of serum triglycerides. In the study of Kasukurti et al. [11], there was a moderate positive correlation of hs-CRP with all lipid parameters which was significant except for triglycerides.

Kimak et al. [12] showed recently that the main problem of a stable coronary angina patients is not the high concentration of total cholesterol and LDL-C but the progressive increase of chronic inflammation and the accompanying increase in triglycerides and apo B lipoprotein concentration but did not examine correlations between parameters of inflammation and the lipid status. Some CVD outcome studies with triglyceride-lowering agents have produced inconsistent results, meaning that no convincing evidence is available that lowering triglycerides by any approach can reduce mortality [13].

During the sub-analysis which included only obese subjects, we found significant changes in correlations between hsCRP and triglycerides and Lp(a). In the group with the highest degree of inflammation (T2DM patients before the initiation of metformin treatment), the relation of hsCRP with triglycerides and Lp(a) is completely opposite to the one observed among NGT obese subjects. Namely, in T2DM patients prior to the therapy initiation, hsCRP levels are accompanied by a decrease in triglycerides (inverse correlation) and by an increase in Lp(a) level (direct correlation), while these relations are completely inverse in NGT obese individuals. It can be speculated that this scenario reflects the role of increased triglyceride production in the anti-inflammatory response, while Lp(a) molecules are favorably low during the attempt of reducing the increased inflammation.

Barcia et al. [14] suggested that triglyceride-rich lipoproteins, apart from their known role in the fat transportation, can interact with different endotoxins, acting as the immunomodulatory agent in the liver and other tissues during the immune response to infections or, in this case, in the course of subclinical inflammation. This recent study with 52 dyslipidemic subjects showed a strong and significant positive correlation between the serum hsCRP Levels with the serum triglycerides [15]. Some other studies showed that CRP and IL-6 levels correlated with significance positively with Lp(a) levels in hemodialysis patients [16]. Lp(a) levels showed no significant correlations with glycemic control parameters nor insulin and triglyceride levels in study with diabetic patients [17]. Some authors suggest that levels of hsCRP are associated with a disorders of lipid profile such as an increase in total cholesterol, triglycerides and LDL cholesterol and lower HDL-but the mechanism is not entirely clear [18]. Bermudez and al. [19] found, among individuals with metabolic syndrome, that only subjects with hypertriglyceridemia exhibit a greater risk of presenting with elevated level of Lp(a).

In our study, high hsCRP levels are associated (direct correlation) with high Lp(a) levels, and also low hsCRP levels are associated to low Lp(a) levels in T2DM group before metformin therapy initiation, which might imply that low levels of Lp(a) reduce levels of inflammation and damage of blood vessels. High levels of Lp(a) might also show inability to reduce inflammation and exhaustion of physiological mechanism of lowering hsCRP levels with lowering of Lp(a) (e.g. consumption at blood vessel damage repairing). Similar to our study Munoz-Torrero et al. [20] and Katsiki et al.[21] found that MetS patients with elevated Lp(a) levels also had significantly higher levels of pro-inflammatory cytokines and hsCRP compared with MetS patients with normal Lp(a) levels

High levels of hsCRP and low levels of Lp(a) might predict onset of T2DM which represents the state of high inflammation (characterized by elevated hsCRP) and hypothetically the condition of good response in minimizing damage and repairing blood vessels (characterized by low Lp(a)). European Prospective Investigation of Cancer (EPIC)-Norfolk and the Diabetes Genetics Replication and Meta-analysis, reported a strong inverse relationship between Lp(a) and the risk of T2DM [22]. In present study, in all groups, except T2DM group before metformin therapy initiation, we can observe an inverse correlation between hsCRP an Lp(a) (e.g. increase in Lp(a) is accompanied with decrease in hsCRP and *vice versa*). This finding might represent the result of presence of lower grade oxidative modification and inflammation and different function of these parameters in all other groups compared to T2DM patients prior to metformin therapy.

A Danish population study found an association between low Lp(a) and incident diabetes [23]. Possible etiology may include the production of large VLDL particles that are less optimal for the assembly of Lp(a) due to its lipid content interfering with interactions of apo(a) kringles repeats with apoB-100. This is supported by the general observation that Lp(a) levels are modestly inversely associated with triglyceride levels in all populations, and indeed, high levels of triglycerides might influence the levels of Lp(a) and most probably its function [24].

Convincing evidence has been presented that the pro-inflammatory and pro-atherosclerotic effects of Lp(a) are largely attributed to different oxidation-specific epitopes (produced in response to reactive oxygen species), present in Lp(a) particles [3]. This might explain a significant change in correlation levels before and after the metformin

treatment. Important changes in linear correlations of Lp(a) and triglycerides with hsCRP point out a possible functional relationship between them, but in a completely opposite direction.

Similar to our study, patients with diabetes have been shown to have lower Lp(a) levels than non-diabetics, in patients with suspected coronary artery disease undergoing coronary angiography [25]. Studies have shown the lower Lp(a) levels are associated with increased risk of incident diabetes. The mechanisms behind these observations are not clear, but imply reverse causality [23].

Recent data show that treatment of patients with rheumatoid arthritis with IL-6 antagonists reduces Lp(a) by ~30% [26]. We also observe significant changes in correlations between two acute phase reactants (Lp(a) an hsCRP), supporting previous statement.

The fact that metformin therapy reduces the relationship of these two parameters to the level present in NGT obese individuals could indicate that the reduction in plasma glucose levels reduces the degree of inflammation and oxidative stress in one's organism, and that the level of damage and the role of Lp(a) varies depending on the level of inflammatory and oxidative damage. Oxidative stress and glycosylation of Lp(a) molecules, in addition to increased levels of triglycerides and insulin, are an assumed explanation for a significant change in the correlation between Lp(a) and hsCRP. Increased plasma levels of Lp(a) have been accepted as an independent, genetically-conditioned risk factor, for the development of CVD in most of the studies. The useful, protective role of low levels of this lipoprotein in the elimination of harmful proinflammatory molecules of oxidative damage, which was hypothetically observed in our research, should be confirmed by the large-scale prospective studies with the long duration of the follow-up.

Considering that Lp(a) was analyzed by the immunoturbidimetric method, its glycosylation could affect the results. However, reviewing the Package insert test (QUANTIA Lp(a), BIOKIT, S.A., Barcelona, Spain) and available literature, we found no clear data about Lp(a) epitopes significant for recognition of this protein by antibodies in the kit, nor could we conclude to what extent their possible glycosylation might impact the result of analysis. The interrogation of the possible effect of glycosylation on applied methodology could be a subject of the future research.

CONCLUSION

In this study, for the first time, we found a significant change in linear correlations for triglycerides and Lp (a) with parameter hs CRP with the onset of diabetes in obese patients and also significant effect of metformin therapy. Oxidative stress and glycosylation of Lp(a) molecules, in addition to increased levels of triglycerides and insulin, are an assumed explanation for a significant change in the correlation between Lp(a) and hsCRP.

In our study, high hsCRP levels are directly associated and correlated with high Lp(a) levels, and also low hsCRP levels are associated to low Lp(a) levels in T2DM group before metformin therapy initiation, which might imply that low levels of Lp(a) reduce levels of inflammation and blood vessels damage. The high levels of Lp(a) might also show inability to reduce inflammation and exhaustion of physiological mechanism of lowering hsCRP levels with lowering of Lp(a) (e.g. consumption at blood vessel damage repairing). The useful, protective role of low levels of Lipoprotein (a) in the elimination of harmful proinflammatory molecules of oxidative damage, which was hypothetically observed in our research, should be confirmed by the large-scale prospective studies with the long duration of the follow-up.

Conflict of interest: None declared.

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Хронична инфламација и параметри липидног статуса код гојазних особа са нормалним и поремећеним метаболизмом глукозе

Радослав Пејин[1,2], Едита Стокић[1,2], Илија Танацков[3], Ђорђе Поповић[1,2], Артур Бјелица[4,2], Александар Јовановић[5,2]

[1]Клинички центар Војводине, Клиника за ендокринологију, дијабетес и метаболичке поремећаје, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Универзитет у Новом Саду, Факултет техничких наука, Нови Сад, Србија;
[4]Клинички центар Војводине, Клиника за гинекологију и акушерство, Нови Сад, Србија;
[5]Клинички центар Војводине, Клиника за неурологију, Нови Сад, Србија

САЖЕТАК

Увод/Циљ У различитим стањима са повишеним степеном хроничне инфламације, као што су гојазност и дијабетес, ране промене у метаболизму липида могу представљати сврсисходан адаптивни одговор у циљу смањивања инфламаторне реакције у организму.

Циљ истраживања је био да се испита утицај гојазности и гликозне регулације на однос хроничне инфламације и липидских параметара метаболизма.

Методе Студија се састојала од четири групе ($n = 30$ за сваку групу): гојазне особе са поремећеним метаболизмом глукозе (субјекти са новодијагностикованим дијабетесом мелитусом типа 2 (ДМТ2)) пре и у току метформинске терапије, гојазне особе са нормалном толеранцијом глукозе (НТГ) и контролне групе здравих субјеката нормалне телесне масе. Одговарајућа антропометријска мерења и лабораторијска тестирања су спроведена код свих учесника.

Резултати Између група гојазних болесника повезаност нивоа високо осетљивог *C*-реактивног протеина (*hsCRP*) са нивоом триглицерида и липопротеина (*a*) (*Lp*(*a*)) нарочито је изражена у групи особа са ДМТ2 пре почетка терапије метформином. У овој групи ниво инфламације је био највиши и корелациони коефицијенти триглицерида ($r = 0,21$ *vs*. $r = -0,36$; $p = 0,0172$) и *Lp* (*a*) ($r = -0,17$ *vs*. $r = 0,36$, $p = 0,0324$) са *hsCRP* се статистички значајно разликују у поређењу са групом гојазних. Линеарне корелације *hsCRP* са триглицеридима ($r = 0,21$ *vs*. $r = 0,38$, $p = 0,2449$) и *Lp*(*a*) ($r = -0,17$ *vs*. $r = -0,27$, $p = 0,3562$) у групама гојазних особа са НТГ и особа са ДМТ2 током терапије нису се статистички значајно разликовале. Третман са метформином је променио однос линерних корелација *hsCRP* са триглицеридима и *Lp*(*a*) слично ономе код гојазних особа са НТГ.

Закључак Код испитаника са новодијагностикованим ДМТ2, који имају највиши ниво запаљења, повећање нивоа триглицерида може представљати део антиинфламаторног одговора, док хипотетички молекули *Lp*(*a*) могу играти улогу у смањењу повишених нивоа инфламације.

Кључне речи: *C*-реактивни протеин; липопротеин (а); триглицериди; метформин, гојазност; дијабетес типа 2

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The advantages of video-assisted thoracoscopic surgery compared to thoracic drainage in the treatment of primary spontaneous pneumothorax

Aleksandar Ristanović[1], Dejan Stojković[1], Vanja Kostovski[1], Nebojša Marić[1], Nataša Vešović[1], Milena Pandrc[2], Slobodan Milisavljević[3]

[1]Military Medical Academy, Clinic for Chest and Cardiac Surgery, Belgrade, Serbia;
[2]Military Medical Academy, Clinic for Cardiology, Belgrade, Serbia;
[3]Kragujevac Clinical Centre, Clinic for General and Chest Surgery, Kragujevac, Serbia

SUMMARY

Introduction/Objective The aim of the study is to analyze the treatment of spontaneous pneumothorax (PSP) through our 10-year experience.

Methods The study included 67 patients with PSP treated with video-assisted thoracoscopic surgery (VATS) or with thoracic drainage (TD) in the Clinic for Chest Surgery at the Military Medical Academy in Belgrade, Serbia in the 2008–2017 period.

Results PSP patients with VATS were younger (33.2 ± 16.4 *vs.* 45.5 ± 21.5 years, p = 0.010), and both groups consisted mainly of males (69.2% *vs.* 78%). VATS-treated patients were hospitalized shorter and wore drains (p < 0.001, p < 0.002). Recurrence after treatment was more common after TD (61% *vs.* 3.8%) and in most cases it was treated with VATS (92%). The incidence of intraoperative complications is similar between groups (p = 0.599, p = 0.636, p = 0.311, p = 0.388, p = 0.388, respectively). Pain was more common in TD (p < 0.001). The early complications in the group of patients treated with TD occurred more often (p < 0.001, p < 0.001), without significant difference in the incidence of pleura infections and intercostal blockade between groups (p = 0.388, p = 0.388, respectively). Patients treated for PSP with the VATS method came to the control follow-up later, compared to patients treated with TD (p < 0.001).

Conclusion VATS proved to be efficient, which was reflected in the optimal duration of surgery, length of hospitalization, tolerable postoperative pain and satisfactory cosmetic effect, and postsurgical relapse in only one case.

Keywords: pneumothorax; bullous lung disease; video-assisted thoracoscopy; thoracic drainage

INTRODUCTION

A pneumothorax is the presence of air in the pleural space, between the lung and the chest wall. It can be classified as spontaneous and non-spontaneous. A non-spontaneous pneumothorax can have iatrogenic or traumatic cause. Spontaneous pneumothorax occurs without apparent underlying lung disease due to a rupture of subpleural bullae, in which case it is a primary spontaneous pneumothorax (PSP). Secondary spontaneous pneumothorax occurs as a complication of underlying lung disease of a pre-existing clinically manifested lung disease, such as chronic obstructive pulmonary disease, cystic fibrosis, or infection. According to the data, the incidence rate among men is about 23 per 100,000 inhabitants, and in women 3.6 per 100,000 per year. PSP is also related to physical constitution. These are usually younger, thin, and tall individuals. Smoking increases the risk of this condition. There is also a high percentage of further episodes, i.e. recurrences, in as much as 67% of cases [1, 2, 3].

Recurrent pneumothorax is a common complication and is seen in about 30% of cases. It usually occurs within six months to two years after the first episode. The main goal of the treatment is evacuation of air from the pleural space and prevention of recurrence. The treatment depends on size, symptoms, whether it is open or closed, primary, secondary, or recurrent. Treatment can be conservative, with needle aspiration, catheter drainage, drainage of the pleural space, sclerosing agent installation, video-assisted thoracoscopic surgery (VATS) or thoracotomic blebectomy, bullectomy, pleural abrasion, pleurectomy and sclerosation [2, 3, 4].

The purpose of this study was to present experience from a 10-year period in the treatment of spontaneous pneumothorax with a minimally invasive thoracic surgery technique.

METHODS

The retrospective cohort study included 67 patients treated for PSP at the Clinic for Thoracic and Cardiac Surgery of the Military Medical Academy in Belgrade, Serbia in the period from 2007 until present, divided into two groups. One group consisted of 41 patients who had been previously treated using drainage after

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Correspondence to:
Milena PANDRC
Military Medical Academy
Crnotravska 17
11000 Belgrade, Serbia
pandrcmilena@yahoo.com

Table 1. Duration of surgery, number of hospital days, and drain-wearing time

Characteristics of the surgical approaches		Group					p
		Arithmetic average	SD	Median value	Percentile 25	Percentile 75	
Duration of surgery (minutes)	TD	29.3	44	15	15	15	< 0.001
	VATS	68.1	20	60	60	60	
Number of hospital days	TD	12	4.7	12	8	16	0.001
	VATS	8.4	5.8	7	5	9	
Drain-wearing time (days)	TD	8.9	4.7	8	6	11	0.002
	VATS	6	4.6	4	3	7	

TD – thoracic drainage; VATS – video-assisted thoracoscopic surgery; Mann–Whitney test

recurrent episodes of spontaneous pneumothorax. The second group of 26 patients was treated by VATS immediately after the first episode. All patients who were treated with the VATS method were informed about the method, the technique, potential risks and complications, and they also signed a standardized consent for patients undergoing surgical procedures at the Military Medical Academy. The monitoring period includes regular clinical and radiographic controls carried out after one month, three months, and one year after hospitalization. Parameters to be monitored in assessing efficiency of the techniques are as follows: duration of surgery, number of hospital days, drain-wearing time, and the percentage of recurrence. Parameters to be monitored in assessing safety of the techniques are as follows: intraoperative complications, early postoperative complications (pain, bleeding, emphysema, wound infection), and late postoperative complications (pleural infection). Complete statistical data analysis was made using the commercial statistical software PASW Statistics, Version 18.0 (SPSS Inc., Chicago, IL, USA). Statistically significant difference was assessed at the minimum level of $p < 0.05$.

RESULTS

PSP patients treated with VATS were of average age of 33.2 ± 16.4 years, while PSP patients treated with thoracic drainage (TD) were 45.5 ± 21.5 years old, from which it follows that patients treated with VATS were significantly younger in comparison with patients treated with TD ($p = 0.010$), and both groups consisted mainly of male patients (69.2% *vs.* 78.0%). Duration of surgery, number of hospital days, and drain-wearing time were compared in the group of patients with PSP who underwent TD or VATS and the results are shown in Table 1.

Duration of surgery using VATS was almost double compared to TD and it was statistically significant (69.8 minutes *vs.* 29.3 minutes, $p < 0.001$). Patients treated with VATS after PSP were hospitalised and wore drains shorter than the patients who underwent TD after PSP ($p < 0.001$, $p < 0.002$).

The PSP recurrence rate as a complication after using VATS and TD methods for the treatment of PSP are shown in Table 2. Recurrence after treatment for PSP is more common after TD (25 patients or 61%) compared to VATS (one patient or 3.8%), and in most cases it is treated with

Table 2. Recurrence distribution according to the method of treatment

Complications of the surgical approaches		Group				p
		TD		VATS		
		n	%	n	%	
Recurrence as complication	no	16	39	25	96.2	< 0.001
	yes	25	61	1	3.8	

TD – thoracic drainage; VATS – video-assisted thoracoscopic surgery; χ^2 test

Table 3. Early complications after surgery

Complications		Group				p
		TD		VATS		
		n	%	n	%	
Wound infection	no	41	100	26	100	-
	yes	0	0	0	0	
Pain	no	6	14.6	17	65.4	< 0.001
	yes	35	85.4	9	34.6	
Bleeding	no	40	97.6	25	96.2	1.000§
	yes	1	2.4	1	3.8	

TD – thoracic drainage; VATS – video-assisted thoracoscopic surgery; χ^2 test; §Fisher test

Table 4. Total early complications after treatment

Complications		Group				p
		TD		VATS		
		n	%	n	%	
Early complications total	No complications	6	14.6%	17	65.4%	< 0.001
	1	28	68.3%	7	26.9%	
	≥2	7	17.1%	2	7.7%	

TD – thoracic drainage; VATS – video-assisted thoracoscopic surgery; χ^2 test

VATS (23 patients or 92% of patients treated with TD). The results show that the incidence of inadequate drainage position, re-drainage, reposition, addition and removal of drains is similar between groups, there is no statistically significant difference ($p = 0.599$, $p = 0.636$, $p = 0.311$, $p = 0.388$, $p = 0.388$). Incidence of intraoperative complications: the use of analgesics, atypical localization of pain, adhesions and the application of open surgery were very similar between the groups in which PSP was treated with VATS or TD ($p = 0.518$, $p = 0.147$, $p = 0.158$).

Pain as an early complication was more common in thoracic drainage, which was statistically significant ($p < 0.001$). Each group had only one patient with bleeding as a complication, so there was no significant difference between the groups (one patient or 2.4% *vs.* one patient or 3.8%, $p = 1.000$) (Table 3).

Table 5. Follow-up control time after intervention

Control time after surgery		Group					p
		Arithmetic average	SD	Median value	percentile 25	percentile 75	
late control (months)	TD	3.7	2.0	3.0.	3.0	6.0	< 0.001
	VATS	5.8	1.0	6.0.	6.0	6.0	

TD – thoracic drainage; VATS – video-assisted thoracoscopic surgery;
SD – standard deviation;
Mann–Whitney test

Early complications were grouped according to their low incidence as follows: wound infection, pain, bleeding, emphysema, reduction in pulmonary function, forced expiratory volume in one second (FEV 1) (Table 4).

One and two and more early complications in the group of patients treated with TD were significantly more common (68.3% *vs.* 26.9%, 17.1% *vs.* 7.7%, respectively; $p < 0.001$, $p < 0.001$). There was no statistically significant difference in the incidence of pleura infections and intercostal blockade between the groups ($p = 0.388$, $p = 0.388$, respectively). Patients treated for PSP with the VATS method came to the follow-up control later, compared to patients treated with TD (5.8 months *vs.* 3.7 months, $p < 0.001$) (Table 5).

DISCUSSION

Our two study groups were composed mostly of younger men, which is in line with the existing epidemiological data on the distribution of primary spontaneous pneumothorax with respect to age and sex [4]. Regarding the duration of the intervention itself, it is optimal and in line with the already published results of prospective studies, with a significantly shorter drain-wearing time and duration of hospitalization, compared to TD [5].

According to some authors, VATS is described as the treatment of choice of PSP with very low recurrence rate, the possibility of bullectomy or apical pleurectomy using mechanical abrasion and the option to switch to open surgery, if needed [6, 7, 8].

In a large European study, the PSP recurrence rate was compared between patients treated with thoracic drainage and VATS with talc pleurodesis. The obtained values are 34% compared to 5% in patients treated with VATS [9]. Ten-year monitoring of PSP patients in one center confirmed the long-term safety and efficiency of VATS with talc pleurodesis, with a 5% recurrence rate in patients with bullae.

Recurrences after treating our patients by VATS were practically negligible, and early and late complications were at approximately the same level as TD, which leads us to the conclusion that the VATS method is at least as safe as the TD method but more effective than it. All of the aforementioned leads also to the explanation of the late first follow-up controls among patients treated with VATS in relation to thoracic drainage, since VATS as a definitive treatment model did not require prior appointment with the surgeon.

Treatment of relapse is unclearly defined, taking into account that TD in the first act is unsuccessful in 15–62% of the cases [10]. Chemical pleurodesis is superior to simple drainage in the prevention of recurrence (recurrence rate of 8–13% and 36%, respectively) [10, 11]. In patients with Vanderschueren's stage II or IV PSP, some authors advocate the advantage of VATS in relation to thoracoscopy, because of the possibility to apply bullectomy or apical pleurectomy. There is no evidence of a preventive effect of bullectomy on the occurrence of relapse, but pleurodesis has proven to be effective. VATS pleurodesis is as efficient as apical pleurectomy, but with less side effects [12].

In patients with previous medical thoracoscopy, there are controversies regarding the repetition of thoracoscopy ipsilaterally due to the fear that the adhesions will interfere with visualization or because of the increased risk of complications. Studies that included a few series of patients treated with repeated thoracoscopy, as well as a group that had previous talc pleurodesis, proved its practicability and safety [11]. In most of them, it was possible to apply talc pleurodesis as part of repeated thoracoscopy. On the other hand, during the analysis of the course of treatment within a small series of 39 patients treated with VATS after previous talc pleurodesis, repeated pleurodesis was successful in almost 70% of the patients [11, 13].

Furthermore, patients treated with VATS benefit from better cosmetic effects and painless procedures. In relation to the earlier method of treating spontaneous pneumothorax with thoracic drainage, the VATS method is a more efficient and significantly safer method of treatment, which is also economically more cost-effective [14].

CONCLUSION

The advantage of VATS in relation to TD is in the fewer number of days of hospital treatment, less postoperative pain, less morbidity, better postoperative gas exchange, faster return to normal physical activity, better cosmetic effect – therefore, VATS has become the gold-standard of treating pneumothorax.

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Предности видеоасистиране торакоскопске хирургије у поређењу са торакалном дренажом у лечењу примарног спонтаног пнеумоторакса

Александар Ристановић[1], Дејан Стојковић[1], Вања Костовски[1], Небојша Марић[1], Наташа Вешовић[1], Милена Пандрц[2], Слободан Милисављевић[3]

[1]Војномедицинска академија, Клиника за грудну хирургију и кардиохирургију, Београд, Србија;
[2]Војномедицинска академија, Клиника за кардиологију, Београд, Србија;
[3]Клинички центар Крагујевац, Клиника за општу и грудну хирургију, Крагујевац, Србија

САЖЕТАК

Увод/Циљ Циљ ове студије је анализа лечења примарног спонтаног пнеумоторакса (ПСП) кроз наше десетогодишње искуство.

Метод Студија је укључила 67 болесника са ПСП-ом лечених видеоасистираном торакоскопском хирургијом (ВАТХ) или торакалном дренажом (ТД) у Клиници за грудну хирургију и кардиохирургију у Војномедицинској академији у периоду 2008–2017.

Резултати Болесници са ПСП-ом лечени ВАТХ-ом су били млађи (33,2 ± 16,4 наспрам 45,5 ± 21,5 година, $p = 0,010$), а у обе групе су већину чинили мушкарци (69,2% наспрам 78%). Такође, оболели третирани ВАТХ-ом су брже завршавали хоспитално лечење и краће носили дрен ($p < 0,001$, $p < 0,002$). Рецидив након лечења се чешће јављао код лечених ТД-ом (61% наспрам 3,8%) и у највећем броју случаја третиран је ВАТХ-ом (92%). Учесталост интраоперативних компликација је била слична између група ($p = 0,599$, $p = 0,636$, $p = 0,311$, $p = 0,388$, $p = 0,388$). Бол као компликација се чешће јављао код лечених ТД-ом ($p < 0,001$), као и ране компликације ($p < 0,001$, $p < 0,001$). Није било разлике у учесталости инфекције плеуре и примене интеркосталне блокаде између група ($p = 0,388$, односно $p = 0,388$). Болесници лечени ВАТХ-ом су касније долазили на контролу у поређењу са болесницима леченим ТД-ом ($p < 0,001$).

Закључак ВАТХ се као хируршка метода показао ефикаснијим у односу на ТД, што се огледа у оптималном трајању операције, дужини хоспитализације, толерабилном постоперативном болу и задовољавајућем козметском ефекту, као и рецидиву у само једном случају.

Кључне речи: пнеумоторакс; булозно плуће; видеоасистирана торакоскопија; торакална дренажа

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Trends in forceps deliveries in a tertiary health care facility in Serbia

Miloš Petronijević[1,2], Svetlana Vrzić-Petronijević[1,2], Danijela Bratić[2], Tatjana Nikolić[2], Zorica Jestrović[2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Centre of Serbia, Clinic of Gynecology and Obstetrics, Belgrade, Serbia

SUMMARY
Introduction/Objective Increased incidence of cesarean sections leads to the reduction of incidence of instrumental vaginal deliveries.
The aim of this study was to analyze the trends of forceps deliveries at the tertiary healthcare facility.
Methods The study was performed at the Clinic of Gynecology and Obstetrics, covering a 30-year period, from 1987 to 2016 with a total of 198,882 births.
Results Forceps delivery rate was significantly lowering during time, while the cesarean section rates were rising.
Conclusion Using linear, cubic and quadratic prediction models, we can estimate that in the year 2020 there will be no more forceps deliveries. However, minding the confidence interval of 95% some forceps deliveries might still be carried out. Since it has been shown that the forceps is a very useful obstetric tool, this very important skill might soon be neglected due to the lack of training.
Keywords: forceps; delivery; vaginal; operative; cesarean section

INTRODUCTION

An increase in cesarean section rates have resulted in a reduction of instrumental vaginal deliveries rates. Nowadays, increased cesarean section rates are becoming an issue, leading to some instances of a renewed interest in forceps delivery, even Kielland's rotational forceps. Nevertheless, a greater use of forceps, especially a rotational one could be associated with a much higher incidence of major maternal trauma, especially to the anal sphincter and levator ani muscles, so its use should be avoided whenever possible [1].

Operative vaginal delivery (forceps and vacuum extraction) and cesarean sections were relatively recently introduced as obstetric operations. Forceps delivery was always considered a great obstetrical challenge. What is expected from contemporary obstetrician is to be able to recognize disorders of natural birth processes following with an active intervention [2].

In some situations, forceps may be the safest option for delivery, for example, with an undiagnosed breech presentation at full cervical dilation or for delivery of the second twin. In these cases, forceps enable the controlled delivery of the fetus's head. Assisted vaginal delivery of a fetus with a face presentation can only be achieved by forceps; vacuum extraction is contraindicated. Forceps is the only option for delivery of premature fetuses because of the risk of cephalohematoma and intracranial hemorrhage with vacuum extraction. Additionally there are medical conditions (cardiac, respiratory, and neurological) that preclude maternal effort, required for successful vacuum extraction, in the second stage of labor. Forceps may also be chosen when maternal effort is minimal secondary to epidural analgesia. Outlet forceps can be useful at caesarean section for controlled delivery of the fetal head.

Typically, forceps is used when a singleton fetus in the cephalic position fails to progress, or when delivery needs to be expedited in the second stage of labor because of fetal distress. In these instances, there may be a real choice between forceps and alternative methods of delivery: caesarean section and vacuum extraction.

Correct placement of the vacuum device or forceps is the key to safety [3]. Instrumental delivery should never be performed when the fetal head is not engaged. Transabdominal ultrasound assessment should be conducted in cases of clinical doubts about the fetal head position [4]. Malrotation and elevated numbers of traction applications may lead to neonatal head injury [5].

Generally, forceps delivery is considered to have higher success rates than vacuum extraction. However, the success rates of operative vaginal delivery will vary regarding other factors, including the range of indication, the approval for subsequent forceps after failed vacuum extraction, and the operator's proficiency and preference [6].

Neonatal sequelae are an important consideration if instrumental vaginal delivery is unsuccessful. A recent prospective study found that neonatal trauma and fetal acidosis were more common after failed instrumental

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Correspondence to:
Miloš PETRONIJEVIĆ
Kičevska 13a
Belgrade, Serbia
petronije@ptt.rs

Table 1. The number of vaginal, cesarean and forceps deliveries in the 1987–2016 period at the Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia in Belgrade, Serbia

Year	Vaginal delivery		Cesarean section		Total	Forceps	
	Number	%	Number	%	Number	Number	%
1987	8,254	92.46	656	7.36	8,910	139	1.87
1988	6,950	92.09	597	7.91	7,547	134	1.92
1989	7,186	91.92	632	8.08	7,818	124	1.72
1990	6,834	90.64	706	9.36	7,540	121	1.77
1991	6,611	89.29	793	10.71	7,404	126	1.91
1992	6,601	89.91	741	10.09	7,342	62	1.04
1993	6,545	89.70	751	10.30	7,296	94	1.29
1994	6,731	88.36	887	11.64	7,618	67	0.99
1995	7,256	90.49	763	9.51	8,019	109	1.50
1996	5,399	86.55	839	13.45	6,238	85	1.57
1997	2,818	78.45	774	21.55	3,592	59	2.09
1998	4,675	83.14	948	16.86	5,623	43	0.84
1999	4,511	81.50	1,030	18.50	5,541	51	1.13
2000	5,099	81.51	1,123	18.49	6,222	43	0.84
2001	5,491	81.42	1,253	18.58	6,744	53	0.96
2002	5,473	78.96	1,464	21.04	6,958	30	0.55
2003	5,415	78.72	1,464	21.28	6,879	52	0.96
2004	5,452	75.39	1,780	24.61	7,232	29	0.53
2005	5,237	74.56	1,787	25.44	7,024	21	0.40
2006	5,283	75.21	1,742	24.79	7,025	20	0.38
2007	5,241	75.86	1,668	24.14	6,909	16	0.30
2008	5,070	72.44	1,929	27.56	6,999	34	0.67
2009	4,556	69.60	1,990	30.40	6,546	16	0.36
2010	4,572	67.75	2,176	32.25	6,748	26	0.57
2011	4,290	68.86	2,224	34.14	6,514	26	0.60
2012	4,475	65.72	2,325	34.28	6,782	15	0.34
2013	4,608	68.93	2,077	31.07	6,685	17	0.36
2014	4,654	67.53	2,238	32.47	6,892	7	0.15
2015	4,026	63.15	2,349	36.85	6,357	5	0.12
2016	4,044	63.26	2,348	36.73	6,392	10	0.25

vaginal delivery than after immediate caesarean section [7]. It remains unclear whether complications in labor result in operative delivery or whether the mode of delivery itself contributes to adverse outcomes. In their large-scale retrospective cohort study, Werner et al. [8] reported that forceps delivery had a lower risk of adverse neonatal outcomes including cephalohematoma, low Apgar score, and neurologic complications and posed a higher risk of facial nerve palsy than did vacuum extraction. Although previous reports suggested that the risk of fetal injury is unacceptable, recent studies demonstrate more favorable outcomes without significant fetal or maternal morbidity, so the training in forceps deliveries should continue [9].

The aim of this study was to analyze the trends of forceps deliveries at a tertiary healthcare facility.

METHODS

This study was performed at the Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia in Belgrade, a tertiary healthcare facility, covering a 30-year period, from 1987 to 2016, with a total of 198,882 births. We analyzed forceps delivery rates, indications for forceps delivery, parity of patients and maternal morbidity after forceps delivery. Regarding neonates, we analyzed average Apgar score, birthweight and neonatal morbidity. At the same time, we analyzed cesarean section rates in same period. Statistical methods we used were descriptive statistics, percentages, as well as linear, cubic, and quadratic prediction models.

This study was conducted in accord with standards of the institutional Committee on Ethics.

RESULTS

In Table 1, the number of vaginal, cesarean and forceps deliveries in the period from 1987–2016 at the Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia in Belgrade, Serbia are shown.

In the analyzed period, there were total of 198,882 births, of which 1,634 were forceps deliveries, and 55,475 were cesareans sections.

Statistically significant decrease in both vaginal and forceps deliveries was noted, while at the same time, the cesarean section rates were statistically significantly increased.

In the analyzed period, the highest forceps delivery rate was noted in the year 1997 (2.09%), and lowest in the

year 2015 (0.12%). The lowest cesarean section rate was observed in the year 1987 (7.36%), and highest in the year 2015 (36.85%).

Using linear ($R^2 = 0.947$), cubic ($R^2 = 0.944$) and quadratic ($R^2 = 0.822$) prediction models we can estimate that in the year 2020 there will be no more forceps deliveries. However, minding the confidence interval of 95%, some forceps deliveries might still be performed.

DISCUSSION

The increase of cesarean section rates is the result of virtually complete elimination of vaginal breech delivery, as well as a significant decrease in operative vaginal deliveries and vaginal birth after cesarean. In our study, covering 198,882 births, we have found a statistically significant decrease in both vaginal and forceps deliveries, and statistically significant increase the cesarean section rates. The number of forceps deliveries is closely associated with the number of vaginal deliveries, which is one of reasons for the decrease in the number of forceps deliveries. Our data is consistent with literature data regarding the decrease in forceps deliveries.

It does not matter whether cesarean section rates are high or low, but whether the appropriate performance of cesarean delivery is part of a system that delivers optimal maternal and neonatal care after consideration of all relevant patient and health system information [10]. The current study suggests, however, that efforts to reduce cesarean section rates may not improve patient outcomes. Caesarean delivery is protective against birth trauma, especially when performed without labor in comparison with vaginal delivery when operative delivery is required in the second stage of labor [11].

After a decline in the use of forceps because of adverse outcomes and fear of litigation, recent evidence suggests that they may be safe and effective in trained hands regarding the increased short and long-term morbidity related to cesarean section compared with the reduced morbidity of subsequent pregnancy after operative vaginal delivery [12].

When complications arise in the second stage of labor, there is a choice between an instrumental vaginal delivery and a caesarean section. Obstetric forceps is potentially dangerous in the hands of untrained or inexperienced obstetricians.

The failures in forceps deliveries are usually related to inaccurate assessment of the fetal position and station, which can be overcome by gaining enough clinical experience and using intra-partum ultrasound scanning to determine the fetal head position in the second stage, and should be part of the core curriculum in obstetric training [13].

Women are more likely (over 75%) to choose a future vaginal delivery after one successful forceps delivery than after a caesarean section (almost 25%) [14].

Instrument-assisted vaginal delivery is a significant risk factor for birth canal lacerations. Protection against extensive perineal tearing may prevent obstetric anal sphincter injuries [15].

In our study, using prediction models we estimated that in the year 2020 there will be no more forceps deliveries, however, minding the confidence interval of 95% some forceps deliveries might still be performed. The limited use of forceps is due to the lack of training and the situation in our facility is no different. This is a new educational challenge for teaching and development of clinician's skills with careful assessment and knowing when to stop if safety criteria are not met [16].

To enable women to make an informed choice about the mode of delivery, obstetricians need to be adequately trained and supervised in the use of forceps.The American College of Obstetrics and Gynecology has recommended training in instrumental delivery to control and reduce the rates of caesarean sections. Current minimum training for forceps delivery is insufficient to ensure obstetricians' competency, leading to the inevitable disappearance of this valuable skill. The prospects are to abandon the attempts to teach forceps and prepare residents for practice, which does not include the availability of forceps delivery, or to prioritize the development of simulation models that would allow them to obtain sufficient training in forceps delivery, which is the only alternative to the inevitable extinction of the forceps [17].

CONCLUSION

After analyzing the trends of vaginal, forceps and cesarean section delivery rates, a statistically significant decrease was found in both vaginal and forceps deliveries, while at the same time, the statistically significant increase of cesarean section rates. Using linear, cubic and quadratic prediction models we can estimate that in 2020 there will be no more forceps deliveries. With the confidence interval of 95% some forceps deliveries, however, might still be performed. The reasons for the decline in the use of a forceps are the fear of maternal and fetal injuries and medicolegal issues. Since it has been shown that the forceps is a very useful obstetric tool, this extremely important skill might soon be neglected due to the lack of training.

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Тренд порођаја форцепсом у терцијарној установи у Србији

Милош Петронијевић[1,2], Светлана Врзић-Петронијевић[1,2], Данијела Братић[2], Татјана Николић[2], Зорица Јестровић[2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија

САЖЕТАК

Увод/Циљ Повећана учесталост царских резова довела је смањења учесталости инструменталног вагиналног порођаја. Циљ студије био је да се анализира тренд порођаја форцепсом у терцијарној установи.

Методе Студија је спроведена у Клиници за гинекологију и акушерство у периоду од 1987. до 2016. године и обухватила је 198.882 порођаја.

Резултати Учесталост порођаја форцепсом се значајно смањила током времена, док је учесталост царског реза у порасту.

Закључак Користећи линеарне, кубне и квадратне моделе предикције, процењује се да у 2020. години више неће бити порођаја форцепсом. Имајући у виду интервал поверења од 95%, могуће је да ће се понеки порођај форцепсом ипак спровести. С обзиром на то да је форцепс веома користан инструмент, вештина његове употребе може нестати због неадекватне обуке акушера.

Кључне речи: форцепс; порођај; вагинални; оперативни; царски рез

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Frequency, severity and type of anemia in children with classical celiac disease

Nedeljko Radlović[1], Zoran Leković[2,3], Marija Mladenović[4], Vladimir Radlović[2], Biljana Vuletić[5,6], Siniša Dučić[2,3], Zoran Golubović[2,3], Dejan Nikolić[2,3], Meho Mahmutović[7], Snežana Petrović-Tepić[8]

[1]Serbian Medical Society, Academy of Medical Sciences, Belgrade, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[4]Valjevo Medical Centre, Valjevo, Serbia;
[5]Kragujevac Clinical Center, Pediatric Clinic, Kragujevac, Serbia;
[6]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia;
[7]Novi Pazar General Hospital, Novi Pazar, Serbia;
[8]University of Banja Luka, School of Medicine, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Anemia is the most common extraintestinal manifestation of celiac disease (CD) in children.

The aim of this study was to determine the frequency, severity and type of anemia in children with a classical CD, as well as the differences between anemic and non-anemic patients in their age, duration of illness, percentile body length or height, percentage of body weight (BW) deviation compared to ideal, and the degree of damage to the small intestine mucosa.

Methods The study was based on a sample of 90 children, 56 females and 34 males, ages 7–90 (18.23 ± 12.7) months with classical CD. The diagnosis of CD is based on the ESPGHAN criteria from 1990 and 2012, and of anemia on the 2011 WHO reference values.

Results Anemia was found in 47 (52.22%) patients, of which it was mild in 23 cases [hemoglobin (Hb) 100–109 g/L] and moderately severe in 24 (Hb 70–99 g/L), in 34 (72.34%) it was microcytic [mean cell volume (MCV) < 70 fl] and normocytic (MCV 70–87 fl) in 13 patients. Low serum iron levels (< 10.7 μmol/L) were found in 68 (75.56%), and hypoferritinemia (< 16 ng/ml) in 77 (85.56%) patients. Except for a greater deficit of BW in patients with anemia compared to those without anemia (-14.64 ± 9.60 *vs*. -8.56 ± 11.87%, $p < 0.01$), differences in other defined features were not significant.

Conclusion Mild or moderate iron deficiency anemia occurs in slightly more than half of children with a classical type CD. In anemic compared to non-anemic patients, there is a significantly higher BW deficit, while differences in other characteristics typical for this type of disease are not significant.

Keywords: classical celiac disease; children; anemia

INTRODUCTION

Anemia is the most common extraintestinal manifestation of celiac disease (CD) [1–5]. Depending on the study, it is found in 16–84% of newly detected patients, more often and more pronounced in severe and prolonged forms of the disease [4–8]. A key role in the pathogenesis of anemia in CD, both in children and adults, is iron deficiency, while the lack of folic acid, vitamin B12, copper, and protein results in a lesser expression [4, 9, 1–12]. In a significant number of cases anemia can be the main, and often the only sign of the disease [9, 13–19]. This clinical presentation of CD is commonly seen in adults and adolescents, although it is not rare in school and preschool children [9]. According to the results of some studies, CD as the etiological factor of sideropenic anemia participates with a prevalence of 6–21.3% [9, 17–19]. Hence, some authors recommend that all patients with sideropenic anemia of unclear etiology, especially those resistant to oral iron therapy, should be tested for CD [13, 17, 19].

The aim of our study was to determine the frequency, severity and type of anemia in children with classical CD. In addition, the objective was to analyze the differences between anemic and non-anemic patients at the age of diagnosis of the basic disease and its previous duration, percentile body length (BL) or body height (BH), percentage of body weight (BW) deviation compared to the ideal, and the degree of damage to the small intestine mucosa.

METHODS

The objectives of the study were analyzed on a sample of 90 children (56 female and 34 male) ages 7–90 (18.23 ± 12.70) months with classical CD, i.e. type of the disease followed by chronic diarrhea (> 2 weeks) and failure to thrive. The diagnosis of CD was based on the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines published in 1990 and 2012 [20, 21]. The diagnosis was preceded by a detailed medical history, complete

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Correspondence to:
Nedeljko RADLOVIĆ
Serbian Medical Society
Džordža Vašingtona 19
11 000 Belgrade, Serbia
n.radlovic@beotel.net

clinical examination, and appropriate laboratory tests. The study protocol was approved by the local ethics committee.

History of the disease for each patient contained exact data related to the onset, duration, and the severity of the underlying disease. According to the data from parents, all respondents had optimally progressed and had normal blood counts before the onset of the disease. During the clinical examination, each patient's BL/BH and BW was measured and the obtained values were compared with the standard for the appropriate age and sex. The values of BL/BH are expressed in percentiles, and deviations in BW in relation to the ideal in percentages.

In accordance with the modified Marsh criteria, small intestinal mucosal damage is classified into infiltrative (I), infiltrative-hyperplastic (II), destructive (III), and hypoplastic (IV) [22]. Depending on the degree of destruction of villi, destructive enteropathies are additionally differentiated into partial (IIIa), subtotal (IIIb), and total (IIIc).

Blood count and serum iron and ferritin concentrations were determined by standard laboratory methods from a blood portion taken in the morning and before breakfast. The diagnostic criterion for anemia was the level of Hb for children up to five years old below 110 g/L, and for children 5–11 years old below 115 g/L [23]. The Hb value of 100–109 g/L was classified as a slight anemia, from 70 to 99 g/L moderate, and below 70 g/L severe [23]. The reference value for red blood cells count (RBCs) was $3.90–5.10 \times 10^{12}$/L, for MCV it was 70–87 fl, for mean cell Hb (MCH) 25–31 pg, and for iron serum concentration 10.7–31.3 μmol/L, of ferritin 16–100 ng/ml [24]. The differentiation of anemia types is based on the values of MCV, MCH, and serum iron concentration.

The differences between the anemic and non-anemic groups of children according to the age of diagnosis and the duration of the underlying disease were tested by Oneway ANOVA (on-the-clock analysis of variance), according to sex by the χ^2 test, according to the degree of small intestinal mucosal damage by the Kruskal–Wallis and Mann–Whitney tests, and the percentile BL/BH and the percentage of BW deviation was compared to the ideal by Student's T-test.

RESULTS

Anemia with Hb values of 71–109 (96.62 ± 9.33) g/L was observed in 47 of 90 or 52.22% of patients. None of them had severe anemia, while the incidence of mild and moderately severe anemia was almost the same (24 *vs.* 23). The number of RBCs in the blood in the whole group of subjects varied 2.56–5.19 (4.29 ± 0.73) $\times 10^{12}$/L, while the MCV value was 50.5–88.0 (64.76 ± 9.18) fl, concentrations of serum iron were 2.1–15.5 (5.96 ± 3.32) μmol/L, and of ferritin 2–18 (7 ± 4.20) ng/ml. In the group of children with anemia, the number of RBCs was low in 15 (31.91%) of them, normal in 27 (57.45%), and elevated in five ($5.11–5.70 \times 10^{12}$/L). In the same group of patients, MCV was decreased in 34 (72.34%) and normal in 13, while MCH was low in 35 (74.47%), and normal in 12. In the entire group of subjects, low serum iron levels were determined in 68 (75.56%) cases, while low ferritin levels were determined in 77 (85.56%) cases. Granulocyte and platelet counts in the blood were normal in all.

The duration of symptoms before the diagnosis was 1–6 (2.21 ± 1.48) months. The majority, 50 children (55.56%), were at the age of 1–2 years, 28 were younger than one year, and 12 were older than two years. The values of BL/BH percentile ranged 5–90 (37.62 ± 26.26), and the BW percentage deviation compared to the ideal for the appropriate age and sex from +18.5 to -33 (-11.58 ± 10.80). Destructive enteropathy (type III) was found in all the patients, seven of which partial (IIIa), 41 subtotal (IIIb), and 42 total (IIIc).

The differences in the age and the duration of the disease, sex, percentile BL/BH, percentage of BW deviation in relation to ideal, and the degree of damage of the obtained small intestine samples among patients with anemia and without anemia are shown in Table 1. As it can be seen, with the exception of significantly higher BW deficit in patients with anemia than in those without it, there were no significant differences.

Table 1. Differences in the age of diagnosis of celiac disease, duration of symptoms, BL/BH percentile, BW percentage deviation compared to the ideal, and the degree of damage of the small intestine mucosa in patients with anemia and in those without it

Observed features	Patients with anemia (No 47)	Patients without anemia (No 43)	Statistical significance
Age (months)	7.5–60 (16.42 ± 10.72)	7.5–90 (16.52 ± 5.96)	n.s.
Duration of symptoms (months)	1–6 (2.37 ± 1.54)	1–6 (2.03 ± 1.42)	n.s.
Percentile of BL/BH	5–90 (40.0 ± 26.37)	5–90 (35.25 ± 16.22)	n.s.
% deviation of BW	+9–-33 (-14.64 ± 9.60)	+18.5–-28 (-8.56 ± 11.87)	$p < 0.01$
Enteropathy (No) IIIa:IIIb:IIIc	2:21:24	5:20:18	n.s.

BL – body length; BH – body height; BW – body weight; n.s. – not significant

DISCUSSION

Anemia in CD is primarily caused by iron deficiency, but also by the lack of other nutritional factors necessary for normal erythropoiesis, such as folic acid, vitamin B12, proteins and copper [10, 12, 25, 26]. Hence, viewed pathogenically, it belongs to the group of nutritive or hypoproliferative anemia [10]. Deficit of iron, protein, and copper results in insufficient Hb synthesis and causes anemia of hypochromic and microcytic type, where the number of RBCs can be normal and elevated, while folic acid and vitamin B_{12} deficiency block normal regeneration of RBCs and result in macrocytic anemia [27]. In the state of a combined deficit of a factor of essential importance for normal erythropoiesis, anemia acquires normocytic features [10]. Folic acid deficiency, in addition to a smaller number of Er and low Hb and the number of reticulocytes, is characterized by high values of MCV and MCH and a reduced number of granulocytes and platelets [10]. An

identical hematological image also has a lack of vitamin B_{12}, but it is, except in the heavy form of the classical CD, rarely seen [4, 27, 28].

The basis of the deficit of the factors necessary for erythropoiesis is the absorption disorder caused by the inflammation of the small bowel mucosa [29]. The morphological and functional damage to the small intestine mucosa to the CD is most pronounced in its proximal part, i.e. in the segment where most of the nutrients are absorbed [29]. Negative nutritional balance in the classical type of CD is also significantly contributed to by insufficient intake caused by anorexia and vomiting [30]. As with other inflammatory diseases, additional involvement in iron malabsorption also has a suppressive effect of hepcidin [12, 30].

The consequences of the disease are more pronounced in children in the first two years of life, i.e. in the period of the most intensive growth and development, especially in the cases of its prolonged duration [4, 9, 29]. The age of our patients was 18.23 ± 12.70 months, and the length of the symptoms until the diagnosis was 2.21 ± 1.48 months, resulting in a significant deficit of BW (-11.58 ± 10.80%), reduced percentage of BL/BH (37.62 ± 26.26) and high representation of subtotal and total enteropathy (92.22%). In accordance with these facts, the prevalence of anemia in our patients was high (52.22%). The mean Hb value in anemic patients was 96.62 ± 9.33 g/L. None of them had severe anemia (Hb < 70 g/L), while the incidence of mild and moderate anemia was almost the same (24 *vs.* 23). According to morphological features, anemia was microcytic and hypochromic in three quarters of cases and normocytic and normochromic in others. In the whole group of subjects, low levels of serum iron were determined in 68 (75.56%) cases, and of ferritin in 77 (85.56%) cases.

Patients with anemia compared to non-anemic ones had a significantly higher deficit of BW. However, the differences in the age of diagnosing the underlying disease, its previous duration, the percentile of BL/BH, and the severity of the histological lesion of the small intestine mucosa were not significant. The explanation for this finding is probably in severe clinical expression of the underlying disease and/or before its onset in lower values of Hb, RBCs, and iron reserves in anemic patients compared to non-anemic ones. In support of the second hypothesis is the fact that the length of time the symptoms had presented themselves before the diagnosis in this sample of patients was almost twice shorter than the average life of RBCs (2:21 ± 1:48 *vs.* four months).

CONCLUSION

Mild or moderate iron deficiency anemia occurs in slightly more than one half of children with the classical type CD. In anemic patients compared to non-anemic ones there is a significantly higher BW deficit, while differences in other characteristics typical for this type of disease, such as its duration, age at which the diagnosis is set, percentile of BL/BH, and the degree of damage to the small intestine mucosa, are not significant.

Conflict of interest: None declared.

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Учесталост, тежина и тип анемије код деце са класичном целијачном болешћу

Недељко Радловић[1], Зоран Лековић[2,3], Марија Младеновић[4], Владимир Радловић[2], Биљана Вулетић[5,6], Синиша Дучић[2,3], Зоран Голубовић[2,3], Мехо Махмутовић[7], Снежана Петровић-Тепић[8]

[1] Српско лекарско друштво, Академија медицинских наука, Београд, Србија;
[2]Универзитетска дечја клиника, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија;
[4]Медицински центар „Ваљево", Ваљево, Србија;
[5]Клинички центар Крагујевац, Клиника за педијатрију, Крагујевац, Србија;
[6]Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија;
[7]Општа болница Нови Пазар, Нови Пазар, Србија;
[8]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Анемија је најчешћа екстраинтестинална манифестација целијачне болести (ЦБ) у дечјој доби.

Циљ рада је био да се утврде учесталост, тежина и тип анемије код деце са класичном ЦД, као и разлике између анемичних и неанемичних болесника у узрасту, дужини трајања болести, перцентилу телесне дужине или висине, проценту одступања телесне тежине (ТТ) у односу на идеалну и степену оштећења слузнице танког црева.

Метод Студијом је обухваћен узорак од 90 деце, 56 женског и 34 мушког пола, узраста 7–90 (18,23 ± 12,70) месеци са класичним ЦД. Дијагноза ЦД је базирана на *ESPGHAN* критеријумима из 1990. и 2012. године, а анемије на референтним вредностима *WHO* из 2011. године.

Резултати Анемија је констатована код 47 (52,22%) болесника и то код 23 лака (*Hb* 100–109 *g/L*) и код 24 средње тешка (*Hb* 70–99 *g/L*), при чему код 34 (72,34%) микроцитна (*MCV* < 70 *fl*) и код 13 нормоцитна (*MCV* 70–87 *fl*). Снижен ниво гвожђа у серуму (< 10,7 *μmol/L*) утврђен је код 68 (75,56%), а феритина (< 16 *ng/ml*) код 77 (85,56%) болесника. Изузимајући већи дефицит *BW* код болесника са анемијом у односу на оне без анемије (-14,64 ± 9,60 односно -8,56 ± 11,87%, *p* < 0,01), разлике у другим дефинисаним обележјима између анемичних и неанемичних испитаника нису биле значајне.

Закључак Лака или умерено тешка сидеропенијска анемија се јавља код нешто више од половине деце са ЦБ. Код анемичности у поређењу са неанемичним болесницима регистрован је значајно већи дефицит ТТ, док разлике у другим карактеристикама типичним за ову врсту болести нису биле значајне.

Кључне речи: класична целијачна болест; деца; анемија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effects of topiramate on cognitive functions of patients with focal epilepsy – the follow-up study in a Serbian sample

Nenad Milošević[1,2], Biljana Salak-Đokić[3], Mirjana Dejanović[1], Mirjana Stojanović-Tasić[1,2], Tatjana Novaković[1,2], Jovana Milošević[1], Zorica Stanojević-Ristić[1], Goran Trajković[4]

[1]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[2]Priština Clinical-hospital Center, Gračanica, Serbia;
[3]Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia;
[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective The aim of this follow-up study was to determine the effects of topiramate therapy on cognitive functions in patients with pharmacoresistant focal epilepsy.

Methods The study sample comprised of 40 topiramate naive patients. The topiramate starting dose was 25 mg, with a fortnightly titration schedule of 25 mg. A wide range of cognitive functions was evaluated through extensive neuropsychological testing at baseline and six months after reaching the target dose (200 mg/day).

Results The most common side effects following the introduction of topiramate were cognitive impairments, reported by 45% of the participants. The neuropsychological scores on attention, executive function, verbal content recall, improved cognitive flexibility, as well as visuospatial ability and speech, obtained at six-month follow-up were significantly lower than at baseline. However, statistically significant correlation between neuropsychological scores and the number of antiepileptic drugs taken alongside topiramate could not be established. Similarly, no statistically significant differences were noted between the percentage of reduced neuropsychological scores at follow-up pertaining to patients with lower and higher baseline cognitive performance. Moreover, regression analysis indicates that the percentage change in the majority of cognitive scores is unrelated to the age at the epilepsy onset, epilepsy duration, presence of brain pathology on magnetic resonance imaging and percentage change in the depression scale score.

Conclusion Despite slow introduction and administration of a relatively small dose, topiramate exhibits adverse effects on a wide range of cognitive functions, which appear unrelated to the number of additional antiepileptic drugs, baseline cognitive functioning, age at the onset of epilepsy and its duration, presence of brain pathology and the extent of depressive symptoms.

Keywords: topiramate; cognitive functions; epilepsy

INTRODUCTION

Topiramate (TPM) is effective as an adjunct treatment for pharmacoresistant focal epilepsy [1]. However, empirical evidence indicated that it can induce various cognitive adverse events (CAEs), including memory and attention problems, as well as poor performance in verbal fluency tasks [2, 3, 4]. Data suggest that up to 10% of patients treated with TPM may complain of cognitive issues [5]. The risk of cognitive complaints is 2–5 times higher in TPM-treated patients compared to those taking placebo [6]. When compared to patients on other antiepileptic drugs (AEDs), cognitive impairments were more frequently reported by patients receiving TPM therapy [7]. Consequently, cognitive impairments during TPM treatment are the most frequently cited reason for therapy discontinuation [8]. It seems that the CAEs that occurred following TPM introduction are at least partly caused by high initial doses and/or rapid drug introduction [9]. Thus, slow titration, administration of the lowest possible doses and monotherapy may decrease the risk of cognitive impairments [10, 11, 12]. However, in extant studies, prolonged therapy, even at low doses of a single drug, was associated with a significant incidence of CAEs [13]. Some authors explain these findings by noting that hippocampal sclerosis, rather than epilepsy duration or polytherapy, is the major risk factor for the development of CAEs [14].

Although the cognitive profile of TPM has been extensively studied, further assessment of cognitive complaints during dose titration using wider range formal neuropsychological tests is necessary.

The aim of the first follow-up study of this kind in a Serbian sample was to determine the effects of topiramate on cognitive function (CF) in patients with pharmacoresistant cryptogenic or symptomatic focal epilepsy.

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Correspondence to:
Nenad MILOŠEVIĆ
University of Priština
– Kosovska Mitrovica
Faculty of Medicine
Vlade Ćetkovića 17/11
38220 Kosovska Mitrovica, Serbia
mmnenad@yahoo.com

METHODS

This follow-up study included 40 TPM naive patients (all of whom spoke Serbian as native language) diagnosed with pharmacoresistant cryptogenic or symptomatic focal epilepsy (according to the ILAE criteria), none of whom had any progressive neurological diseases, psychiatric comorbidity or mental retardation. Study participants were prospectively recruited from the outpatient clinic of the Epilepsy Department of the Neurology Clinic, Clinical Center of Serbia in Belgrade.

The study protocol was done in accord with standards of the Institutional Committee on Ethics. All participants were informed of the purpose, procedures, and the scope of the neuropsychological evaluations and provided written informed consent for their inclusion in the study. The TPM starting dose was 25 mg, with fortnightly titration of 25 mg to reaching a stable dose of 200 mg/day. At the study onset, the therapy prescribed to the participants comprised of one or more of the following AEDs: carbamazepine, valproic acid, lamotrigine, phenobarbital, clobazam and phenytoin.

Demographic and clinical data (gender, age, and level of education, age at seizure onset, epilepsy duration, and current antiepileptic therapy) were obtained from each patient at the beginning of the study. Patients' written records regarding epileptic seizures and accompanying side effects, starting two months prior to the TPM introduction and covering the entire study period, were also collected. Seizure frequency before commencing TPM therapy, as well as that when patient was on a stable dose was classified as 1–10/11–20/> 20 seizures/2 months. Cognitive and other side effects after the introduction of TPM were arbitrarily classified as mild or severe according to their interference with daily activities. CAEs that were not present before the introduction of TPM included impaired memory, impaired attention, and slower thinking, among others. At the end of the study, the patients self-rated their general condition in relation to the period before the introduction of TPM as much better, better, unchanged, or worse.

In addition to the above procedures, study participants underwent neuroimaging using a 1.5 T MRI scanner (Siemens Avanto, Siemens AG, Erlangen, Germany). A standardized scanning protocol was adopted, with the option of detecting hippocampal sclerosis and other pathologies of the temporal and non-temporal lobes, as well as other parts of the brain. However, a scan was not performed on patients that underwent brain MRI on the same machine utilizing the same scanning protocol within six months prior to the start of this study, as this information was used in the analyses.

Each patient was subjected to neuropsychological assessment at baseline (i.e., before the introduction of TPM), and six months after reaching a stable dose. None of the patients experienced seizures in the 24-hour period prior to testing. An objective CF assessment was conducted using a battery of flexible neuropsychological tests [15]. All tests were conducted in a standardized manner and were adapted for Serbian population [15]. The battery of tests included Mini-Mental State Exam (MMSE) as a CF screening test [16]. Wisconsin Card Sorting Test (WCST) was used for assessment of executive function [17]. Rey Auditory Verbal Learning test (RAVLT) focused on verbal learning and episodic verbal memory [17]. Rey–Osterrieth Complex Figure test (ROCF) assessed visuospatial ability and visual memory [18, 19]. Trail Making Test Part A (TMT-A) end Part B (TMT-B) examined psychomotor speed and attention, and cognitive flexibility [17]. Wechsler Memory Scale–Revised (WMS–R) focused on attention [20]. Verbal and Category Fluency measured capacity for verbal divergent thinking [15]. Boston Diagnostic Aphasia Examination (BDAE) focused on speech [21]. In addition, the depression level was assessed via Hamilton Depression Rating Scale (HDRS) [22].

Statistical analyses were performed using SPSS Statistics (Statistical Package for Social Sciences) for Windows, version 20. The results were reported as the arithmetic mean ± standard deviation, as well as maximum and minimum values. The obtained data were further subjected to the Student's t-test, χ^2 test, the Spearman's correlation, the sign test, linear regression models, and the McNemar's test, where appropriate. Differences and correlations were considered statistically significant at $p < 0.05$.

RESULTS

Study participants' demographic data and general clinical characteristics at the start of the study are shown in Table 1. As can be seen from the tabulated results, most patients experienced a significant reduction ($p = 0.001$; sign test) in the total number of seizures in the two-month period of TPM treatment at target doses (15.8 ± 54.3) compared to the two-month period before TPM was introduced (21 ± 61.4). Once the target TPM dose of 200 mg/day was reached, 40% of the patients were seizure-free. Among the remaining patients, a significant reduction of seizure incidence (> 50%) was observed in 11 (27.5%) cases, while 13 (32.5%) patients experienced a < 50% reduction. On the other hand, depression incidence at the end of the study (14 patients) was not statistically significantly different ($p = 0.243$; McNemar's test) from that at baseline (18 patients). The difference in depression scores before and after the administration of TPM was not statistically significant either (t-test -0.46, $p = 0.648$). Based on their

Table 1. Demographic and clinical data of the patients on start of the study

Parameters	Value
Sex (female/male)	24/16
Age, years (range)	41 ± 14.1 (18–68)
Patients with education ≤ 11 years (%)	10 (25)
Age at seizure onset, years (range)	25.9 ± 17.9 (2–68)
Duration of epilepsy, years (range)	14.8 ± 12.2 (1–50)
Seizure frequency before TPM (2 months), 1–10/11–20/> 20	27/5/8
Patients with depression, mild/severe	8/10
Patients with lesioned brain MRI (%)	19 (47.5)

TPM – topiramate; MRI – magnetic resonance imaging

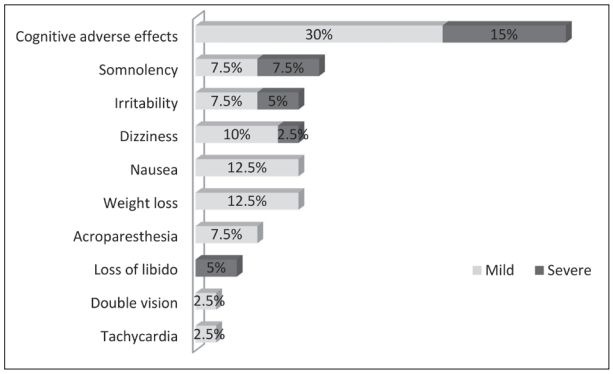

Figure 1. The frequency of adverse effects after reaching target dose of topiramate

self-assessment of general health status after achieving a stable dose of TPM, five (12%) patients felt significantly better, 17 (43%) felt better, two (5%) felt worse than before the introduction of TPM, and 16 (40%) patients reported no changes in their condition.

Figure 1 shows the adverse effects the patients reported after reaching the TPM target dose. It can be seen that cognitive impairments were by far the most common adverse effects experienced, and were reported by 18 (45%) patients. At the end of the study, six months after reaching the target TPM dose, most patients (38.9%) reported multiple CAEs. Specifically, 16.7% participants complained of impaired memory, impaired attention, and word-finding difficulties, while slower thinking was experienced by 11.1% of the sample. None of the participants reported remission of any of the cognitive impairments after their onset until the end of the study. Table 2 shows the number of patients that reported cognitive impairments during the TPM dose titration period.

Table 2. The number of patients with complaints on cognitive difficulties during titration dose of topiramate

Type of cognitive impairment	[a]25 mg n (%)	[a]50 mg n (%)	[a]100 mg n (%)	[a]150 mg n (%)	[a]200 mg n (%)
Impaired memory	-	-	7 (17.5)	9 (22.5)	10 (25)
Impaired attention	-	2 (5)	7 (17.5)	10 (25)	10 (25)
Slowed thinking	-	2 (5)	2 (5)	4 (10)	7(17.5)
Word-finding difficulties	-	-	-	3 (7.5)	5 (12.5)

n – number of patients;
[a]two weeks after reaching a given dose of topiramate

The results of the applied neuropsychological tests and corresponding statistical findings are presented in Table 3. The six-month follow-up scores related to measurements of attention, executive function, verbal content recall, enhanced cognitive flexibility, as well as visuospatial abilities and speech, obtained when the patients had been receiving the TPM target dose of 200 mg/day for six months, were statistically significantly lower than at baseline. On the other hand, differences in scores on visual memory tests at baseline and at six-month follow-up were not statistically significant (Table 3). Table 4 shows the percentage changes in the cognitive scores after the introduction of TPM with respect to the baseline, in relation to the independent variables, such as the age at the epilepsy onset, duration of epilepsy, presence of pathology on the brain MRI, and the percentage change in the depression scale score. Regression analysis findings indicated that the percentage change in the majority of cognitive scores was unrelated to the aforementioned independent variables. In addition, percentages of patients whose cognitive performance declined at the six-month follow-up relative to the baseline were examined separately for each test. The mean MMSE score served as the baseline CF level, as it provided a measure of the patients' overall cognitive status. When the participants were grouped by their MMSE baseline score (≤ 27 *vs.* > 27), no statistically significant differences were found in the percentage of patients whose individual test scores declined on 6-month assessment relative to the corresponding baseline values.

In 31 of the 40 participating patients (77%), TPM was added to a preexisting medication, with valproic acid (VPA) (13 patients), carbamazepine (CBZ) (14 patients), lamotrigine (LTG) (14 patients) and phenobarbital (PHB) (five patients) identified as the most frequently used comedications. However, no correlation between neuropsychological scores and the number of AEDs used alongside TPM was established.

DISCUSSION

The findings yielded by the present study indicate that TPM therapy can compromise a wide range of CFs in patients with pharmacoresistant focal epilepsy. Patients' subjective complaints were the first indication of the adverse neuropsychological profile of TPM, which was, subsequently, confirmed thought comprehensive neuropsychological assessments. Fortunately, the results reported in this paper also reveal that TPM was effective in reducing the frequency of epileptic seizures. This could be the reason why patients on a stable TPM dose predominantly rated their health condition as better or significantly better compared to the period before the introduction of the drug.

In the clinical evaluation of newer AEDs, the highest incidence of adverse effects was noted among patients taking TPM [23]. In the present study, cognitive impairments were by far the most common reason for patients' complaints, and involved multiple CAEs in most cases. In addition, the first reports of CF impairments (primarily slow thinking and attention difficulties) were noted at the low dose of only 50 mg/day, while speech disorders became more prevalent at the target dose of 200 mg/day (Table 2). This dose-related incidence of cognitive impairments was previously confirmed in a pooled analysis of clinical trials in which TPM was used as an adjuvant therapy in the treatment of pharmacoresistant focal epilepsy [3].

In addition to evaluating patients' subjective cognitive complaints, the formal neuropsychological assessment conducted as a part of this investigation also revealed adverse effects of TPM on CF. The assessment of verbal

Table 3. Neuropsychological test results before and 6 months after achievement of the 200 mg of TPM;
Data are presented as arithmetic mean with simple standard deviation; results were compared by Student's t-test; a higher score means a better result, except on TMT-A and TMT-B (opposite)

Measure	Before TPM	After six months	t-test	p
MMSE	27.4 ± 2.4	24.7 ± 4.6	4.42	0.001
RAVLT (immediate recall)	42.7 ± 9.8	40.8 ± 11.0	1.94	0.060
RAVLT (recall after 20 minutes)	7.3 ± 3.3	6.5 ± 3.6	2.32	0.026
RAVLT (recognition)	11.2 ± 2.9	11.2 ± 3.5	-0.18	0.857
TMT-A	60.1 ± 31.4	63.2 ± 34.7	-0.83	0.413
TMT-B	143.3 ± 59.8	172.6 ± 81.4	-3.34	0.002
WCST (categories completed)	3.7 ± 2.0	4.1 ± 2.1	-1.59	0.121
WCST (perseverative responses)	34.0 ± 18.8	25.6 ± 20.7	2.76	0.009
WCST (inability to maintain set)	1.2 ± 1.3	1.1 ± 1.7	0.36	0.722
Test of phonemic fluency (S)	8.2 ± 2.6	7.0 ± 2.8	2.98	0.005
Test of phonemic fluency (K)	9.9 ± 4.0	7.6 ± 3.5	3.53	0.001
Test of phonemic fluency (L)	7.7 ± 2.7	5.4 ± 2.8	5.14	0.001
Test of categorical fluency	14.3 ± 4.3	12.2 ± 4.1	3.73	0.001
ROCF (copying)	26.9 ± 5.2	23.8 ± 6.0	3.56	0.001
ROCF (drawing by recall)	12.2 ± 6.5	11.0 ± 6.7	1.71	0.095
BDAE (complex ideational material)	9.8 ± 1.8	9.3 ± 1.7	2.10	0.042
BDAE (repetitive speech)	6.8 ± 1.2	6.7 ± 1.5	0.26	0.793
BDAE (orders)	14.9 ± 0.4	14.4 ± 0.9	3.73	0.001
WMS-R (attention index)	71.2 ± 15.3	59.1 ± 17.5	6.76	0.001
WMS-R (digit span)	5.7 ± 0.9	4.7 ± 1.0	6.02	0.001
WMS-R (visual span)	4.6 ± 0.8	3.8 ± 1.0	4.49	0.001

TPM – topiramate; MMSE – Mini Mental State Examination; RAVLT – Rey Auditory Verbal Learning Test; TMT-A – Trail Making Test Part A; TMT-B – Trail Making Test Part B; WCST – Wisconsin Card Sorting Test; S, K and L – words beginning with letter S, K, and L; ROCF – Rey-Ostterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS–R – Wechsler Memory Scale–Revised

Table 4. Linear regression models with percent change in cognitive tests performance as dependent variables

Dependent variable (Neuropsychological tests)	Independent variables			
	Age on onset of disease	Duration of epilepsy	Presence of MRI brain patology	Percentage change on HDRS
MMSE	-0.31	0.07	-1.42	-0.02
RAVLT (immediate recall)	-0.02	0.02	-3.28	0.06
RAVLT (recall after 20 minutes)	-0.32	0.53	4.15	0.02
RAVLT (recognition)	-0.32	-0.13	-5.15	-0.05
TMT-A	0.52	-0.68	-2.44	-0.01
TMT-B	0.33	0.35	-4.19	-0.15
WCST (categories completed)	-1.73	0.07	6.52	0.61
WCST (perseverative responses)	0.62	0.46	-11.57	-0.20
WCST (inability to maintain set)	-0.26	-0.77	8.78	0.97*
Test of phonemic fluency (S)	-0.21	0.72	7.26	0.11
Test of phonemic fluency (K)	0.43	1.34*	2.85	-0.23
Test of phonemic fluency (L)	0.47	1.58*	-2.65	-0.35*
Test of categorial fluency	0.15	-0.07	-9.15	-0.03
ROCF (copying)	0.19	0.28	-3.30	0.00
ROCF (drawing by recall)	-0.08	0.10	-15.11	0.17
BDAE (complex ideational material)	0.25	0.19	-1.56	-0.10
BDAE (repetitive speech)	0.19	-0.10	-8.91	-0.12
BDAE (orders)	0.05	0.03	2.36	0.02
WMS-R (attention index)	-0.04	0.29	2.24	-0.05
WMS-R (digit span)	0.10	0.17	-13.05	-0.09
WMS-R (visual span)	-0.34	0.27	3.76	-0.10

MMSE – Mini Mental State Examination; RAVLT – Rey Auditory Verbal Learning Test; TMT-A – Trail Making Test Part A; TMT-B – Trail Making Test Part B; WCST – Wisconsin Card Sorting Test; S, K and L – words beginning with letter S, K, and L; ROCF – Rey-Ostterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS–R – Wechsler Memory Scale–Revised; MRI – magnetic resonance imaging; HDRS – Hamilton Depression Rating Scale;
*$p < 0.05$

memory and learning by RAVLT showed that patients on TPM obtained lower delayed-recall scores at six-month follow-up relative to baseline. It was also proved that this aspect of memory was affected by TPM in the study conducted by Thompson et al. [4]. Attention deficit after TPM introduction was confirmed by lower scores on the Digit Span and Visual Memory Span measures, as well as by WMSR (attention index). In an earlier study, Burton and Harden [24] confirmed the adverse effect of TPM on Digit Span scores in adults with epilepsy who had been treated with TPM for ≥ 3 months. These authors also established an inverse link between TPM dose and the Digit Span scores.

Although speech disorders were the least frequently reported cognitive complaints, findings yielded by the formal neuropsychological assessment revealed significantly lower test scores while patients were undergoing TPM therapy. In addition to deteriorating speech recognition results, TPM also had an adverse effect on the verbal fluency scores, which is consistent with the findings of other studies on patients with epilepsy [25].

When executive functions were evaluated through the WCST, a significantly higher number of perseverative responses in the second measurement confirmed their susceptibility to TPM. This result indicated a reduced ability to suppress previous choices, including the non-adaptive ones, and to switch to the correct choice, which is one of the important characteristics of impaired executive functions [26]. The deterioration of multiple CFs observed in the present study can likely be attributed to the impaired working memory, which is at the core of executive functions and represents a critical step in almost all cognitive processes [27]. The working memory impairment suggested by the test findings could arise due to the reduced information processing speed, stemming from the potentiation of inhibitory processes in the brain by gamma-aminobutyric acid (GABA). Indeed, ample body of evidence indicates that TPM increases GABA levels in the brain [28]. This simplified mechanism is further supported by the fact that AEDs that do not primarily impact GABA neurotransmission, such as lamotrigine, are rarely associated with serious cognitive impairments [29].

In analyzing the risk factors that contribute to the emergence of cognitive impairments following TPM introduction, some authors speculated that the adverse effect of TPM on mood may result in an increased number of cognitive complaints [30, 31]. Others are of view that the effect of TPM on cognition can be attributed to the synergistic effect of polytherapy [8]. Extant studies also suggest that cognitive abnormalities prior to adding TPM to the epilepsy therapy could predispose patients to CF impairments [32]. Even though a statistically significant relationship between the percentage changes in cognitive scores and independent variables (age at the onset of epilepsy, epilepsy duration, presence of brain pathology and depression severity) examined in this study were noted with respect to a small number of measurements, this did not provide sufficient evidence to propose a causal link between these factors and the observed changes in CF. In addition, a significant correlation between neuropsychological scores and the number of AEDs taken alongside TPM was not supported by our findings. Similarly, it has not been established that lower cognitive performance at baseline is associated with a more pronounced CF deterioration when patients are treated with a stable TPM dose. Therefore, the impact of TPM on CF is independent of the observed variables.

Generally, given that TPM is an effective AED, the greatest clinical importance should be placed on determining the mechanisms and the factors that can contribute to the onset of CAEs. We thus believe that further studies are needed to determine the profile of patients in whom topiramate administration would have a therapeutically beneficial effect without significant cognitive impairment.

CONCLUSION

The findings reported in this work indicate that TPM, despite slow introduction as adjuvant therapy and low-dosage titration, has an adverse effect on the CF in patients with pharmacoresistant focal epilepsy. In our sample, attention, verbal memory, executive function, visuospatial ability, and speech were affected by TPM treatment. We also established that the adverse effects of topiramate are independent of the number of antiepileptic drugs taken alongside topiramate, baseline cognitive functioning, age at the epilepsy onset, epilepsy duration, presence of brain pathology, and depression severity. Despite occurrence of the aforementioned adverse TPM effects, most patients had a positive assessment of their condition following TPM treatment, most probably due to its effectiveness in controlling seizures, which was confirmed in our study.

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Утицај топирамата на когнитивне функције болесника са фокалном епилепсијом – студија праћења у српском узорку

Ненад Милошевић[1,2], Биљана Салак-Ђокић[3], Мирјана Дејановић[1], Мирјана Стојановић-Тасић[1,2], Татјана Новаковић[1,2], Јована Милошевић[1], Зорица Станојевић-Ристић[1], Горан Трајковић[4]

[1]Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;
[2]Клиничко-болнички центар Приштина, Грачаница, Србија;
[3]Клинички центар Србије, Клиника за неурологију, Београд, Србија;
[4]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ ове студије био је да се утврди ефекат топирамата на когнитивне функције болесника са фармакорезистентном фокалном епилепсијом.

Методе Студија је обухватила 40 болесника који раније нису лечени топираматом. Почетна доза топирамата била је 25 *mg*, са брзином повећања дозе од 25 *mg* на сваких 14 дана. Широк спектар когнитивних функција процењен је обимним неуропсихолошким тестирањем у два одвојена интервала, пре него што је уведен топирамат и шест месеци после достизања циљне дозе (200 *mg*/дан).

Резултати Најчешћи нежељени ефекти после увођења топирамата биле су когнитивне сметње, које је пријавило 45% болесника. Неуропсихолошки скорови добијени после увођења топирамата су знатно нижи него пре топирамата на мерењима пажње, егзекутивних функција, присећања вербалног садржаја, брзине когнитивне флексибилности, као и визуоспацијалне способности и говора. Међутим, није нађена значајна корелација између неуропсихолошких скорова и броја антиепилептичких лекова додатих топирамату. Поред тога, није нађена значајна разлика у учесталости погоршања неуропсихолошких скорова између болесника са нижим и вишим базичним когнитивним перформансама. Такође, вредност проценатне промене на већини когнитивних мерења није значајно повезана са годинама на почетку епилепсије, трајањем епилепсије, присуством можданих лезија видљивих на нуклеарној магнетној резонанци и процентуалном променом на скали депресије.

Закључак Упркос постепеном увођењу и примени релативно ниских доза, топирамат изазива нежељене ефекте на широк спектар когнитивних функција, чија појава није повезана са бројем додатих антиепилептичких лекова, базичним когнитивним функционисањем, узрастом на почетку епилепсије и њеним трајањем, присуством можданих лезија и степеном депресије.

Кључне речи: топирамат; когнитивне функције; епилепсија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The influence of the dynamics and the level of maturity of the cortical functions as a prerequisite for the development of speech in children

Maja Davidović[1], Jadranka Otašević[2], Nada Dobrota-Davidović[2], Ivana Petronić[3], Dragomir Davidović[1], Lana Jerkić[4],

[1]Dr Laza Lazarević Clinic for Psychiatric Diseases, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia;
[3]University Children's Clinic, Belgrade, Serbia;
[4]Dr. Cvetko Brajović Institute of Psychophysiological Disorders and Speech Pathology, Belgrade, Serbia

SUMMARY

Introduction/Objective The development of speech is the result of interaction of different systems of the cortex, which gradually acquires the ability of phonological presentation and motor control, in the presence of a series of physical and physiological changes in the morphology of the articulation system. The objective of the study was to examine the impact of laterality and cortical responses on the development of speech in children.

Methods Research is a quasi-experimental design with two groups. The sample covered 60 children from Belgrade, of both sexes, ages 5.5–7 years, divided into two groups, experimental (30) and control (30). We used the following instruments: test for assessing laterality and ascertaining evoked potentials.

Results On the visual lateralization subtest there was a statistically significant difference ($\chi^2 = 7.56$, $p < 0.05$) between the observed groups. The visual evoked potentials on all measured parameters gave a statistically significant difference between the groups: waveform cortical responses – left ($\chi^2 = 30.00$, $df = 1$, $p < 0.05$); cortical responses – right ($\chi^2 = 6.667$, $df = 1$, $p < 0.05$); waveform amplitude – left ($\chi^2 = 13.469$, $df = 1$, $p < 0.05$); amplitude – right ($\chi^2 = 40.00$, $df = 1$, $p < 0.05$), somatosensory potentials ($\chi^2 = 18.261$, $df = 1$, $p < 0.05$); waveform amplitude ($\chi^2 = 12.000$, $df = 1$, $p < 0.05$); waveform latency ($\chi^2 = 5.455$, $df = 1$, $p < 0.05$).

Conclusion Visual laterality, as well as visual and somatosensory cortical responses to stimuli is better in children without the present articulation disorder, which could be used for timely prevention planning.

Keywords: speech; laterality; children; articulation disorder; evoked potentials

INTRODUCTION

What distinguishes people from animals is evolution of the brain. The brain is the manager of all physical and psychological activities. Due to the complex organization of the nervous system, man can produce a large number of voices with meaning and use hands to perform fine movements. Language allows man to control his behavior and behavior of others [1]. The brain is anatomically divided into two hemispheres that are approximately identical. Despite the relative similarity of brain hemispheres, they do not perform the same function. Due to the fact that the hemispheres have specialized, some skills became possible [2]. The left hemisphere plays a role in the creation of language, which is confirmed by a series of research. It has been found that in 95% of right-handed people speech is controlled by the left hemisphere, as well as in 70% of the left-handed people, while in 15% of others speech is controlled from both hemispheres [3]. The exact role of the right hemisphere is not known. It is considered to be responsible for performing visual-spatial tasks and for processing information simultaneously and holistically. In addition, its role in controlling and processing musical abilities is indisputable [4, 5]. Neurons have to be stimulated in order to develop new synaptic connections. The development of new connections creates new opportunities for neural communication. Each new skill contributes to the new element of sensory perception and motor skills of the child. As a child's number of neural connections increases, it becomes more capable of learning [6]. Functional brain differentiation indicates that different aspects of language and speech are located in different regions of the cortex [7, 8]. This points to the genetic basis of the development, during which different aspects of language are distributed in different brain regions [9].

Laterality is determined simultaneously with the determination of the hemisphere domination. Through motor development, bilateral control is established first, followed by unilateral control. Laterality is established between the age of three and four years. It is achieved gradually during maturation and the accumulation of experience acquired by observation, kinesthesia, manipulative activity, and finally the realization that this laterality has occurred [10]. In the next phase of maturation, the dif-

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Correspondence to:
Jadranka OTAŠEVIĆ
Faculty of Special Education and Rehabilitation
University of Belgrade
Dobrinovićeva 10
11000 Belgrade, Serbia
jadrankastevovic@yahoo.com

ferentiation of laterality occurs when it becomes dominant for one side and subdominant for the other side of the body – it is recognized that one extremity or sensory organ leads and thus dominates the other [11]. Harmonic laterality implies identical dominant laterality level with the arm, eye, ear, and leg. The category of disharmonic lateralization consists of subjects with complete discrepancy between the dominance of the arm, the eye, the ear, and the leg. The process of developing the ambivalence of the movement to selecting a leading right or left hand can be considered a process of maturation, because from laterality we are going to dominate the hemispheres and movements in the manipulative field, from the lower forms of organizing activities to more complex and more suitable levels, of the differentiated sensory needs and the enforcement of intelligence [12, 13]. Assessment of laterality and dominant laterality indicates the organization of the ability of senses and movements in the function of voluntary motor activity and the level of practicality of the cortex in relation to the development of the dominance of the hemisphere [14].

The processes that precede the development of proper articulation are swallowing, sucking, and chewing. Proper stimulation of these functions in the earliest age affects the good development of oral practice and, consequently, the smooth development of articulation [15, 16]. The child, by vocalization, elaborates the movements and coordination of peripheral speech organs. The speech production mechanism undergoes significant changes during growth, and the progressive maturation of motor control capabilities is the basis of this process [17]. Motor control of the articulation mechanism, as in adults, reaches the middle of childhood. More complex motor patterns require longer time for automation, and such are the patterns of articulation movements. The speed of automation is also affected by the plasticity of the nervous system. Automated articulation movements constitute the articulation base of native speakers of a language [18, 19].

The pathological articulation is a deviation in the pronunciation of the voices of the mother tongue, both on the visual and on the acoustic and the kinesthetic level [20]. Poorly placed voice organs misjudge the air current, leading to articulation disorders. Parents and the environment often find that the child speaks well of a certain voice, not knowing that the visual presentation of this voice is not good and that for this reason the pronunciation of a certain voice is considered pathological [21, 22]. This is due to ignorance of motor patterns that are necessary for the proper pronunciation of the given voice [23].

The aim of the study was to examine the impact of laterality and cortical responses on the development of speech (articulation) in children.

METHODS

The basic method of organization of research is a quasi-experimental design with two groups. The sample included 60 children, of both sexes, aged 5.5–7 years of age. The research was performed at the Children's Outpatient Department of the Voždovac Community Health Center and University Children's Clinic in Belgrade, from 2015 to 2016. The research was carried out in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The Ethical Committee approved the research and, taking into account that the research subjects were children, the informed consent was obtained from their parents/guardians. The experimental group (E) consisted of 30 children with articulation disorders diagnosed with Articulation Test, who were on continuous logopedic treatment, which lasted six months on average. The control group (C) of 30 children consisted of children from the general population who did not have any articulation disorders. We used the individual testing technique for both E and C group.

The instruments used in the research included: specialized test for lateralization assessment and evaluation of evoked potential recordings. Lateralization test consists of questions and tasks classified according to the levels for the assessment of usage and gesture laterality of extremities, sight, and hearing. The tested child was supposed to ask the questions by showing certain action or complete a specific task using the appropriate equipment offered.

Evoked potentials [visually evoked potential (VEP) and somatosensory evoked potential (SSEP)]: the VEP challenge was performed by the rhythmic repetition of the light signal of a certain intensity, duration, and defined distance of the light source from the subject. Light stimuli are structured or unstructured, and the test is performed by binocular, whole field of vision, and half of the field of view. The series contains at least 128 stimuli that are analyzed and moderated by soft-technique, while responses contaminated by artifacts are rejected. Registration is done using surface electrodes at the head position determined by the 10–20 EEG system. Examined: configuration of the induced response, waveform amplitude, P100 waveform latency, and interocular latency P100 waveform.

SSEPs were tested by stimulating both *n. medianus* individually, averaging 512 stimuli of low intensity (5–15, mA), frequency of three stimuli per second, duration of 0.2 ms. Detection of the induced responses was performed above the Erb's point (brachial plexus), at C7 and C2, spinal cord segments, as well as on the scalp above the contralateral sensory cortical field. *N. medianus* is stimulated in the wrist, while the electrodes on the scalp are positioned according to the international 10–20 system. The following parameters were analyzed: absolute primary cortical response waveform latency (N20), configuration and waveform amplitude of the primary complex (N20–P25).

Statistical processing and analysis were performed in IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). The measure of descriptive statistics used the arithmetic mean with the corresponding standard deviation, as well as the minimum and the maximum. Frequency and percentage were used. Chi-squared test was used to examine the relationship of two categorical variables, as well as to determine the cross-ratio of the results of the applied instruments.

RESULTS

Table 1 shows that the age of the subjects ranged 5.5–7 years. After the categorization of these variables into three categories (5.5–6 years, 6.1–6.5 years, and 6.6–7 years) we obtained the following percentile representation of respondents by category: 60% of the experimental group is 5.5–6 years old, 13.3% are 6.1–6.5 years old, and 26.7% of the group are 6.6–7 years old. Within the control group, 23.3% of the respondents belong to the group 5.5–6 years old, 46.7% belong to the group 6.1–6.5 years old, and 30% belong to the group 6.6–7 years old.

Table 2 shows that the average age of the E group was M = 6.07 ± 0.5 years of age, while the average age of the C group was M = 6.34 ± 0.46 years of age.

Figure 1 shows that E group comprised more respondents of male sex (76.7%), while the C group comprised more female sex respondents (56.7%).

Figure 2 shows that a statistically significant difference exists only on visual laterality ($\chi^2 = 7.56$, $p < 0.05$). The statistical significance is below the limit of 0.05. A statistically significant difference between the experimental and the control group does not exist on other laterality tests.

Table 3 shows that when we categorize the results obtained on VEP, we obtain statistically significant differences on all measured parameters, between the experimental and the control group of the respondents.

Table 4 shows that when categorizing the results of E and C groups measured on SSEP, statistically significant differences are obtained on all measured parameters, except on the waveform cortical response – right.

Figure 3 shows that respondents with lower waveform amplitude on the left eye dominantly use the right eye (68.4%). Those who use this waveform amplitude have a regular dominant use of the left eye (54.5%). The finding of VEP (amplitude to the left) is statistically significant in relation to visual laterality ($\chi^2 = 7.56$, df = 2, $p = 0.023$).

Figure 4. shows that respondents with lower waveform amplitude are predominantly left-handed (50%), while subjects with a regular waveform amplitude are predominantly right-handed (70%), indicating that the finding on the SSEP (amplitude) is in a statistically significant relationship with gestural laterality ($\chi^2 = 6.72$, df = 2, $p = 0.035$).

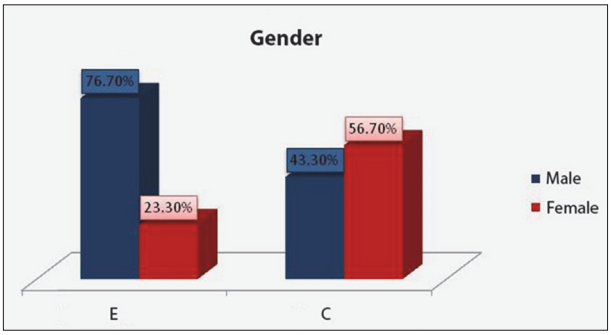

Figure 1. Sample structure according to the sex of the respondents

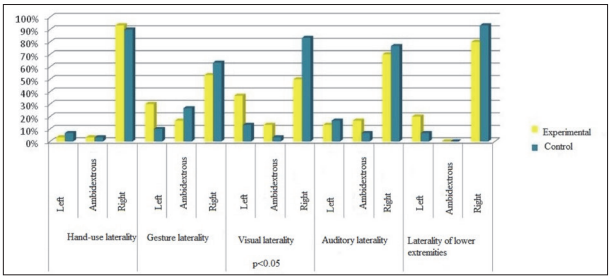

Figure 2. Test of assessment of laterality – the difference between the experimental and the control group

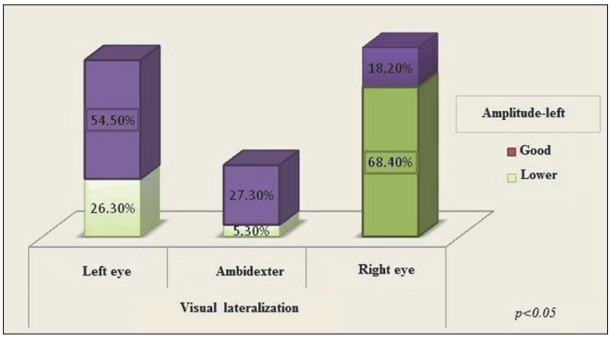

Figure 3. Cross-ratio of visually evoked potential findings (amplitude on the left) and visual laterality

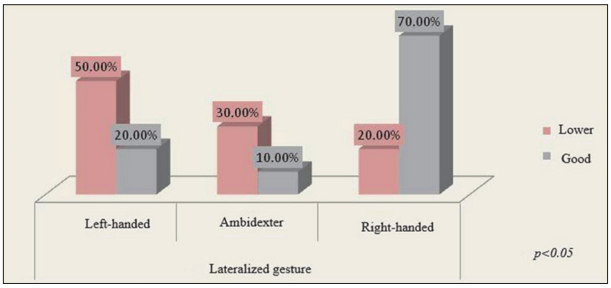

Figure 4. Cross-sectional relationship between somatosensory evoked potential (amplitude) and gestural laterality

DISCUSSION

The study included children 5.5–7 years of age. This age was observed because it is considered that the development of articulation should be finished at 5.5 years of age. The sample was divided into three subgroups, at the age of half the age of children (Table 1). The average age of E group was M = 6.07 ± 0.5 years, while the average age of C group was M = 6.34 ± 0.46 years (Table 2). All the achievements of the examinees were analyzed collectively for both subgroups and individually for each subgroup. We started from the fact that speech (articulation) and laterality, as cortical functions of the developmental category, are adopted by learning and intensively develop during the pre-school period.

The analysis of the results in relation to sexes (Figure 1) showed that there were more boys (76.7%) than girls (23.3%) in E group, while the number of girls in C group was larger (56.7%) compared to the number of boys (43.3%). As a prospective section study, the sample structure by sex reflects the numerical representation of groups in the population. The results of the laterality test show that a statistically significant difference exists on the visual laterality subtest ($\chi^2 = 7.56$, $p < 0.05$). By analyzing

Table 1. Structure of the sample according to the age categories of the respondents

Parameter			Age of respondents (years)			Total
			5.5–6	6.1–6.5	6.6–7	
Group	Experimental	Total (n)	18	4	8	30
		%	60	13.3%	26.7%	100
	Control	Total (n)	7	14	9	30
		%	23.3	46.7%	30.0%	100
Total		Total (n)	25	18	17	60
		%	41.7	30.0%	28.3%	100

Table 2. Sample structure according to average age of the respondents

Group	n	Min.	Max.	M	SD
Experimental	30	5.50	7	6.0700	0.50729
Control	30	5.50	7	6.3433	0.46065
Total	60	5.50	7	6.2067	0.49979

Min. – sample minimum variable value; Max. – sample maximum variable value; M – sample arithmetic mean (sample average variable value); SD – standard deviation (average deviation of individual sample variable values)

the percentage representation of certain categories, we can see that both groups are predominantly right lateralized. The analysis shows that there were more left-handed individuals in E group (36.7%) than in C group (13.3%). The number of ambidextrous respondents was higher in E group (13.3%) compared to C group (3.3%), which shows the existence of a larger number of respondents with undifferentiated lateralization within E group (Figure 2). This indicates the existence of disharmonic laterality and slow maturation of certain functions in these subjects. The category of disharmonic laterality consists of subjects with complete discrepancy between the dominance of the arm, the eye, the ear, and the leg. In addition, we registered the presence of undifferentiated lateralization, i.e. the presence of an ambient, within the group [24–27]. The results of evoked potentials show that both groups of subjects are at the physiological age limits, but that certain differences within these values exist. The results of VEP show that waveform cortical responses to the left were less formed in 66.7% of the subjects in E group, and 33.3% were well formed; in C group, 100% of the respondents were well formed, which gave statistically significant difference ($\chi^2 = 30$, df = 1, $p < 0.05$). A better waveform cortical response to the left was present in the subjects in C group. Waveform cortical responses to the right were less formed in 20% of the examinees of E group, and they were well formed in 80% of the respondents; within C group, cortical responses were 100% well-formed, and there was a statistically significant difference ($\chi^2 = 6.667$, df = 1, $p < 0.05$). The waveform amplitude was on the right in 20% of E group examinees, while it was regular in 80% of the subjects.

Table 3. Visually evoked potential – the difference between the experimental and the control group on the measured parameters

Parameter		Experimental		Control		χ^2	Df	p
		Total (n)	%	Total (n)	%			
Cortical response – left	Well formed	10	33.3%	30	100%	30.000	1	0.000
	Less formed	20	66.7%	0	0%			
	No response	0	0%	0	0%			
Cortical response – right	Well formed	24	80%	30	100%	6.667	1	0.010
	Less formed	6	20%	0	0%			
	No response	0	0%	0	0%			
Amplitude – right	Lower	6	20%	30	100%	40.000	1	0.000
	Good	24	80%	0	0%			
Amplitude – left	Lower	19	63.3%	30	100%	13.469	1	0.000
	Good	11	36.7%	0	0%			
Latency	Within physiological limits	30	100%	30	100%	/	/	/
Interocular difference	Equal	0	0%	4	13.3%	5.795	2	0.050
	Prolonged at the cost of the left side	24	80%	17	56.7%			
	Prolonged at the cost of the right side	6	20%	9	30%			

Df – degrees of freedom

Table 4. Somatosensory evoked potential – the difference between the experimental and the control group on the measured parameters

Parameter		Experimental		Control		χ^2	Df	p
		Total (n)	%	Total (n)	%			
Cortical response – left	Well formed	16	53.3%	30	100%	18.261	1	0.000
	Less formed	14	46.7%	0	0%			
	No response	0	0%	0	0%			
Cortical response – right	Well formed	29	96.7%	30	100%	1.017	1	0.313
	Less formed	1	3.3%	0	0%			
	No response	0	0%	0	0%			
Amplitude	Lower	10	33.3%	0	0%	12.000	1	0.001
	Good	20	66.7%	30	100%			
Latency	Within physiological limits	25	83.3%	30	100%	5.455	1	0.020
	Prolonged latency	0	0%	0	0%			

Df – degrees of freedom

In 100% of C group, waveform amplitude on the right is regular ($\chi^2 = 40.000$, df = 1, $p < 0.05$). Waveform amplitude on the left 63.3% of the examinees in E group is lower, and in 36.7% of the examinees it is regular, while in 100% of the C patients it is regular ($\chi^2 = 13.469$, df = 1, $p < 0.05$) (Figure 3). Waveform latency is within the physiological limits of the examinees of both groups. In the assessment of the waveform cortical response of the left eye, the results showed that the cortical response was worse in 43.3% of the subjects of E group, while 56.7% of the subjects were without clear lateralization (equal to the left and right eye); there was a statistically significant difference between the groups ($\chi^2 = 16.596$, df = 1, $p < 0.05$), as in 100% of patients in group C the response was without clear laterality – equable.

The distribution of the results for interocular difference shows that 80% of the examinees in E group had poorer results on the left eye and 20% of them had poorer results on the right eye. In C group, in 13.3% of the examinees there was no interocular difference, 56.7% of the examinees confirmed poorer result on the left eye, while 30% of them had poorer result on the right eye. In the final analysis of the results, the difference would be reflected in the larger number of subjects with a balanced interocular latency of 13.3% within C group, which is a better result. This result can be observed through the functional localization of parts of the body in the cerebral cortex (eye, mouth-tongue, arm, leg) [28].

The SSEP results show that waveform cortical responses on the left side were less formed in 46.7% of the respondents in E group, and in 53.3% they were well formed; in C group, 100% of the respondents had well-formed waveform cortical responses on the left side ($\chi^2 = 18.261$, df = 1, $p < 0.05$) (Figure 4). A better waveform cortical response on the left is present in C group subjects. Waveform cortical responses on the right were less formed in 3.3% of the respondents in E group, and 96.7% of respondents were well formed; within C group, waveform cortical responses on the right side were 100% well-formed ($\chi^2 = 1.017$, df = 1, $p > 0.05$). Sophisticated and coordinated movements of the hands affect the sensorimotor development of the central nervous system and, by doing so, the development of speech, which requires a higher level of sensorimotor coordination [26].

The waveform amplitude is lower in 33.3% of E group of examinees, while it is regular in 66.7% of the subjects. In 100% of group C respondents, the amplitude is regular, which gives a statistically significant difference ($\chi^2 = 12$, df = 1, $p < 0.05$). Waveform latency is in 83.3% of the experimental group in the physiological limits, while in 16.7% of the subjects, latency is at the limit value (which implies latency at the physiological limit for the age); in 100% of examinees of C group, latency is at physiological limits ($\chi^2 = 5.455$, df = 1, $p < 0.05$). After evaluation of the waveform cortical response, the left *n. medianus* results of 46.7% of subjects in E group were inferior, and in 53.3% of the subjects the results showed no clear laterality (equal), in the control group, the waveform cortical response was equal ($\chi^2 = 18.261$, df = 1, $p < 0.05$). These results suggest that there was mild dysfunction of the central afferents on the left hand in some patients of E group, within the physiological limits. We tested with the χ^2 test whether the results of the applied tests were statistically significant. Connection testing was done in E group. The reason for this is that C group generally had unified results so that is no point in doing comparison (numbers are constants). VEP (amplitude of waves of the left eye) is statistically significant with visual laterality ($\chi^2 = 7.56$, df = 2, $p = 0.023$) (Figure 3). Respondents with lower waveform amplitude on the left side dominantly use the right eye (68.4%). Those with a regular amplitude have a regular dominant use of the left eye (54.5%). SSEP (*n. medianus,* cortical wave amplitude) is in a statistically significant connection with gestural laterality ($\chi^2 = 6.72$, df = 2, $p = 0.035$). Respondents with a lower amplitude were predominantly left-handed (50%), while subjects with a regular amplitude were predominantly right-handed (70%) (Figure 4). Considering that gestural lateralization of the hand is seen here, we can conclude that laterality did not succumb to sociocultural pressure and reflects spontaneous, individual maturation, which is precisely the reason for this result [29].

CONCLUSION

Articulation disorders are manifested more often in boys than it is in girls. Diffusion of visual lateralization is more pronounced in children with articulation disorders than in children with normally developed speech. Results of visual and somatosensory waveform cortical test responses, which are within the physiological values for the respective age, represent better results for children with well-developed articulation than for children with articulation impairment in mutual comparison. Consequently, neuropsychological and neurophysiological indicators give us the possibility of detecting risks in speech development in pre-school children. This result suggests that further monitoring of findings could provide data that could be used to timely plan prevention.

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Утицај динамике и нивоа зрелости кортикалних функција као предуслов за развој говора код деце

Маја Давидовић[1], Јадранка Оташевић[2], Нада Доброта-Давидовић[2], Ивана Петронић[3], Драгомир Давидовић[1], Лана Јеркић[4]

[1]Клиника за психијатријске болести „Лаза Лазаревић", Београд, Србија;
[2]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[3]Универзитетска дечија клиника, Београд, Србија;
[4]Завод за психофизиолошке поремећаје и говорну патологију „Др Цветко Брајовић", Београд, Србија

САЖЕТАК

Увод/Циљ Развој говора од рођења до одраслог доба је резултат интеракције различитих система коре великог мозга, помоћу којих се постепено стичу способности фонолошке презентације и моторне контроле, уз присуство низа физичких и физиолошких промена у морфологији артикулационог система.

Циљ истраживања је био испитати утицај латерализованости и кортикалних одговора на развој говора код деце.

Методе Истраживање је квазиекспериментални дизајн са две групе. Узроком је обухваћено 60 деце (30 у експерименталној и 30 у контролној групи) из Београда, оба пола, узраста од пет и по до седам година. Од инструмената смо користили тест за процену латерализованости и налаз евоцираних потенцијала.

Резултати На суптесту визуелна латерализованост постоји статистички значајна разлика ($\chi^2 = 7{,}56$, $p < 0{,}05$) између посматраних група. Визуелни евоцирани потенцијали на свим мереним параметрима су дали статистички значајну разлику између експерименталне и контролне групе кортикални одговори – лево ($\chi^2 = 30{,}00$, $df = 1$, $p < 0{,}05$); кортикални одговори – десно ($\chi^2 = 6{,}667$, $df = 1$, $p < 0{,}05$); амплитуда – лево ($\chi^2 = 13{,}469$, $df = 1$, $p < 0{,}05$); амплитуда – десно ($\chi^2 = 40{,}00$, $df = 1$, $p < 0{,}05$). Соматосензорни потенцијали су дали статистички значајну разлику код кортикалних одговора – лево ($\chi^2 = 18{,}261$, $df = 1$, $p < 0{,}05$), амплитуде ($\chi^2 = 12{,}000$, $df = 1$, $p < 0{,}05$), латенција ($\chi^2 = 5{,}455$, $df = 1$, $p < 0{,}05$).

Закључак Визуелна латерализованост, као и визуелни и соматосензорни кортикални одговори на стимулусе су бољи код деце без присутног поремећаја артикулације, што би се могло искористити за благовремено планирање превенције.

Кључне речи: говор; латерализованост; деца; артикулациони поремећаји; евоцирани потенцијали

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pregnant woman survives aortic dissection, dies later of coronary embolism – a unique case of a non-compliant patient

Andrej Preveden[1,2], Golub Samardžija[1,2], Stamenko Šušak[1,2], Aleksandra Ilić[1,2], Aleksandar Redžek[1,2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia

SUMMARY

Introduction The incidence of aortic dissection ranges 3–5 cases per 100,000 person-years. In women under the age of 40 who acquire aortic dissection, almost half of the cases happen during pregnancy.

Case outline We report a case of a 22-year-old pregnant woman in the 16th gestational week with a history of arterial hypertension and known aortic dilatation, who was admitted with aortic dissection. She underwent the Bentall procedure, in which her aortic valve, ascending aorta, and proximal part of the aortic arch were replaced using valved composite graft. On the next day, the evacuation abortion was made, since the fetus didn't survive the operation. Six years later, the patient stopped taking anticoagulation therapy and was admitted for prosthetic valve thrombosis, which was successfully treated with intravenous heparin. One year later, the patient died of a myocardial infarction due to coronary thromboembolism, confirmed on autopsy.

Conclusion Preconceptional counseling in women with a known aortic disease is of the utmost importance. Aortic dissection in pregnant women is an acute life-threatening condition for both mother and fetus that should be managed by a multidisciplinary team. After a mechanical heart valve implantation, lifetime oral anticoagulants are mandatory.

Keywords: aortic dissection; pregnancy; anticoagulation therapy; prosthetic valve thrombosis; coronary embolism

INTRODUCTION

Aortic dissection (AD) is not a common disease, its incidence ranges 3–5 cases per 100,000 person-years [1]. Although almost two thirds of patients are male, an important fact is that in women under the age of 40 who acquire AD, almost half of the cases happen during pregnancy [2, 3].

The most important risk factor is arterial hypertension, while the others include aortic dilatation and aneurysm, aortic coarctation, bicuspid aortic valve, and connective tissue diseases like Marfan syndrome [2, 4].

Hypertension is considered to be a common disorder during pregnancy. About 1% of pregnant women have preexisting hypertension and about 5% develop gestational hypertension [5].

CASE REPORT

In June 2008, a 22-year-old pregnant woman in the 16th gestational week (GW) was admitted with heavy back and chest pain of sudden onset. She had a history of hypertension for the last five years and had her regular checkups. The last transthoracic echocardiography (TTE) had been performed two years prior to her admittance, when the ascending aorta was found to be dilated with the inner diameter of 43 mm. The patient stopped taking her antihypertensive medications at the start of her pregnancy. Her ambulatory and home-monitored blood pressure (BP) did not exceed 135/95 mmHg.

Admission electrocardiogram (ECG) was normal. TTE revealed dilated ascending aorta (52 mm in diameter on the 2D parasternal long axis view), with a clearly visible intimal flap (Figure 1) that originated from the area of the right aortic cusp. Significant aortic regurgitation grade 3/4 was registered with color Doppler. Fetal echocardiography registered normal fetal heart activity with the frequency of 165 bpm.

An interdisciplinary team consisting of cardiologist, cardiac surgeon, anesthesiologist and

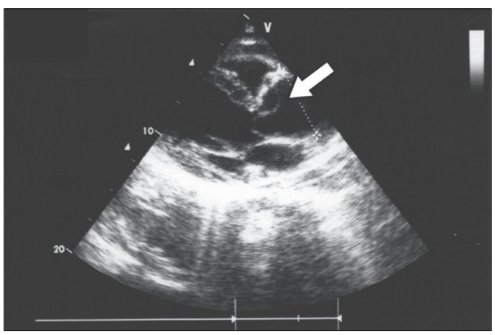

Figure 1. Transthoracic echocardiography (parasternal long axis view): image demonstrating dilated ascending aorta, the intimal flap (arrow) originating in the area of the right aortic cusp, prolapsing into the left ventricle outflow tract

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Correspondence to:
Andrej PREVEDEN
Jirečekova 3
21000 Novi Sad
Serbia
andrej.preveden@mf.uns.ac.rs

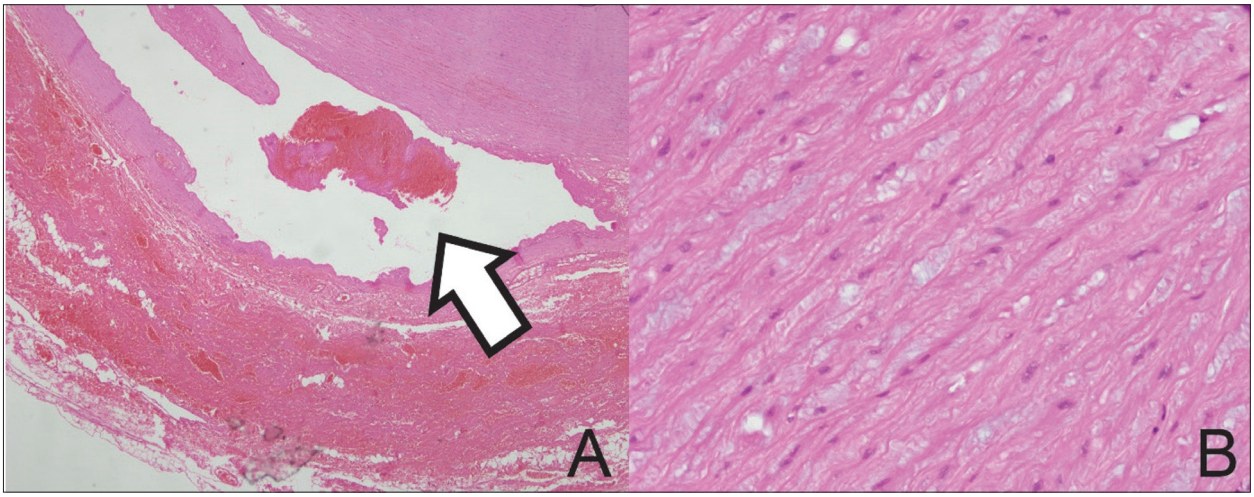

Figure 2. Light microscopy histopathology of the aortic wall: A – dissection of the aortic wall: dissection spreads characteristically along the laminar planes of the aorta, between the middle and outer thirds, fibrin thrombus is present in the false lumen (arrow), the adventitia is permeated with blood (H&E, 4×); B – cystic medial degeneration with elastic tissue fragmentation and separation of the elastic and fibromuscular elements of the tunica media by small cleftlike spaces with an absence of the normal elastic tissue; these areas are filled with an amorphous extracellular matrix of connective tissue (H&E, 40×)

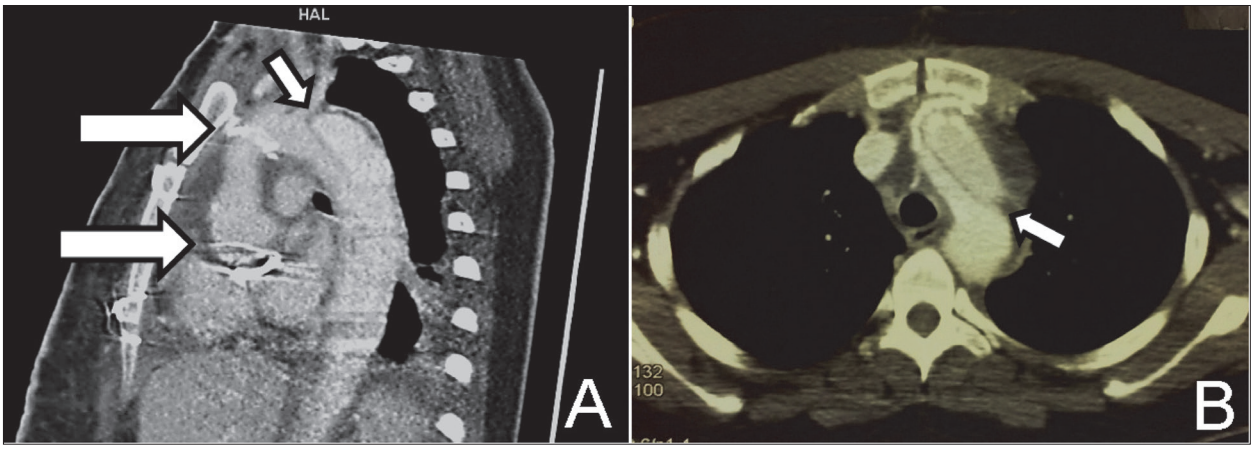

Figure 3. Postoperative computed tomography angiography of the aorta (A – sagittal plane and B – transversal plane): proximal and distal anastomosis of the graft with the prosthetic valve (large arrows) and intimal flap in the aortic arch (small arrows)

gynecologist decided to perform an urgent operation, with the fetus left inside the uterus. The Bentall operation was carried out replacing the aortic valve, ascending aorta, and the proximal part of aortic arch with valved composite graft. Light microscopic analysis of the aortic tissue showed a presence of cystic medial necrosis with elastic fibers that were torn and moved apart, as well as a large amount of mucoid substance (Figure 2). The aortic valve had all three cusps, but they were myxomatously degenerated on histology.

The patient left the operating room in a stable condition, but fetal echocardiography on the first postoperative day (POD) showed no heart activity. The team of doctors met once again and decided to terminate the pregnancy, considering the intrauterine death of the fetus and the patient's general condition. The dead fetus and the placental tissue were removed by dilatation and curettage on the second POD. Autopsy and histopathology showed maceration of the fetus without any malformations and abnormalities.

Further postoperative course was uneventful. Postoperative TTE showed normal prosthetic valve function with normal velocities [mean pressure gradient (PG) 8.5 mmHg]. Computerized tomography (CT) of the aorta on the 14th POD confirmed normal position of the tubular graft, but also an existing intimal flap in the aortic arch that extended all the way to the bifurcation of the aorta (Figure 3). After a 24-hour BP monitoring, the patient's antihypertensive therapy was adjusted. She was dismissed on the 20th POD in a good general condition with carvedilol, losartan and methyldopa. Acenocoumarol as an oral anticoagulant with a target internationalized normalized ratio (INR) of 2.0–3.0 was initiated.

Four months later, after heavy physical activity, the patient developed dehiscence of the sternal wound, which was hence resutured. The wound still failed to heal, so several weeks later another resuture had to be undertaken, after which the sternum was finally successfully managed.

The patient was free of symptoms on her medications for the next six years and went to checkups regularly, until July 2014, when she was admitted to the intensive care unit with severe shortness of breath and chest pain. Six days before she had carelessly stopped taking oral anticoagulant therapy.

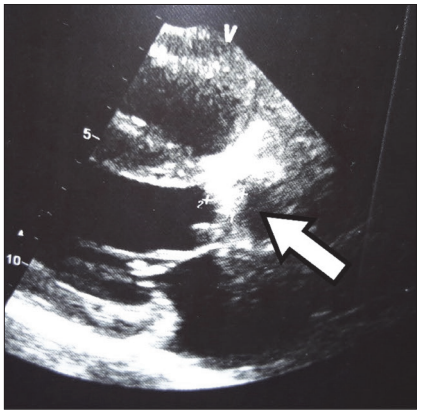

Figure 4. Transthoracic echocardiography (parasternal long axis view): thrombus on the ventricular side of the prosthetic valve in the aortic position (arrow)

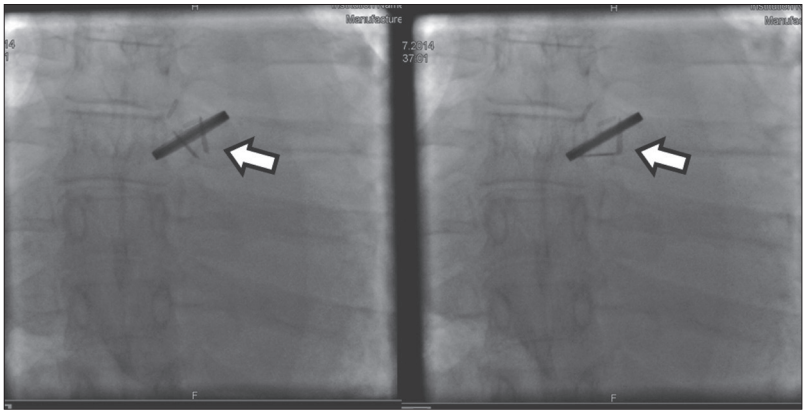

Figure 5. Cinefluoroscopy of the prosthetic valve: one of the leaflets is immobile in both systole and diastole (arrows)

TTE revealed severe dysfunction of the prosthetic valve with an echo formation measuring 15 × 10 mm in size, attached on the ventricular side with thrombus characteristics and a large embolic potential (Figure 4). The measurements showed obstruction across the valve with high PG (maximum PG 99 mmHg, mean PG 49 mmHg, V_{max} 5 m/s), along with a significant insufficiency that had a central regurgitation jet. Cinefluoroscopy revealed one completely immobile leaflet (Figure 5). CT scans of the aorta showed the progress of the false lumen in the descending aorta with a significant parietal thrombosis. The diameter of the descending aorta on CT was 45 mm in total, out of which only 5 mm was the true lumen, since the false lumen was 21 mm and the thrombosis 19 mm.

The patient was considered to have a high risk for a redo operation (EuroSCORE II was 18.97%), so she was treated conservatively with an intravenous unfractionated heparin (UFH) infusion. The UFH dosage had been adjusted in the 1,200-1,700 IU/h interval, depending on the values of APTT that was checked on a regular basis.

Further TTE exams showed graduate lysis of the previously registered echo mass, normalization of the prosthetic valve function, and a PG decrease. After 40 days of continuous intravenous UFH infusion and regular periodic TTE exams, oral anticoagulation therapy with acenocoumarol was continued. Because of the prolonged heparin use and its potential effect on heparin-induced thrombocytopenia (HIT), platelet count was checked regularly. Nonetheless, it remained normal the entire time. The patient was dismissed from the hospital in a clinically stable condition with target INR between 2.0 and 3.0.

One year later, in April 2015, the patient was admitted as an emergency case once again because of chest pain and serious shortness of breath. The admission ECG raised a suspicion for a myocardial infarction (MI) (Figure 6) and laboratory tests revealed elevated cardiac enzymes. Shortly upon admission, the patient had cardiac arrest with pulseless electrical activity. Cardiopulmonary resuscitation was performed, but the patient died.

The autopsy discovered that the reason for the MI was a thromboembolus in the left anterior descending coronary artery (LAD) without any atherosclerotic changes. There

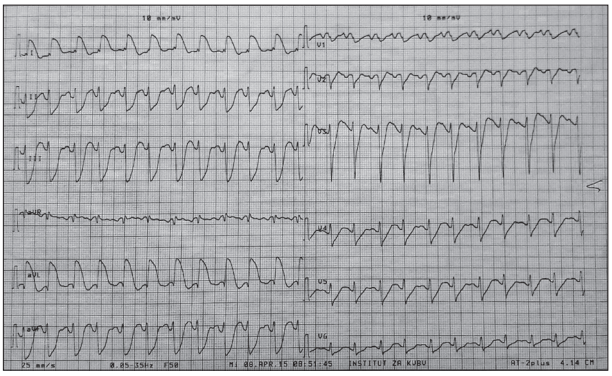

Figure 6. Electrocardiogram on admission: sinus rhythm, heart rate 100 bpm, widened QRS complexes – left bundle brunch block type

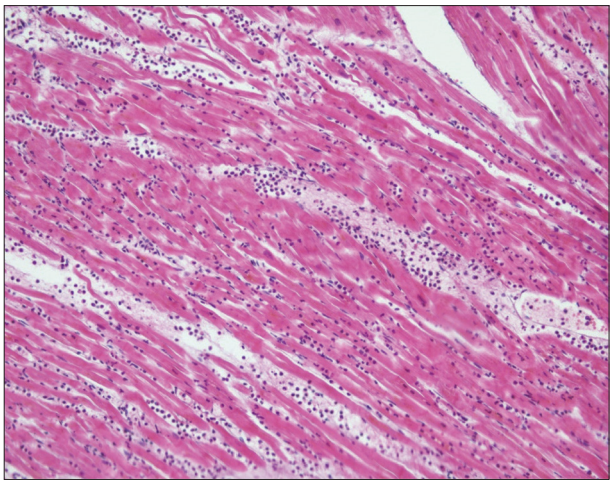

Figure 7. Light microscopy histopathology of the specimen from the anterior wall of the left ventricle: necrotic cardiomyocytes with the loss of nuclei and striations, the interstitium is edematous with the presence of a dense infiltrate of neutrophils (H&E, 20×)

were signs of acute transmural MI in the anterior and lateral wall of the myocardium. On the cross pathology, the area of the MI was pale yellow and soft, surrounded by a hyperemic zone. On the histologic section, cardiomyocytes were necrotic with the loss of nuclei and striations, the interstitium was edematous with the presence of a dense infiltrate of neutrophils (Figure 7). The prosthetic valve was correctly positioned. The inner wall of the aortic graft was covered with a large thrombi formation.

DISCUSSION

AD in pregnant women can be explained by hormone-mediated and hemodynamic changes during pregnancy that increase the aortic wall stress. Tachycardia and rise in cardiac output are the most prominent ones, because of their effect on hemodynamic stress on the arterial walls. Stimulation of the estrogen receptors in aortic tissue causes connective fiber fragmentations and acid mucopolysaccharides reduction, leading to the reduced wall elasticity. The aortic stress can also be increased by the gravid uterus that compresses the aorta [6].

Our patient had neither a positive family history of aortic diseases nor the other Marfan features like spine or chest deformities that would indicate the presence of this syndrome [7, 8]. Previously diagnosed hypertension and dilated aorta were the risk factors that immediately raised the suspicion for the right diagnosis in this case. Hypertension in pregnancy is often related to preeclampsia and eclampsia, however in this case it was present from before and there was no proteinuria [9]. The latest discoveries suggest that the loss of nocturnal BP drop (the so called non-dipping pattern) may be the main cause of cardiovascular dysfunction and hemodynamic impairment in pregnancy, rather than just hypertension by itself [10].

Most of the antihypertensive drugs are avoided during pregnancy because of their side effects on the fetus. Drugs that are recommended are methyldopa, nifedipine, and labetalol, while angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated [11]. According to the current guidelines, antihypertensive therapy in pregnant women who are without any symptoms and signs of organ dysfunction is recommended when the BP levels reach > 160 mmHg for systolic or > 110 mmHg for diastolic BP, and may be considered for BP ≥ 150/95 mmHg [9, 11]. Considering that our patient did not have BP levels above 140/90 mmHg during pregnancy according to the history data and home-based measurements, stopping her antihypertensive therapy was justified and according to guidelines.

Dilated ascending aorta in our patient was noticed two years prior to her pregnancy, 43 mm in diameter on TTE. An indication for elective surgery of the ascending aortic aneurysm is the diameter ≥ 55 mm, but for patients with Marfan syndrome or other risk factors, this threshold can be lowered to 45 mm according to the current guidelines [12]. As a separate recommendation, it is stated that lowering this threshold even more may be considered in the case of planned pregnancy, but thresholds are not specified.

TTE should be performed monthly or every other month during pregnancy in patients with known dilated ascending aorta to identify the potential progress of the aortic diameter, and if indicated undertake surgery on time, thus preventing potential unwanted incidents [13]. Unfortunately, our patient hadn't had a TTE exam during the pregnancy, so possible progressive dilatation of her ascending aorta couldn't have been recognized.

Management of AD involving ascending aorta (Stanford type A) is an urgent surgery, because of high mortality in patients who are not operated on, which reaches 50% in the first 48 hours [12, 13]. In the case of acute AD during pregnancy, management protocols depend on the gestational age. If the pregnancy is older than 28 GW (third trimester), it is indicated to deliver the baby with caesarean section first, and then perform surgery of the aorta [14]. Our patient was in the 16th GW and the caesarean section was not an option, so the urgent surgery of the aorta was undertaken immediately.

Echocardiography is a basic diagnostic modality for aortic diseases. However, a negative TTE does not rule out AD. Other imaging techniques such as transesophageal echocardiography (TEE), CT, and magnetic resonance have a greater field of view and may provide additional information important for the operation [15], but in this case the diagnosis of the dissection and the decision for surgical treatment was made using solely TTE, which, according to the literature, has a sensitivity and specificity of 75% and 90%, respectively [4]. Precious time was saved by skipping TEE and CT scan, and the negative effects of CT radiation and contrast agents were avoided.

The patient survived the cardiac surgery, but the stress on the fetus was apparently too strong and it died, so the evacuation abortion was undertaken the next day. There is a limited number of similar cases in the literature. Majority of them describe the dissection in the third trimester, which is in fact the most vulnerable period [16, 17, 18]. Only two case reports describe the surgical repair of Stanford type A AD before the third trimester with maternal and fetal survival in both of them [19, 20]. Liu et al. [21] reported five cases of Bentall operation in Stanford type A AD during pregnancy, only one of which happened before the third trimester (22 GW), with both mother and fetus diseased.

There are multiple possible reasons for the fetal death. The main ones being the dissection itself, with the intimal flap potentially compromising the placental perfusion, as well as the factors associated with the operation, including cardiopulmonary bypass and circulatory arrest. Hypothermia during bypass has also shown to worsen the fetal prognosis [22].

The tissue sample of the ascending aorta that was sent to light microscopic histopathology showed cystic medial necrosis, which is a typical finding in Marfan syndrome [7]. Considering the significantly higher burden of acute aortic syndromes in Marfan patients, recognizing this syndrome in our patient could have improved her follow-up. She had an aneurysm of the ascending aorta, which is a major criterion for Marfan syndrome diagnosis, yet criteria on other organ systems (skeletal, ocular, respiratory, skin) were not fulfilled [8].

The patient was released from hospital with a combined antihypertensive therapy including losartan. A number of studies on animal and human models have demonstrated that losartan improves endothelial function and has a positive effect on aortic root stabilization [23].

The necessity of a lifetime anticoagulation therapy after mechanical valve implantation is clearly demonstrated in this case [24]. The patient had stopped taking oral anticoagulants for an unknown reason, and during that period of

time she was not protected with a low-molecular-weight heparin. This led to valve thrombosis in only a few days, causing its malfunction and resultant heart failure.

The diagnosis of prosthetic valve thrombosis was based on the findings of TTE and cinefluoroscopy. TTE provided a proper diagnostic assessment with 2D echo when an echo mass (15 × 10 mm) attached at the ventricular side of the prosthetic valve was registered. High velocity and elevated transprosthetic gradients were measured with Doppler echo.

Usually, urgent surgery is the treatment of choice in such critically ill patients with obstructive valve thrombosis [24]. Therapeutic strategy in this case was mainly influenced by the risk assessment, which was too high for a redo operation, so being aware of the prosthesis location, the presence of a valvular obstruction, and the patient's clinical status, heparin infusion was started. This led to prosthetic valve function recovery after two months. The prolonged heparin use did carry an increased risk of complications like hemorrhage and HIT; however, they were fortunately avoided. From the aspect of HIT, low-molecular-weight heparin might have been a better choice over UFH. Recent studies show lower incidence of HIT with the use of low-molecular-weight heparin in comparison to UFH, without a significant difference in therapeutic effect [25].

Nine months later, the cause of death was a massive transmural MI. The autopsy showed that the MI was caused by thromboembolism in the LAD. There were no atherosclerotic plaques in coronary arteries. The reported incidence of thromboembolism after Bentall operation is around 0.7% events per year, which is mainly associated with inadequate anticoagulation [26]. The main cause of coronary thromboembolism is atrial fibrillation [27]. Although our patient was in sinus rhythm, she did have a few other risk factors, including previous cardiac surgery, non-infected thrombi on prosthetic valve, and intraluminal thrombosis inside the chronic dissection of the descending aorta, which are all described as rare but possible causes of coronary thromboembolism [27, 28]. There is scarce data in literature describing coronary thromboembolism after Bentall operation [29, 30]. As in our case, coronary thromboembolism was also caused by prosthetic valve thrombosis due to inadequate coagulation in the described cases.

In conclusion, we can say that even though this pregnancy could have been classified as a high-risk one, considering the patient's hypertension and known aortic disease, the follow-up was not as thorough as it should have been and the preconceptional counseling failed. Taking everything into account, it might have been wise to consult the patient against pregnancy. BP levels during pregnancy probably haven't been monitored regularly since the antihypertensive therapy was discontinued, which might have contributed to the damage of the aorta. In the setting of acute chest pain and distress in pregnancy, AD should always be suspected.

Echocardiography is rapid, accurate, and cost-effective in the diagnosis and follow-up of aortic diseases. In contrast to the poor pregnancy follow up, the reaction of the multidisciplinary team managing AD was prompt and appropriate to this life-threatening condition, saving the woman's life but unfortunately losing the baby. Mandatory lifetime oral anticoagulants after a mechanical valve implantation is clearly demonstrated in this case.

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Трудница преживела дисекцију аорте, а касније умрла због коронарне емболије – јединствен случај несарадљивог болесника

Андреј Преведен[1,2], Голуб Самарџија[1,2], Стаменко Шушак[1,2], Александра Илић[1,2] Александар Рељек[1,2]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за кардиоваскуларне болести Војводине, Сремска Каменица, Србија

САЖЕТАК

Увод Учесталост дисекције аорте се креће између три и пет случајева на 100.000 људи годишње. Од жена млађих од 40 година које добију дисекцију аорте готово половина су труднице.

Приказ болесника Приказан је случај 22-годишње трудице у 16. гестацијској недељи са историјом артеријске хипертензије и дилатираном аортом, која је примљена због дисекције аорте. Урађена јој је операција по Бенталу, којом су јој замењени аортни залистак, асцедентна аорта и проксимални део лука аорте коришћењем композитног графта са заliском. Плод није преживео операцију, те је сутрадан начињена евакуациона киретажа. Шест година касније код болеснице је, услед престанка узимања антикоагулантне терапије, дошло до тромбозе механичког заliска, која је успешно излечена интравенском применом хепарина. После годину дана болесница је умрла због инфаркта миокарда узрокованог коронарном тромбоемболијом, што је потврђено обдукцијом.

Закључак Код жена са познатом болешћу аорте веома је важно саветовање пре зачећа. Дисекција аорте код трудница је акутно, животно угрожавајуће стање како за мајку тако и за фетус, у чијем збрињавању треба да учествује мултидисциплинарни тим. После уградње механичког заliска неопходна је доживотна антикоагулантна терапија.

Кључе речи: дисекција аорте; трудноћа; антикоагулантна терапија; тромбоза механичког заliска; коронарна емболија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Osseous metaplasia in an inflammatory polyp of the anal canal – a case report and a review of literature

Dejan Stevanović[1], Vuk Aleksić[2], Dragoš Stojanović[1], Nebojša Mitrović[1], Damir Jašarović[1], Zorana Bokun-Vukašinović[3]

[1]University of Belgrade, Faculty of Medicine, Clinical Hospital Center Zemun, Department of Surgery, Belgrade, Serbia;
[2]Clinical Hospital Center Zemun, Department of Neurosurgery, Belgrade, Serbia;
[3]Clinical Hospital Center Zemun, Department of Pathology, Belgrade, Serbia

SUMMARY
Introduction Osseous metaplasia is a heterotopic formation of bone and its appearance in benign gastrointestinal polyps is exceedingly rare. The mechanism responsible for this type of metaplasia is not fully understood, however it seems to be an innocent rare phenomenon.
Case outline We present a case of a 31-year-old male with mesenchimal osseal metaplasia in a large inflamatory polyp measuring 57 × 23 × 20 mm in diameter, located in the anal canal region.
Conclusion According to our knowledge, this is the largest gastrointestinal polyp with osseous metaplasia described so far. Although a rare phenomenon, there are certain characteristics of this disease, so we conducted a literature review and summarized these characteristics.
Keywords: osseous metaplasia; gastrointestinal polyps; inflamatory polyps

INTRODUCTION

Heterotopic formation of bone (mesenchymal osseous metaplasia) is rarely found in the gastrointestinal tract. Most cases are associated with colon adenocarcinoma, but also can be found in the benign lesions of the bowel wall, such as necrosis, chronic inflammation foci, and mucin extravasation [1]. The appearance of heterotopic bone in benign colon polyps is exceedingly rare, and only a few cases have been reported in literature. The first case of heterotopic bone formation in gastrointestinal polyp was described by Todd [2] in 1963. The mechanism responsible for this type of metaplasia is not yet fully understood [3].

Herein, we shall describe a case of mesenchymal osseous metaplasia (OM) in a large inflammatory polyp located in the anal canal region in a 31-year-old male, after which we shall make an accompanying literature review.

CASE REPORT

We report a case of a 31-year-old male who visited the hospital with a chief complaint of pain and evacuation of fresh blood from the anal canal during defecation. Clinical exam revealed a polypoid tumefaction with contact bleeding in the anal canal region. Concomitant clinical findings were grade I internal hemorrhoidal nodules without signs of bleeding or inflammation. Total colonoscopy confirmed lobulated and vulnerable polyp about 5 cm in diameter, located at 1–2 cm from the anocutaneous line. Colonoscopy biopsy revealed an inflammatory pseudopolyp. The patient underwent a transanal electrosurgical resection of the polyp. The polyp was sent to pathohistological analysis. The postoperative course was uneventful, and the patient was discharged on the first postoperative day.

The tissue fragment submitted for pathohistological analysis, was macroscopically a soft greyish white polyp measuring 57 × 23 × 20 mm in diameter. Histological analysis showed fragments of an inflammatory polyp of the large bowel mucosa, partly overlaid with superficial cylindrical epithelium and partly with fibrin deposits and groups of neutrophils. The stroma of the described specimen was edematous with florid fibrovascular granulation tissue and numerous foci of dilated and congested blood vessels, as well as with moderately intense mixed inflammatory infiltrate, made mostly of granulocytes and lymphocytes. In the central parts of the polyp, numerous foci of mineralized osteoid lined by osteoblasts without extramedullary hematopoiesis signs were found (Figure 1). The lesion was diagnosed as an inflammatory polyp of the anal canal with foci of OM.

DISCUSSION

Stromal ossification can occur in gastrointestinal cancers from the stomach to the anal canal and it seems to be result of bone morphogenetic protein production of tumor cells.

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Correspondence to:
Vuk ALEKSIĆ
Department of Neurosurgery
Clinical Hospital Center Zemun
Vukova 9, 11000 Belgrade, Serbia
aleksicvuk@hotmail.com

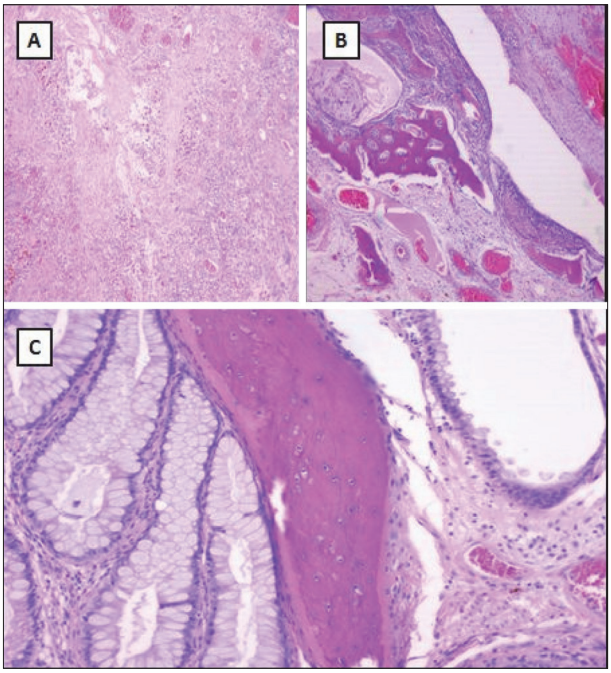

Figure 1. Microscopic pictures of H&E stained sections of the inflammatory polyp of the anal canal with focus of OM; (A) 10× magnification, (B) 10× magnification, (C) 20× magnification

Ossification in benign colon tumors has been documented only rarely, and only a few cases have been documented [1]. We reviewed and summarized the related literature on OM in gastrointestinal polyps (Table 1). We found 24 cases described in literature, of which 16 were male and five were female patients, while in three cases gender as well as age were not specified. Patient age ranged 3–85 years, with mean age of 34 years. Our patient was a 31-year-old male. Out of 24 described polyps, three were smaller than 10 mm, 11 were 10–20 mm in diameter, and six were larger than 20 mm, while in four cases size was not specified. The mean size was 17.05 mm (range: 3–50 mm). In our case, the polyp was very large with 57 mm in diameter, which is to our knowledge the largest gastrointestinal polyp with OM described so far. The most frequently involved site was the rectum where 60% of polyps (12/20) were found. In 30% (6/20) polyps were located in the colon, and in 10% (2/20) polyps were found in the junction of the sigmoid colon and the rectum. In four remaining cases, exact location was not defined. Our patient had a polyp in the anal canal, which is another curiosity of our case. Histologically, seven lesions were neoplastic (four tubular adenomas, and three tubulovillous adenomas), while 15 lesions were non-neoplastic (seven juvenile polyps, six inflammatory polyps, and two serrated adenomas). In two lesions histology finding was not specified [1, 3–8]. Our patient had non-neoplastic inflammatory polyp.

The pathogenesis of heterotopic ossification is still not fully investigated. Many theories about pathogenesis are published. At the beginning of the 20th century, Charles Brenton Huggins [9] conducted a set of experimental studies on dogs and demonstrated OM in soft tissue of abdominal wall after transplantation of bladder tissue with

Table 1. Summary of our and previously reported cases of OM in gastrointestinal polyps

Case	Author	Year	Sex	Size (mm)	Location	Age	Histology
1	Todd	1963	NI	NI	NI	NI	NI
2	Marks	1964	M	NI	NI	10	Juvenile polyp
3	Sperling	1981	M	10	Rectum	25	Inflammatory polyp
4	Castelli	1992	F	10	Rectum	22	Inflammatory polyp
5	Drut	1992	M	10	Rectosigmoid	5	Juvenile polyp
6	Drut	1992	M	5	Rectum	4	Juvenile polyp
7	Groisman	1994	M	18	Rectum	67	Tubulovillous adenoma
8	Groisman	1994	F	20	Rectum	3	Juvenile polyp
9	Cavazza	1996	NI	NI	NI	NI	Tubulovillous adenoma
10	Monzon	1997	M	12	NI	59	Tubular adenoma
11	McPherson	1999	M	20	Cecum	73	Tubulovillous adenoma
12	Rothstein	2000	NI	25	Sigmoid colon	NI	Tubular adenoma
13	Al-Daraji	2005	F	15	Sigmoid colon	85	Tubular adenoma
14	White	2008	F	NI	Transverse colon	63	Tubular adenoma
15	Oono	2009	M	12	Rectum	39	Inflammatory polyp
16	Ahmed	2009	M	10	Rectum	15	Juvenile polyp
17	Wilsher	2010	M	25	Rectosigmoid	50	Serrated adenoma
18	Bowman	2012	M	45	Descending colon	28	NI
19	Odum	2012	M	7	Ascending colon	74	Inflammatory polyp
20	Montalvo	2012	M	50	Rectum	62	Serrated adenoma
21	Bhat	2012	F	14	Rectum	5	Juvenile polyp
22	Bhattachary	2013	M	10	Rectum	14	Juvenile polyp
23	Garg	2013	M	15	Rectum	6	Inflammatory juvenile polyp
24	Zemheri	2015	M	8	Rectum	9	Inflammatory polyp
25	Our case	2016	M	57	Anal canal	31	Inflammatory polyp

NI – not informative

intact epithelium to abdominal wall fascia. These studies provided evidence that some component of the epithelial tissue may induce mesenchymal tissue ossification. Van Patter and Whittick [10] presented a series of OM cases in gastrointestinal tumors and suggested theory that the ossification resulted from the interaction between local physicochemical factors, such as mucin and calcium salts, and proliferating connective tissue. Zemheri et al. [3] noticed that OM, especially in benign lesions, is most often seen in lesions with active chronic inflammation and/or ulceration. Therefore, the pathogenesis might be a reactive change due to repeated local trauma, or be a peculiar characteristic of the intestinal mucosa itself [1]. One of the possible mechanisms of bone formation could be the ability of fibroblasts to achieve the phenotype of other types of cells of mesodermal tissue by the process of metaplasia, especially osteoblasts [3, 8, 11]. Recent studies showed important role of the bone morphogenetic proteins (BMPs) in the tissue where the formation of heterotopic bone takes place [3]. BMPs are members of the TNF-β group, and they have an important role in the new bone formation. Imai et al. [12] conducted an immunohistochemistry study of BMP expression in colon carcinoma with heterotopic ossification. They found that BMP-5 and BMP-6 were strongly stained in tumor cells but weakly stained in osteoblast-like cells on the surface of the bone matrix. In addition, BMP-2 and BMP-4 were found in tumor cells, but staining was week. Authors concluded that BMPs might have a significant role in heterotopic ossification in colon adenocarcinoma. The study of Kypson et al. [13] showed BMP-2 overexpression in rectal adenocarcinoma tumor cells with OM compared to rectal adenocarcinomas without bone production. Later on, Liu et al. [14] found BMP-1, BMP-4, and BMP-6 expression in stroma as well as epithelium in different cancers with OM. Genetic studies of Takahashi et al. [15] demonstrated that mouse somatic cells and human dermal fibroblast cultures, by transduction of four transcription factors ($Oct^{3/4}$, Sox2, Klf4, and c-myc), can be generated in induced pluripotent stem cells, which are similar to human embryonic stem cells. Additionally, these cells could differentiate into cell types of the three germ layers in vitro and in teratomas [3, 16, 17]. Other genetic studies found increased expression of bone matrix synthesis markers e.g. collagen type I, osteocalcin and osteonectin in the foci of metaplastic bone formation [8, 18].

All of the above point to the fact that the interaction between either neoplastic or non-neoplastic epithelium of the large bowel with the surrounding mesenchymal tissue is the key factor for the formation of bone tissue in the stroma, but their relationship and the precise mechanism of OM are still confusing the clinicians as well as pathologists. Most importantly, the majority of authors agree that clinically, the presence of the metaplastic bone seems to be an innocent phenomenon [1].

Confilct of interests: None declared.

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Коштана метаплазија у инфламаторном полипу аналног канала – приказ болесника и преглед литературе

Дејан Стевановић[1], Вук Алексић[2], Драгош Стојановић[1], Небојша Митровић[1], Дамир Јашаровић[1], Зорана Бокун-Вукашиновић[3]

[1]Универзитет у Београду, Медицински факултет, Клиничко-болнички центар Земун, Служба хирургије, Београд, Србија;
[2]Клиничко-болнички центар Земун, Служба неурохирургије, Београд, Србија;
[3]Клиничко-болнички центар Земун, Служба патологије, Београд, Србија

САЖЕТАК

Увод Коштана метаплазија представља хетеротопично формирање коштаног ткива и њена појава у бенигним гастроинтестиналним полипима је ретка.

Механизам настанка ове врсте метаплазије није потпуно разјашњен, али изгледа да представља само редак доброћудни феномен.

Приказ болесника Приказујемо мушкарца, старог 31 годину, са мезенхималном коштаном метаплазијом у великом инфламаторном полипу промера 57 × 23 × 20 *mm* у аналном каналу.

Закључак Према нашим сазнањима, ово је највећи до сада описан гастроинтестинални полип са коштаном метаплазијом. Иако редак феномен, постоје извесне карактеристике ове болести, због чега смо урадили преглед литературе и сумирали карактеристике.

Кључне речи: коштана метаплазија; гастроинтестинални полипи; инфламаторни полипи

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Laparoscopic sleeve gastrectomy in a superobese patient with restenosis of the trachea

Miroslav Ilić[1,2], Srđan S. Putnik[3]

[1]Institute for Pulmonary Diseases of Vojvodina, Clinic for Thoracic Surgery, Sremska Kamenica, Serbia
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Vršac General Hospital, Department of General Surgery, Vršac, Serbia

SUMMARY
Introduction Superobese group of patients with body mass index (BMI) ≥ 50 kg/m^2 have higher technical intraoperative problems, higher morbidity, and mortality. Indications for the metabolic procedure are widening and minimally invasive operation dictates that both patients and surgeons face previously assumed "general contraindication" for a surgical bariatric/metabolic procedure.
Case outline We present a superobese patient with restenosis of the trachea, chronic obstructive pulmonary disease, sleep apnea, and cardiomyopathy with panniculus grade IV, in whom, as a multidisciplinary team, we simultaneously performed permanent tracheostomy, laparoscopic sleeve gastrectomy, and panniculectomy.
Conclusion Quality of life after the bariatric operation must be a leading factor in regard to the approach to a difficult patient, with the operation adaptable enough to fit all demands.
Keywords: superobese; laparoscopic sleeve gastrectomy; bariatric surgery

INTRODUCTION

In recent decades, obesity has become a significant health and surgical problem worldwide [1]. The superobese group of patients with body mass index (BMI) ≥ 50 kg/m^2 have more pronounced technical intraoperative problems, more postoperative complications, and higher mortality [2, 3]. Indications for metabolic operation are widening and successful management of comorbidities after minimally invasive operation dictates that both patients and surgeons face previously assumed "general contraindication" for a surgical bariatric/metabolic procedure. Is elective surgery justified in a selected group of patients who experience dysfunction of several vital organs?

We present a high-risk superobese patient with chronic respiratory failure, cardiomyopathy, and restenosis of previously resected trachea, who came to the surgeon for removing panniculus (grade IV), refused for surgery in non-referral surgical centers [4]. We performed a successful laparoscopic sleeve gastrectomy after re-tracheostomy with a synchronous panniculectomy.

CASE REPORT

The patient was a male Caucasian, 54 years old, weighing 160 kg, 175 cm tall, BMI of 52.3 kg/m^2 (Figure 1A). His neck's circumference was 49.5 cm. He complained of large panniculus and inspiratory stridor. In a tertiary institution, he was refused for panniculectomy operation due to restenosis of the upper trachea, respiratory chronic failure, and chronic cardiomyopathy with 10 years' medically history of hypertension with arrhythmia. Previously (11 years prior), he had a surgical repair of the stenotic trachea after a prolonged intubation due to the attempt of suicide with local pesticide poison containing parathion during a psychical paranoid episode (Figure 2). After his recovery, he started to gain weight. At his admittance to the Clinic, the patient was an active smoker and consumed 15 cigarettes per day during the previous 25 years.

At the University Clinic for Thoracic Surgery, Department for Esophageal and Laparoscopic Surgery, Sremska Kamenica, Serbia, we performed multi-slice computed tomography (MSCT) of the neck and thorax and tracheobronchoscopy. Preoperative MSCT showed restenosis of the trachea 12 mm beyond the glottis. Endoscopic findings suggested restenosis immediately beneath the vocal cords, which appeared immobilized and showed disarrangement of the whole larynx. Respiratory function showed global respiratory insufficiency due to alveolar hypoventilation and chronic obstructive pulmonary disease. Cardiac function was estimated with echocardiogram (ejection fraction of 65%) and dilatation of the left atrium and hypertension were noted. Sleep apnea study was not done due to restenosis of the trachea, but the patient was previously treated with ventilator support during the night. The patient lived without suicidal thoughts for the previous 10 years, living in a stable social relationship with his wife, working as an agricultural laborer. After the multidisciplinary

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Correspondence to:
Srđan S. PUTNIK
Vršac General Hospital
Department of General Surgery
Abraševićeva bb
26300 Vršac, Serbia
putniksrdjan@outlook.com

Figure 1. The superobese 54-year-old patient before the operation (A) and one year later (B)

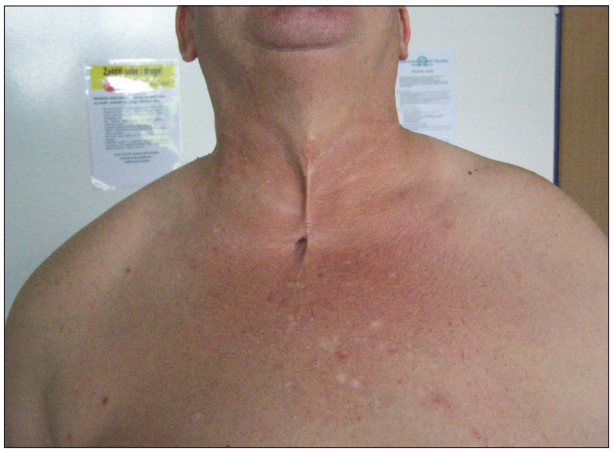

Figure 2. The scar from the previous tracheal operation

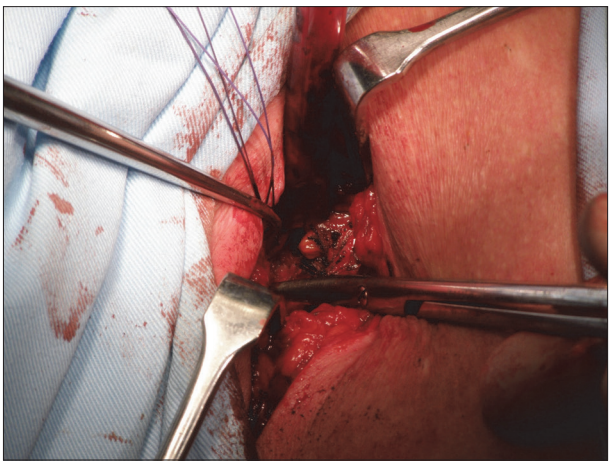

Figure 3. Re-tracheostomy

surgical and the otorhinolaryngology team provided explanations, the patient accepted the reasonable risk and the operation.

The operation begins with intraoperative direct and rigid laryngoscopy and temporary intubation with tracheal tube No. 6. Excision of the scar tissue was done after identification of the tracheal restenosis *in loco* of the subglottic-tracheal junction (Figure 3). Re-tracheostomy was performed and cannula No. 9 was placed and fixed for further airway support for the procedure. The patient was placed in the French position and laparoscopic sleeve gastrectomy was done with the four-trocar technique. After completing the laparoscopic procedure, panniculectomy was done in the standard fashion (Figure 4). Postoperative period was uneventful and the patient spent 14 days in the hospital.

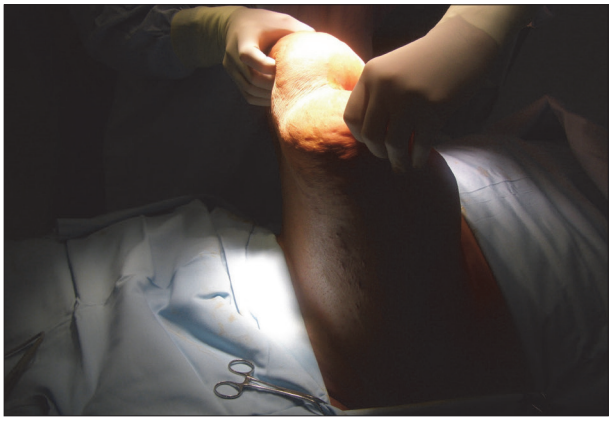

Figure 4. Preparation for panniculectomy

After 12 months, the patient's body weight was 93 kg, BMI of 30.4 kg/m^2, percentage of excess weight loss of 71.4 (Figure 1b). The patient adapted to the permanent metal tracheal cannula and spoke routinely by closing the cannula opening. He was very satisfied with his quality of life.

DISCUSSION

Superobese patients with BMI ≥ 50 kg/m^2 and neck circumference > 42 cm are considered to be 50 times more likely to experience difficulties in intubation [5]. In our patient, restenosis of the previously resected trachea was a factor for refusing anesthesia and any elective surgery in non-experienced centers. This patient's only hope was an experienced center specialized in tracheal surgery and obesity surgery. His primary health demand was the removal of panniculus, but the explanation of the multidisciplinary team resulted in the acceptance of simultaneous surgical tracheal, metabolic, and plastic intervention. At every step, as a team, we considered discontinuing the intervention in case of any complications.

Difficult intubation during operation for morbid obesity is a relatively uncommon situation, which requires emergency tracheostomy in very few cases [6]. However, a very difficult situation arises with stenosis of the trachea, as was the case in our patient. This poses a problem not the only to the anesthesiologist, but also to the patient, as unsolved restenosis of the trachea permanently damages the patient's health. This is why an otorhinolaryngologist was included in solving the problem with permanent tracheostomy.

The question of the patient's psychological status is also important for the success of the entire postoperative period. Our patient was cooperative, with social, family life, and able to work. He reasonably inquired not only about panniculectomy but also about the reduction of weight. The question was what operation to choose. We decided to perform a simple but effective operation, with possible

eventful recovery, which would not dependent on continuous therapy of supplementation. Simultaneously, we did panniculectomy since it was the patient's primary demand. Several authors suggest that panniculectomy should be performed after patients stabilize body weight, but there are some exceptions, as in cases with panniculus grade IV and V [4, 7]. Perhaps there is a special indication in patients with tracheostomy and difficult approach to airways. The cosmetic result in our patient supports this thesis.

The result regarding sleeve gastrectomy and weight loss is good after one year. The patient was on surgical check-ups at regular intervals and his attitude regarding the quality of life was superior.

In the era of the modern, team approach, morbidly obese patients could be treated successfully even with serious comorbidities nondependent on obesity. The quality of life after the bariatric operation is a factor which must be a leading one in the concern as to how to approach a difficult patient, with operation adaptable enough to fit all demands.

Confilct of interest: None declared.

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Лапароскопска рукавна гастректомија код супергојазног болесника са рестенозом трахеје

Мирослав Илић[1,2], Срђан С. Путник[3]

[1]Институт за плућне болести Војводине, Клиника за грудну хирургију, Сремска Каменица, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Општа болница „Вршац", Служба опште хирургије, Вршац, Србија

САЖЕТАК

Увод Супергојазна група болесника са индексом телесне масе ≥ 50 kg/m^2 има веће техничке и интраоперативне проблеме, већи морбидитет и морталитет. Индикације за метаболичке процедуре се повећавају и минимално инвазивне операције захтевају како од болесника тако и од хирурга да се суоче са претходно подразумеваним „општим контраиндикацијама" за хируршку баријатријску/метаболичку процедуру.

Приказ болесника Представљамо супергојазног болесника са рестенозом трахеје, хроничном опструктивном болешћу плућа, опструктивним апнеја синдромом и кардиомиопатијом и паникулусом четвртог степена, ког кога је мултидисциплинарни тим урадио истовремено трајну трахеостомију, лапароскопску рукавну гастректомију и паникулектомију.

Закључак Квалитет живота после баријатријске операције мора бити водећи фактор у начину приступања тешком болеснику, са операцијом прилагођеном свим захтевима.

Кључне речи: супергојазни, лапароскопска рукавна гастректомија, баријатријска хирургија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Meningoencephalitis as a complication of acute otis media in an 11-year-old child

Zoran Dudvarski[1,2], Nenad Arsović[1,2], Snežana Ješić[1,2], Vladimir Nešić[1,2], Biljana Međo[1,3], Dimitrije Nikolić[1,4]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Center of Serbia, Clinic of Otorhinolaryngology and Maxillofacial Surgery, Belgrade, Serbia;
[3]University Children's Hospital, Intensive Care Unit, Belgrade, Serbia;
[4]University Children's Hospital, Department of Neurology, Belgrade, Serbia

SUMMARY

Introduction Acute otitis media is a very common disease in the early childhood age, with typical symptoms such as otalgia and fever. Otogenic complications are divided into extracranial and intracranial. Although the introduction of antibiotics has significantly reduced the incidence of intracranial complications, they are still present. Clinical picture usually develops fast, with the predominance of neurologic symptoms.

Case outline An 11-year-old boy was admitted to a tertiary health care children's hospital because of fever, agitation, altered behavior and disorder of consciousness. Based on the anamnesis, clinical examination, CT, MRI, and lumbar puncture, it has been established that it is a case of meningoencephalitis as complications of acute otitis media. Besides intense antibiotic and symptomatic therapy, surgical treatment too was conducted as well. Firstly, mastoidectomy with the implantation of ventilation tube was done, followed by radical tympanomastoidectomy, because there was no improvement. The treatment was followed by numerous complications, such as toxic hepatitis, mycoplasma pneumoniae infection, and hemolytic anemia. The treatment lasted for 71 days, and the patient was discharged from the hospital in a good general condition, without the focal motor failure.

Conclusion Meningoencephalitis is unusual and rare complication of acute otitis media that requires urgent diagnostic procedure and multidisciplinary approach to the treatment. Surgical treatment of the ear that caused complications should not be postponed, and the choice of surgical method must be adapted to each patient individually. Hospital treatment of these patients is often prolonged and auditory and neurological sequelae are substantial and require long-term treatment.

Keywords: acute otitis media; intracranial complications; children

INTRODUCTION

Acute otitis media (AOM) is characterized by a sudden onset of symptoms and signs of the middle ear inflammation. This disease is very common in early childhood, and typical symptoms include otalgia and fever. Otoscopic finding of hyperemic, bulging or perforated tympanic membrane with secretion, indicate AOM. When AOM diagnosis is uncertain, it is necessary to perform pneumatic otoscopy or tympanometry in order to assess the presence of secretion in the middle ear. The application of the adequate guides greatly helps the diagnostics and treatment of AOM, and represents the integral part of a routine clinical practice [1, 2]. The occurrence of complications in AOM depends on several factors, such as age, virulence of pathogens, immunological system of the patient, presence of comorbidities and previous therapy. Otogenic complications are the most common in recurrent acute bacterial otitis and exacerbation of chronic inflammatory processes of the middle ear. Sometimes they can be the first sign of inflammation of the middle ear. The most common extracranial complications (ECC) of AOM are mastoiditis and subperiosteal abscess, while the most common intracranial complications (ICC) of AOM are meningitis, cerebral abscess, epidural abscess and sigmoid sinus thrombosis [3, 4].

Despite the introduction of an effective antibiotic therapy, the rate of otogenic ICC is still about 8%, and the mortality rate is 5–26% [5, 6]. Symptoms and signs that indicate the development of otogenic ICC are dizziness, instability of walk, headache, vomiting, fever, visual field disorders, altered behavior, and disorder of consciousness. In cases of AOM with ICC, clinical picture usually develops quickly, with a predominance of neurological symptoms. High degree of clinical suspicion of ICC, computed tomography (CT) with intravenous contrast, magnetic resonance imaging (MRI) with venography and lumbar puncture with the analysis of cerebrospinal fluid enable an early diagnosis. Therapeutic approach in these cases has to be multidisciplinary and adapted to each patient individually, and besides intense antibiotic and symptomatic therapy, surgical treatment is required as well. In spite of all measures taken in treatment, the prognosis is sometimes uncertain.

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Correspondence to:
Zoran DUDVARSKI
Clinic of Otorhinolaryngology and Maxillofacial Surgery
Clinical Center of Serbia
2 Pasterova Street
11000 Belgrade, Serbia
zdudvarski@open.telekom.rs

The objective of this paper is to show fulminant course of AOM with the development of meningoencephalitis in an 11-year-old boy, dilemmas, and complications that existed during treatment, as well as significant auditory and neurological sequelae.

CASE REPORT

In December 2014, an 11-year-old boy was admitted to a tertiary-care children's hospital, because of fever, agitation, altered behavior, and disorder of consciousness. The score on the Glasgow Coma Scale was 5/15. The previous day, the patient complained of headache and pain in the left ear, and then he vomited. During the night, the boy woke up confused, agitated, and vomited again. Other than that, patient's personal and family history had no particularities, no data on previous ear disease, and he was regularly vaccinated according to the calendar of vaccination. The blood test on admission showed: total leukocytes 12.3×10^9/L (94.5% neutrophils); C-reactive protein 249 mg/L; procalcitonin 51.2 ng/mL. CT scan showed moderate diffuse cerebral edema and signs of inflammation in the left middle ear, mastoid and petrosal apex, without tegmen erosion (Figure 1). After that, lumbar puncture was performed: cerebrospinal fluid was turbid with a mass of leukocytes (94% polymorphonuclear). The treatment started with vancomycin, meropenem, and metronidazole, according to recommendations from the literature [7].

In the cerebrospinal and blood samples, the cause of infection was not detected. On the second hospital day, there was a spontaneous perforation of the tympanic membrane and purulent secretion from the left ear. *Streptococcus pneumoniae* was detected in swab taken from the left ear. Due to the appearance of convulsions, phenobarbital and midazolam were introduced into therapy. Electroencephalography showed signs of severe encephalopathy. Cerebral MRI with angiography showed meningitis and disseminated multiple inflammatory and ischemic changes in brain tissue. Cranial venous sinuses had a normal caliber and blood flow, with no signs of thrombosis (Figure 2).

On the fifth hospital day, mastoidectomy was done with myringotomy and implantation of ventilation tube. During surgery, we found that tympanic membrane had healed where it spontaneous perforated and after myringotomy, abundant purulent content was obtained from the middle ear. Mastoid cavity was completely filled with inflamed mucosa and granulation tissue. Osteolytic changes were present in the intercellular septa, but bone integrity to the middle and posterior cranial fossa was preserved. Histopathologic findings pointed to a non-specific granulation tissue. Postoperatively, the patient showed an improvement concerning his consciousness and motor skills, but after a few days, we registered an increase in laboratory parameters of inflammation and fever. The antibiotic therapy was changed to cefepime and clindamycin, but without significant improvement in the clinical picture. Medical advisory board had decided that radical tympanomastoidectomy must be performed in order to provide a more complete removal of the pathological process, and it was done eight days after the first operation.

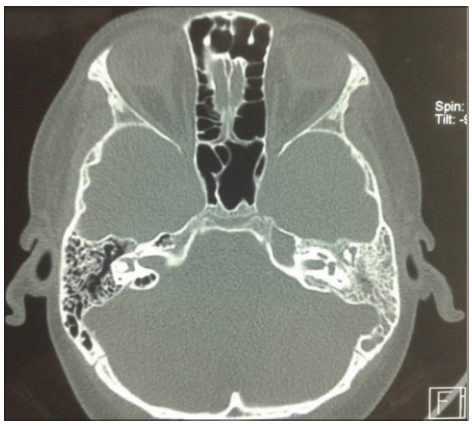

Figure 1. Axial computed tomography scan showed soft tissue opacity of the middle ear, mastoid and petrosal apex on the left side

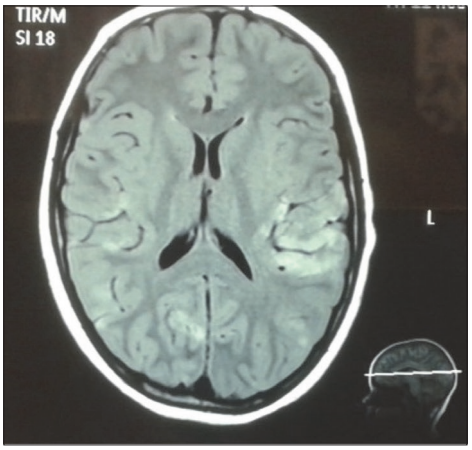

Figure 2. Axial magnetic resonance imaging showed multiple inflammatory and ischemic changes in brain tissue

During hospitalization, the patient received parenteral antibiotic therapy for seven weeks. Because of the long-term antibiotic treatment, toxic hepatitis had developed (AST 620 U/L, ALT 575 U/L). *Mycoplasma pneumoniae* infection, as one of the complications was serologically proven during hospitalization, when azithromycin was included in the treatment. The infection was complicated by hemolytic anemia and the patient received two doses of concentrated red blood cells.

The patient spent 71 days in hospital. He was discharged from the hospital in a good general condition, without the focal motor failure. By applying intensive physical therapy the patient was able to walk independently, sphincter control was normal, he understood orders, but aphasia was present. Due to the inability of oral feeding, the patient was discharged with nasogastric tube that was well tolerated. Finally, the immunological tests performed during hospitalization showed that the patient was immunocompetent.

After he left the hospital, our patient began intensive therapy with a psychologist and a speech therapist. The results were good and this boy has successfully completed

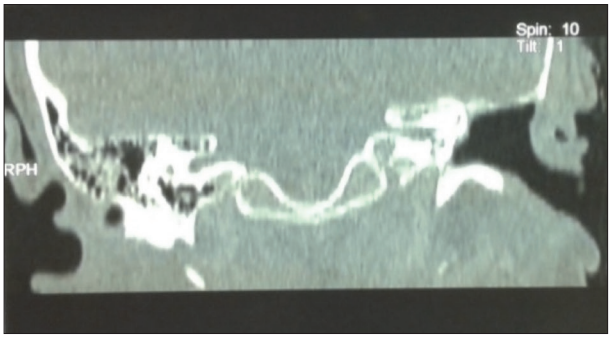

Figure 3. Coronal Computed Tomography scan after radical tympanomastoidectomy showed normal findings

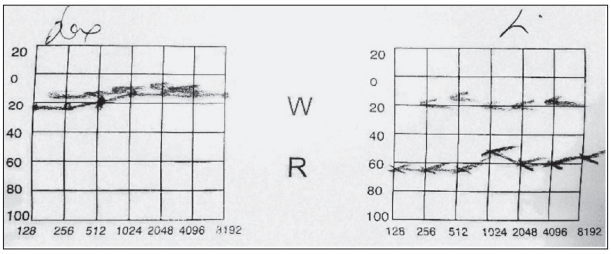

Figure 4. Pure tonal audiogram after treatment showed moderate conductive hearing loss in the left ear

fifth grade. On the last medical checkup that was done a year and a half after hospital treatment: clinical and CT findings (Figure 3) were normal and audiometric finding corresponded to surgery performed (Figure 4).

DISCUSSION

The diagnosis of AOM is not always easy, especially when considering the fact that this disease is most common in the first two years of life, and that clinical picture can be dominated by the respiratory and gastrointestinal tract symptoms. For children over six months with the presence of very prominent symptoms and signs of AOM (intense pain that lasts more than 48 hours and body temperature ≥ 39°C), as well as for children of 6–23 months with bilateral AOM and moderate symptoms and signs of disease, the antibiotic therapy is recommended. In addition, the choice of antibiotics, adequate dose and the length of therapy are very important [1, 2]. Unfortunately, we are still unable to predict which patient will have a poor response or develop severe complications.

Streptococcus pneumoniae is the most common cause of complications of AOM in children and some studies present disturbing data on increasing resistance to antibiotics [4, 8, 9]. Recent studies confirm the hypothesis that serotypes with high invasive potential causes invasive pneumococcal disease in younger patients with less comorbidity [10]. In our case, *Streptococcus pneumoniae* was isolated from the secretions of the left ear, but serotyping had not been done for technical reasons. Clinicians should recommend pneumococcal conjugate vaccine and annual influenza vaccine to all children according to updated schedules [1].

According to literature data, other causes of complications in AOM are *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Haemophilus influenzae,* and *Staphylococcus aureus* [3, 4]. Some studies indicate a possible role of anaerobic bacteria in the occurrence of ICC in pediatric population with acute mastoiditis [8].

The development of otogenic ICC is thought to occur by one of three pathophysiological mechanisms: direct extension of infection through bone weakened by osteomyelitis or cholesteatoma; retrograde spread of infection by thrombophlebitis; or extension of infection along preformed pathways, such as the oval and round windows, or through dehiscence that is the result of congenital malformations. Histological research on temporal bones of the infants who died due to otogenic meningitis, have shown the presence of chronic inflammatory cells in the round window membrane, perilymph, modiolus and cochlear aqueduct, which indicates a possible "silent" route of the infection spread from the middle ear towards the endocranium [11]. Later research on temporal bones indicates the connection between the presence of bacteria in fibrous matrix in the ear with chronic pathologic changes and tympanogenic meningitis in infants. In 82% of the cases, the presence of bacteria was detected in fibrous matrix at different locations in the middle and inner ear, and most often around oval and round window [12]. Chronic inflammatory changes in the middle ear behind the intact eardrum and the absence of otologic symptoms can lead to occurrence of serious complications in infants [11, 12]. In our case, the fulminant course of the disease indicates a possible hematogenic spread of the infection from the middle ear to the endocranium, with the occurrence of a severe form of meningoencephalitis. All data point to an accidental infection in an immunocompetent child.

Chronic otitis media with cholesteatoma is the most common cause of ICC [13, 14]. Đerić et al. [13] recorded 114 cases of otogenic ICC in an extensive retrospective study over the period of 23 years. The most common was meningitis, followed by brain abscess and lateral sinus thrombosis. Half of the patients had two or more complications at the same time, and otogenic abscess were often combined with meningitis. For that reason, the authors emphasize the importance of CT scan in the diagnostics of the ICC, especially in the abscesses of a "silent" clinical course, when the treatment of the active phase of chronic otitis with antibiotics can conceal early symptoms of the occurrence of this complication [15]. Dankuc et al. [16] describe a simultaneous existence of ECC and ICC in an adult patient with the exacerbation of chronic suppurative otitis. The authors described the protective role of the dura mater in the localization of subdural abscess, but also a possibility of further spread of the infection by hematogenic way into the brain tissue with the creation of the encephalitis focus and brain abscess later.

In the era of antibiotics, ICC of AOM is rarely seen. De Oliveira Penido et al. [3] recorded only ten cases of AOM with ICC during the period of 22 years, and observed that the complications generally occur in people younger than 15, as well as in the elderly population. Mattos et al. [4]

recorded 26 cases of ICC in children with AOM during the 15-year period. Interestingly, meningitis was recorded in one case only, while encephalitis was not recorded in any case. Leskinen and Jero [17] in a 10-year retrospective study at pediatric population described extradural abscess with meningitis as the only ICC of AOM. Zernotti et al. [18] describe one case of encephalitis and subdural empyema as a complication of AOM. In contrast, Krivopalov et al. [19] recorded meningoencephalitis as a complication of AOM in 15.4% of adult patients.

During the treatment of our patient, we were faced with several dilemmas. How long does one need to wait for surgical treatment, due to the fact that the patient is comatose? Which surgical method is the right choice in such a case? Zanetti et al. [20] in a study of 45 children with acute mastoiditis discovered ICC in 28.9% of cases. They advised mastoidectomy in the first 48–72 hours, if neurological status allows this. In two cases with severe ICC was performed a surgery of the canal wall down. Other authors also propose extended mastoidectomy in the treatment of meningoencephalitis, which is the result of AOM [19]. In a study published by De Oliveira Penido et al. [3] all patients with AOM and ICC were surgically treated. Neurosurgical treatment was performed in six patients in order to evacuate the cerebral abscess, while four patients were treated with otosurgical procedures (tympanocentesis in three patients and tympanomastoidectomy in one patient). In our case, convulsive seizures and neurological status did not allow the surgery in the first few days, and mastoidectomy with the implantation of ventilation tube did not lead to an improvement of consciousness and general condition of the patient. Consequently, it raises the following question whether it was necessary to perform radical surgery immediately in order to have a more complete removal of the pathological process, considering the cause of infection and inflammation, which is affecting deep retrofacial and infracochlear cell tract together with retrolabyrinthine cells and petrous apex.

During the treatment of our patient, we met a number of complications, such as the inability of oral feeding, inability to control sphincter, confinement to bed, toxic hepatitis, infection by *Mycoplasma pneumoniae*, and hemolytic anemia. Considering all the above, it is not surprising that our patient stayed in the hospital for 71 days, which is significantly higher compared to some data from the literature [3]. Some authors recorded that 29.4% of patients with otogenic ICC has neurological sequelae in the form of abducens nerve palsy, reduction of intellectual capacity, dysmetria, and dysarthria [3]. In our patient neurological sequelae in the form of occasional agitation and aphasia significantly improved by adequate medical teamwork, while unilateral conductive hearing loss is only auditory sequelae.

To conclude, meningoencephalitis is an unusual and rare complication of AOM. Fulminant course of the disease requires urgent diagnostic procedure and multidisciplinary approach to the treatment. Surgical treatment of the ear, which caused the complication, should not be delayed, and the choice of surgical method must be adapted to each patient individually. Hospital treatment of these patients is often prolonged and auditory and neurological sequelae are substantial and require long-term treatment.

Conflict of interest: None declared.

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Менингоенцефалитис као компликација акутног запаљења средњег ува код 11-годишњег детета

Зоран Дудварски[1,2], Ненад Арсовић[1,2], Снежана Јешић[1,2], Владимир Нешић[1,2], Биљана Међо[1,3], Димитрије Николић[1,4]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клинички центар Србије, Клиника за оториноларингологију и максилофацијалну хирургију, Београд, Србија;
[3]Универзитетска дечја болница, Јединица интензивне неге, Београд, Србија;
[4]Универзитетска дечја болница, Одељење неурологије, Београд, Србија

САЖЕТАК

Увод Акутно запаљење средњег ува је веома често обољење у раном дечјем узрасту. Отогене компликације се деле на екстракранијалне и интракранијалне. Увођење антибиотика је значајно смањило учесталост интракранијалних компликација, али оне још увек постоје. Клиничка слика се обично брзо развија уз предоминацију неуролошких симптома.

Приказ болесника Дечак стар 11 година је примљен у терцијерну здравствену установу због повишене телесне температуре, узнемирености, измењеног понашања и поремећаја стања свести. На основу анамнезе, клиничког прегледа, компјутеризоване томографије, магнетне резонанце и лумбалне пункције утврђено је да се ради о менингоенцефалитису као компликацији акутног запаљења средњег ува. Осим интензивне антибиотске и симптоматске терапије, спроведено је и хируршко лечење: најпре мастоидектомија са имплантацијом вентилационе цевчице, а потом радикална тимпаномастоидектомија, јер није дошло до очекиваног побољшања. Лечење је било праћено бројним компликацијама, као што су токсични хепатитис, инфекција са *Mycoplasmom pneumoniae* и хемолитичка анемија. Лечење је трајало 71 дан, а болесник је отпуштен из болнице у добром општем стању, без фокалних моторних испада.

Закључак Менингоенцефалитис је неуобичајена и ретка компликација акутног запаљења средњег ува, која захтева хитну дијагностику и мултидисциплинарни приступ у лечењу. Хируршко лечење ува не треба одлагати, а избор хируршке методе мора бити прилагођен. Болничко лечење је често продужено, а аудиторне и неуролошке секвеле су значајне и захтевају дуготрајан третман.

Кључне речи: акутно запаљење средњег ува; интракранијалне компликације; деца

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Isolated dislocation of the pisiform bone in a 10-year-old boy

Siniša Dučić[1,2], Nikola Bojović[3], Vladimir Radlović[1], Goran Đuričić[1], Bojan Bukva[1]

[1]University Children's Hospital, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Niš Clinical Center, Pediatric Surgery and Orthopedics Clinic, Niš, Serbia

SUMMARY

Introduction Isolated dislocation of the pisiform bone is a very rare condition due to robust ligamentous attachments that stabilize the pisiform to the carpus. This type of injury is usually a result of direct trauma to the ulnar and volar aspect of the wrist.

Case outline We present an isolated dislocation of the pisiform, with no other carpal bone injuries, treated successfully with closed reduction. Diagnosis was based on clinical findings, plain radiographs, and computer tomography examination of the wrist. Elongation and partial rupture of the pisometacarpal ligament was found on magnetic resonance imaging.

Conclusion Fracture and dislocation of the pisiform is an extremely rare injury in children, which could be easily neglected or misdiagnosed. Closed reduction with plaster cast immobilization should always be considered as the first method of treatment in the pediatric population, since the conservative approach provides excellent results.

Keywords: dislocation; pisiform; children

INTRODUCTION

Pisiform bone dislocation is a rare injury reported mostly in young male adults and literature is void of reports on this type of injury in children [1]. Isolated dislocation of carpal bones is rare, except for the lunate and the perilunate bone. Dislocation of the pisiform bone is particularly rare because of the sturdiness of the ligamentous complex which stabilizes the pisiform to the carpus [2, 3, 4]. In this paper, we present a case of isolated pisiform dislocation in a young boy, successfully treated by closed reduction.

CASE REPORT

A 10-year-old boy injured his left wrist in a fall and was admitted to hospital due to a suspected fracture of the pisiform bone. Clinical examination revealed swelling around the ulnar aspect of the left wrist joint, with local tenderness and painful restriction of all wrist movements. The neurovascular examination of ulnar artery and nerve was normal. The radiographs (anteroposterior and lateral view) of the left wrist showed an isolated dislocation of the pisiform bone (Figure 1) on the lateral radiographs. Further diagnostic tests followed. Computed tomography showed isolated anteroradial displacement of the pisiform of 7 mm. There were no other injuries of bones, soft tissues, or blood vessels (Figure 2). Additionally, a magnetic resonance imaging scan confirmed the 7 mm anteroradial dislocation of the pisiform bone but also revealed an elongation and partial rupture of the pisometacarpal ligament (Figure 3). Closed reduction of the pisiform was performed under an X-ray image intensifier, direct pressure was applied to relocate the bone with a slightly dorsiflexed position and a stable reduction was achieved. The wrist was immobilized with a long arm plaster cast in dorsiflexion for four weeks. Four weeks after the procedure, the cast was removed and radiographs revealed correct position of the pisiform bone. At the 12-month follow-up, the patient was clinically well, without any pain or limitation of motion, and X-ray imaging showed normal results (Figure 4).

DISCUSSION

We searched the literature in English on PubMed for terms 'pisiform,' 'fracture,' 'dislocation,' and 'children,' and, to the best of our knowledge, three pisiform dislocations associated with type I and II Salter–Harris fracture of the distal radius fracture in children have been reported [1, 5, 6]. As of yet, no isolated fracture and dislocation of the pisiform bone in children has been reported.

The pisiform bone lies in the proximal row of the carpal bones and forms a synovial joint by articulating with the triquetrum. Its stability is ensured by a complex structure composed of 10 soft tissue attachments [7]. This may be the reason why injuries of the pisiform are generally rare. When pisiform dislocations occur, it is usually due to direct trauma to the ulnar and

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Correspondence to:
Siniša DUČIĆ
University Children's Hospital
Tiršova 10
11000 Belgrade, Serbia
sinisaducic@gmail.com

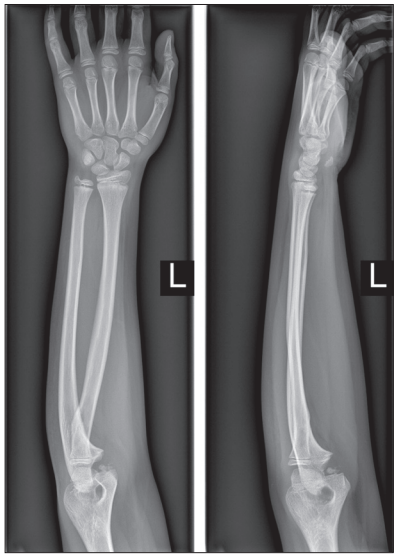

Figure 1. Initial radiographic presentation: X-ray clearly shows the pisiform bone dislocation

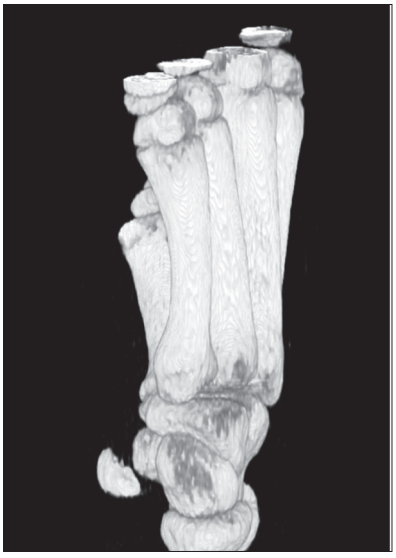

Figure 2. Three-dimensional volume rendering of spiral computed tomography scan shows dislocation of the pisiform bone

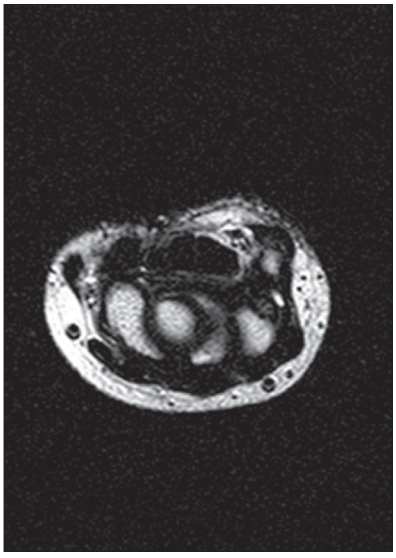

Figure 3. Transversal plane T2-weighted magnetic resonance imaging; the pisometacarpal ligament is elongated and heterointense, with partial interstitial rupture

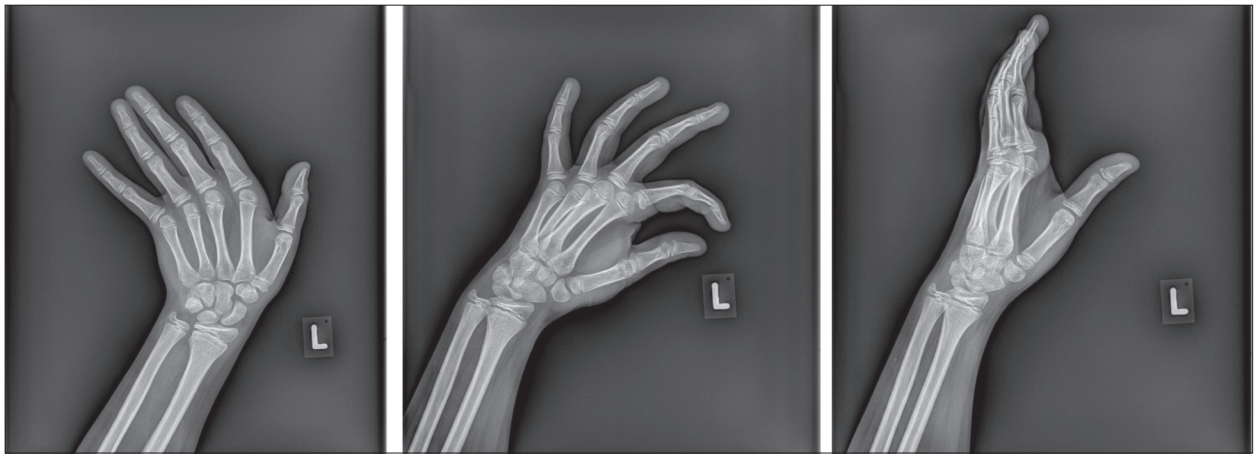

Figure 4. X-ray at the one-year follow-up: correct position of the pisiform bone

volar aspect of the wrist or as a consequence of an indirect force such as a forceful muscular contraction in a minority of cases [4]. As the center of ossification of the pisiform bone appears between 7.5 and 10 years of age and the pisiform is not always clearly visualized, diagnosing pisiform fracture and dislocation in children could be very challenging [6].

Different modalities of treatment in adults have been reported in literature, such as closed reduction and immobilization, open reduction with internal fixation and excision of the pisiform [5, 6, 8]. In regard to pediatric population, all reported pisiform dislocations have been managed conservatively. Mancini et al. [5] performed closed reduction of the pisiform in both of their cases. Hurni et al. [1] and Ashkan et al. [5] also reported a closed reduction with immobilization as the method of choice in a pediatric patient. They suggest that this type of injury in children should be primarily treated with closed reduction and immobilization, and a more aggressive approach, such as pisiform bone resection, should be used in case the conservative treatment fails [1]. Furthermore, Sharma and Massraf [4] and Kwon et al. [8] also support conservative treatment unless recurrent dislocations occur or the disability remains after conservative treatment, in which case resection of the pisiform is recommended. Sharma and Massraf [4] reported an ulnar nerve compression as a consequence of isolated pisiform dislocation in an adult male. No ulnar injuries have been reported in children with pisiform dislocations. In such a case, emergency reduction of the pisiform is required.

Taking everything into consideration, fracture and dislocation of the pisiform is an extremely rare injury in children, which could be easily neglected or misdiagnosed, firstly because physicians usually do not consider this condition, and secondly due to unspecific clinical signs and challenging interpretation of radiographs. Closed reduction with plaster cast immobilization should always be considered as the first method of treatment, as it is a conservative approach that provides excellent result in the pediatric population.

Conflict of interest: None declared.

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Изолована дислокација писиформне кости код дечака узраста 10 година

Синиша Дучић[1,2], Никола Бојовић[3], Владимир Радловић[1], Горан Ђуричић[1], Бојан Буква[1]

[1]Универзитетска дечја клиника, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Клинички центар Ниш, Клиника за дечју хирургију и ортопедију, Ниш, Србија

САЖЕТАК

Увод Изолована дислокација писиформне кости је изузетно ретка имајући у виду робусност лигаментарног апарата који је стабилизује у ручју. Обично је овај тип повреде резултат директне трауме на улнарну и воларну страну ручја.

Приказ болесника Представљамо изоловану дислокацију писиформне кости, без повреда осталих костију ручја, која је успешно лечена затвореном репозицијом. Дијагноза је потврђена клиничким прегледом, радиографијом и налазом компјутеризоване томографије ручја. Елонгација и парцијална руптура писометакарпалног лигамента су утврђене помоћу магнетне резонанце.

Закључак Прелом и дислокација писиформне кости је изузетно ретка повреда код деце, која се лако може превидети или дијагностички лоше протумачити. Затворену репозицију са гипсаном имобилизацијом треба увек сматрати методом избора у лечењу овог типа повреда код деце, имајући у виду да конзервативни третман даје одличне резултате.

Кључне речи: дислокација; писиформна кост; деца

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The treatment of hemangioma of the larynx in children is still a dilemma

Anđelka Stojković[1,2], Dragan Milovanović[1,3], Stevan Stojanović[1,4], Katerina Dajić[1], Zlatan Elek[5], Maja Vulović[6], Aleksandra Simović[1,2]

[1]University of Kragujevac, Faculty of Medicine, Department of Pediatrics, Kragujevac, Serbia;
[2]Clinical Centre of Kragujevac, Clinic of Pediatrics, Kragujevac, Serbia;
[3]Clinical Centre of Kragujevac, Department of Clinical Pharmacology, Kragujevac, Serbia;
[4]Clinical Centre of Kragujevac, Clinic for Otorhinolaryngology, Kragujevac, Serbia;
[5]Clinical Hospital Center, Department of Child Surgery, Kosovska Mitrovica, Serbia;
[6]University of Kragujevac, Faculty of Medicine, Department of Anatomy, Kragujevac, Serbia

SUMMARY
Introduction The laryngeal hemangioma in children is a benign vascular neoplasm but it could become malignant after localization.
Case outline After two weeks of corticosteroid treatment in a 15-month-old boy, there were no desired results. This case report is a small contribution to the research of targeted Propranolol treatment in infantile laryngeal hemangioma and the role of Epinephrine in the initial treatment in life-threatening conditions.
Conclusion When laryngeal hemangioma has "bad" localization and any surgical treatment is denied in spite of the vital risk, the choices of treatment are epinephrine (as the first choice) and propranolol.
Keywords: laryngeal disease; neoplasm; vascular tissue; child

INTRODUCTION

The hemangioma of the larynx in children is rare benign vascular neoplasm, which by its localization may have malign clinical course. Last year the American Academy of Pediatrics (AAP) made recommendations for the treatment of infantile hemangioma while calling for additional research of the treatment of hemangioma in the airways of young children [1].

CASE REPORT

We rarely encounter a larynx hemangioma, especially if there is no accompanying hemangioma of the skin [2]. However, we report a case of a male child aged 15 months with the diagnosis of larynx hemangioma. We were even more confused by the normal findings of fiber-laryngoscopy. However, the pediatricians had to treat the child until fiber-bronchoscopy was performed. The question is which drug to use? Which drug may contribute to a successful differential diagnosis of the mentioned condition in a primary health care, before fiber-bronchoscopy is done? Are the AAP recommendations absolutely relevant [1]?

A brief description of the clinical course of hemangioma of the larynx in a boy will be the basis for monitoring the treatment course and making conclusions. Before admission to the Pediatric Clinic, the 15-month-old boy had a cough, breathing difficulty and a fever of 38.6°C, which was treated by nebulized bronchodilator with fenoterol and ipratropium Bromide (FIB) and a steroid therapy (Table 1). On admission, the boy had signs of respiratory insufficiency. The majority of biochemical, hematological and microbiological analyses (Table 2) were within border references for his age [3]. At back-front chest X-ray in the projection of the larynx a hyperdense zone could be seen (Figure 1), asymmetrical, with successive extensions first to the left, then to the right, followed with air bronchogram and the strip-blotchy shadows in the lung parenchyma on both sides. The X-ray of the trachea in two directions and a contrast X-ray of the esophagus did not present any abnormal findings.

After three days of therapy (Table 1), a pediatrician considered that the child's condition was improving and did not need further epinephrine inhalation. However, about eight hours after epinephrine was excluded, his condition deteriorated. Since the finding of fiberoptic laryngoscopy to the borders of the larynx were a normal, fiberoptic bronchoscopy was performed (Table 1) as multidetector computed tomography (MDCT) (Figure 2). MDCT at the level of cervical vertebral body 2–3, on the left airway wall, discovered a thickening and hypodense, polypoid change, which asymmetrically narrowed the lumen of the border between the larynx and the trachea to a minimum diameter of under 2 mm. After that, Propranolol was introduced to the therapy, and after four days, oxygen therapy was no longer needed. After ten days of propranolol treatment, fiberoptic bronchoscopy was

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Correspondence to:
Anđelka STOJKOVIĆ
University of Kragujevac
Faculty of Medicine
Svetozara Markovića 69
34000 Kragujevac, Serbia
andja410@mts.rs

Table 1. The clinical course and treatment of hemangioma of the larynx in a boy with body weight of 9.5 kg

Level of health care	Primary care				Pediatric Clinic							Institute for Mother and Child Healthcare					
Day of treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 con
Some clinical features and additional diagnostic findings per days	Day 1: cough, breathing difficulty, fever 38.6°C Day 2–3: cough, breathing difficulty Day 4: more powerful cough, hoarse, fever 38.8°C				Day 5: cough, dyspnoea, inspiratory stridor, pallor of skin and visible mucous membranes, fluttering nostrils, SaO_2 89–96% (according to the phase of the respiratory cycle and waking/sleeping child), RR 36/min, and HR 150/min. Apart from hyperglycemia (8.1 mmol/l), other biochemical, hematological and microbiological analyses were within border references for the child's age [3]. Back–front chest X-ray: In the projection of the larynx, a hyperdense zone could be seen, asymmetrical, with successive extensions first to the left then to the right, followed with air bronchogram and the strip-blotchy shadows in the lung parenchyma on both sides. Day 8: Improvement, then 8h after epinephrine was excluded there was deterioration: hard wheezing, alertness of the child, RR 56/min, SaO2 < 91% (irrespective of the phase of the respiratory cycle). Day 9: biphasic stridor, SaO_2< 89%, RR 28/min, HR 90/min. X-ray of the trachea in two directions and contrast x-ray of the esophagus did not present abnormal findings.							Day 12: Respiratory failure and inspiratory stridor continued to worsen; Fiberoptic bronchoscopy revealed a cystic tumor covered with normal mucous membrane color, capillary with a strong drawing, located under false vocal cords on both sides predominantly to the right, where it occupied the entire space between the anterior and posterior commissure, and left behind the last commissure with a tumor on the right almost completely obstructing aditus of larynx, leaving a breathing crack in the back commissure, which corresponds to the findings of hemangioma of the larynx. MDCT scanners neck and chest(native and with i.v. application of contrast medium): precisely determined the level of localization of lesions in C2–3 vertebral body, on the left wall, in the form of thickening and polypoid hypodense change which narrowed asymmetrically the lumen of the larynx to the smallest diameter of about 2 mm. Day 17: discharged home					
Drugs:																	
Oxygen					continuously												
FIB, sol. (ml), nebulized	0.2/12h							0.2/6h	0.2/6h	0.2/6h							
Salbutamol, sir.(ml), p.o	2.5/8h		2.5/8h	2.5/8h													
Epinephrine 1:10000 (+ panthenol + saline) (mg/kg/dosis) nebulized					0.1/4h	0.1/4h	0.1/4h										
Aminophylline, i.v. (mg/kg/8h)									3								
Salbutamol, sol. (mg) nebulized											0.2/4h						
Ipratropium bromide, sol. for inhalation (µ/kg)											5/4h						
Magnesium sulfate, i.v. (mg/kg)											50/6h						
Budesonide (µ/12h), nebulized	250		250	250	500	500	250	500	500	500	500	500	500	500	500	500	
Dexamethasone i.v. (mg/dosis/d divided in two doses)					8	8											
Methylprednisolone i.v. (mg/kg/d divided in three doses)								3	3	3	3	3	3	3	3	3	
Antibiotics			Azithromycin, p.o														
												Ceftriaxone, i.v.					
							Clarithromycin, p.o										
Propranolol (mg/kg/d) divided in 2 doses, p.o.													2	2	2	2	2 con

FIB – fenoterol and ipratropium bromide; p.o. – orally; SaO_2 – percutaneous oxygen saturation; RR – respiratory rate; HR – heart rate; MDCT – multiple detector computed tomography; C – cervical; i.v. – intravenous; con – continued; – interrupted

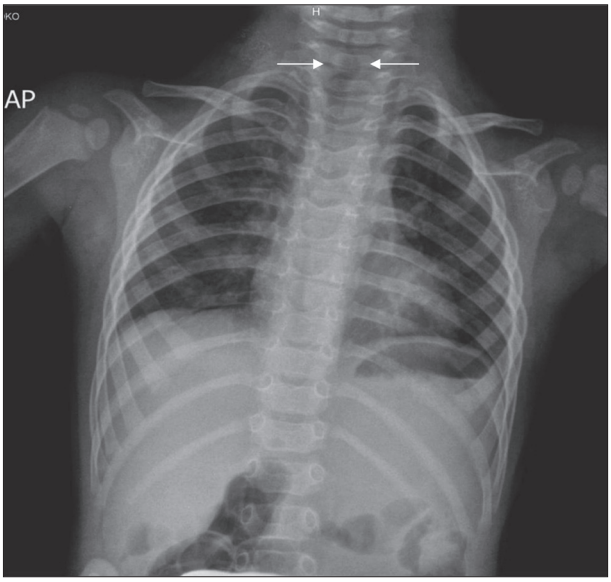

Figure 1. The chest X ray in the posterior anterior position of the 15-month-old boy (on admission)

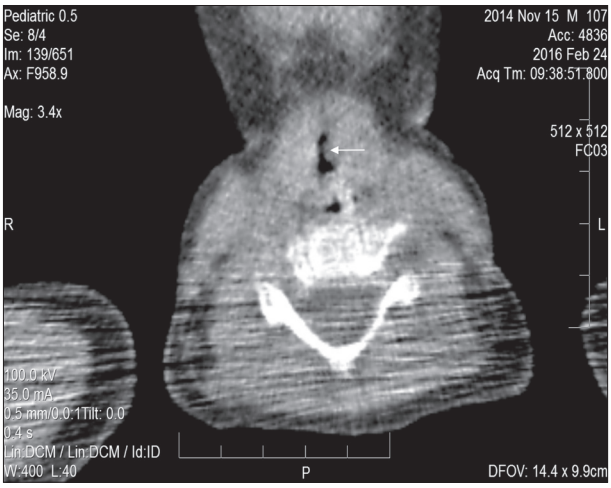

Figure 2. The multidetector computed tomography at the level of C2–3 vertebral body of the 15-month-old boy (4th hospitalization day) – on the left airway wall (arrow) discovered thickening/hypodense/polypoid change which narrowed asymmetrically the lumen of the border larynx/trachea to the smallest diameter of 2 mm

repeated revealing a significant reduction in tumor tissue and the reappearance of sufficient breathing space (Table 1). The child was discharged home with the same dose of Propranolol (for the total of six weeks), which resulted in recovery.

DISCUSSION

In a 15-month-old boy with hemangioma of the larynx, there was a good therapeutic response after administration of epinephrine and propranolol. There was no improvement of respiratory failure after the administration of corticosteroids (systemic not inhaled), which is recommended in many textbooks of pediatrics and is placed as the first therapeutic option for laryngeal hemangioma [2]. There was no desired therapeutic response after the administration of a bronchodilator (beta-2-agonists, theophylline), or a broad-spectrum antibiotics (Cephalosporins 3rd generation, Macrolides). Epinephrine treatment in inhalation for three days resulted in clinical improvement. Epinephrine therapy was discontinued because no therapeutic protocol in pediatrics recommends the use of a multi-day inhalation of this drug [2].

Table 2. The 15-month-old boy's laboratory findings on admission to the Pediatric Clinic [2]

Gas analysis by Astrup from venous blood: pH 7.34, pO_2 5.7 kPa, pCO_2 5.9 kPa, sodium ionized 138 mmol/l, potassium ionized 4.3 mmol/l, calcium ionized 1.14 mmol/l, bicarbonate 24 mmol/l, base excess -2 mmol/l
Sedimentation rate 10, C-reactive protein 9.9 mg/l Complete blood count: WBC 5.1x10/$^{-9}$l, neutrophils 0.53, lymphocyte 0.43, monocytes 0.05, PLT 267x10/$^{-9}$l, RBC 4.64x10/$^{-12}$l, Hb 117 g/l, Hct 36%
Urinalysis – normal
Glycemia 8.1 mmol/l, magnesium 1 mmol/l, aspartate aminotransferase 42 U/l, alanine aminotransferase 17 U/l, urea nitrogen 4.6 mmol/l, creatinine enzymatic 46 µmol/l
Immunoglobulin (Ig) E 5.2 kIU/l, Vitamin D 25 ng/ml
Smear pharynx and nose, and aspirate – normal flora; IgM-mycoplasma pneumoniae – negative titer

WBC – white blood cells; RBC – red blood cells; PLT – tromboytes

Epinephrine causes vasoconstriction of arterioles and the dilatation of airway smooth muscle that in a short period of a few hours can impose beneficial effects on blood vessels in the hemangioma, and the dilatation of the larynx. However, systemic and daily use of epinephrine for seven days causes ischemic effect on the soft tissues, which is a powerful stimulus for neovascularization [4, 5]. This effect is not desirable in the treatment of hemangioma of the larynx, which leads us to think that epinephrine should be administered for a very short period, i.e. until the clinical improvement of respiratory insufficiency becomes definite. At the same time, the speed of therapeutic response to epinephrine helped us in the differential diagnosis of inspiratory stridor and a hoarse cough. The duration of epinephrine administration is not defined in the recommendations of the AAP, so future research is needed [1].

The peripheral effects of propranolol are used to "shrink" a hemangioma and to prevent the differentiation of infantile hemangioma stem cells to endothelial cells and pericytes [1, 6]. The recommendation is that the initial dose of propranolol *per os* for the larynx hemangioma would be the same like for skin hemangioma: 1–3.4 mg/kg/d with a gradual reduction in dose during 3–12 months, until the child reaches the age (8–12 months of age) when a spontaneous resolution of infantile hemangioma occurs [1, 2]. However, we have applied a dose of propranolol 2 mg/kg/d, continuously to the patient for six weeks only and achieved a complete resolution of hemangioma of the larynx without any side effects like drowsiness or hypoglycemia.

Despite the official recommendations concerning the effective application of steroids in the treatment of infantile hemangioma of the larynx, our experience was not positive [1, 2] (Table 1). Only after adding propranolol for four days, the need for oxygen was eliminated and the child

clinically recovered. During the six weeks of treatment, systemic steroid was not administered simultaneously with Propranolol, which is contrary to the recommendations, but it turned out to be the right and successful therapeutic approach [1, 2]. In life-threatening situations, with progressive deterioration of respiratory insufficiency of the child, parents and pediatricians do not have the patience to wait for prolonged effect of corticosteroids, which is achieved in the course of 4–12 weeks, but insist on a swift and targeted therapy of laryngeal hemangioma that is achieved by propranolol [1, 2]. Bearing in mind the so-called "bad" localization of hemangioma in the larynx, the classic surgical removal of hemangioma and/or the epinephrine application locally were not possible in this infant.

We wish to note outlooks of other pediatric institutions. The recommendation of one colleague from the Children's Hospital of Philadelphia does not include epinephrine, but has based his opinion exclusively on the effects of propranolol, corticosteroids (Intralesional), microdebrider excision, laser, and surgical therapy, all of which implies certain risks of such therapy [7]. American authors published a recommendation related to the therapeutic options for infantile hemangioma, with the exception of the above noted, and the Interferon alfa-2band, a biologic immune response modifier, but not epinephrine [8]. French authors put propranolol as the first choice in the treatment of infantile laryngotracheal hemangioma, still suspecting in conclusion, about the unsuccessful treatment of this type of hemangioma with propranolol [9].

After two years of treatment of hemangioma of the larynx, a boy, now four years old, does not exhibit a stridor, but only wheezing as part of the clinical picture of asthma in a child under the age of five years. We shall continue to follow this child.

To conclude, we suggest epinephrine as the first choice in the therapy course for hemangioma of the larynx in children. The current pediatric recommendations suggest that the larynx hemangioma treatment of choice is propranolol, as this therapy lasts much shorter. Epinephrine and propranolol may be the treatment of choice when the surgical treatment is not indicated because of the life-threatening localization of hemangioma.

Conflict of interest: None declared.

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Лечење хемангиома ларингса код деце је још увек дилема

Анђелка Стојковић[1,2], Драган Миловановић[1,3], Стеван Стојановић[1,4], Катерина Дајић[1], Златан Елек[5], Маја Вуловић[6], Александра Симовић[1,2]

[1]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за педијатрију, Крагујевац, Србија;
[2]Клинички центар Крагујевац, Клиника за педијатрију, Крагујевац, Србија;
[3]Клинички центар Крагујевац, Служба за клиничку фармакологију, Крагујевац, Србија;
[4]Клинички центар Крагујевац, Клиника за оториноларингологију, Крагујевац, Србија;
[5]Здравствени центар, Одељење дечје хирургије, Косовска Митровица, Србија;
[6]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за анатомију, Крагујевац, Србија

САЖЕТАК

Увод Хемангиом ларингса код деце је бенигна васкуларна неоплазма, али по локализацији може постати малигна.

Приказ болесника У току две недеље кортикостероидне терапије није било жељеног ефекта код дечака старог 15 месеци. Овај приказ болесника је мали допринос истраживању о хемангиому код деце и циљаној терапији пропранололом. Поред овога, расветлили смо улогу епинефрина у иницијалној терапији хемангиома ларингса код животно угрожене деце.

Закључак Када хемангиом има „лошу" локализацију и није индиковано хируршко лечење упркос виталном ризику, терапија избора су епинефрин (први избор) и пропранолол.

Кључне речи: обољење гркљана; неоплазма; васкуларно ткиво; дете

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CASE REPORT / ПРИКАЗ СЛУЧАЈА

Fatal consequences caused by prolonged chloroform inhalation in a child

Miroslav Milić[1,2], Aleksandra Antović[1,2], Milena Trandafilović[2,3], Miodrag Zdravković[1,2]

[1]University of Niš, Faculty of Medicine, Department of Forensic Medicine, Niš, Serbia;
[2]University of Niš, Faculty of Medicine, Niš, Serbia;
[3]University of Niš, Faculty of Medicine, Institute of Anatomy, Niš, Serbia

SUMMARY

Introduction Chloroform intoxication as a result of inhalation is usually associated with occupational exposure. Fatal cases of accidental and intentional chloroform poisoning are extremely rare.
The aim of this work was to report a case with fatal consequences caused by prolonged chloroform inhalation in a child.

Case outline We report a case of a three-month-old child found dead by its mother in their home. Investigation provided the data about two refrigerators in the house, which were not entirely functional, and were filled with a refrigerant based on chloroform, and about a recent house spraying with a pesticide also based on chloroform. Forensic autopsy was performed the following day. Autopsy established the existence of malnutrition, dehydration, brain and lungs edema, the presence of very scarce contents in the digestive tract, and the enlargement of the abdominal lymph nodes. The initial stage of liver degeneration was noted on histopathological examination. Chemical-toxicological analysis of organ tissue samples (brain, lungs, spleen, liver with gall bladder, kidney and bladder, stomach, small and large intestine) performed using the techniques of headspace gas chromatography with mass detector, confirmed chloroform poisoning.

Conclusion The emaciation underlying the dysfunction of organ systems provided a grim frame for a child to succumb to chloroform toxicity. The proper use and maintenance of domestic appliances, and careful application of chemical agents indoors is an imperative, especially in the vicinity of children. Low levels of chloroform inhaled from the room air may have fatal consequences in a susceptible individual.
Keywords: chloroform; intoxication; toxicology; autopsy; forensic pathology

INTRODUCTION

Chloroform (trichloromethane – $CHCl_3$) is a colorless, volatile liquid, whose potent anesthetic properties were recognized early after its synthesis during the 1830s [1]. However, soon after the first described applications of chloroform as an anesthetic during surgical procedures in clinical context, its acute toxicity was observed, and chloroform was determined to be the cause of death in a number of physically fit patients [2]. In spite of the fatal complications, chloroform continued to be used as a potent anesthetic agent over the next 50 years. Only in 1912, the Committee on Anesthesia of the American Medical Association proclaimed that the use of chloroform as the anesthetic for major surgery was no longer justifiable [3]. The use of chloroform as an anesthetic is abandoned because exposing the organism to high concentrations may cause hypotension and fatal cardiac arrhythmias [4, 5]. Fatal cardiac arrhythmias may be also induced by inhalation abuse of toxic substances such as chloroform. From the 1960s, deaths caused by inhalation of toxic substances have been termed "sudden sniffing death" [6, 7].

Nowadays, chloroform has a wide application in industry, and is a subject to strict regulations as a hazardous substance. The main use of chloroform is the production of fluorocarbons used in the synthesis of tetrafluoroethylene and polytetrafluoroethylene, as a refrigerant and propellant. It is also used as an organic solvent in industry and in analytical laboratories, as an ingredient of pharmaceuticals, drugs, cosmetics, grain fumigants, dyes, and pesticides [4]. Before 1989 and the Montreal Protocol on Substances that Deplete the Ozone Layer, chloroform was also a popular refrigerant [8].

Acute chloroform poisoning, resulting in respiratory and central nervous system depression, has been described in accidental, suicidal, and homicidal cases [9, 10, 11]. Intentional fatal chloroform intoxications usually concern self-poisoning acts, while homicides by chloroform are very rare. Accidental poisoning more frequently occurs in the setting of occupational exposure, but may also be encountered in a domestic environment [11, 12]. Chronic inhalation of chloroform leads to liver damage, and causes central nervous system depression as well [3, 8].

The aim of this paper was to present a case of a child death by accidental prolonged chloroform poisoning at home, under unusual circumstances.

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Correspondence to:
Miroslav MILIĆ
Institute of Forensic Medicine
81 Dr Zorana Đinđića Blvd.
Niš 18000, Serbia
pantelija76@gmail.com

CASE REPORT

Circumstances of chronic exposure to chloroform inhalation

In the early morning, mother found her three-month-old child dead. She called the police, and a forensic autopsy was ordered. During the investigation, data about underprivileged, multi-member family (four adult persons and six children) who lived in a house with two rooms was obtained. There were two refrigerators in the house, which were not entirely functional, and were filled with a refrigerant based on chloroform. A short period before the relevant event, the house was sprayed with a disinsection agent, a pesticide also based on chloroform. This information was obtained from investigative authorities but the name of the compound used on that occasion was not specified. The child was found on the mattress on the floor, where he slept, in the room with the refrigerators. The event took place in the winter, and because of the poorly ventilated rooms in this period, chloroform poisoning of the infant was suspected.

Autopsy findings

The autopsy was performed on the following day. The three-month-old male child was malnourished, with signs of dehydration. The weight of the body was 3 kg, and the length was 49 cm, which, according to the table of development of infants, corresponds to the age of about a month. The cadaver had reduced muscle and bone mass, with almost complete absence of subcutaneous adipose tissue (Figures 1 and 2). On the skin of the lower part of the back, decubitus wounds were noted. No signs of injury were found on the body of the child. The examination revealed signs of brain and lungs edemas. Inside the digestive tract, only slight amounts of content were found. Abdominal lymph nodes were enlarged. The examination of the bones revealed no fractures or any other remarkable changes. In addition to pulmonary edema, the histopathological analysis demonstrated the hydropic liver degeneration. Cytoplasmic vacuolation, and swelling of the hepatocytes, with a mild architectural disarrangement of the plates, was observed in the liver tissue (Figure 3). The rest of the morphological findings were unremarkable and classified as normal.

Chemical-toxicological analysis of internal organ samples (brain, lungs, spleen, liver with gall bladder, kidney and bladder, stomach, small and large intestine) showed the presence of chloroform. We performed chemical-toxicological analysis using the techniques head space gas chromatography with flame ionization detection (HS-GC/FID) and head space gas chromatography mass spectrometry (HS-GC/MS).

The following chemicals were used in the process: chloroform and isopropanol, GC purity (J. T. Baker, Mallincrodt, Netherlands).

The basic standard chloroform solution was prepared at a concentration of 1 mg/mL in methanol. A series of dilutions for calibration curve, in the range of 1–50 mg/L, was prepared out of the basic solution. Isopropanol was used as the internal standard at a concentration of 0.5 mg/mL in water. The identification was done by comparing mass sample spectra with mass spectra databases Willy 7 and Pfleger Maurer Weber, and the quantification was done by the internal standard method.

Conditions for gas chromatographic determination were as follows:

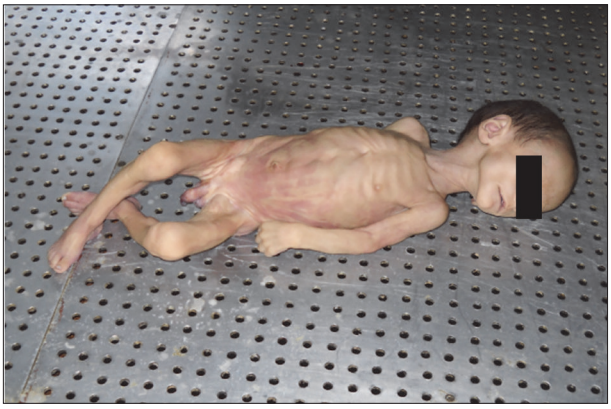

Figure 1. The deceased child aged three months with a reduced mass of bones and muscles and almost complete absence of subcutaneous adipose tissue – external findings

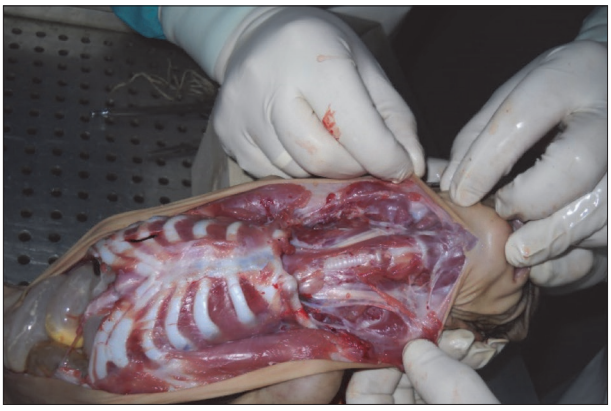

Figure 2. Reduced mass of bones and muscles and almost complete absence of subcutaneous adipose tissue – internal findings in the deceased child

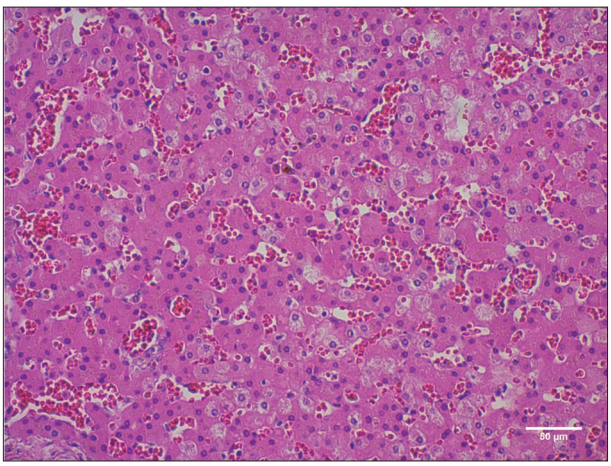

Figure 3. Cytoplasmic vacuolation and swelling of the hepatocytes (H&E, ×20)

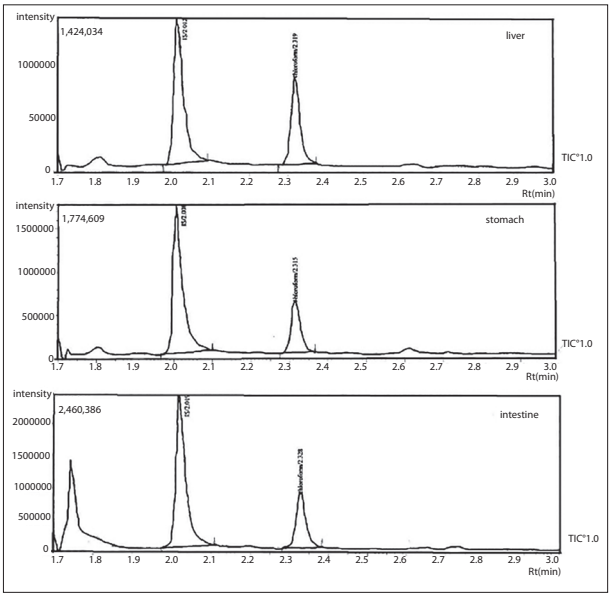

Figure 4. Chromatogram of chloroform concentration detected in the liver with gall bladder, stomach, small and large intestine

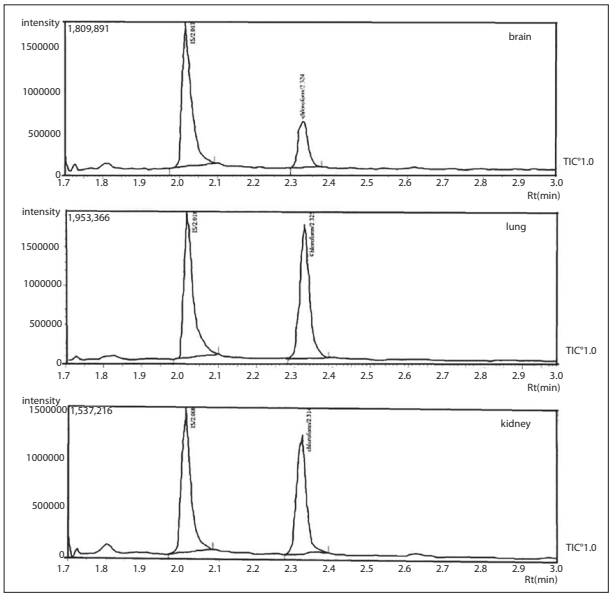

Figure 5. Chromatogram of chloroform concentration detected in the brain, lungs, and kidney and bladder

HS-GC/FID, Shimadzu QP 2010, Ultra, Autosampler AOC -5000: GC column: InterCap 624 (30 m × 0.53 mm i.d., film thickness 3 μm). The temperature program starts at 40°C, and lasts 1 minute; the temperature is then raised to 120°C, at a rate of 50°C/minute; injector 250°C, split ratio 20; detector FID 260°C; carrier gas He, 30 mL/minute flow, hydrogen, 40 mL/minute flow, air 400 mL/minute flow.

HS-GC/MS, Shimadzu QP 2010, Ultra, Auto sampler AOC-5000: GC column: DB-5 ms (30 m × 0.25 mm i.d., film thickness 0.25 μm), isocratic at 40°C for 3 minutes, at a flow rate of 0.55 mL/minute; injector 200°C, split ratio 30; ion source 200°C; interface 200°C; scan range m/z 28–100, scan rate 0.5 scans/second; incubation temperature 55°C; incubation time 900 seconds; syringe temperature 90°C; agitator speed 300 rpm; fill speed 500 μL/s; injection speed 500 μL/s; pre-inject delay 500 ms; post-inject delay 500 ms; flush time 10 seconds; GC runtime 180 seconds.

Chloroform concentrations detected in organ samples were the following: in the liver with gall bladder 17.35 mg/kg (Figure 4), in the stomach 10.29 mg/kg (Figure 4), in the small and large intestine 10.58 mg/kg (Figure 4), in the brain 27.64 mg/kg (Figure 5), in the lungs 27.64 mg/kg (Figure 5), and in the kidney and bladder 25 mg/kg (Figure 5). The results of this analysis led to the conclusion that chloroform poisoning was the cause of death.

DISCUSSION

In the case of acute chloroform poisoning, sings as edematous swelling of the lips, focal mummifications of the facial skin and the chloroform-soaked soft covering of the airways could be very useful in determination of the cause of death [12]. In chronic poisoning, there are no previous nor indicative signs.

In case of exposure to poison in the gaseous state, blood levels already peak within a few minutes after exposure because of the extensive capillary surface area of the lungs. Because of their lipid solubility, volatiles, including chloroform, quickly cross lipid membranes and distribute to well-perfused organs such as the brain, liver, heart, and kidneys. This condition is retained if sudden death occurs, but if exposure is prolonged, toxic substance will slowly also accumulate in poorly perfused parts, such as muscles and fat tissue [13].

In fatal chloroform poisoning cases, its concentration ranges were 10–48 μg/ml in the blood, 50.4–156 μg/g in the brain, 16–27 μg/g in the kidney, 6–86.2 μg/g in the liver, and 0–60 μg/ml in urine [14]. In the case reported herein, only the concentration of chloroform in the brain (27.64 mg/kg) was below the fatal level.

Non-fatal chronic inhalation of chloroform is usually associated with features of hepatic damage that develop 2–5 days after exposure [15, 16, 17]. These pathological changes are similar to those noted in cases of the prolonged anesthesia. Signs of hepatic injury have been reported after occupational industrial exposure, up to workplace air chloroform concentrations of 205 ppm (1,005 mg/m^3) [18]. Pathologic changes that may be observed in the liver tissue probably reflect the major role of hepatocytes and cytochrome P-450 enzymes in chloroform metabolism. Depending on the concentration and the quantity of oxygen, chloroform can be metabolized in the body by oxidative or reductive processes. The oxidative metabolism of chloroform, which is more commonly encountered, creates phosgene by CYP2E1 (high affinity – low capacity enzyme), while the reductive metabolism produces a dichloromethyl free radical. Both metabolic products of chloroform are highly cytotoxic and, due to their liposolubility, they rapidly penetrate into cells causing necrosis primarily of liver and kidney cells and tissue [5, 19, 20, 21]. *A priori*, it might be expected that the oxidative pathway of chloroform metabolism would predominate *in vivo*, because tissues of healthy individuals are oxygenated. Moreover, the toxic

effect of chloroform includes manifestations as ventricular fibrillation, respiratory paralysis, and even multi-organ failure caused by chloroform-induced systemic inflammatory response syndrome [11, 22].

Fat liver degeneration that begins on the periphery and progresses to the center of the lobe, infiltration of lymphocytic lymphocytes and plasmocytes, and compression of the liver sinus with initially expressed fibrosis represent the basic microscopic characteristics of liver changes in malnutrition [23]. In the present case, unlike the foregoing, as a result of prolonged chloroform intoxication, the microscopic examination showed the hydropic liver degeneration with a mild architectural disarrangement of the plates. This suggests that liver changes were more likely to be caused by prolonged chloroform poisoning (Figure 3).

The circumstances recorded at the scene of death suggest that the deceased infant might have been constantly exposed to chloroform inhalation in its home. The age of the infant, the cold in the winter months when death occurred, chloroform concentrations in tissue samples, and the findings of skin decubitus on the lower part of the back point to the conclusion that the child stayed for a prolonged period of time where it was found dead. However, other family members, including the older children in the presented case, showed no signs of intoxication and did not complain of any health problems. The fact is that they went out of the house every day, which was the way of detoxification for them, thus their exposure was not constant. During the investigating procedure, the sample of the air from the family house had not been taken; therefore, we do not have the data on gas analysis and chloroform level in the air in the room where the child was found dead.

The hepatic damage as an effect of chloroform toxicity occurs more frequently in patients with predisposing factors, such as hypoxia, hypercapnia, dehydration, acidosis, and alcoholism [1, 3]. During the external and internal examination of the body of the child, signs of severe dehydration and malnutrition were registered, which were certainly a predisposing factor for faster appearance of toxic effects of chloroform. The emaciation underlying the dysfunction of organ systems provided a grim frame for a child to succumb to chloroform toxicity.

In the context of mental function disorders that occur during chronic chloroform poisoning, a wide range and different degrees of disturbances have been described, from a lack of concentration to the most severe ones, such as stupor and coma [1, 15]. It is possible that the child showed some signs of passivity, but the parents failed to correctly recognize them.

In recent times, chloroform intoxication has been mostly limited to professional exposure, and it has been mainly related to the period prior to the adoption of regulations on ventilation of the working area. This accidental chronic chloroform poisoning implies that the use of products containing even small amounts of chloroform in the household can have fatal consequences. The proper use and maintenance of domestic appliances, and careful application of chemical agents indoors, is imperative.

Conflict of interest: None declared.

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Фатални исход изазван пролонгираним тровањем детета хлороформом

Мирослав Милић[1,2], Александра Антовић[1,2], Милена Трандафиловић[2,3], Миодраг Здравковић[1,2]

[1]Универзитет у Нишу, Завод за судску медицину, Ниш, Србија;
[2]Универзитет у Нишу, Медицински факултет, Ниш, Србија;
[3]Универзитет у Нишу, Медицински факултет, Институт за анатомију, Ниш, Србија

САЖЕТАК

Увод Тровање услед удисања хлороформа је обично повезано са професионалним излагањем хлороформу. Смртни случајеви задесног и намерног тровања хлороформом су веома ретки.

Циљ овог рада је био да прикаже случај тровања детета хрлороформом са фаталним исходом.

Приказ случаја Тромесечно дете је мајка пронашла мртво у кући. Истрагом је утврђено да су у кући постојала два непотпуно исправна фрижидера са расхладним гасом на бази хлороформа и да је у кући недавно коришћен пестицидни спреј на бази хлороформа. Судско-медицинска обдукција је извршена наредног дана и утврђено је постојање потхрањености, дехидратације, отока мозга и плућа, присуства веома оскудног садржаја у дигестивном тракту и увећања трбушних лимфних чворова. Хистопатолошким прегледом нађен је почетни степен дегенерације јетре. Хемијско-токсиколошка анализа узорака органа (мозак, плућа, слезина, јетра са жучном кесом, бубрег са бешиком, желудац, танко и дебело црево), применом технике гасне хроматографије са масеним детектором, потврдила је тровање хлороформом.

Закључак Исцрпљеност и дисфункционалност система органа утицали су на околности под којима је дете подлегло токсичном ефекту хлороформа. Неопходни су адекватна употреба и одржавање кућних апарата и пажљива употреба хемијских супстанци у затвореном простору, нарочито у близини деце. Ниске концентрације хлороформа удахнутог из ваздуха у просторији могу бити фаталне код осетљивих појединаца.

Кључне речи: хлороформ; тровање; токсикологија; обдукција; форензичка патологија

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Prevalence of spondyloarthritis and its subtypes – are they really comparable?

Mirjana I. Zlatković-Švenda[1,2], Roksanda M. Stojanović[1], Sandra B. Šipetić-Grujičić[3], Marija M. Radak-Perović[1], Francis Guillemin[4]

[1]University of Belgrade, Faculty of Medicine, Institute of Rheumatology, Belgrade, Serbia;
[2]University of East Sarajevo, Faculty of Medicine, East Sarajevo, Republic of Srpska, Bosnia and Herzegovina;
[3]University of Belgrade, Faculty of Medicine, Institute of Epidemiology, Belgrade, Serbia;
[4]University of Lorraine, University Hospital, INSERM-CIC-EC and EA 4360 APEMAC, Nancy, France

SUMMARY

Introduction/Objective Increasing spondyloarthritis (SpA) prevalence in the last several decades cannot be attributed to disease manifestations alone.
The objective of this paper is to review the prevalence of SpA and its subtypes: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel disease (IBD) and undifferentiated SpA (UnSpA).

Methods MEDLINE literature search was done via PubMed, Google Scholar, and Embase databases, using terms for spondyloarthritis, and prevalence, with an additional hand searching.

Results As compared with southern European countries, northern European countries (Scotland, Sweden, France) showed lower SpA prevalence rates (0.21–0.45% *vs.* 1.06% and 1.35% in Italy and Turkey, respectively). The lowest world SpA prevalence was in African and Southeast Asian countries (0–0.19%), and the highest was in Alaska (2.5%). The widest variability in PsA prevalence was in Europe (northern 0.02–0.19%, southern 0.42%). The lowest world PsA prevalence was in Japan (0.001%), followed by China (0.01–0.10%). The European ReA prevalence ranged from 0.04% in Greece to 0.10% in Serbia and Germany, and the European UnSpA prevalence varied from 0.02% in Serbia to 0.67% in Germany; the highest world UnSpA prevalence was in Lebanon (3.4%). Studies aimed at estimating the SpA prevalence differed in sampling strategy and confirmation criteria, different cutoffs for age groups inclusion, presentation of standardized or row results, etc.

Conclusion Variation in the SpA prevalence cannot be attributed to genetic or geographic distribution only. Differences in methodology of studies add to the diversification, described more in-depth in this review.
Keywords: epidemiology; prevalence; spondyloarthritis; ankylosing spondylitis; psoriatic arthritis

INTRODUCTION

Spondyloarthritis (SpA) comprises ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel diseases (IBD), such as Crohn`s disease or ulcerative colitis, and undifferentiated SpA (UnSpA). Common SpA clinical features are spinal, sacroiliac, and peripheral joint inflammation, enthesitis and some extra-articular manifestations (uveitis, skin or mucosal changes, cardiovascular or pulmonary changes).

SpA prevalence estimates range widely both in developed and developing countries, from 0.03% in the APLAR region (New Zealand in Oceania to Jordan in the Middle East) to 2.5% in Russian and Alaskan Eskimos [1, 2, 3] (Figure 1). Particularly, African black people populations have shown virtually non-existent SpA prevalence, as in Sub-Saharan Africa, Zimbabwe, and Nigeria [4, 5].

Differences in the prevalence of SpA and its subtypes, apart from geographic, racial, and cultural influences, could also be due to differences in the methodology used in studies (various sampling and case identification strategy with different classification criteria, diverse age groups included, presentation of row or standardized results, etc.). For example, in the last decades, PsA has been identified by a number of different criteria [6, 7].

This study aimed to review the estimates of prevalence of SpA and its subtypes: AS, PsA, ReA, IBD SpA, and UnSpA, specifically emphasizing differences in methodology and variations in geography.

METHODS

Review involved a search of MEDLINE literature via PubMed, Google Scholar, and Embase databases with the terms spondyloarthritis, spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease spondyloarthritis, undifferentiated spondyloarthritis and prevalence, with an additional hand search. A total of 15,325 titles and abstracts were reviewed; the full text of 292 articles was read thoroughly; and data for 67 reports are presented and compared here.

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Correspondence to:
Mirjana ZLATKOVIĆ-ŠVENDA
University of Belgrade
Faculty of Medicine
Institute of Rheumatology
Resavska 69
11000 Belgrade, Serbia
mirjanazlatkovicsvenda@gmail.com

Table 1. Spondyloarthritis prevalence

Reference	Country	Year	Age	Population, area, Number of participants	Criteria	Prevalence [%]		
						Men	Women	All
EUROPE								
Steven [14]	Scotland	1992	15+	Mixed, Scotish islands	Doctor dg			0.21*
Saraux [15]	France	2001	18+	Mixed, France 9,395	Doctor dg	0.31	0.29	0.30*
Constantino [16]		2010	35+	Gazel Cohort, 18,757	ASAS			0.43*
Zlatković-Švenda [17]	Serbia	2008	18+	Mixed, Serbia 6,213	Doctor dg	0.34	0.31	0.32*
Haglund [18]	Sweden	2011	15+	Mixed, south Sweden	Register[P]			0.45
Trontzas [19]	Greece	2005	19+	Mixed, 7 areas, 10,647	ESSG			0.49*
Adomaviciute [20]	Lithuania	2008	18+	Urban, Lithuania, 6,542	Doctor dg	1.36	1.34	0.84*
De Angelis [21]	Italy	2007	18+	Mixed, Marche, 3,664	ESSG			1.06
Bruges-Armas [22]	Portugal	2002	50+	Mixed, Terceira, Azores, 936	ESSG	2.7	0.4	1.6
Braun [23]	Germany	1998	18+	Blood donors, 1,871	ESSG			1.9
AFRICA								
Adebajo [4]	Sub-Saharan Africa	1994	A	Negro, rural	Doctor dg			0.00
Mijiyawa [5]	Togo	2000	A	Negro, rural	Doctor dg			0.00
APLAR region [south-east Asia and Pacific]								
Davatachi [1]	Phillipines	1997	15+	Urban, Manila, 3,006	Doctor dg			0.03
Akhter [6]	Pakistan	2011	15+	Rural, 2,090	/			0.10
Veerapen [7]	Malasya	1992	15+	Rural, Banting, 2,594	Doctor dg			0.12
Davatachi [1]	Tailand	1998	15+	Rural, 2,463	/			0.12
Dai [9] Zeng [10]	China China	2003 1995	15+ 16+	Urban, Shangai, 7,603 Urban, Shantou 2,040	Doctor dg			0.11 0.26
Davatachi [1]	Iran	1995	15+	Urban, 7,000	/			0.34
Onen [12]	Turkey	2008	20+	Urban, Izmir, 2,887	ESSG	0.88	1.22	1.05*
Onen [13]		2015		University Employees, 381	ASAS			1.35
Davatachi [1]	APLAR	2006	15+	APLAR	/			0.19*
Alexeeva [2]	Russia	1994	P	Chukotka, Russia				2.5
NORTH AMERICA								
Strand [24]	USA	2013	18+	Mixed, pt.records, 816	ASAS			0.70
Helmick [25]	USA	2005	18+	NHIS	Doctor dg			0.35–1.31
Boyer [3]	Alaska	1994	20+	Eskimos, 6,749	ESSG/AMOR			2.50

*Prevalence estimates standardized for age and sex in terms of the country population; Doctor dg, diagnosis made by a doctor;
ESSG – European Spondyloarthropathy Study Group Classification criteria; ASAS – Assessment of SpondyloArthritis international Society criteria;
AMOR – Spondyloarthropathy criteria by Amor et al; A – adult; P – population

SPONDYLOARTHRITIS PREVALENCE

The Asian SpA prevalence ranged from 0.03% in Manila to 1.05–1.3% in Turkey [1, 8–13]. The SpA standardized prevalence in the whole APLAR region was 0.19% [1]. The SpA prevalence in Europe ranged from 0.21% in Scotland to 1.9% in Germany [14–23]. In Serbia, it was 0.32% [17] (Table 1). The estimated SpA prevalence in the United States was 0.35–1.31% [24, 25]. The Australian urban SpA prevalence was 0.21%, but was 0.50% in Australian Aboriginals [1].

Comparison of the world SpA prevalence was limited by methodology discrepancies: various sample sizes, different age limitations (15, 16, 18, 20 years), and different presentation of the achieved results (row or standardized) (Table 1). However, the prevalence was lower in tropical zone countries [Africa or South Asia and Southeastern Asia (Philippines, Pakistan, Malaysia, Thailand, China)] than in northern countries, with the highest rate in Alaska (Figure 1) [2, 4, 7–10]. However, prevalence was lower in northern Europe (Scotland, Sweden, France) than in southern Europe (Italy and Turkey) (Figure 1), which contrasted with the reported rheumatoid arthritis prevalence [12, 13, 14, 16, 18, 21, 26]. Inequalities in methodologies of SpA studies are described in Table 1.

ANKYLOSING SPONDYLITIS PREVALENCE

A wide range of AS prevalence was reported as well (Table 2, Figure 2). The highest AS prevalence was found in Canadian Indigenous Haida people, 6% [27]. However, no AS cases were found in African countries: Zimbabwe, Nigeria, and Togo [28, 29, 30]. For Southeast Asian and Pacific regions, AS prevalence estimates ranged from 0.01% in Japan to 0.49% in Turkey [12, 31, 32, 33] (Table 2). The European AS prevalence ranged from 0.08% in France and Serbia to 0.86% in Germany [23] [15, 17, 18, 21, 22, 34–40] and was 1.1–1.4% in Norway (Table 2, Figure 2). The AS population prevalence in the United States was estimated at 0.35% and 0.52% (e.g., 0.13% for Caucasians only [24, 25, 41]). The Alaskan Eskimo AS prevalence was 0.4% [3].

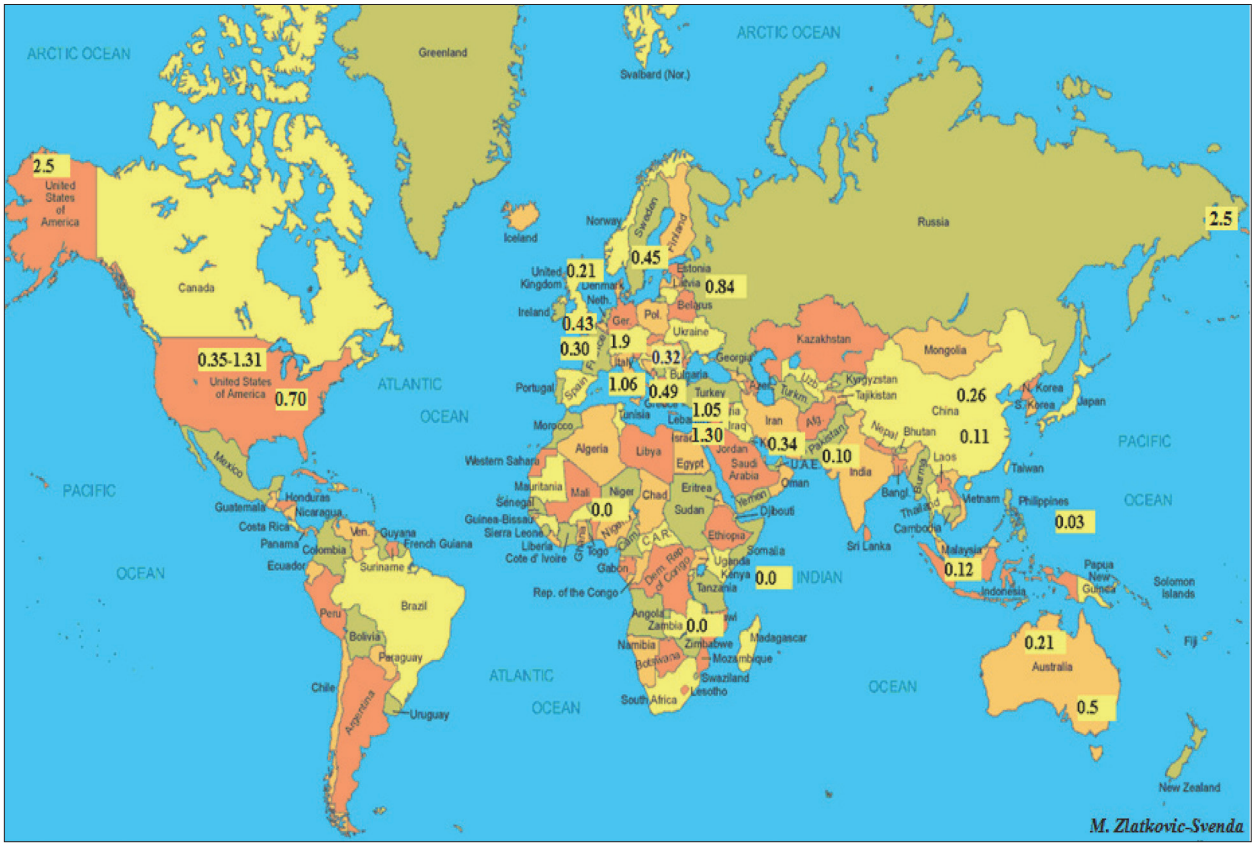

Figure 1. Spondyloarthritis prevalence in the world given in percentages

NOTE: The specific population estimate may not represent the full population estimate for a particular country (see Table 1)

AS prevalence estimates were lower in African and South and Southeast Asian countries than in northern Europe and the United States [25, 27–33, 40] (Figure 2). Differences in the studies are further evaluated in Table 2.

PSORIATIC ARTHRITIS PREVALENCE

The widest variability in SpA prevalence was for PsA and was the highest in Europe: 0.42% in Italy [21] (Figure 3). As one of the SpA-related diseases, PsA was not found in certain African countries either (in accordance with the virtual non-existence of SpA), and the non-existence of PsA was confirmed by the studies from Uganda and Sub-Saharan Africa [29, 42]. PsA prevalence was low in Southeast Asia and Pacific regions as well: 0.001% in Japan and 0.10% in China [43, 44]. Europe had the widest PsA prevalence range, lower in the northern than southern part, ranging from 0.02% in Sweden to 0.42% in Italy [15, 17, 21, 23, 34, 36, 37, 45–50] (Figure 3, Table 3). The PsA prevalence was 0.09% in Serbia. The prevalence ranged from 0.07–0.25% in the United States and was 0.12% in Minnesota and 0.10% in Alaskan Eskimos [3, 41, 51, 52]. The prevalence in South America was 0.07% [53].

Differences in PsA prevalence studies are described in more detail in Table 3.

REACTIVE ARTHRITIS PREVALENCE

Results of the ReA prevalence estimation studies cannot be generalized because of periodic and geographic variations in "disease trigger factors," such as *Salmonella, Shigella, Yersinia,* and *Campylobacter* bacteria species, as well as *Chlamydia* and *Mycoplasma* subspecies. In fact, only a few ReA prevalence studies were performed, mostly under the SpA disease prevalence estimation. The ReA prevalence was 0.04% in Greece, 0.09% in Italy and 0.10% in Serbia and Germany [17, 19, 21, 23].

INFLAMMATORY BOWEL DISEASE SPONDYLOARTHRITIS PREVALENCE

The prevalence of IBD SpA (Crohn`s disease or ulcerative colitis) has not been studied much, and was less frequently reported than IBDs themselves. According to the few reported studies, the IBD SpA prevalence ranged from 0.01% in Sweden to 0.03% in Serbia, 0.04% in Greece and 0.09% in Italy [17, 18, 19, 21]. It was 0.05–0.25% in the United States [25].

Prevalence related to IBD type was evaluated by one US study: the prevalence of ulcerative colitis SpA was 0.03% and Crohn`s disease 0.01% [41]. Karreman et al. [54] found a SpA prevalence of 13% in IBD patients, with the pooled prevalence for AS of 3%, peripheral arthritis 13% and sacroiliitis 10%.

Table 2. Ankylosing spondylitis prevalence

Reference	Country	Year	Age	Method	Prevalence [%]
EUROPE					
Saraux [15]	France	2001	18+	Questionnaire	0.08*
Zlatković-Švenda [17]	Serbia	2008	18+	Questionnaire	0.08*
Hanova [34]	Czech Republic	2003	16+	Register	0.09
Haglund [18]	Sweden	2011	15+	Register	0.12
Kaipiainen [35]	Finland	1997	30+	Sample	0.15
Trontzas [36] Anagnostopoulos [37] Alamanos [38]	Greece	2005 2010 2002	19+ A 16+	Questionnaire Questionnaire Register	0.24* 0.29 0.29*
Backland [39] Gran [40]	Norway	2005 1985	20+	Register Urban	0.26 1.1–1.4
De Angelis [21]	Italy	2007	18+	Questionnaire	0.37
Bruges-Armas [22]	Portugal	2002	50+	Questionnaire	0.6
Braun [23]	Germany	1998	18+	Blood donors	0.86
AFRICA					
Stein [28]	Zimbabwe	1990		Population	0.00
Adebajo [29]	Nigeria	1991		Population	0.00
Mijiyawa [30]	Togo	1993		Population	0.00
APLAR region (south-east Asia and Pacific)					
Hukuda [31]	Japan	2001	A	Register	0.01
Dai [10] Yao-Jun [32]	Shangai China	2003 1985 1995 2005	 16+ 16+ 16+	Urban Rural Urban Urban	0.11* 0.22 0.2 0.2*
Chou [33]	Taiwan	1994	20+	Urban Suburban Rural	0.4 0.19 0.54
Onen [12]	Turkey	2008	20+	Urban	0.49*
Alexeeva [2]	Chukotka, Russia	1994	P	Population	1.1
NORTH AMERICA					
Boyer [3]	Alaska	1994	20+	Register	0.4
Strand [24]	USA	2013	18+	Pt records	0.35
Helmick [25]		2005	18+	NHIS	0.52*
Lawrence [41]	USA, Caucasians	1998	A	Sample	0.13*
Gofton [27]	Canada, Haida People	1964	15+	Population	6.2

*Prevalence estimates standardized for age and sex in terms of the country population;
P – population; A – adult

UNDIFFERENTIATED SPONDYLOARTHRITIS PREVALENCE

The UnSpA impact and its clinical manifestations are not yet fully understood. In general, UnSpA should be considered in patients presented with inflammatory back pain or peripheral joint arthritis, enthesopathy or alternative buttock pain, not accompanied by some SpA-disease specific features such as spondylitis, psoriasis, Crohn's disease, ulcerative colitis, or previously proven urogenital or gastrointestinal infection.

The highest UnSpA prevalence was in Lebanon, 3.4% [55]. In Asia, the representative China had 0.24% prevalence [56]. In Europe, the UnSpA prevalence estimate for Serbia was 0.02%, Greece, 0.03%, France, 0.04%, Sweden, 0.10%, and Germany, 0.67% [15, 17, 18, 19, 23]. The UnSpA prevalence in the United States was 0.37% and in Alaskan Eskimos 1.3% [3, 25, 57].

DISCUSSION

Although historically considered sporadic cases of rheumatoid arthritis and reported at the beginning as "rheumatoid spondylitis" or "seronegative variants of RA," AS and PsA have over time been shown not only as separate diseases, but also diseases of constantly increasing impact and importance. When the SpA concept was promoted for several seronegative diseases characterized by certain common features, thereby enabling different diseases to be classified into a unified diagnosis a few decades ago, they may have been classified as SpA.

SpA prevalence has increased in the past decades. With the universal health system in France, the AS prevalence was estimated at 0.005% in 1994, 0.08% in 2001 (French population study) and 0.43% in 2015 (French population-based study) [15, 16, 58].

The 21st century European studies showed high SpA prevalence as well: Sweden 0.45%, France 0.43%, Greece 0.49%, Lithuania 0.84%, Turkey 1.05%, Italy 1.06%, and Portugal 1.6%. In the last century, SpA prevalence even

Figure 2. Ankylosing spondylitis prevalence in the world given in percentages;

NOTE: The specific population estimate may not represent the full population estimate for a particular country (see Table 2)

Table 3. Psoriatic arthritis prevalence

Reference	Country	Year	Age	Method	Prevalence [%]
EUROPE					
Hellgren [45]	Sweden	1969	P		0.02
van Romunde [46]	Netherlands	1984	20+	Sample	0.05
Zlatković-Švenda [17]	Serbia	2008	18+	Questionnaire	0.09
Pedersen [47]	Denmark	2002	Twins	Questionnaire	0.15
Madland [48]	Norway	2002	A	Register	0.19*
Hanova [34]	Czech Republic	2003	16+	Register	0.05*
Saraux [15]	France	2001	18+	Questionnaire	0.19*
Braun [23]	Germany	1998	18+	Blood donors	0.29
Alamanos [49] Trontzas [37] Anagnostopoulos [38]	Greece	2001 2005 2010	A 19+ A	Register Questionnaire Questionnaire	0.06* 0.17* 0.35
Salaffi [50] De Angelis [21]	Italy	2005 2007	18+ 18+	Questionnaire Questionnaire	0.37 0.42
AFRICA					
Adebajo [29]	Subsaharial Africa	1990			0.00
Lamurezo [42]	Uganda	1980			0.00
APLAR region (south-east Asia and Pacific)					
Hukuda [43]	Japan	2001	A	Register	0.001
Zeng [44]	China	2006	A	Study	0.01–0.1
NORTH AMERICA					
Lawrence [41] Gelfand [51]	USA white race	1998 2005	A P	Sample Questionnaire	0.07* 0.25
Shbeeb [52]	Minesota	1991	A	Register	0.16*
Boyer [3]	Alaska	1994	20+	Register	0.1
SOUTH AMERICA					
Soriano [53]	Argentina	2006	P	Register	0.07

*Prevalence estimates standardized for age and sex in terms of the country population
A – adult; P – population

Figure 3. Psoriatic arthritis prevalence in the world given in percentages;

NOTE: The specific population estimate may not represent the full population estimate for a particular country (see Table 3)

exceeded rheumatoid arthritis (as one of the most prevalent inflammatory rheumatic diseases) in Japan, Germany, Turkey, Lithuania, China, Italy, Australian Aboriginals and the United States, but was similar to the rheumatoid arthritis prevalence in France and Serbia [17, 59]. This fact could be explained by a better understanding of the SpA concept both by the patients and physicians, as well as by introducing new classification criteria, the European Spondyloarthropathy Study Group Classification criteria (ESSG) [60]. The newest Assessment of SpondyloArthritis international Society (ASAS) classification criteria was used by several studies, reporting high SpA prevalence estimates as well: 0.43% in France (0.36% for axial SpA and 0.12% for peripheral SpA), 1.35% in Turkey and 0.70% for axial SpA alone in the United States [13, 16, 24, 61].

The first study on the prevalence of pooled SpA and its subtypes was conducted in 2016 by Stolwijk et al. [62]. The general population pooled prevalence of SpA ranged from 0.20% in Southeast Asia to 1.61% in northern Arctic communities; the AS prevalence ranged from 0.02% in Sub-Saharan Africa to 0.35% in northern Arctic communities; and the PsA prevalence ranged from 0.01% in the Middle East to 0.19% in Europe [62]. However, only a few studies from this meta-analysis were truly representative of the general population, due to a high risk of bias in addition to other methodological variations described more in depth in the article [62].

The limitation of our review is that we could not track the human leukocyte antigen B27 (HLA-B27) prevalence in all studies included, and connect its range with prevalence differences. According to the DESIR (*DEvenir des Spondylarthropathies Indifférenciées Récentes*) cohort, diagnostic delays are less common in HLA-B27-positive than in B27-negative patients [63]. High HLA-B27 prevalence is generally positively correlated with SpA prevalence, especially axial SpA [64]. Our review found the highest SpA prevalence in Alaskan Eskimos, 2.5% [3], of whom 25–40% are HLA-B27–positive [64]. In the current review, second-place SpA prevalence was found in Russian Chukotka Eskimos, 2.5%, with HLA-B27 prevalence at 34%. The highest AS prevalence (6%) was found in Haida Indians living in the Queen Charlotte Islands of Canada, of whom 50% are HLA-B27-positive [27]. However, although the HLA-B27 prevalence varies from 10–16% in northern European countries, the latest studies have shown an AS prevalence of 0.12% in Sweden, 0.15% in Finland and 0.26% in Norway [18, 35, 39, 64].

CONCLUSION

In conclusion, although the wide SpA prevalence range in different geographic regions could partially be attributed in part to HLA-B27 positivity, other factors may also play the role, such as geographic differences [59]. In addition, prevalence variations could only partially be due to genetic or environmental factors or geographic distribution and are certainly affected by differences in case definition and case confirmation strategy as well as by other variations in applied methodologies [65, 66].

Conflict of interest: None declared.

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Преваленција спондилоартритиса и његових подтипова – да ли је заиста упоредива?

Мирјана И. Златковић-Швенда[1,2], Роксанда М. Стојановић[1], Сандра Б. Шипетић-Грујичић[3], Марија М. Радак-Перовић[1], Франсис Гилман[4]

[1]Универзитет у Београду, Медицински факултет, Институт за реуматологију, Београд, Србија;
[2]Универзитет у Источном Сарајеву, Медицински факултет, Република Српска, Босна и Херцеговина;
[3]Универзитет у Београду, Медицински факултет, Институт за епидемиологију, Београд, Србија;
[4]Универзитет у Лорени, Универзитетска болница, *INSERM-CIC-EC* и *EA 4360 APEMAC*, Нанси, Француска

САЖЕТАК

Увод/Циљ Пораст преваленције спондилоартритиса у последњих неколико деценија не може се приписати само манифестацијама болести.

Циљ овог рада је преглед преваленције спондилоартритиса (СпА) и његових подтипова: анкилозирајућег спондилитиса (АС), псоријазног артритиса (ПсА), реактивног артритиса (РеА), СпА повезаног са инфламаторним болестима црева и недиферентованог СпА (НеСпА), са посебним освртом на методолошке разлике и географске варијације.

Методе Претражена је литература са базама података *PubMed, Google Scholar* и *Embase* уз додатно ручно претраживање у односу на термин спондилоартритис и његове подтипове у комбинацији са преваленцијом.

Резултати Земље северне Европе (Шкотска, Шведска, Француска) имају ниже стопе преваленције СпА (0,21–0,45%) у поређењу са јужним (Италија – 1,06% и Турска – 1,35%). Најнижа преваленција СпА у свету забележена је у афричким и југоисточним азијским земљама (0–0,19%), а највиша на Аљасци (2,5%). Највећа варијабилност у преваленцији ПсА запажена је у Европи (северни део 0,02–0,19%, јужни 0,42%). Најнижа преваленција ПсА у свету забележена је у Јапану – 0,001%, а затим у Кини 0,01–0,1%. У Европи се преваленција РеА креће од 0,04% у Грчкој до 0,1% у Србији и Немачкој, док је преваленција УнСпА од 0,02% у Србији до 0,67% у Немачкој. Највиша преваленција УнСпА у свету нађена је у Либану – 3,4%. Студије које одређују преваленцију СпА разликују се у бројним карактеристикама: различит метод формирања узорака и употребљених критеријума, укључивање различитих старосних група, различит приказ резултата итд.

Закључак Варијације у преваленцији СпА не могу се приписати само генетским или географским разликама. Различита преваленција делимично је условљена и неуједначеним методама истраживања, детаљније описаним у овом чланку.

Кључне речи: епидемиологија; преваленција; спондилоартритис; анкилозирајући спондилитис; псоријазни артритис

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Minimal invasive coronary bypass surgery – the robotic total endoscopic approach

Duško Terzić[1], László Göbölös[2], Jehad Ramahi[2], Johannes Bonatti[2]

[1]Clinical Center of Serbia, Clinic for cardiac surgery, Belgrade, Serbia;
[2]Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

SUMMARY
The aim of this paper is to present the latest recommendations for practitioners for preoperative preparation, surgical procedures and postoperative treatment in patients with myocardial revascularization using robotic total endoscopic coronary artery bypass grafting (CARG), which is applied as daily clinical routine practice at the Heart and Vascular Institute, Cleveland Clinic Abu Dhabi. Many patients indicated for coronary bypass surgery may be candidates for robotic total endoscopic CARG. The paper illustrates eligibility criteria of this procedure, preoperative assessment and preparation principles, peripheral access for cardiopulmonary bypass and port insertion, then graft harvesting procedure, initiation of cardiopulmonary bypass and application of endoaortic clamping, identification and exposure of the target vessels, anastomosis procedure and postoperative care in this group of patients.
Keywords: robotic; endoscopic; coronary artery bypass; TECAB

INTRODUCTION

In recent years, cardiac surgery has shifted its focus to developing and using minimally invasive procedures. These procedures differ from conventional approaches in incision size and level of invasion. Some of the advantages that these methods have are pain relief, improved cosmetic outcome, better postoperative respiratory function, faster rehabilitation and reintegration of the patient into his/her social community. After various minimally invasive procedures using small thoracotomy, robotic coronary artery bypass grafting (CARG) is a new and upgraded type of surgical myocardial revascularization.

This robotic CARG technique is both single and a multi-vessel procedure that can be performed on a beating heart as well as the arrested heart. Moreover, totally endoscopic coronary artery bypass surgery (TECAB), can also be done with percutaneous coronary interventions at the same time [1].

The da Vinci™ surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) consists of a surgeon's console, a vision cart, and a surgical cart. The master remote console has two master handles that are manipulated by a surgeon in order to achieve three-dimensional, binocular, high-resolution magnified view of the operative field that is equivalent to the one in the open surgery. The system can also be downscaled by tuning the handles' motion ratio to the one of surgical instruments. Also, there is a motion filter for the prevention of unintended movements that are caused by human tremor. Thanks to these previously mentioned technological advantages, it's possible to achieve high-precision micro sutures. It usually takes about six hours for the procedure to be completed. When it comes to perioperative results, they are similar to those that CABG procedures through sternotomy have. Also, the long-term survival and lower risk for major adverse cardiac and cerebral events are similar too (96% and 73% at five years, respectively) [1, 2] (Figure 1).

The most commonly used TECAB procedures are left internal mammary artery (LIMA) to the left anterior descending (LAD) artery or right internal mammary artery (RIMA) to LAD artery combined with LIMA to the left coronary arteries [circumflex (Cx) or diagonal] and creation of Y anastomosis whereby the LIMA is anastomosed to LAD and RIMA to RCA or Cx artery.

Eligibility criteria

The absolute contraindications for this procedure are cardiogenic shock, diffusely diseased coronary arteries, or intra myocardial coronary arteries, significant peripheral vasculopathy, pulmonary hypertension, severe lung impairment chest deformities, ascending aortic diameter > 3.8 cm and severe aortoiliac calcification, hemodynamic instability. The procedure carries the increased risk for complications and possible forced Intra-aortic balloon pump, previous heart surgery, previous severe chest trauma and chest irradiation as adhesions severely impaired left ventricular function [3, 4].

Preoperative assessment and preparation

The preoperative preparation is no different than the one for full sternotomy CABG. This

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Correspondence to:
Duško TERZIĆ
Clinic for Cardiac Surgery
Clinical Center of Serbia
8 Dr. Koste Todorovića Street
11000 Belgrade, Serbia
terzic.dusko@gmail.com

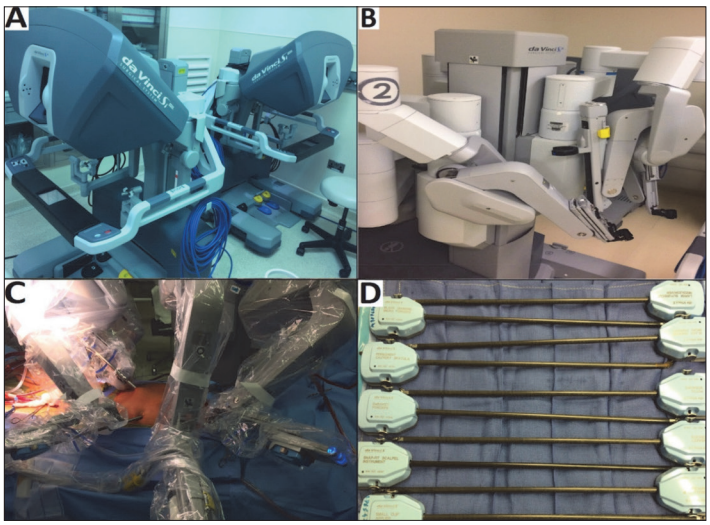

Figure 1. A) The da Vinci™ surgical system – surgeon's console, surgical cart and vision cart; B) the da Vinci™ surgical system – surgical robot; C) surgical robot is docked to the patient; D) different technical variable "hand" devices contribute to high-precision surgical work (forceps, scissors, cautery spatula...)

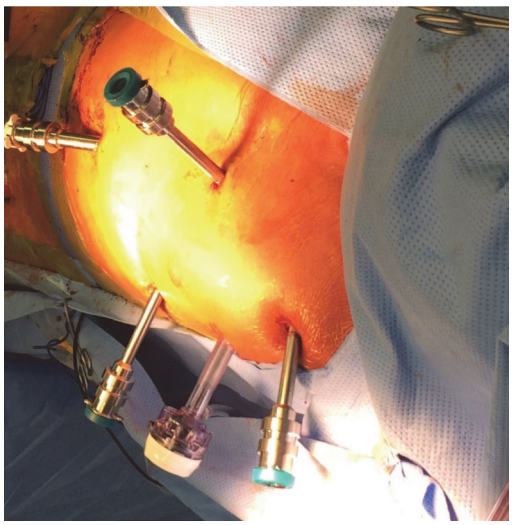

Figure 2. Thoracic cavity with the instrument ports in place

preparation also includes double lumen intubation or bronchial blocker, TEE during the procedure, percutaneous defibrillator pads as well as NIRS monitoring.

The essential tool for monitoring the overall heart function is transesophageal echocardiography (TEE). TEE is also used to check the position or detect the incidental migration of the endoballoon during cardioplegic TECAB. It is also important to determine the initiation of a single lung ventilation as well as setting the level of CO_2 inflation pressure [5, 6].

Peripheral access cardiopulmonary bypass and port insertion

Based on our experience, the Cx or right CARG is reliable only on the arrested heart since it is completely flaccid and the it can be rotated to the adequate position for the procedure. Also, the equipment for the open CABG should be at your disposal all the time during the procedure.

In case of cardioplegic TECAB, the usual vascular exposure target is the left groin or subclavian-axillar artery. In this case, the venous drainage is achieved through 25 Fr cannula that is forwarded to the superior vena cava under the TEE guidance while the arterial perfusion cannula (21 or 23 Fr, equipped with the side arm) is placed into the femoral artery. [7, 8, 9].

After the anesthesiologist confirms that the left wing is completely deflated, the ports are placed on the left side of the thorax.

The camera port is placed on the fifth intercostal space, at the level of the anterior axillary line. The CO_2 should be insufflated at the pressure of 8 mmHg. If sudden hypotension or any other hemodynamic instability happens during this phase, the CO_2 pressure should be adjusted in order to avoid the venous return hindrance. The thoracic cavity should be inspected under the scope in order to properly place the right and left instrument ports (Figure 2). After this, the surgical robot is docked to the patient with the cautery spatula and forceps mounted on the left and right manipulator arm, respectively (Figure 1c) [7, 8, 9].

Graft harvesting procedure and utility port placement

The internal mammary artery (IMA) can be visualized in "camera up" view of the 30° angled robotic device. IMA can be harvested in either pedicle or skeletonized form. If both IMAs have to be harvested retro sternal robotic endoscopic dissection is done in order to access the right pleural cavity [10]. If you're harvesting both LIMA and RIMA, the RIMA should be harvested before the left one. If not, there's a high chance that the LIMA will compromise surgeon's view and accessibility for the rest of the procedure. After the IMA is harvested, a 5 mm utility port is placed under the scope control in the left parasternal region, on the opposite side of the camera port. This port will allow the delivery of supplies for the surgical procedure [8, 9, 10].

Initiation of the cardiopulmonary bypass and application of endoclamp (ballon) occlusion.

It is important that there is no significant atherosclerosis in the thoracic aorta. Also, the ascending diameter should not exceed 38 mm and the aortic valve has to be fully functional in order to place the endoballoon (guide wire is inserted through a special arterial cannula side-arm under continuous ultrasound control) above the aortic valve in case of the endoclamp occlusion. The endoballoon system has a special line for management of cardioplegia, which is connected with the extracorporeal device. The system possesses manometers, which measure the endoballoon and root pressures precisely [11].

If significant atherosclerosis of lower arterial trunk is present, the left subclavian artery should be used for cannulation. Initial suturing of 8 mm Dacron graft to subclavian artery or axillary artery is suggested, which serves to connect the arterial line.

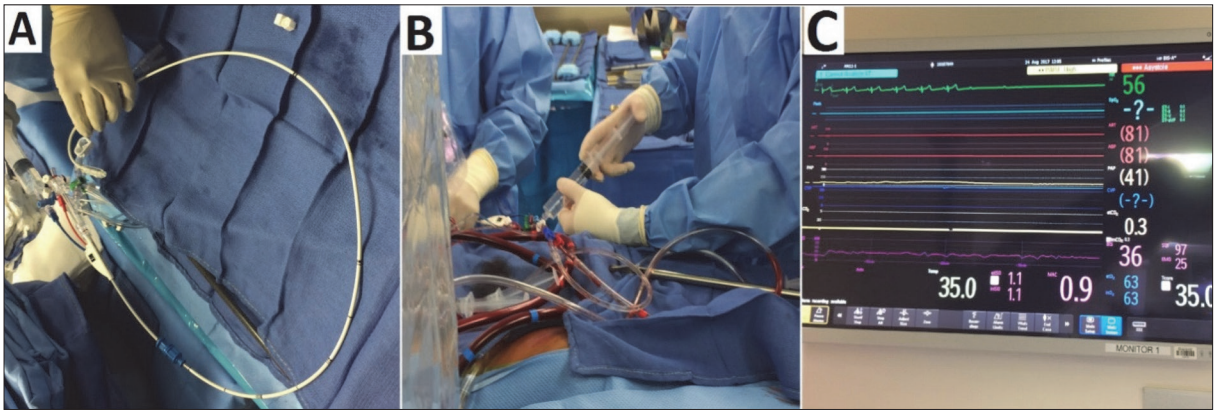

Figure 3. A) The endoballoon system; B) rapid cardioplegic induction can be established by the administration of adenosine; C) ECG confirmation of stopping the heart immediately after adenosine infusion

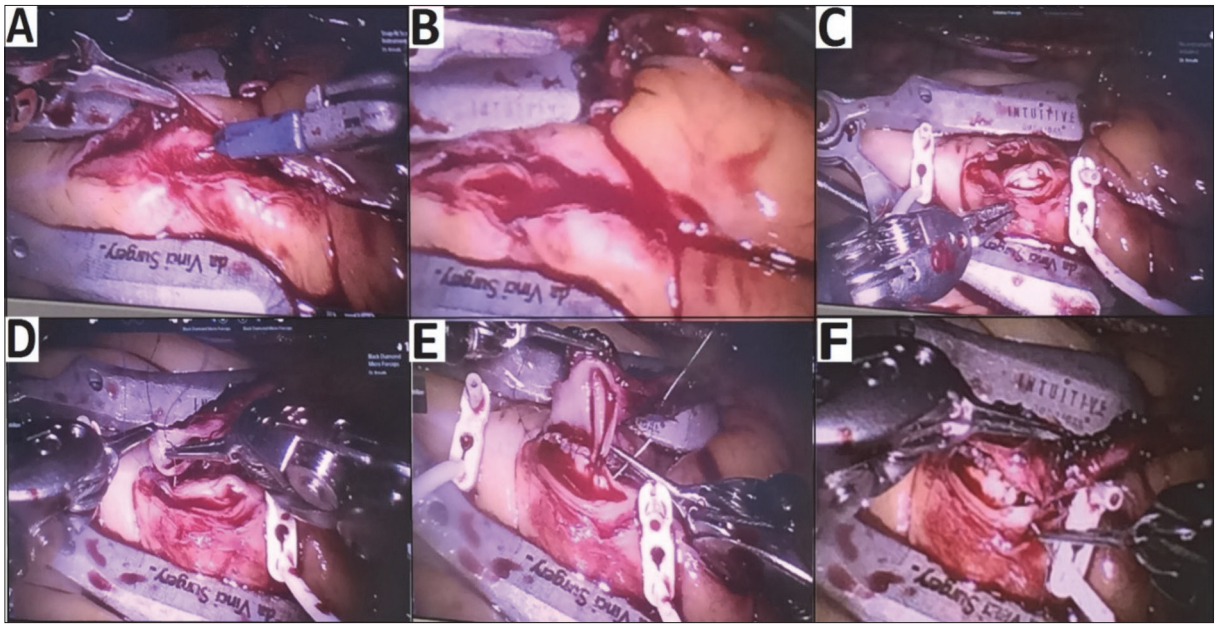

Figure 4. A) With DeBakey forceps and a robotic beaver knife the target vessel is opened; B) incision is extended to approximately 4 mm; C) the blood flow of the vessel has to be ensured; D) the initial stitch is placed "back hand" on the toe of the coronary in an inside-out fashion; E) after the first three throws the graft is parachuted down to the coronary level; F) adequate suture line tension on the back wall in order to avoid leaks

The endoballoon catheter might still be inserted in most cases through a separate 19 Fr cannula placed into the common femoral artery [12, 13]. If the insertion of endoballoon through the femoral artery is assessed to be an extremely high-risk procedure, the method of choice would be a beating heart TECAB with formerly provided support of extracorporeal circulation (stand-by cannula in axillary artery) [12, 13].

The endoballoon is inflated when a sufficient venous drainage is achieved along with low blood pressure and no ventricular ejections. The correct position of the endoballoon in the aortic root can be echocardiographically confirmed. The cardioplegic solution is administered after the inflation of the endoballoon. The fast cardioplegic induction can be achieved by administration of adenosine (6 mg/20 mL of normal saline). After the stable position of the endoballoon is confirmed, the cooling process can be initiated. The cardioplegia should be repeated once every 20 minutes [1, 2, 13] (Figure 3).

Identification and exposure of the target vessels

In "camera down" view, the pericardium is opened just above the right ventricular outflow tract. The incision is made towards the substernal part of the pericardial reflection, and extended laterally. In cranial direction, the aperture goes towards the phrenic nerve, which needs to be identified always [1, 3].

The robotic endostabilizer, inserted through a 12 mm port that is located two fingers away to the left side of the xiphoid, provides an effective support for different structures on the surface of the heart. The insertion process is guided by the robotic camera in "up facing" view. The subcostal port is connected to the fourth arm of the da Vinci™ system (Figure 4).

In order to have the optimal view and access to the target coronary arteries, the camera is set in the "face down" position. The LAD and Cx coronary artery branches can be adequately reached with the aid of subcostal endostabilizer

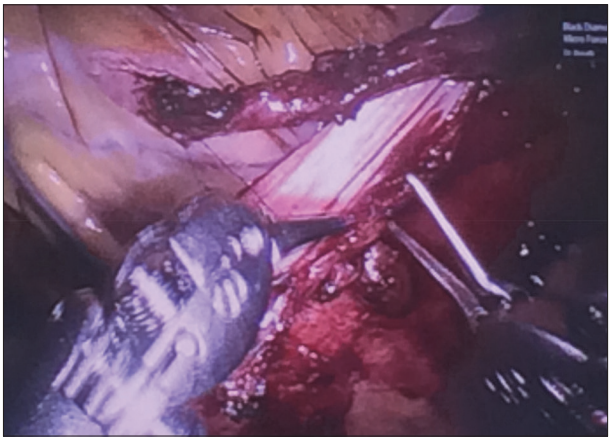

Figure 5. Final result – completed anastomosis

device. The endostabilizer is activated by a dedicated foot pedal while the suction pods are lined-up along the target area. This way, the local immobilization is achieved and the target coronary arteries are moved into position that is suitable for a surgeon [13]. The right ventricular acute margin can be lifted up with the aid of the endostabilizer, this provides an excellent access to the posterior descending artery or posterolateral artery. It should be noted that we've applied this method only for TECAB on the arrested heart. In case of a beating heart procedure, the endostabilizer has to be used cautiously on the right ventricular surface since there's a risk for accidental perforation [14, 15].

Robotic endoscopic coronary anastomosis procedure

After re-checking the graft suitability, the facet of the graft that was previously occluded by a bulldog is shaped in an oblique manner and opened for 4 mm in total length in order to achieve a "cobra head" anastomotic profile. The blood flow of the vessel has to be ensured.

After this, the incision is extended to about 4 mm in length while the 7 cm long double-armed polypropylene suture is supplied via parasternal utility port.

The initial stitch is placed "back hand" on the toe of the coronary in an inside-out fashion (Figure 4d, 4e, 4f). At the end of creation of anastomosis, the completed suture line has to be meticulously inspected for slings. Slings can be corrected with the aid of suture needles (Figure 5) [7, 10].

Detailed video presentation of the distal anastomosis creation with a review of technical challenges may be found on the following link: http://www.youtube.com/watch?v=l6DiBz2JUnY

In case of beating heart procedures, proximal occlusion devices for bleeding control and intraluminal shunts providing distal flow during anastomosis creation are applied. Beta blockers are used to slow down heart frequency, which in turn ensures better visual control. Before clinical practice, during a surgeon's specialized training, he/she should be provided, with sufficient number of training hours in dry- and wet-lab settings [16].

Final tasks and postoperative care

The left pleural drainage is a must before ending the procedure. If necessary, it should be done with the right pleural cavity too, by using the thoracic drains. The robot is docked and the instruments are parked in the IMA bed after the anastomoses are created and patient is taken off the cardiopulmonary bypass machine. This step is necessary because the heart is filling with blood after decannulation. Also, it may be required to insert instruments again. After this, the last robotic inspection of the thoracic cavity is done, followed by an observation from both console surgeons and the tableside team. Once the sufficient hemostasis is achieved, the robotic system is undocked but the ports are still left in position. This is done in order to avoid the leakage of CO_2. Then the ports are removed under the scope vision, and the portholes are cauterized and packed with surgical hemostat material. The chest drain is inserted via the camera porthole. This procedure should be carried out with the inflated left lung in order to avoid graft injuries at the final phase of the operation. [3, 7, 13].

CONCLUSION

Nowadays, about 30% of CABG patients can be done in a robotic endoscopic fashion, and it is possible to revascularize any coronary artery at institutions that provide a competent practice in this field of medicine. Multi-vessel TECAB definitely takes more time than a single vessel procedure. Moreover, the rate of conversion to sternotomy is high due to the technical complexity of the procedure. Some of the most important advantages of multi-vessel TECAB are much shorter recovery, completely preserved sternum and utilization of double IMA.

Conflict of interest: None declared.

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Минимално инвазивна хируршка реваскуларизација миокарда применом ендоскопске робот технологије

Душко Терзић[1], Ласло Гебелеш[2], Џехад Рамахи[2], Јоханес Бонати[2]

[1]Клинички центар Србије, Клиника за кардиохирургију, Београд, Србија;
[2]Кардиоваскуларни институт, Клиника Кливленд Абу Даби, Абу Даби, Уједињени Арапски Емирати

САЖЕТАК

Циљ рада је да се прикажу најновије препоруке везане за преоперативну припрему, хируршке процедуре и постоперативни третман код болесника којима је учињена реваскуларизација миокарда методом минимално инвазивне хируршке реваскуларизације употребом робот технологије, а која се свакодневно примењује као рутинска пракса на Кардиоваскуларном институту на Клиници Кливленд Абу Даби. Многи болесници са индикацијом за реваскуларизацију миокарда могу се разматрати као кандидати за робот ендоскопску процедуру реваскуларизације срца. У раду су представљени критеријуми за одабир болесника, принципи преоперативне припреме, периферни приступ за канулацију и успостављање екстракорпоралног крвотока, пласирање портова за уређај, покретање вантелесне циркулације, методе привременог заустављања срчаног рада, идентификација коронарних крвних судова, принципи креирања анастомоза и постоперативна нега ове групе болесника.

Кључне речи: робот; ендоскопски; коронарни артеријски бајпас; *TECAB*

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UDC: 61:929 Радуловић Д.; 61:796(497.11)(091)

ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE

Др Димитрије Радуловић, пионир у области спортске медицине – живот и дело

Нена А. Васојевић[1,2], Снежана Кирин[2,1], Мирко Филиповић[3], Предраг Ј. Марковић[4]

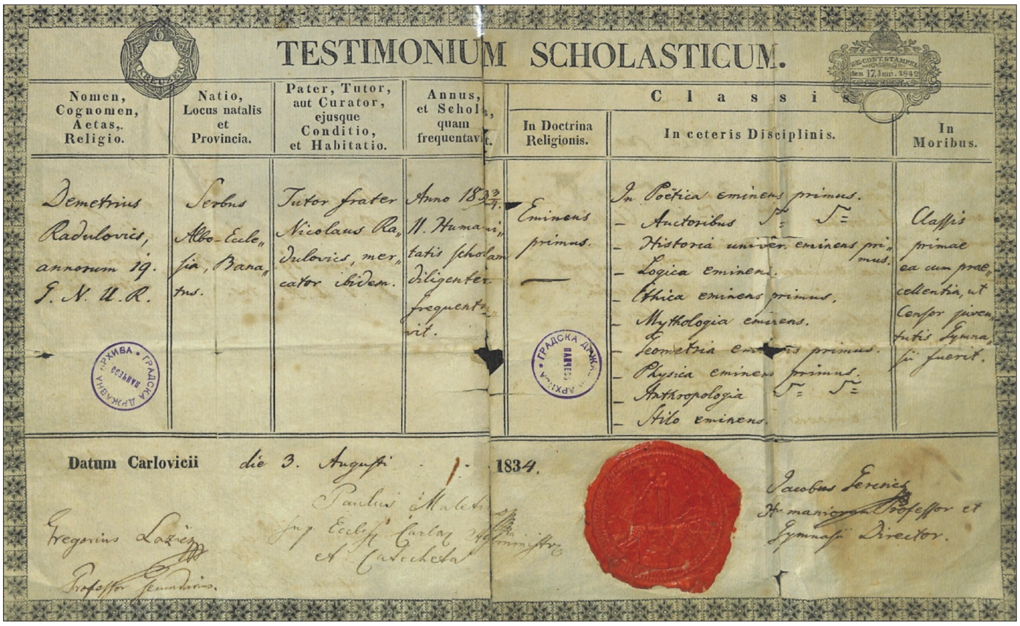
[1]Универзитет у Београду, Историја и филозофија природних наука и технологије, Београд, Србија;
[2]Универзитет у Београду, Машински факултет, Иновациони центар, Београд, Србија;
[3]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[4]Институт за савремену историју, Београд, Србија

САЖЕТАК

У историографији српске медицине малобројни су подаци о животу и раду др Димитрија Радуловића. Др Радуловић припадао је првој генерацији Срба лекара деветнаестог века. Рођен је 1814. године у Белој Цркви, а студије медицине завршио је у Пешти, у којој је стекао звање доктора медицине. После Пеште одлази у Беч, где се специјализује у области породиљства. Међу Србима је био аутор првог рада из области коју данас називамо спортском медицином. Тим радом, као и својим каснијим деловањем, поставио је темеље спортске медицине међу Србима. Први је писао о важности телесног вежбања и утицају различитих спортова на физички развој деце, омладине и одраслих; на тај начин дао је допринос дефинисању оптималних физичких оптерећења и хигијенско-дијететских режима. Циљ му је био да се очува и унапреди здравље, односно да се побољшају превенција и куратива различитих обољења и повреда, али и рехабилитација пацијената.
Кључне речи: медицина; спортска медицина; стипендија; Текелијанум; породиљство

УВОД

Др Димитрије Радуловић био је један од првих лекара Срба у деветнаестом веку. Рођен је 23. октобра 1814. године по јулијанском календару у Белој Цркви, тадашњем насељу Банатске војне границе. Потицао је из породице посрбљених Румуна, а његов отац био је сиромашни ћурчија (крзнар) Георгије [1]. Основну школу похађао је у Белој Цркви, док је свих шест разреда гимназије завршио у Сремским Карловцима. Да се радило о натпросечном ученику (Слика 1) сведочи и чињеница „да је у једној школској години (1829/30) завршио два разреда гимназије (I и II), а остала четири до школске 1833/1834. године“. Већ у првом разреду гимназије био је тако добар ученик да је после Ускрса 1830. године премештен у други разред [1]. У гимназији је стекао изванредно знање немачког и латинског језика, а показао је таленат за реторику и писање. О томе сведоче говори које



Слика 1. Сведочанство Димитрија Радуловића о завршеном шестом разреду Карловачке гимназије, 1834; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 1. Dimitrije Radulović's school certificate of the completed sixth grade of the Gymnasium of Karlovci, 1834; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

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Correspondence to:
Нена А. ВАСОЈЕВИЋ
Радована Симића-Циге 34/64
Београд
nenavasojevic@hotmail.com

је држао у то доба. Године 1833, на дан оснивања гимназије (27. децембра по јулијанском календару), беседио је у част митрополита Стефана Стратимировића „Говор одржан на рођендан (Његове) екселенције архиепископа и митрополита Стефана Стратимировића“ (*Oratio die onomastico excellentissimi archiepiscopi ac metropolitae Stephani Stratimirovics habita*). Беседу је започео цитирањем Ехелијада: „Свакога свој очекује дан, свима је време живота кратко и неповратно, али је посао врлине да (добрим) делима продужи славу“ (*Stat sua cuique dies; breve et irreparabile tempus omnibus est vitæ; sed famam extendere factis, hoc virtutis opus*). Исте године одржао је беседу на латинском језику на тему „Школе треба да дају допринос у увећању и побољшању благостања појединца“ (*Scholae multum conferunt ad uniuscuiusque salutem augendam et amplificandam*), а наредне године (1834) тема његове беседе била је: „О жељи да се врлина повеже са науком“ (*De virtutis studio cum litteris coniugendo*) [2].

Радуловић је матурирао у Винковцима или Осијеку, јер у то доба ђаци Карловачке гимназије нису имали могућност да испит зрелости полажу у својој школи. По завршеном шестом разреду, одлазили су у Винковце или Осијек и тамо слушали припремна предавања на немачком језику, на коме су полагали и завршне испите. Тако је било све до 1873. године, када су добили право да испит зрелости полажу у матичној школи. По завршеној матури, Димитрије Радуловић је уписао студије медицине у Пешти на предлог директора Велике српске гимназије Герчића. Радуловић је у свом директору имао пријатеља и помагача, што се види из писма које му је упутио. Из писма се такође види да се испомагао дајући корепенције студентима филозофије. Али, када је осетио да му здравље услед тога попушта, замолио је за стипендију од митрополита Стефана Стратимировића, и овај му је обећао. Када пак стипендија није долазила, замолио је свог бившег директора да митрополиту каже о њему коју добру реч [1]. Важно је напоменути да је тада Карловачком гимназијом управљао Патронат под окриљем Српске православне цркве, који је и бирао чланове овог тела до 1921. године, када је Карловачка гимназија постала државна реална школа.

До стипендије вероватно није дошло, пошто је Радуловић убрзо после овог писма као студент медицине 1838. године изабран за стипендисту Текелијанума – Задужбине Саве Текелије, која је управо те године започела са радом. Од дванаест питомаца Задужбине изабраних за студије у Пешти Радуловић је био други. Тада је слушао трећу годину медицине и истицао се срчаним друштвеним ангажовањем [3].

У то доба студенти из Војводине често су се кретали између Пеште, Пожуна (Братиславе), Прага и Беча, градова који су се налазили у истој држави (Аустријској монархији), и у којима се настава одвијала на немачком језику [4]. Димитрије Радуловић био је стипендиста Текелијанума пуне три године, од 1838. до 1841. Докторирао је, односно промовисан је у доктора медицине (*medicinae doctor*), на Пештанском медицинском факултету, 26. фебруара 1842. године.

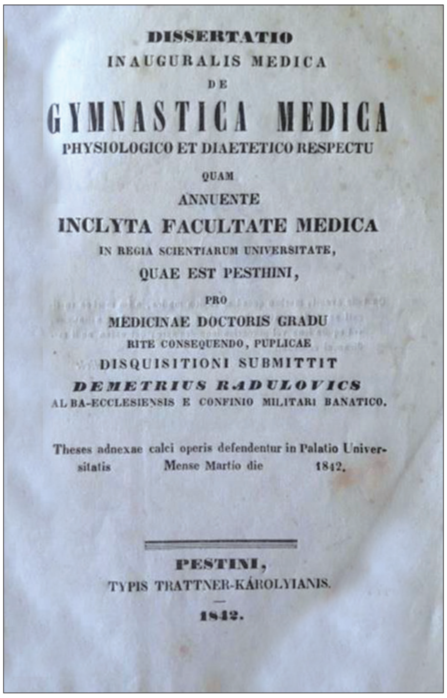
ЖИВОТ У ТЕКЕЛИЈИНОМ ЗАВОДУ – ТЕКЕЛИЈАНУМУ

Завод Текелијанум (цивилни интернат за српску омладину у Будимпешти) основао је Сава Текелија[1] у својој 77. години, како би сиромашним, интелигентним и учења жељним српским младићима омогућио наставак школовања [5]. Критеријуми за избор стипендиста били су добар успех у претходном школовању, припадност православној вероисповести и слабо материјално стање. Сава Текелија омогућио је великом броју сиромашних људи да о трошку Задужбине своју децу школују на универзитетима широм Аустријске царевине, касније Аустроугарске монархије.

Сава Текелија је говорио да су Србима потребни образовани људи који ће српски народ упознавати са новим приликама у Европи и судбину српског народа све више везивати за судбину народа Европе. Следећи идеје просветитељства, одлучио је да целокупну имовину остави Матици српској, као задужбину која ће омогућити образовање сиромашних Срба [5]. Зграда Завода[2], у којој су били смештени питомци, налазила се недалеко од Пештанског универзитета (ул. Великог крста бр. 276). У Заводу су питомцима били обезбеђени стан и огрев, а сваки од њих добијао је по стотину форинти за храну и универзитетске трошкове. Текелија није имао потомке. О „својим питомцима“ старао се лично; надзирао је њихово владање и учење и водио рачуна да буду задовољене и њихове остале потребе. Међутим, у то доба харале су многе болести за које није било лека. Иако су поседовали лекарско уверење да су здрави, многи од питомаца долазили су у Текелијанум већ начети неком болешћу, пре свега туберкулозом [6]. Известан број питомаца преминуо је током школовања, али њихова имена нису забележена у списима Матице српске, јер нису умрли у Текелијином заводу (дому), већ у кућама својих родитеља [7]. Ни сама зграда Задужбине није обезбеђивала најбоље услове за живот, посебно приземље, које је било влажно. Међутим, без обзира на то, Текелијанум је изнедрио значајан део српске елите која је снажно допринела модернизацији живота међу српским живљем. У периоду од 1838. до 1878. године 179 питомаца Текелијанума завршило је студије. Већина њих је завршила филозофију или права, а 32 питомца завршило је студије медицине. Преглед спискова са именима питомаца довољан је да се каже да је Текелијанум изнедрио значајан део српске лекарске елите 19. и 20. века. Они су по завршетку студија живели и радили на подручју тадашње војвођанске границе, као и на подручју Кнежевине Србије, потом Краљевине Србије.

1 Сава Поповић Текелија (1761–1842) потицао је из два века старе и веома угледне породице Поповић-Текелија која је припадала српском војном племству Аустроугарске монархије. Образован у духу европског рационализма, Сава Текелија је био присталица реформи цара Јозефа II, као и идеја Доситеја Обрадовића, кога је познавао лично и са којим се дописивао [5]. Године 1786. промовисан је у доктора права на Пештанском универзитету.

2 „Дом за своје Заведение“, односно Текелијанум, Сава Текелија је купио 21. августа 1838. године.


DISSERTATIO
INAUGURALIS MEDICA
DE
GYMNASTICA MEDICA
PHYSIOLOGICO ET DIAETETICO RESPECTU
QUAM
ANNUENTE
INCLYTA FACULTATE MEDICA
IN REGIA SCIENTIARUM UNIVERSITATE,
QUAE EST PESTHINI,
PRO
MEDICINAE DOCTORIS GRADU
RITE CONSEQUENDO, PUPLICAE
DISQUISITIONI SUBMITTIT
DEMETRIUS RADULOVICS
ALBA-ECCLESIENSIS E CONFINIO MILITARI BANATICO.

Theses adnexae calci operis defenduntur in Palatio Universitatis Mense Martio die 1842.

PESTINI,
TYPIS TRATTNER-KÁROLYIANIS.
1842.

Слика 2. Насловна страна докторске дисертације др Димитрија Радуловића, 1842.
Figure 2. Cover page of the doctoral dissertation of Dr. Dimitrije Radulović, 1842

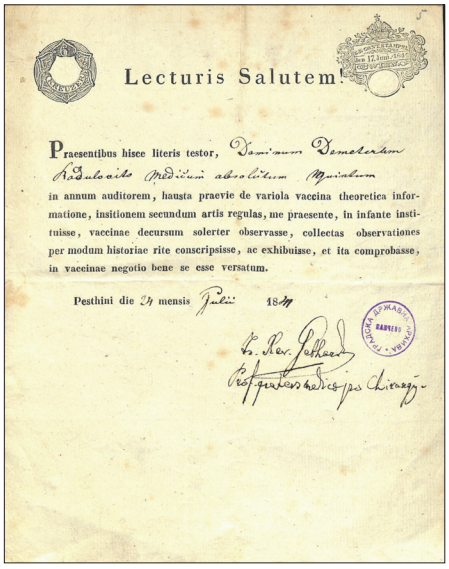

NOS PRAESES
DECANUS ET FACULTAS MEDICO-CHIRURGICA IN ANTIQUISSIMA AC CELEBERRIMA
UNIVERSITATE VINDOBONENSI

Слика 3. Диплома др Димитрија Радуловића о стеченом знању магистра породиљства (Универзитет у Бечу, Медико-хируршки факултет, 1842. године); Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 3. Dr. Dimitrije Radulović's diploma on the acquired knowledge of the Master of Obstetrics (University of Vienna, Faculty of Medicine and Surgery, 1842); Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

Слика 4. Печат Универзитета у Бечу са дипломе др Димитрија Радуловића, 1842; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 4. Stamp of the University of Vienna on Dr. Dimitrije Radulović's diploma, 1842; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

Осим др Димитрија Радуловића, који је одбраном своје докторске дисертације направио прве кораке у области спортске медицине код Срба, међу питомцима су били и касније познати лекари: Јован Стејић, Иларион Анђелковић, Стеван Васић, Никола Дада, Ђорђе Ивановић, Љубомир Радивојевић, Милош Радојчић, Ђорђе Јаконић, Милан Јовановић Батут и Илија Огњановић.

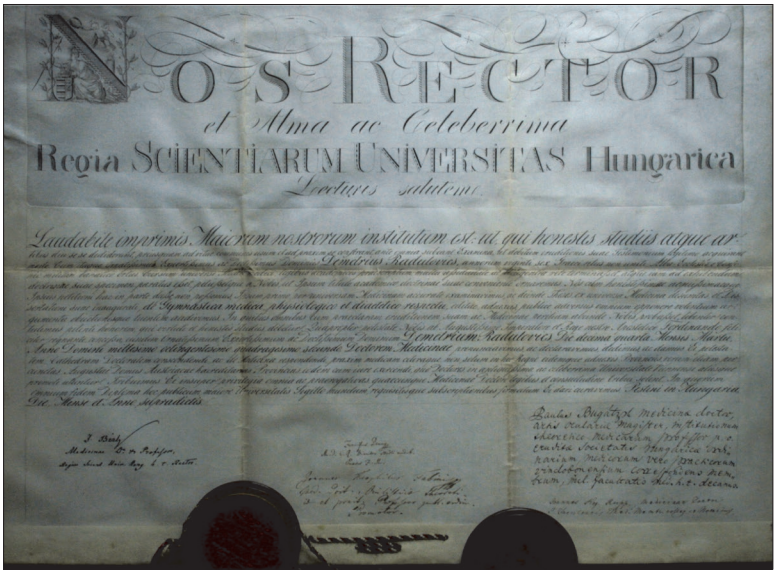
По доласку у Текелијанум, Димитрије Радуловић се суочио са новим и потпуно другачијим начином живота, коме се ипак брзо прилагодио. Године 1838. у Будиму је организована свечаност у част Симе Милутиновића Саралије. На тој свечаности Радуловић је као представник студената медицине и питомаца Текелијанума одржао поздравни говор. Наредне године (1839) говор је одржао на прослави празника Светог Саве, где је беседио на тему „Слово-Високопочитајмо Сабрание“ [2]. Као студент, био је пренумерант (претплатник) на велики број књига које су штампане у то доба. У Заводу је остао до 1842. године, када је на пештанском универзитету одбранио дисертацију под насловом „О медицинској гимнастици са становишта физиологије и дијететике“ (*De gymnastica medica physiologico et diaetetico respectu*). Дисертацију, коју је написао и исте године објавио на латинском језику, посветио је добротвору Сави Текелији [8] (слике 2, 3 и 4). Нажалост, о лику и делу др Димитрија Радуловића данас се зна веома мало. У тексту Хрватског друштва за спортску медицину наведено је да „спортска медицина у Хрватској има дугу традицију која, према документима, сеже у последње десетлеће прве половине 19. столећа. Доктор Димитрије Радуловић је 1842. године одбранио докторску дисертацију са темом „*De gymnasstica medica physiologica et diaetetico respectu* (Физиолошки и прехрамбени аспекти медицинске гимнастике)“, која је објављена у Пешти, а похрањена у Националној и свеучилишној књижници у Загребу. Аутор се због наведене дисертације сматра једним од доајена у знаности медицине спорта у нашој земљи. У свом квалификацијском раду Радуловић не


Lecturis Salutem!

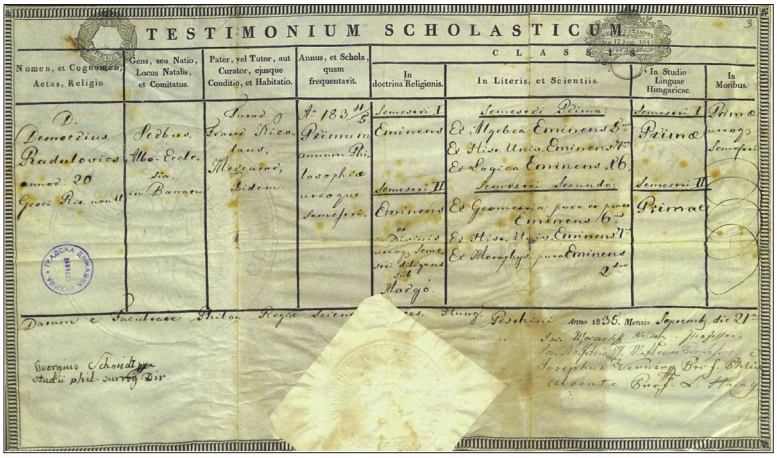
Praesentibus hisce literis testor, Dominum Demetrium Radulovits Medicum absolutum Muriahum in annum auditorem, hausta praevie de variola vaccina theoretica informatione, insitionem secundum artis regulas, me praesente, in infante instituisse, vaccinae decursum solerter observasse, collectas observationes per modum historiae rite conscripsisse, ac exhibuisse, et ita comprobasse, in vaccinae negotio bene se esse versatum.

Pesthini die 24 mensis Julii 1841

Слика 5. Уверење о завршеном курсу о лечењу великих богиња. Пештански универзитет 1841. године; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 5. Certificate for the completed course on treatment of smallpox, Pesta University, 1841; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1


NOS RECTOR
et Alma ac Celeberrima
Regia SCIENTIARUM UNIVERSITAS Hungarica
Lecturis salutem

Слика 6. Докторска диплома др Димитрија Радуловића стечена на Универзитету у Пешти 1842. године; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 6. Dr. Dimitrije Radulović's doctoral degree diploma, obtained at the University of Pest, 1842; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

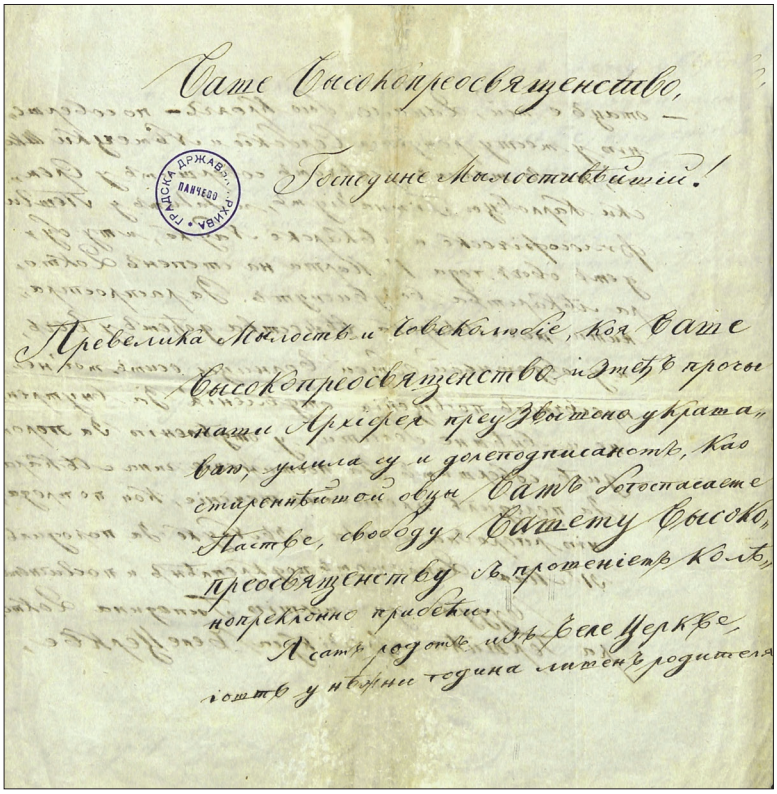

TESTIMONIUM SCHOLASTICUM

Слика 7. Сведочанство др Димитрија Радуловића са прве године филозофије (за 1. и 2. семестар), 1835; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 7. Dr. Dimitrije Radulović's school certificate for the first year of Philosophy Studies (for the first and second semester), 1835; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

расправља само о медицинској гимнастици као таквој већ и о могућностима превенције и лијечења болести суставном примјеном тјелесне активности, при чему сасвим субремено оцјењује важност кретања за људско здравље" [9]. Важно је поменути да се примерци дисертације др Димитрија Радуловића чувају и у Народној библиотеци Србије, у Библиотеци Матице српске и у Историјском архиву у Панчеву. Литература о доктору Радуловићу настајала је и у Србији и у Хрватској, али под сложеним друштвено-политичким околностима 20. века. У „хрватском" делу те литературе неки аутори чак оспоравају Радуловићеву припадност српском националном корпусу. Међутим, неоспорна је чињеница да у свим његовим документима пише да је он Србин. Др Радуловић је био заинтересован за различите области медицине. Године 1841. завршио је курс лечења богиња на Пештанском универзитету (Слика 5). Осим инфективних болести, интересовало га је и породиљство, о чему сведочи диплома од 11. јуна 1842. године о стеченом знању магистра породиљства на бечком Медицинском факултету [2] (Слика 6). Поред медицине, Радуловић је изучавао и „филозофске науке" на Пештанском универзитету. Ради се заправо о двогодишњем лицејском школовању, које је уобичајено претходило упису студија (Слика 7). О овоме сведоче сведочанства (*testimonium*) о положеним испитима из прве и друге године 1835/1836, као и писмо које је упутио 1. јуна 1842. године (по јулијанском календару) епископу вршачком (Јосифу Рајачићу) док се налазио у Бечу. У писму истиче да је изучио филозофију и да студира медицину, да ће студије завршити „ове године" и моли да га епископ Рајачић препоручи властима како би био именован за физика у Белој Цркви (Слика 8). У то време није било необично да студенти стичу знања из више области на више универзитета Аустријске монархије.

НАУЧНИ И СТРУЧНИ РАД И КАРИЈЕРА

У првој половини XIX века физичко и духовно здравље српског народа било је озбиљно нарушено великим и тешким ратним сукобима (Први и Други српски уста-



Слика 8. Молба др Радуловића епископу вршачком (Јосифу Рајачићу) да га препоручи властима за физика у Белој Цркви, 1842, Беч; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 8. A request letter written by Dr. Radulović to the bishop of the City of Vršac (Josif Rajačić) asking for his recommendation to the authorities for the position of a physician in Bela Crkva, 1842, Vienna; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

нак), док је здравствена просвећеност народа била на изузетно ниском нивоу. Биле су распрострањене многе болести за које није било лека. Младе животе је на првом месту односила туберкулоза. Често се дешавало да не буду у могућности (попут Јована Јовановића Змаја) да помогну члановима својих породица и себи. Честе су биле епидемије колере и трбушног тифуса [10]. За „правим лекарима се осећала највећа глад" [11]. Те велике народне потребе били су свесни младићи који су на пештански универзитет долазили из свих крајева у којима су живели Срби.

У време када је Димитрије Радуловић постао доктор медицине, на територији данашње Војводине, као и у Србији, гимнастика и вежбање нису се пропагирали као активности значајне за људско здравље. То је уследило тек после 1850. године. Следбеници др Радуловића у Војводини били су др Ђорђе Натошевић (1821–1887), др Радивоје Симовић (1858–1950), др Урош Чаковац (1898–1976) и др Петар Швар (1890–1981) [12]. Вест о промовисању Димитрија Радуловића у доктора медицине објављена је у „Србским народним новинама" 1. марта 1842. године [8]. Те новине излазиле су у Пешти, а њихов уредник и издавач био је др Теодор Павловић.[3] Извори за Радуловићеву дисертацију била су дела античких лекара Хипократа, Целзуса, Галена и других, као и дела Фридриха Лудвига Јана (*Friedrich Ludwig Jahn*), Франца Фулера (*Franz Fuller*), Карла Линеа (*Carl Liné*), Кристофа Вилхелма Хуфеланда (*Christoph Wilhelm Hufeland*) итд. [13]. Посебно је било значајно сазнање, схватање и писање о гимнастици и гимнастичком вежбању, како код деце, тако и код одраслих. Значајан део дисертације Димитрија Радуловића био је посвећен раду мишића приликом вежбања, као и функционисању нервног система и осталих система и органа. Вежбање је било сачињено од телесних покрета, како оних активних, тако и пасивних. Другим речима, вежбе су биле терапеутска гимнастика, којом су могли да се баве и деца и одрасли. Међутим, приликом избора вежби било је неопходно да се узму у обзир физичке карактеристике и физичка спремност човека коме су намењене. Посебно је интересантно Радуловићево објашњење о „вежбама дисајних органа" и њиховом значају. Тако се у часопису „Сербски народни лист" из 1842. наводи да се таквим вежбама „'бела цигерица' снажно шири и зато у њу много више ваздуха улази, а отуда је и проток крви много бржи. У ово вежбање дисајних путева спадају говор, декламовање, певање, свирање у двојницу или флауту" [14].

По стицању звања доктора медицине, др Димитрије Радуловић је покушао да упозна српску јавност са значајем гимнастике, вежбања и спорта [3]. У пештанском „Сербском народном листу" објавио је чланак у четири наставка под насловом „Лекарска гимнастика" [15]. Ти чланци били су засновани на појединим деловима његове докторске дисертације.

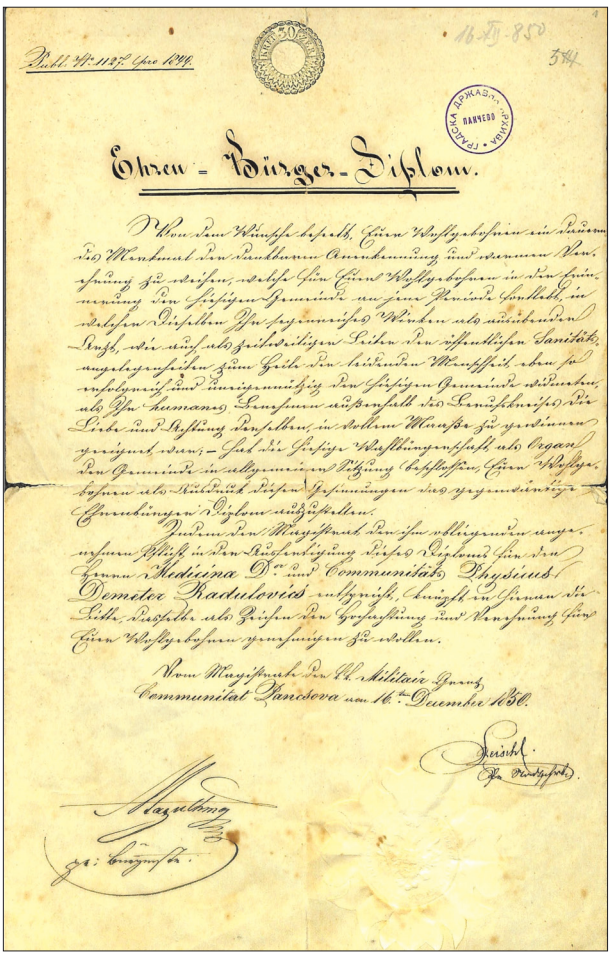
Први део Радуловићевог чланка штампан је у „Сербском народном листу" 26. јула 1842. године [16]. У њему су Олимпијске игре и олимпизам први пут поменути на просторима на којима су живели Срби. У уводу је дат кратак преглед телесног вежбања код Грка и Римљана. Поделу телесних вежби извршио је по Галену (129–200. н. е.), познатом римском лекару и филозофу грчког порекла. Чланак је употпуњен цитатима Хипократа, Целзуса, Галена и других старих и значајних лекара, а поделу телесних вежби др Радуловић је извршио следећи Јана и Гутсмутса (*Gymnastik für d. Jugend 1801.-Deutsche Turnkunst 1816*). Радуловић се у раду бави лекарском гимнастиком која се заснива на телесним вежбама за децу („педагошка (лекарска) медицинска гимнастика") и гимнастиком одраслих („гимнастиком за одрасле"). Препоручио је да се деца баве гимнастиком од своје прве године. „Будући да се између треће и шесте године детета кретање његових ногу и руку доста утврђује, гимнастика у то доба треба тежити, да се дечији чланци покретима покрећу" [15]. У делу чланака који се односи

3 Теодор Павловић (1804–1854) био је први секретар Матице српске у Новом Саду.

на вежбање одраслих нарочито је истицао да интензитет и тежина сваке вежбе морају бити прилагођени телесним могућностима појединца.

Последњи чланак о спортској медицини др Димитрије Радуловић објавио је у „Сербском народном листу“ 20. августа 1842. године [14].

По завршетку студија, Димитрије Радуловић је упутио молбу епископу вршачком Јосифу Рајачићу да га препоручи властима како би био именован за физика (градског лекара) у Белој Цркви [2]. Није познато да ли је Рајачић препоручио Радуловића властима или није. Међутим, Радуловић је октобра 1842. године поднео молбу за добијање дозволе за приватну праксу у Панчеву. У њој је навео да је по образовању доктор медицине и магистар породиљства (бабичлука). Дозволу за рад добио је од Генералне команде 21. децембра 1842. године [17]. Био је први лекар акушер у Панчеву. Међутим, 29. децембра исте године Радуловић је преко панчевачког магистрата упутио молбу Дворском ратном савету у Бечу да буде постављен на упражњено место лекара у земунском контумацу. За исто место су конкурисале и његове колеге из Панчева – др Петровић и др Коларовић, али ниједна молба није уважена, па су сва тројица остала да живе и раде у Панчеву. Свој живот др Димитрије Радуловић посветио је приватној лекарској пракси, гинекологији и акушерству. Велики напор је улагао у здравствено образовање мајки да би своју децу подизале на прави начин. Био је сарадник листа „Зимзелен“, који је излазио у Суботици. Године 1848. у том часопису је објављен његов чланак под насловом „О погрешкама и празноверицама при неговању деце“, који је штампан у оквиру Народног лекарског календара [18]. Календари су у то време сматрани за најважнију књигу коју народ треба да чита. Чланак др Радуловића био је подељен на осам целина са следећим насловима: „Дете не треба дати мати, докле се не крсти, јер ће прождрљиво бити; Што пре мати новорођено дете пољуби, тиме ће га више волети, нити ће му се икакво зло догодити; Не ваља децу у ново, него у старом месецу одбити, јер у новом месецу одбијена деца-зло и споро расту!; Дете не треба у зиму, када снег земљу покрива, одбити, јер ће рано оседети; Дете до треће године много разумније бива од другог; Дете млађе од године, не ваља да у огледало гледа, јер ће касније ослепети и полудети; Дете пузећи не ваља прекорачити, јер неће добро расти; Не ваља у огњене дане (*hundstage*) крв пустати, нити средство за столицу узети, јер ко то чини полуди“. Својим чланцима настојао је да у српском народу развије свест о значају лекара и укаже на недостатке и слабости видара. О проблему видара известио је Дирекцију штабног лекарства 1852. године. Добио је одговор да је у области Границе видарима дозвољен рад, и да тек у случају тешких и компликованих болести они имају обавезу да се за савет обрате дипломираним докторима медицине [2]. Међутим, лекари у Србији, за разлику од колега у Аустрији, били су дужни да пријаве надрилекаре властима, јер је проблем надрилекарства у Србији био регулисан Наставленијама за окружне лекаре и физикусе.


Ehren - Bürger - Diplom.

Слика 9. Повеља почасног грађанина града Панчева из 1850. године; Историјски архив у Панчеву, Збирка професора Ђорђа Живановића, Ф1
Figure 9. Muniment of the honorary citizen of the town of Pančevo from 1850; Historical Archive in Pančevo, Collection of Professor Đorđe Živanović, F1

Деветог априла 1850. године Генерална команда из Темишвара послала је панчевачком магистрату обавештење да је панчевачки лекар др Димитрије Радуловић постављен за комунитетског физикуса на упражњено место у Сремским Карловцима. Магистрату је наложено да Радуловића обавести о његовом постављању на место државног физикуса (службеника) и о обавези да положи заклетву. Тај налог магистрат је извршио и априла или маја исте године др Димитрије Радуловић је прешао на нову дужност [2]. Због пажње коју је посвећивао оболелима и своје стручности, 1850. године изабран је за почасног грађанина Панчева. У повељи коју је том приликом добио наведено је да је „током свог седмогодишњег рада као практични лекар, својом хуманошћу стекао поштовање у овом комунитету“ [2] (Слика 9). Међутим, пошто је у време добијања те повеље већ био на дужности у Сремским Карловцима, она му је уручена у том граду. Ово признање указује на то да је др Димитрије Радуловић оставио посебан траг у Панчеву. Пре њега као ни после њега ниједан лекар није постао почасни грађанин Панчева, иако је лекара на служби у том граду било много.

О ЛИЧНОСТИ ДР ДИМИТРИЈА РАДУЛОВИЋА

Др Радуловић је осим за медицину био талентован и за писање и реторику. Био је аутор неколико песама у десетерцу, насталих у периоду од 1833. до 1835. Са групом младих људи у Панчеву је 1843. покушао да организује позоришну дружину која би давала представе на српском језику [19]. Године 1847. венчао се са Јелисаветом Ристић, ћерком угледног белоцркванског трговца Христофа Ристића. У том браку имао је једно дете, које није живело дуго. Убрзо после смрти детета умрла је и његова жена (после 1850. године). После тога, др Димитрије Радуловић био је потпуно посвећен свом послу. После седам година живота и преданог рада у Панчеву, прешао је у Сремске Карловце, у којима је, као градски физик, радио до краја живота [20] (Слика 10). Школске 1860/61. године био је изабран за члана Патроната Карловачке гимназије, који је управљао гимназијом под окриљем Српске православне цркве. Др Димитрије Радуловић био је члан Патроната до смрти, 14. априла 1865. године (по јулијанском календару) [21]. У некрологу објављеном у листу „Напредак" 1865. године записано је: „Опет имадосмо жалосну дужност, да великог човека из наше средине до града допратимо; то беше др Димитрије Радуловић варошки физик и члан гимназијског патроната. Спровод беше свечан и леп, као што га и покојник заслужује, чинодржаше млоги свештеници са три архимандрита на челу и сам св. Патријарх при опелу био и очитао јеванђеље и молитве. Том приликом г. Протосинђелић Теофан Живковић изговори лепу надгробну беседу у вештом слогу пуну садржине и осећања, иза њега прочитао је професор Стојановић покојников живопис; сва господа варошка са целим отменим грађанством и гомилом осталог становништва као и многа господа из Варадина и Новог Сада стекоше се, да умрлом последњу пошту учине. У другу Радуловићу изгубило је наше место поштеног и честитог грађанина и лекара, што се по општој жалости за њиме најбоље види. Патронат гимназијски изгубио је члана, који је настојао око свога звања, одликовао се добрим срцем и савеснушћу и био примчив за изискивање напредујућег времена. Покојник је у млађе доба свој рад и на књижевном пољу, чланака његових било је у Павловићевом Србском народном листу, у Зимзелену итд. Лака му земља и велико хвала!" [22].


No 440

CERTIFICAT

Für den hierortigen ... welcher in ... Angelegenheit von hier nach ... zu reisen wünscht.

Demselben wird dieses Certificat zur Hin- und Rückreise auf ... Tage hiemit ertheilt.

Pr. k. k. Polizey Amt
Karlowitz den 21 März 1851.

Слика 10. Дозвола за рад у Сремским Карловцима [14]; Српска академија наука и уметности, Архив у Сремских Карловцима, КМА, 440

Figure 10. Work permit for Sremski Karlovci [14]; Serbian Academy of Sciences and Arts, Archives in Sremski Karlovci, KMA, 440

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Dr. Dimitrije Radulović, pioneer in the field of sports medicine – life, work and achievements

Nena A. Vasojević[1,2], Snežana Kirin[2,1], Mirko Filipović[3], Predrag J. Marković[4]

[1]University of Belgrade, History and Philosophy of Natural Sciences and Technology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Mechanical Engineering, Innovation Centre, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia;
[4]Institute for Contemporary History, Belgrade, Serbia

SUMMARY

In the historiography of Serbian medicine, there is little data on the life and work of Dr. Dimitrije Radulović. He belonged to the first generation of Serbian doctors of the 19th century. He was born in 1814, in Bela Crkva, completed his studies of medicine in Pest, where he received his title Doctor of Medicine. After Pest, he went to Vienna, where he specialized in obstetrics. Among Serbs, he was the author of the first work in the field which we today call sports medicine. With this work, as well as with his later work, he established important foundations of sports medicine among the Serbian people. He was the first to write about the importance of physical exercise and the impact of different sports on the physical development of children, adolescents, and adults, thus contributing to the definition of optimal physical activity and hygienic-dietary regimes. His goal was to preserve and improve health, i.e. to improve the prevention and curative of various diseases and injuries, as well as the rehabilitation of patients.

Keywords: medicine; sports medicine; scholarship; Tekelijanum; obstetrics

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење, прегледне радове, сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад, метаанализа, претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навесити као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор метаанализе и прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине - насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5.000 речи, а за претходно и кратко саопштење, приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и претплатници на часопис за годину у којој се рад предаје Уредништву, или измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3.000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

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AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100-250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

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TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) - if any - should be translated into English as well.

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All enclosures (tables, graphs, photographs, etc.) should be placed at the end of the manuscript, while in the body of the text a particular enclosure should only be mentioned and its preferred place indicated. The final arrangement (position) of the enclosures will depend on page layout.

ABBREVIATIONS. To be used only if appropriate, for very long names of chemical compounds, or as well-known abbreviations (standard abbreviations such as DNA, AIDS, HIV, ATP, etc.). Full meaning of each abbreviation should be indicated when it is first mentioned in the text unless it is a standard unit of measure. No abbreviations are allowed in the title. Abbreviations in the summary should be avoided, but if they have to be used, each of them should be explained when first mentioned in the text of the paper.

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UNITS OF MEASURE. Length, height, weight and volume should be expressed in metric units (meter – m, kilogram – kg, gram – g, liter – l) or subunits. Temperature should be in Celsius degrees (°C), quantity of substance in moles (mol), and blood pressure in millimeters of mercury column (mm Hg). All results of hematological, clinical and biochemical measurements should be expressed in the metric system according to the International System of Units (SI units).

LENGTH OF PAPER. The entire text of the manuscript - title page, summary, the whole text, list of references, all

enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian - must not exceed 5,000 words for original articles, review articles and articles on history of medicine, and 3,000 words for case reports, preliminary and short communications, current topics, articles for practitioners, educational articles and articles for "Language of medicine", congress and scientific meeting reports; for any other section maximum is 1,500 words.

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ARTICLE ENCLOSURES are tables, figures (photographs, schemes, sketches, graphs) and video-enclosures.

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Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
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