

СРПСКИ АРХИВ

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА ОСНОВАН 1872. ГОДИНЕ

ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

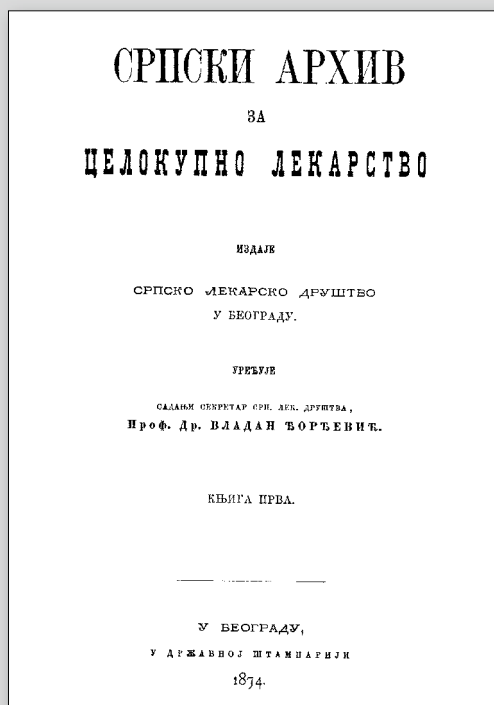


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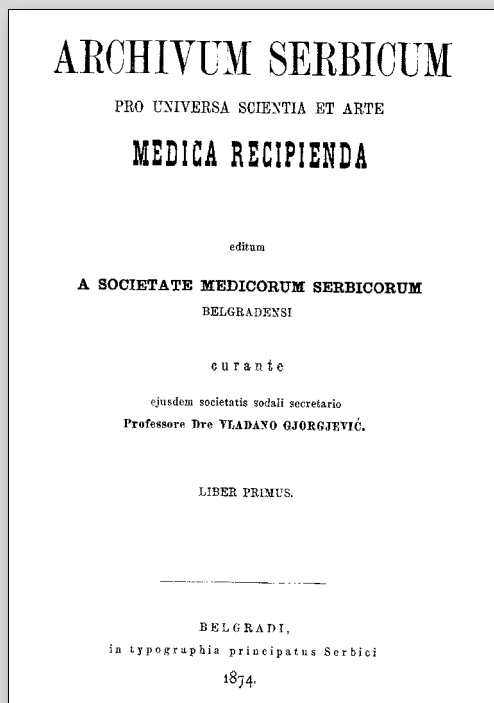
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Факсимил текста на српском језику на првој страници прве свеске часописа, објављене 1874. године (две године после оснивања часописа).



Facimile of the text in Latin language of the title page of the first Journal edition published in 1874 (two years after the Journal was founded)

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основан 1872. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Часопис објављује: оригиналне радове, саопштења, приказе болесника, прегледе литературе, актуелне теме, радове из историје медицине, радове за праксу, радове који се односе на језик медицине, радове из медицинске етике (клиничка етика, етика публиковања, регулаторни стандарди у медицини), извештаје с конгреса и стручних састанака, стручне вести, приказе књига и дописе за рубрике *Сећање*, *In memoriam* и *Promemoria*, као и коментаре и писма Уредништву у вези с објављеним радовима.

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Председник: академик Радоје Чоловић
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Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Телефон: +381 (0)11 3245 149
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Serbian Medical Society

Džordža Vašingtona 19, 11000 Belgrade, Serbia

Phone: +381 (0)11 3245 149

E-mail: srparhiv@bvcom.net

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The Correlation between Pain Perception among Patients with Six Different Orthodontic Archwires and the Degree of Dental Crowding

Evgenija Marković¹, Janko Fercec², Ivana Šćepan¹, Branislav Glišić¹, Nenad Nedeljković¹, Jovana Juloski¹, Rebeka Rudolf³

¹University of Belgrade, School of Dental Medicine, Department of Orthodontics, Belgrade, Serbia;

²University of Maribor, Faculty of Mechanical Engineering, Maribor, Slovenia;

³Zlatarna Celje, d.d., Celje, Slovenia

SUMMARY

Introduction Forces generated in orthodontic treatment with fixed appliances create tension and compression zones in the periodontal ligament resulting in a painful experience for patients. In the first phase of orthodontic treatment, when leveling of teeth is needed, nickel-titanium (NiTi) archwires can be completely engaged in brackets, even in the cases of extreme crowding, exerting small forces. There is a great individual variation in the pain perception related to the application of orthodontic forces.

Objective The aim of this study was to investigate the pain perception among patients with dental crowding after insertion of six different NiTi orthodontic archwires as a part of fixed appliances in the first stage of orthodontic treatment.

Methods The study was conducted on a sample of 189 orthodontic patients receiving one of six different either superelastic or heat activated NiTi archwires, in the first phase of orthodontic treatment. Pain perception was evaluated in groups of patients with different degree of crowding. The modified McGill Pain Questionnaire with Visual Analogue Scale was used to evaluate the quality and intensity of pain. Statistical analysis was performed using simple descriptive statistics, and Pearson's chi-square test with statistical significance of $p < 0.05$.

Results Majority of patients reported pain as discomfort or pressure of moderate intensity caused by chewing or biting, started within 12 hours, carried on for 3-4 days, and decreased over time without self-medication.

Conclusion No correlation was found between pain perception among patients with different types of NiTi archwires and the degree of crowding.

Keywords: nickel-titanium archwires; pain; dental crowding; orthodontics

INTRODUCTION

The initial discomfort experienced during orthodontic treatment for the first couple of days after force application is generally accepted as inevitable. Most orthodontic appliances deliver a relatively complicated set of forces and moments that are indeterminate and not quantitatively predictable. Many factors have been assumed to affect the perception of pain, namely the intensity and duration of applied forces, age and gender, degree of crowding, structure of wires, patient's psychological background and past experiences. There is a traditional belief of the existence of a relationship between the amount of force applied to the tooth and the degree of pain experience. Existing literature has indicated that patients may feel tension, pressure, soreness of teeth, and pain as a result of orthodontic treatment [1, 2, 3]. The prevalence of experiencing at least some degree of pain among subjects ranges from 70% to 95% [4].

Nickel-titanium (NiTi) alloys have been widely used in orthodontics, especially at the beginning of orthodontic treatment. This is

mainly due to their good mechanical properties, biocompatibility and ductility, resistance to corrosion, lower elastic modulus, superelasticity and shape memory effect (SMA). The superelasticity is the property of NiTi alloy to deflect on loading without plastic deformation, and return to its preformed shape after unloading. The alloy can be deformed up to 8% strain, which is useful in leveling severely misaligned teeth. Shape memory heat-activated NiTi archwires can return to their original shape, recovering from large strains throughout heating. While superelasticity is induced by stress, shape memory is initiated when the alloy in martensite phase is warmed and transformed to stable austenite phase in the specific range of temperature transformation. The deflection of heat activated alloy can generate locally stress induced martensite, which is unstable at oral temperature and undergoes reverse transformation to austenite as soon as the stress from misaligned teeth is relieved.

Wire is very pliable in the areas of crowded teeth exerting continuous force until the teeth move into a new position and reduction in deflection occurs [4-9].

Correspondence to:

Evgenija MARKOVIĆ
Gastona Gravijea 2
11000 Belgrade
Serbia
evgenijam@hotmail.com

OBJECTIVE

The aim of this study was to investigate pain perception among patients with dental crowding after insertion of six different NiTi orthodontic wires in the first stage of orthodontic treatment with fixed appliances.

METHODS

The scientific protocol was approved by the Ethic Committee of the School of Dental Medicine, University of Belgrade, and all subjects signed informed consent form to participate in this study.

The investigation was conducted on a sample of 189 orthodontic patients (84 male and 105 female) treated at the Department of Orthodontics, University of Belgrade satisfying the following criteria: 12-30 years of age, permanent dentition, no systemic medical or chronic conditions, no caries and periodontal disease and no history of chronic pain, depression and anxiety. Conventional 0.018 inch slot stainless steel brackets – Ricketts prescription (Equilibrium II metal brackets, Dentaaurum, Germany) were bonded. The following initial archwires (0.014 inch diameter) were randomly inserted and ligated: 1) Rematitan (Dentaaurum, Germany) – superelastic archwire; 2) Sentalloy (GAC, Japan) – superelastic archwire; 3) Truflex (Ortho Technology, USA) – superelastic archwire; 4) Rematitan Thermo NiTi (Dentaaurum, Germany) – heat activated archwire; 5) Truflex Thermo (Ortho Technology, USA) – heat activated archwire; 6) Damon Copper NiTi (Ormco, USA) – heat activated archwire.

At the end of bonding appointment all subjects were given the modified McGill Pain Questionnaire with Visual

Table 1. Distribution of individuals with different degree of crowding

Archwires	Mild crowding		Moderate crowding		Severe crowding	
	n	%	n	%	n	%
<i>Rematitan</i>	4	12.90	18	58.06	9	29.03
<i>Sentalloy</i>	11	31.43	13	37.14	11	31.43
<i>Truflex</i>	6	23.08	11	42.31	9	34.62
<i>Rematitan Thermo</i>	12	38.71	8	25.81	11	35.48
<i>Truflex Thermo</i>	17	53.13	8	25.00	7	21.88
<i>Damon</i>	10	29.41	15	44.12	9	26.47

n – number of subjects; % – percentage of subjects

Analogue Scale (VAS) and asked to fill it out until the next appointment (Figure 1). The Questionnaire consisted of questions concerning the cause of pain, type, location, duration, intensity, initiation of pain perception as well as the level of self-medication.

All patients received one of six either superelastic or heat activated archwires from different manufacturers. The patients were allocated to one of six groups with the same archwire and divided in regard to the degree of dental crowding in three groups: mild crowding (less than 4 mm of space deficiency), moderate crowding (from 4-6 mm of space deficiency) and severe crowding (more than 6 mm of space deficiency) (Table 1).

Statistical analysis was performed using simple descriptive statistics and Pearson's chi-square test with statistical significance of $p < 0.05$.

RESULTS

Mild crowding (Tables 2 and 3): The most frequently reported cause of pain (statistical significance) was chewing

Table 2. Distribution of pain parameters in patients with mild crowding and superelastic archwires

Superelastic archwire	<i>Rematitan</i> (n=4)			<i>Sentalloy</i> (n=11)			<i>Truflex</i> (n=6)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Rest	33	0.34	Biting	37	<0.05	Chewing	45	<0.05
Description	Discomfort/pressure	50/50	<0.05	Pressure	42	<0.05	Discomfort/pressure	20/20/20	0.52
Beginning	Immediately	50	1.00	After 6 days	60	0.20	After 6 hours	67	0.22
Duration	4 days	100	0	4 days	50	0.22	3/4 days	33/33	0.88
Intensity	4/5	50/50	1.00	4	40	0.41	2	33	0.96
Site/teeth location	Posterior teeth	50	1.00	All teeth	40	0.57	Anterior teeth	34	0.88
Medication	No	67	0.56	No	70	0.21	No	83	0.10
End of pain	Decreased	67	0.56	Decreased	60	0.53	Decreased	83	0.10

n – number of subjects; % – percentage of subjects; p – level of statistical significance

Table 3. Distribution of pain parameters in patients with mild crowding and heat activated archwires

Heat activated archwires	<i>Rematitan Thermo</i> (n=12)			<i>Truflex Thermo</i> (n=17)			<i>Damon</i> (n=10)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Chewing	41	<0.05	Chewing	52	<0.05	Biting	61	<0.05
Description	Sharp	42	0.07	Pressure/tingling	25/25	<0.05	Discomfort	40	0.52
Beginning	After 12 hours	55	0.18	After 6 hours	62	0.32	After 6 hours	80	<0.05
Duration	4 days	55	0.31	2 days	44	0.21	2 days	50	0.51
Intensity	7	36	0.59	4	44	<0.05	3/4	30	0.74
Site/teeth location	Anterior teeth	64	<0.05	Anterior teeth	44	0.57	Anterior teeth	40	0.57
Medication	No	90	<0.05	No	88	<0.05	No	90	<0.05
End of pain	Decreased	72	0.13	Decreased	50/50	1.00	Decreased	50/50	0.10

Patient name			
Age			
Crowding	Mild	Moderate	Severe
Extractions	NO	YES	
	Teeth		
	7 6 5 4 3 2 1	1 2 3 4 5 6 7	
	7 6 5 4 3 2 1	1 2 3 4 5 6 7	
Date of archwire insertion			
Type of archwire			
PLEASE ANSWER THE FOLLOWING QUESTIONS			
What was the pain trigger?			
1. No pain 2. Chewing 3. Biting 4. Cold food or liquid 5. Hot food or liquid 6. At rest 7. Only during the night 8. Physical activity			
Where did you perceive pain?			
1. Frontal teeth 2. Posterior teeth 3. All teeth 4. Upper jaw 5. Lower jaw 6. Head			
Describe the pain:			
1. Discomfort 2. Pressure 3. Tingling 4. Dull 5. Sharp 6. Pulsating 7. Headache			
On the scale from 0 to 10 (0 – no pain; 10 – the strongest pain you have ever experienced) please mark the pain you perceived after archwire insertion.			
0	1	2	3
4	5	6	7
8	9	10	
When did the pain start?			
1. Immediately after insertion of an archwire 2. 6 hours later 3. 12 hours later 4. Two days later 5. More than two days later			
Duration of pain			
• 1 day • 2 days • 3 days • 4 days • Longer			
Has the intensity of pain decreased over time?		YES	NO
Have you taken any pain medication?		YES	NO

Figure 1. Modified McGill Pain Questionnaire (MPQ) with Visual Analogue Scale (VAS)

Table 4. Distribution of pain parameters in patients with moderate crowding and superelastic archwires

Superelastic archwires	Rematitan (n=18)			Sentaloy (n=13)			Truflex (n=11)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Biting	38	<0.05	Biting	33	<0.05	Chewing	33	0.06
Description	Pressure	35	<0.05	Pressure	37	<0.05	Pressure	50	<0.05
Beginning	After 12 hours	39	0.29	After 6 hours	50	0.17	Immediately	40	0.90
Duration	4 days	33	0.49	2 days	50	0.11	4 days	38	0.27
Intensity	3	22	0.86	8	42	<0.05	5	30	0.86
Site/teeth location	All teeth	44	0.89	Upper jaw	58	<0.05	All teeth	63	0.36
Medication	No	75	<0.05	Yes	69	0.17	No	60	0.53
End of pain	Decreased	83	<0.05	Decreased	54	0.78	Decreased	78	0.09

Table 5. Distribution of pain parameters in patients with moderate crowding and heat activated archwires

Heat activated archwires	Rematitan Thermo (n=8)			Truflex Thermo (n=8)			Damon (n=15)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Biting	36	0.08	Rest	39	<0.05	Rest	33	<0.05
Description	Pressure	20	0.79	Pressure	43	<0.05	Pressure	38	<0.05
Beginning	After 12 hours	57	0.37	After 12 hours	50	0.60	Immediately	40	0.27
Duration	4 days	29	0.93	4 days	38	0.88	3 days	40	0.51
Intensity	6	29	0.98	7	25	0.99	7	33	0.37
Site/teeth location	Upper jaw	43	0.67	All teeth	75	<0.05	All teeth	47	0.18
Medication	Yes	57	0.70	No	50	1.00	No	60	0.44
End of pain	Decreased	57	0.70	Decreased	63	0.48	Decreased	87	<0.05

Table 6. Distribution of pain parameters in patients with severe crowding and superelastic archwires

Superelastic archwires	Rematitan (n=9)			Sentaloy (n=11)			Truflex (n=9)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Chewing	62	<0.05	Chewing	58	<0.05	Chewing	33	0.08
Description	Pressure	36	<0.05	Pressure	38	<0.05	Pulsating	30	0.05
Beginning	After 6 hours	56	0.26	After 6 hours	72	0.13	After 6 hours	50	0.42
Duration	4 days	67	0.09	4 days	37	0.63	4 days	88	<0.05
Intensity	4	33	0.80	4	27	0.76	7	50	0.39
Site/teeth location	All teeth	44	0.39	All teeth	27	0.70	Anterior teeth	63	0.19
Medication	No	78	0.09	No	72	0.13	No	50	1.00
End of pain	Decreased	75	0.16	Decreased	72	0.13	Decreased	50	1.00

Table 7. Distribution of pain parameters in patients with severe crowding and heat activated archwires

Heat activated archwires	Rematitan Thermo (n=11)			Truflex Thermo (n=7)			Damon (n=9)		
	Parameter	%	p	Parameter	%	p	Parameter	%	p
Trigger	Chewing	47	<0.05	Chewing	33	0.36	Chewing	50	<0.05
Description	Pressure	29	<0.05	Discomfort	38	0.17	Discomfort	40	0.09
Beginning	Immediately	55	0.18	Immediately	86	0.06	Immediately/ after 6 hours	33/33	0.75
Duration	3 days	36	0.80	2 days	43	0.67	2 days	56	0.26
Intensity	3	55	0.11	3	57	0.28	3	33	0.82
Site/teeth	All teeth	45	0.29	Anterior teeth	28	0.93	Anterior teeth	38	0.74
Medication	No	63	0.37	No	86	0.06	No	89	<0.05
End of pain	Decreased	64	0.337	Decreased	57	0.70	Decreased	67	0.32

in groups with Truflex, Truflex Thermo and Rematitan Thermo wires. Pain triggered by biting with statistically significant appearance was present in groups with Damon and Sentaloy archwires. Discomfort and pressure was present in all patients with mild crowding, except in subjects with Rematitan Thermo wire who reported sharp pain. Pain started immediately only in the group with Rematitan arcwire, whereas other groups of patients perceived pain after 6-12 hours of bonding appointment. Intensity of pain diversified between 2-7 on VAS. Sub-

jects usually perceived pain as a discomfort in anterior teeth which decreased in 2-4 days with no pain medication taken.

Moderate crowding (Tables 4 and 5): After ligation of archwire, pain in most of the patients was provoked either by chewing or biting, with exception to patients with Truflex Thermo and Damon archwire who perceived constant pain. All subjects perceived pain as pressure initiated right after insertion of wire or with delay of 6-12 hours. Discomfort with intensity ranging from 3-8 on VAS lasted 4 days

except in patients with Damon wire who were relieved after 3 days.

Severe crowding (Tables 6 and 7): Chewing was the dominant cause of pain in patients with all 6 archwires, with statistical significance in patients with Rematitan, Sentaloy, Rematitan Thermo and Damon archwire. Pain was perceived significantly as pressure and discomfort in groups with Rematitan, Sentaloy and Rematitan Thermo archwires. No statistical significance was found in reported site of pain as well as in intensity, which was 3-4 on VAS. Only subjects in the group with Truflex Thermo archwire perceived pain as pulsating and very strong (intensity 7). Most of the time, subjects did not take any medication for pain that decreased with time.

Generally, the majority of patients reported pain of moderate intensity that was triggered by biting or chewing and started within 12 hours after bonding appointment with no relationship to crowding. The types of pain, most commonly described by subjects, were pressure and discomfort that lasted 3-4 days and decreased in intensity over time without self-medication.

DISCUSSION

The present study was performed on a sample of 189 orthodontic patients who were given the modified McGill Pain Questionnaire with VAS to assess the quality and intensity of pain after insertion of initial NiTi orthodontic wire as a part of fixed appliances. It is well-known that correct measurement of pain is an essential part of its evaluation, and adaptation of methods to control it.

Various approaches have been used to measure and evaluate pain perception in orthodontic patients. The methods adopted vary from traditional surveys with pre-tested questionnaires to rating with Visual Analogue Scale (VAS) [10], McGill Pain Questionnaire (MPQ) [11], and Verbal Rating Scale (VRS) [12]. None of the proposed approaches on its own have provided a precise pain assessment in orthodontics and a miscommunication and poor management of pain in orthodontic patients were reported [13]. For that matter, the modified McGill questionnaire with VAS for orthodontic purposes was proposed in this study. The questionnaire included all aspects of pain quality such as: type of pain, timing, duration, location and intensity as well as necessity for pain management. The questionnaire was found to be accurate, appropriate and clear even to younger subjects who completely understood all questions.

Following insertion and ligation of six different NiTi wires subjects perceived pain. The mechanisms by which pain arises when orthodontic force is applied are not completely understood. It has been suggested that pain perceptions are due to blood flow changes in the periodontal ligament (PDL) [14, 15]. Other studies have indicated the presence of prostaglandins, substance P, and other substances to be associated with discomfort. Two types of pain have been described in the past literature including the immediate and delayed pain responses to

orthodontic treatment [16, 17]. Immediate response can be explained by the initial compression of the PDL. The delayed response is due to the partial compression of the PDL that still allows blood flow and over time results in hyperalgesia of the PDL which lowers the patient's pain tolerance. This type of pain develops a few hours after appliance placement and is caused by an increased sensitivity to prostaglandins, histamines, and substance P [18].

It has been previously reported that the magnitude of the force applied to teeth corresponds to the experienced pain [4, 19]. Therefore, the use of lighter forces has been recommended to reduce pain. However, other studies have found no relationship between the applied force and associated pain [20-23], and the controversy on whether or not light forces will decrease the degree of pain during tooth movement remains unanswered.

In the present study, 0.014 inch diameter wires were used for leveling in the first phase of orthodontic treatment in order to produce light forces even in cases with the most severe crowding. No differences in pain perception between patients with 0.014 and 0.016 inch NiTi archwires were found in a recent study [24]. The difference in pain response was not found when superelastic NiTi wires, conventional NiTi wires and stainless steel wires were compared [25].

A distinctive kind of force activation in superelastic and heat activated NiTi wires prompted their use in present study in order to determine if there were any differences in pain perception among patients with different wires. No statistical analysis was undertaken to compare perception of pain between patients with different types of archwire and the same degree of crowding due to a small number of subjects in each group.

In the present study, the quality and intensity of pain was not in correlation to the degree of dental crowding as well as the type of archwire. Since the pain during orthodontic treatment is mostly associated with the level of compression of the PDL, it may be hypothesized that both superelastic and heat activated NiTi archwires generate equal response of the periodontal ligament and blood vessels initiating the similar type of pain perception. Clinical and anecdotal observations have suggested a correlation between the degree of dental crowding (the intensity of forces applied by a fully engaged initial archwire) and pain. Studies revealed that the crowding at the start of treatment or the magnitude of force applied to the teeth by the archwire did not appear to affect the discomfort experienced by patients [12, 20], which was in agreement with the present study.

Two previous studies that attempted to compare pain intensities associated with application of different force magnitudes using a split-mouth design, found that higher forces were associated with stronger pain [22, 23]. In places where superelastic wire was engaged in the brackets of severely misaligned teeth, the wire did not follow the Hooke's law and exerted the same amount of force (stress) independent of the degree of activation (strain) [26]. Thus, it was expected that the amount of force applied to teeth would be the same no matter of the degree of crowding.

Results of the present study indicated that there were no significant differences in pain response in subjects with a different degree of crowding. Heat activated archwires undergo phase transformation at oral temperature. In the mouth, the wire is in austenite phase. In case of crowding teeth, stress is applied to wire and stress induced martensite is formed. Stress induced martensite is unstable at oral temperature and could be easily transformed into austenite when teeth change their position and stress is relieved. The amount of strain in the wire ligated in the slots of brackets of irregular teeth, again, is not the same as the amount of forces that wire applies to teeth. Therefore, the same amount of force was expected to be applied to teeth in mild and severe crowding [7]. Another explanation to similar pain perception in the patients with different degree of crowding would be that the force generated in the archwire is not the same (i.e. the force is higher in severe crowding), but the response from the PDL was the same if necrosis and hyalinization did not occur. Another study reported that the same degree of forces caused variations in blood flow in the PDL [27]. The authors questioned the validity of using the degree of force and pain response as a guide to the determination of the amount of hyalinization and damage to the PDL. Even if higher degree of deflection of archwire engaged in the brackets of misaligned teeth produces higher force to the PDL, the perception of pain is the same which is in agreement with the results of the present study.

The pain triggered by chewing and biting was most frequently reported by the patients. These results were consistent with findings of other studies that assessed the perception of pain during orthodontic treatment [3, 4, 12, 15, 28]. In the current investigation, the patients reported pain immediately after insertion of archwire or within the

next 6-12 hours with tendency to decrease. These findings were in agreement with previous studies in which pain increased and peaked between 4 and 24 hours after the application of force and then decreased [1, 3, 12, 24, 29]. The majority of patients from various studies reported pain as pressure or discomfort that lasted for 7 days with a gradual decrease which is in agreement with the present study [1, 3, 4, 30].

CONCLUSION

The patients of all six groups with different archwires and degrees of crowding had reported a similar perception of pain at the beginning of orthodontic treatment with fixed appliances. The pain perceived as pressure or discomfort was predominantly triggered by biting or chewing, started within 12 hours of archwire insertion, lasted up to 4 days with moderate intensity and decreased over time without self-medication. In an attempt to describe if the degree of crowding was associated with different pain perception no significant correlation was found. Information obtained from the questionnaire can help practitioners in patients' education of the quality and intensity of expected pain as well as adequate pain management.

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Зависност између перцепције бола код пацијената са шест различитих ортодонтских жица и тескобе зубних низова

Евгенија Марковић¹, Јанко Ферцеџ², Ивана Шћепан¹, Бранислав Глишић¹, Ненад Недељковић¹, Јована Јулоски¹, Ребека Рудолф³

¹Универзитет у Београду, Стоматолошки факултет, Клиника за ортопедију вилица, Београд, Србија;

²Универзитет у Марибору, Машински факултет, Марибор, Словенија;

³Златарна Цеље, д.д., Цеље, Словенија

КРАТАК САДРЖАЈ

Увод Ортодонтске силе којима се током терапије фиксним апаратима померају зуби доводе до истезања и компресије пародонталних влакана, те појаве бола код пацијената. У првој фази ортодонтског лечења, када се зуби нивелишу, жице од легуре никл-титанијума производе релативно малу силу и могу се потпуно лигирати у слотове бравица, чак и у случајевима велике тескобе. Постоје веома велике индивидуалне варијације у перцепцији бола приликом примене ортодонтских сила.

Циљ рада Циљ истраживања је био да се испита перцепција бола код особа с тескобом у зубним низовима након лигирања шест различитих ортодонтских жица у склопу прве фазе терапије фиксним апаратима.

Методе рада Студија је урађена на узорку од 189 пацијената којима је у оквиру ортодонтског лечења фиксним апаратима била лигирана једна од шест различитих супереластичних или термо жица од легуре никл-титанијума.

Перцепција бола је процењивана код особа с различитом израженошћу тескобе. Коришћен је модификовани Макгилов (*McGill*) упитник за бол с Визуелном аналогном скалом ради описивања квалитета и интензитета бола. Статистичка обрада података је обухватила дескриптивну статистичку анализу и примену χ^2 -теста са статистичком значајношћу од $p < 0,05$.

Резултати Највећи број испитаника је описао бол као непријатност или притисак средњег интензитета изазван жвакањем или додиром, који је почињао до 12 сати од лигирања жице, трајао је три-четири дана и смањивао се без примене лекова.

Закључак Није утврђена статистички значајна разлика у перцепцији бола код особа с различитом израженошћу тескобе зубних низова којима су биле лигиране супереластичне и термо жице од легуре никл-титанијума.

Кључне речи: легура никл-титанијума; бол; тескоба; ортодонција

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Regional Reference Values of Thyroid Gland Volume in Turkish Adults

Ertan Şahin¹, Umut Elboğa², Ebuzer Kalender²

¹Namık Kemal University Hospital, Department of Nuclear Medicine, Tekirdağ, Turkey;

²Gaziantep University Hospital, Department of Nuclear Medicine, Gaziantep, Turkey

SUMMARY

Introduction It is important to know the size of the thyroid gland, and its normal value may vary among different geographic regions.

Objective In this study, we aimed to establish reference ranges for thyroid volume in euthyroid adults and to compare these results with the literature data.

Methods Between June 2011 and June 2012, 461 patients with normal laboratory results (serum TSH, anti-TG, anti-TPO antibodies and urine iodine level) that underwent thyroid gland ultrasound examination were retrospectively analyzed. Two hundred and 92 patients were females and 169 were males; the age range was 18-61 years with mean age 30.84 ± 9.97 years. Length, breadth and thickness were measured, and the volume of each lobe was estimated using the ellipsoid formula.

Results The overall mean thyroid volume in all patients who were examined was 12.98 ± 2.53 mL. The mean thyroid volume in females and males was 12.09 ± 2.05 mL and 14.53 ± 2.55 , respectively ($p < 0.05$). The right thyroid lobe volume was greater than the left in all patients of both sexes. In addition, the study establishes a significant correlation between the thyroid volume and height, weight and body surface area of the subjects of both sexes ($p < 0.05$). In the light of our findings we can provide reference values in order to evaluate patients who have thyroid hyperplasia or who are considered as normal.

Conclusion We consider that further studies are necessary to establish national references thyroid volume for each country.

Keywords: thyroid; ultrasound; thyroid volume

INTRODUCTION

Accurate estimation of thyroid size is important for the evaluation and management of thyroid disorders. The ultrasonographic measurement of thyroid size is more accurate than palpation for the diagnosis of goitre [1]. According to its superficial anatomical location, the thyroid gland is easily accessible by sonography. Ultrasound is commonly used in epidemiologic studies, as a quick, safe, and non-invasive technique to estimate thyroid volume [2, 3, 4]. Computed tomography and magnetic resonance imaging provide structural information of the thyroid gland just like ultrasound but are relatively more expensive. In areas without significant iodine deficiency disorders, where the prevalence of visible goiter is low, the sensitivity and specificity of palpation are poor and goiter prevalence can be estimated using thyroid ultrasound [5, 6]. In recent decades, sonography has improved with the development of high frequency transducers, which allow a more detailed study of the thyroid gland [7]. On the other hand, intra and inter-observer variation can lead to differences in volume calculation on ultrasound. Small differences in ultrasound technique may introduce substantial errors in the measurements of thyroid volume, and the inter-observer variation can be high, even among experienced examiners [8]. Volumetric evaluation of the thyroid gland is

based on the use of the ellipsoid model. Hence, a value is obtained that replaces the clinical evaluation of volume. With the ellipsoid model, the length, width, and depth of each lobe are measured and multiplied. The obtained result is then multiplied by the correction factor [9].

OBJECTIVE

Several factors are known to be involved in the regulations of thyroid volume and different reports of the thyroid volume normal range are presented for different populations [10]. Suggestions are presented as to population-specific references for thyroid volumes and their determinants for each area [11]. In Turkey, there is absence of domestic reference for thyroid volumes. The aim of this study was to set normal values of thyroid volume in euthyroid adults of Turkey sonographically.

METHODS

This study was conducted as a retrospective cross-sectional study at the Nuclear Medicine Department of Gaziantep 25 Aralık Hospital. A total of 461 adults, consisting of 292 females and 169 males were included in the study. The age of the subjects ranged from 18-61 years; mean age was 30.84 ± 9.97 years. The study was

Correspondence to:

Ertan ŞAHİN
Namık Kemal University Hospital
Department of Nuclear Medicine
Tunca Street, 59100, Tekirdağ
Turkey
er_ahin@yahoo.com

retrospective and extended during the period June 2011 – June 2012. The study was approved by the University Medical Faculty Ethics Committee.

The criteria of subjects included in the study were: normal laboratory results (serum TSH, Anti-TG, Anti-TPO antibodies and urine iodine level), normal ultrasonography of thyroid parenchymal texture and absent nodule confirmed by sonography. Subjects with anterior neck swelling or clinical evidence of thyroid disease were excluded from the study. The following subjects were also excluded from the study: smokers, persons on lithium, phenytoin, oral contraceptive drugs, women during menstruation, pregnant women or women who had delivered within the last 12 months and persons with any systemic disorder.

Data were collected on age, sex, height, weight, thyroid size by sonography. Body weight and height were measured using standard anthropometric techniques. For the measurements of weight and height, the subjects removed their shoes and emptied their pockets. In all subjects body weight (kg) and height (cm) were measured to determine the body surface area (BSA). The BSA was calculated by the DuBois and DuBois formula [12]:

$$\text{BSA (m}^2\text{)} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$$

The ultrasound system which is a grey scale real-time ultrasound machine (Logiq 5 Pro, General Electric (GE) Healthcare, Milwaukee, USA), fitted with a 7.5 MHz transducer, was used for the study. The patients were examined in a supine position with hyperextended cervical spine. Ultrasound gel was applied over the thyroid area. The transducer was directly placed on the skin over the thyroid gland and the images of each lobe were obtained in transverse and longitudinal planes. The craniocaudal and the sagittal dimensions of both lobes were measured on the longitudinal image. The transverse dimension was measured on the transverse image. The thyroid gland volume was calculated using the formula below (AP diameter – depth; ML diameter – width; CC diameter – length):

$$\text{Tvol lobe} = \text{AP diameter} \times \text{ML diameter} \times \text{CC diameter} \times 0.479 \text{ (conversion factor)}$$

Statistics

The data was collected and analyzed using SPSS for Windows version 11. Thyroid volume was represented by the value of median and mean $\pm$ standard deviation. Student T-test was used for comparison in both sexes and Pearson's correlation coefficient was used to relate the thyroid volume to height, weight and BSA. $P < 0.05$ was taken as significant.

RESULTS

We studied 461 subjects, of whom 292 (63.3%) were females and 169 (36.7%) males, representative of healthy population, according to history, palpation, ultrasonography and laboratory results. The mean age of the subjects

Table 1. Volume (mean and SD) of thyroid glands in females, males and all cases

Subjects (number)	Thyroid volume (mL)	Right lobe volume (mL)	Left lobe volume (mL)
Females (292)	12.09 $\pm$ 2.05	6.48 $\pm$ 1.84	5.61 $\pm$ 1.58
Males (169)	14.53 $\pm$ 2.55	8.17 $\pm$ 1.53	6.36 $\pm$ 1.44
All (461)	12.98 $\pm$ 2.53	7.01 $\pm$ 1.94	5.97 $\pm$ 1.76

was 30.84 $\pm$ 9.97 years with a range of 18–61 years. The overall mean thyroid volume in all the patients who were studied was 12.98 $\pm$ 2.53 mL. The mean thyroid volume in females and males was 12.09 $\pm$ 2.05 mL and 14.53 $\pm$ 2.55 mL, respectively ($p < 0.05$). The mean volume of the right and left lobes of the thyroid gland in all of the patients were 7.01 $\pm$ 1.94 mL and 5.97 $\pm$ 1.76 mL, respectively. In females, the right and the left lobes of the thyroid gland volumes were 6.48 $\pm$ 1.84 mL and 5.61 $\pm$ 1.58 mL. In males, the right and the left lobes of the thyroid gland volumes were 8.17 $\pm$ 1.53 mL and 6.36 $\pm$ 1.44 mL. The right thyroid lobe volume was greater than the left in all patients of both sexes ($p < 0.05$). Table 1 shows the volume of the thyroid glands in females, males and all cases.

In our study, thyroid volume (mL) was positively correlated with weight, height and BSA in both sexes by Pearson's correlation which is presented in Graphs 1 and 2 (p values). By analysis the following results were obtained.

Males

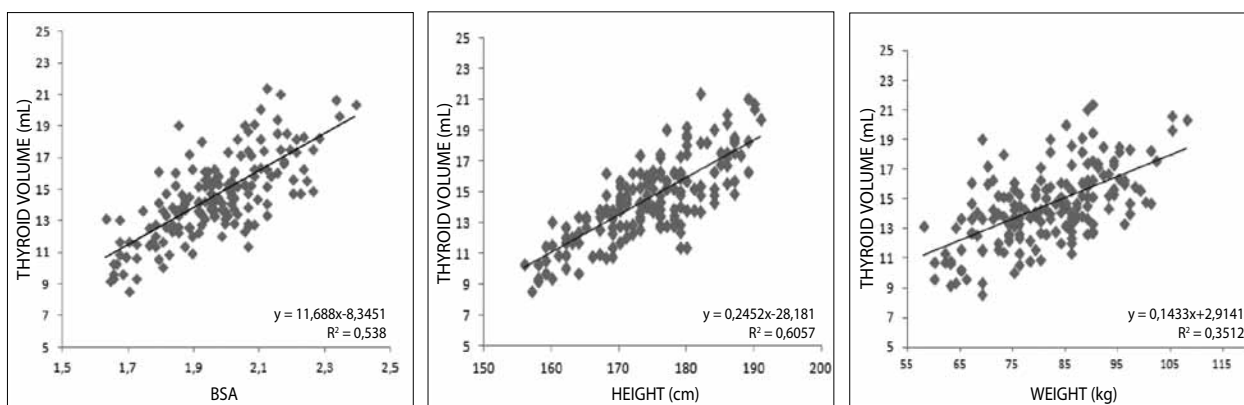
Pearson's correlation coefficient (r) showed strong, positive correlation between thyroid volume and subject's height (R: 0.78, $p < 0.00001$ and the result is significant at $p < 0.05$) with a linear regression equation of $y = 0.2452x - 28.191$, $R^2 = 0.6057$, where y is total thyroid volume (TTV) and x is height.

Pearson's correlation coefficient (r) of thyroid volume against subject's weight and BSA, respectively, showed a moderate positive correlation of thyroid volume with weight (R: 0.59, $p < 0.00001$ and the result is significant at $p < 0.05$) and BSA (R: 0.73, $p < 0.00001$ and the result is significant at $p < 0.05$). With a linear regression equation for weight as $y = 0.1433x + 2.9141$, $R^2 = 0.3512$, where y = TTV and x = weight and or BSA $y = 11.688x - 8.3451$, $R^2 = 0.538$, where y = TTV and x = BSA.

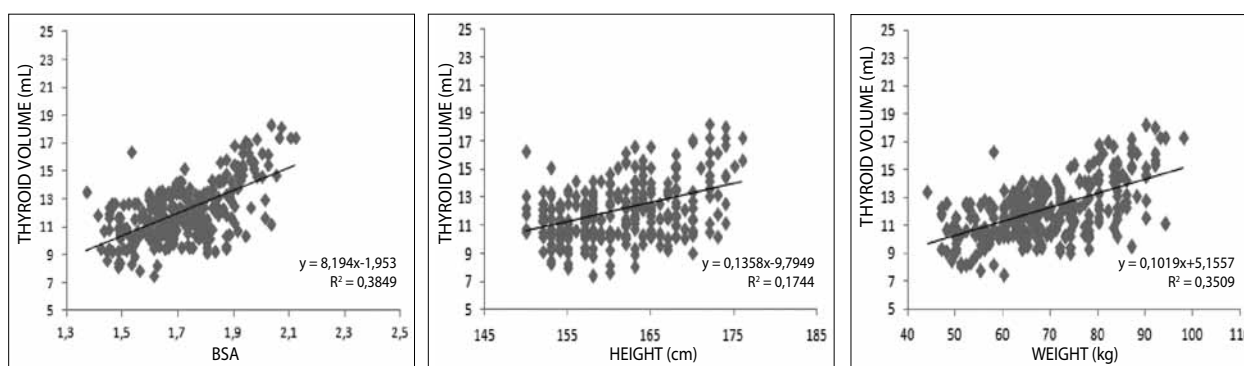
Females

Pearson's correlation coefficient (r) showed weak, positive correlation between thyroid volume and subject's height (R: 0.42, $p < 0.00001$ and the result is significant at $p < 0.05$) with a linear regression equation of $y = 0.1358x - 9.7949$, $R^2 = 0.1744$, where y = TTV and x = height.

Pearson's correlation coefficient (r) of thyroid volume against subject's weight and BSA, respectively, showed



Graph 1. The scattered plot of Pearson's correlation of thyroid volume against the subject's body surface area (BSA), height and weight in males



Graph 2. The scattered plot of Pearson's correlation of thyroid volume against the subject's body surface area (BSA), height and weight in females

a moderate positive correlation of thyroid volume with weight ($R: 0.59$, $p < 0.00001$ and the result is significant at $p < 0.05$) and BSA ($R: 0.62$, $p < 0.00001$ and the result is significant at $p < 0.05$). With a linear regression equation for weight as $y = 0.1019x + 5.1557$, $R^2 = 0.3509$, where $y = \text{TTV}$ and $x = \text{weight}$ and or BSA $y = 8.194x - 1.953$, $R^2 = 0.3849$, where $y = \text{TTV}$ and $x = \text{BSA}$.

DISCUSSION

As mentioned earlier, accurate estimation of thyroid size is important for the evaluation and management of thyroid disorders. According to its superficial anatomical location and the gland which has a different echogenicity compared with adjacent soft tissues, the thyroid gland is easily accessible by sonography [13].

Some factors such as iodine intake, genetic and geographic region affect the values of thyroid volume. Especially, consumption of oral iodine is the most important factor in thyroid volume and function. Therefore, patients with normal urinary iodine levels have included in our study.

Also, it is known that thyroid volume values vary in some physiological condition such as pregnancy. The thyroid size was found to increase during pregnancy and decreases up to 12 months postpartum period [14, 15]. The menstrual cycle also seems to associate with cyclical alteration of thyroid size in healthy women [15, 16]. That is why these subjects were excluded from our study.

In our study, the overall mean volume of the thyroid gland in all the patients was 12.98 ± 2.53 mL. According to our knowledge, there was no previous local study for comparison in our country. The thyroid volume among the Chinese that was studied by Hsiao and Chang [17] was 7.7 ± 3.3 mL, and this value is slightly lower than ours. This may be explained by the short height of the Chinese population in general because, as already established, the height of an individual correlates well with the thyroid size [17, 18]. As further discussed, in our study a strong positive correlation was found between the subject's height and thyroid volume. Also, our values are higher than those reported by studies conducted in Sudan, Nigeria and Iran populations [19, 20, 21]. The TTV in our study was obviously lower than that in Hegedus et al. study, which was conducted in Copenhagen with reported volumes found 19.6 mL and 17.5 mL in males and females, respectively [22]. It could be speculated that the Danish subjects were in fact iodine deficient to some degree or could be explained by the tall height of the Danish population [23].

It has been shown in many other studies such as these, the thyroid volume is associated with anthropometric measurements such as height and weight. In our study, the thyroid volume was positively related to body weight, height and BSA.

Especially in the males, a strong positive correlation between the subject's height and thyroid volume was found ($R: 0.78$, $p < 0.00001$).

Of course, the thyroid volume could not be entirely explained by weight and height, but also the thyroid volume is determined by other factors such as ethnicity. Genetic background and environmental factors could contribute to the variations of the results in these different geographic areas [21]. Therefore, previous reports suggest the need for population-specific reference.

Similarly to most previous studies, we found that the thyroid gland to be greater in males (14.53 ± 2.55 mL) compared to females (12.09 ± 2.05 mL). This difference between both sexes was statistically significant ($p < 0.05$). We conclude that the sex difference in the thyroid volume due to the structural anatomy is larger in males than that in females irrespective of BMI [10, 17, 22].

The volumes of the thyroid lobes obtained in this study showed that the right thyroid lobe volume was greater than the left and with significant statistical difference between the right and the left lobe volumes in both sexes ($p < 0.05$). These findings are similar to other studies [17, 24, 25, 26].

The mean thyroid volume in the males was greater than in the females. The volume of the right lobe of the gland was greater than the left in both sexes. These findings were similar to most of previous studies. On the other hand, ultrasonography is a technique dependent on the observer, and also genetic and environmental factors have influence on the thyroid volume.

CONCLUSION

In this study, we present the normal values of adults' thyroid volumes in the south-east region of Turkey. The overall mean volume of the thyroid gland in all the patients was 12.98 ± 2.53 mL, which was found to be significantly correlated with subjects' height, weight and BSA. Thyroid gland volume values were significantly different between males and females. The mean thyroid volume in females and males was 12.09 ± 2.05 mL and 14.53 ± 2.55 mL, respectively. To our knowledge, this is the first reference of thyroid volume measured by ultrasonography in Turkey. These values are recommended as reference values for use in south-east region of Turkey. According to this data, we tried to contribute to the establishment of the reference values in our country.

As the thyroid volume is associated with anthropometric measurements, genetic and environmental factors, we consider that further studies are necessary to establish national references for thyroid volume in Turkey and other countries.

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Регионалне референтне вредности волумена штитасте жлезде код одраслих особа у Турској

Ертан Шахин¹, Умут Елбога², Ебузер Календер²

¹Универзитетска болница „Намик Кемал“, Одељење за нуклеарну медицину, Текирдаг, Турска;

²Универзитетска болница у Газиантепу, Одељење за нуклеарну медицину, Газиантеп, Турска

КРАТАК САДРЖАЈ

Увод Важно је познавање величине штитасте жлезде, као и чињенице да њене нормалне вредности могу да се разликују зависно од географске регије.

Циљ рада Циљ истраживања је био да се утврде граничне референтне вредности волумена штитасте жлезде код еутиреоидних особа, а затим ови резултати упореде с подацима из литературе.

Методе рада Од јуна 2011. до јуна 2012. године ретроспективно је анализиран 461 болесник с нормалним лабораторијским резултатима (*TSH* у серуму, анти-*TG* анти-*TPO* антитела и вредности јода у мокраћи) који је подвргнут ултразвучном прегледу штитасте жлезде. Испитивану групу болесника чиниле су 292 жене и 169 мушкараца старости од 18 година до 61 године и средње старосне доби од 30,84±9,97 година. Мерени су дужина, ширина, дебљина и волумен лобуса штитасте жлезде помоћу формуле за елипсу.

Резултати Целокупна средња вредност волумена штитасте жлезде код свих испитаника била је 12,98±2,53 ml. Само код жена била је 12,09±2,05 ml, а код мушкараца 14,53±2,55 ml ($p<0,05$). Волумен десног лобуса био је већи од левог код свих болесника без обзира на пол. Сем тога, истраживањем је код испитиваних особа оба пола утврђена значајна корелација између волумена штитасте жлезде и висине, тежине и целокупне телесне површине испитаника ($p<0,05$). У светлу налаза наших испитивања можемо да наведемо референтне вредности у сврху вредновања болесника с хиперплазијом штитасте жлезде или оних код којих се ове вредности сматрају нормалним.

Закључак Сматрамо да је потребно да се обаве даља истраживања, како би се утврдиле националне вредности волумена штитасте жлезде за сваку поједину земљу.

Кључне речи: штитаста жлезда; ултразвук; волумен штитасте жлезде

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Risk Factors for the Development of Metabolic Syndrome in Obese Children and Adolescents

Nevena Folić¹, Marko Folić^{2,3}, Slavica Marković^{1,3}, Marija Andjelković^{3,4}, Slobodan Janković^{2,3}

¹Pediatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia;

²Department of Clinical Pharmacology, Clinical Centre Kragujevac, Kragujevac, Serbia;

³University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia;

⁴Department of Laboratory Diagnostics, Clinical Centre Kragujevac, Kragujevac, Serbia

SUMMARY

Introduction High prevalence of metabolic syndrome (MetS) in children and adolescents is a great concern of the modern society.

Objective Our aim was to determine the influence of previously investigated, but also and potentially novel risk factors for the development of metabolic syndrome in children and adolescents.

Methods Observational case-control clinical study was conducted involving children and adolescents with obesity/metabolic syndrome, treated on inpatient basis from January 2008 to January 2012 at the Pediatric Clinic of the Clinical Centre Kragujevac, Kragujevac, Serbia. The group of "cases" (n=28) included patients aged 10-16 years with the diagnosis of metabolic syndrome according to the International Diabetes Federation (IDF) criteria, while the control group included twice as many obese patients (n=56) matched to the compared group.

Results Presence of maternal gestational diabetes (OR_{adjusted}: 39.426; 95% CI: 1.822-853.271; p=0.019), and/or lack of breastfeeding in the first six months of life (OR_{adjusted}: 0.079; 95% CI: 0.009-0.716; p=0.024) were significant predictors for developing MetS. Also, microalbuminuria is associated with MetS in obese children and adolescents (OR_{adjusted}: 1.686; 95% CI: 1.188-2.393; p=0.003).

Conclusion Presence of maternal gestational diabetes and/or lack of infant breastfeeding are considered as relevant factors that may contribute to the increased risk of developing MetS syndrome, while microalbuminuria is frequently associated with MetS in obese children and adolescents.

Keywords: metabolic syndrome; child obesity; adolescent obesity; risk factors

INTRODUCTION

Metabolic syndrome (MetS) is a complex medical condition involving multiple inter-related factors that directly increase the risk of developing cardiovascular disease and type 2 diabetes mellitus, and includes abdominal obesity, dyslipidemia, glucose intolerance and hypertension [1]. Even though the current literature describes a wide range of cut-off criteria values used to define MetS in the pediatric population [2, 3, 4], the definition of the International Diabetes Federation (IDF) is generally accepted [5].

Obesity is considered one of the major components of MetS in the pediatric population. Rise in the prevalence of obesity in children and adolescents presents a global and severe problem of modern era, since excess weight is associated with various health problems in the pediatric population, and at the same time presents a significant risk factor for morbidity and mortality in adulthood [6].

Physical inactivity, inadequate and unhealthy diet and modern, "sedentary" lifestyle are the leading causes of the increase in childhood obesity, especially in developing countries [1]. According to the 2004 data of the International Obesity Task Force [7], 10% of schoolchildren aged 5 to 17 are overweight, and it is estimated that the prevalence of child-

hood obesity will continue to increase, as has been the case in recent years. In 2003/2004, percentage of obese children aged 2-19 in the USA was 17.1% [8]. It is interesting to note that among adolescents obesity is slightly higher in countries of Western and Southern Europe in comparison to Central and Northern Europe [9]. The prevalence of MetS varies not only depending on the population, but also the criteria defined for syndrome diagnosis. Cook et al. [3] estimated that the prevalence of the syndrome among youths aged 12 to 19 is 4.1%. According to the Bogalusa Heart Study [10], in the population aged 8-17 the prevalence is 3.6%. However, there is consensus that it is significantly higher in obese children [2].

Certain circumstances, beginning with birth (or even earlier), are linked to obesity and glycemic disorders, or MetS. The presence of maternal gestational diabetes [11], low/high birth weight [12], certain kinds of diet of newborns [13], early rise in "fats" [14], genetic factors, growing up in an "obesogenic" environment and the impact of socio-economic factors [15] are only some of the factors that may contribute to the increased risk for the development of these disorders in children. Early identification of children at risk of MetS, and prevention of progression to type 2 diabetes mellitus and cardiovascular disease later in life, is of great importance for their future wellbeing.

Correspondence to:

Marko FOLIĆ
Faculty of Medical Sciences
University of Kragujevac
Svetozara Markovića 69
34000 Kragujevac
Serbia
markof@medf.kg.ac.rs

OBJECTIVE

The aim of our study was to further evaluate risk factors for the development of MetS in children and adolescents.

METHODS

The study was designed as an observational case-control clinical study involving children and adolescents of Serbian nationality with obesity/metabolic syndrome, treated on an inpatient basis from January 2008 to January 2012 at the Endocrine Department of the Pediatric Clinic at the Clinical Centre Kragujevac, Kragujevac, Serbia. The study was approved by the Ethics Committee of the Clinical Centre Kragujevac.

The group of "cases" included 28 patients during the study period aged 10 to 16 years with the diagnosis of MetS according to the IDF criteria [5]. The control group included 56 obese patients (obesity was defined as waist circumference $\geq 90^{\text{th}}$ percentile for age and sex, according to Yugoslav standards [16]), randomly selected from the source population, matched to cases by gender, age and comorbidity (allergic rhinitis, asthma or epilepsy). Written informed consent was obtained from the parents of the participants, and an oral consent from each child.

In order to properly identify the risk factors and potential confounders for the development of MetS in children and adolescents, the following variables were monitored and analyzed in the study: patient's basic characteristics and clinical parameters/signs on admission (age, gender, comorbidities, waist circumference, body weight, height, BMI, blood pressure, heart rate, presence/absence of *Acanthosis nigricans*); basic blood chemistry panel (blood glucose, urea, creatinine, uric acid, alkaline phosphatase, direct bilirubin, total bilirubin, C-reactive protein, lipid profile (cholesterol, HDL, LDL, triglycerides), ALT, AST, GGT, HbA1c); fasting blood glucose levels, and levels at 120 minutes after glucose load, or fasting insulin levels and levels at 120 minutes (oral glucose tolerance test - OGTT with insulin levels); homeostatic indices of insulin sensitivity: HOMA and QUICKI; morning cortisol levels; microalbuminuria - in the quantitative urinalysis (24-hour urine).

The parent-related variables determined by the questionnaire were as follows: body weight, height, parental BMI; mother's pregnancy (controlled, special-care, use of medications in pregnancy, smoking, specific diseases such as gestational diabetes, pregnancy-induced hypertension, etc.); the presence of significant co-morbidities (assessing the existence of chronic diseases in the child's parents and immediate family); socioeconomic living conditions, family living area (rural/urban); level of parental education; birth order of children in the family; family diet (type of food, regularity of meals); smoking (active/passive); physical activity ("sedentary" lifestyle); existence of stressogenic family events (divorce, loss of a close person, loss of job, change of residence...); family attitude towards obesity.

The child-related variables that were determined by interviewing parents and children, were the following: birth weight, APGAR score; diet during the first months of life (breast/formula milk); physical activity/"sedentary" lifestyle; significant child comorbidity (existence of chronic diseases); significant co-medication in children (chronic drug therapy); diet - types of food, regularity of meals.

Patients from both groups underwent clinical examination on admission to hospital. Height and weight were measured without the subjects wearing shoes or heavy outer clothing. Standing height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Waist circumference was measured at the level of the narrowest point between the lower costal border and the iliac crest with non-stretchable measuring tape (produced by local Serbian manufacturer) while the patient exhaled slightly. While the patients were sitting, relaxed for more than 10 minutes, blood pressure (BP) was measured twice (each measurement 5 minutes apart), and the final BP was presented as the mean value of these measurements. *Acanthosis nigricans* was diagnosed by a dermatologist independent from the investigators. Blood chemistry was performed in the Laboratory Diagnostics Department of the Clinical Centre Kragujevac (according to standard operating procedure for laboratory diagnostics at the Clinical Centre Kragujevac), while the remaining components of the clinical study were conducted at the Pediatric Clinic of the Clinical Centre Kragujevac, pursuant to applicable hospital protocols.

HOMA index (Homeostasis Model Assessment) was calculated using a formula suggested by Matthews et al. [17]: $(\text{Gly0}(\text{mmol/L}) \times \text{Ins0}(\mu\text{IU/mL})) / 22.5$. On the other hand, the QUICKI index (Quantitative Insulin Sensitivity Check Index) was based on a logarithmic transformation model: $1 / (\log(\text{Ins0}(\mu\text{IU/mL})) + \log(\text{Gly0}(\text{mg/dL})))$ [18]. To calculate the index, a conversion of glycemic units from mmol/L into mg/dL with the mathematical formula: $\text{mg/dL} = \text{mmol/L} \times 18.0182$, was used.

For continuous variables, the significance of differences in cases of normal data distribution was tested by parametric tests (Student's t test), whereas in the case of irregular data distribution non-parametric tests were used (Mann-Whitney U test). For categorical variables, Pearson's χ^2 test was used to assess the significance of differences. The difference in the compared data was considered statistically significant if the probability of the null hypothesis was less than 5% ($p < 0.05$). The variables which turned out to be significant predictors/markers of the followed outcome of interest after the univariate logistic analysis were included in multivariate binary logistic regression. The SPSS statistical software was used for all calculations (SPSS Inc, version 18, Chicago, IL, USA).

RESULTS

In regard to the basic characteristics of patients in both the MetS study group and the obese control group, a significant difference between the study groups in body weight

(84.29±21.85 vs. 76.34±14.03 kg, $p=0.047$), waist circumference (95.46±9.58 vs. 91.04±8.41 cm, $p=0.033$), systolic blood pressure (134.11±14.60 vs. 128.39±8.26 mmHg, $p=0.024$) and diastolic blood pressure (83.57±11.21 vs. 78.84±9.63 mmHg, $p=0.048$) was identified using the Student's t test, while χ^2 test was used to determine the frequency of *Acanthosis nigricans* (35.7% vs. 10.7%, $p=0.006$) (Table 1). Regarding the age (12.93±1.96 vs. 12.43±2.07 years), BMI (31.77±4.93 vs. 30.14±3.06 kg/m²), heart rate (86.79±11.24 vs. 82.84±8.61 per minute), and the frequency of female subjects (57.1% vs. 53.6%), no statistical difference between the groups was observed ($p>0.05$).

A detailed analysis of blood chemistry panel in both groups using the Student's t test showed a significant difference between the MetS group and the group of obese patients in serum uric acid (356.32±32.70 vs. 340.98±32.30 $\mu\text{mol/L}$, $p=0.044$), glycosylated hemoglobin A1c (5.55±0.69 vs. 5.24±0.54 %, $p=0.030$) and GGT (22.39±10.64 vs. 18.37±6.99 U/L, $p=0.041$). Since irregular distribution of data related to the levels of AST and ALT was found, the difference between the compared groups in AST values (27.50±17.68 vs. 24.71±9.97 U/L, $p>0.05$) and in ALT values (26.04±20.30 vs. 19.93±11.04 U/L, $p=0.020$) was tested by the Mann Whitney U test. Student's t test showed significant difference in the values of total cholesterol (5.02±1.43 vs. 4.54±0.66 mmol/L, $p=0.035$), LDL (3.33±1.25 vs. 2.78±0.74 mmol/L, $p=0.013$) and a highly significant difference in the compared values of HDL (0.94±0.34 vs. 1.31±0.18 mmol/L, $p<0.001$), and triglycerides (1.95±1.10 vs. 1.12±0.42 mmol/L, $p<0.001$). Statistical difference between the observed groups was not detected ($p>0.05$) in values of urea (4.50±1.22 vs. 4.26±1.06 mmol/L), creatinine (69.39±18.03 vs. 62.45±16.83 $\mu\text{mol/L}$),

alkaline phosphatase (195.43±63.89 vs. 204.96±44.20 U/L), direct bilirubin (1.73±0.83 vs. 1.85±0.87 $\mu\text{mol/L}$), total bilirubin (13.21±3.20 vs. 14.45±3.46 $\mu\text{mol/L}$) and CRP (3.83±1.73 vs. 3.23±1.29 mg/l), which were mainly within reference ranges.

Comparison of cortisol values measured at 8 am and 4 pm, (within assessment of characteristic endocrine glands functions) using the Student's t -test identified the statistically significant difference in morning cortisol (measured at 8am) between the group with MetS and obese group (472.04±129.53 vs. 412.39±118.51 nmol/L, $p=0.038$), while this difference was not observed for 4pm values (243.21±74.36 vs. 217.14±54.72 nmol/L, $p>0.05$).

Regarding the comparison of differences in 24-hours microalbuminuria, significantly higher values were detected in the group of patients with MetS (7.04±4.96 vs. 3.05±1.81 mg/L, $p<0.001$).

Using the Student's t -test, the analysis of blood glucose and insulin values during OGTT showed a statistically significant difference between the study groups in blood glucose values at 120 minutes (6.93±1.18 vs. 6.38±0.93 mmol/L, $p=0.023$), but not in the values of fasting glucose (4.66±0.71 vs. 4.43±0.51 mmol/L, $p>0.05$). From the standpoint of statistical approach to fasting blood insulin levels and levels at 120 minutes, it was determined that the values of monitored parameters in both typical observation time points during OGTT were significantly higher in MetS patients (20.28±7.02 vs. 14.95±3.77 $\mu\text{IU/mL}$, $p<0.001$ and 140.41±49.98 vs. 100.45±39.76 $\mu\text{IU/mL}$, $p<0.001$). Using the Student's t -test, a highly significant difference was found when comparing the homeostatic indices of insulin sensitivity, HOMA (4.25±1.81 vs. 2.97±0.95, $p<0.001$) and QUICKI (0.312±0.013 vs. 0.327±0.014, $p<0.001$).

Table 1. Basic patient characteristics, typical blood chemistry profile of subjects and the values of glucose tolerance test with insulin levels by groups

Parameter/sign	Metabolic syndrome (n=28)	Obese group (n=56)	Test value; p value
Weight (kg)	84.29±21.85	76.34±14.03	$t=2.019$; $p=0.047$
Waist circumference (cm)	95.46±9.58	91.04±8.41	$t=2.171$; $p=0.033$
Systolic pressure (mmHg)	134.11±14.60	128.39±8.26	$t=2.293$; $p=0.024$
Diastolic pressure (mmHg)	83.57±11.21	78.84±9.63	$t=2.009$; $p=0.048$
<i>Acanthosis nigricans</i> (n, %)	10 (35.7)	6 (10.7)	$\chi^2=7.566$; $p=0.006$
Uric acid ($\mu\text{mol/L}$)	356.32±32.70	340.98±32.30	$t=2.043$; $p=0.044$
ALT (U/L)	26.04±20.30	19.93±11.04	$Z=-2.332$; $p=0.020$
GGT (U/L)	22.39±10.64	18.37±6.99	$t=2.073$; $p=0.041$
HbA1c (%)	5.55±0.69	5.24±0.54	$t=2.211$; $p=0.030$
Total cholesterol (mmol/L)	5.02±1.43	4.54±0.66	$t=2.138$; $p=0.035$
HDL (mmol/L)	0.94±0.34	1.31±0.18	$t=-6.505$; $p<0.001$
LDL (mmol/L)	3.33±1.25	2.78±0.74	$t=2.540$; $p=0.013$
Triglycerides (mmol/L)	1.95±1.10	1.12±0.42	$t=4.980$; $p<0.001$
Cortisol – 8 AM (nmol/L)	472.04±129.53	412.39±118.51	$t=2.108$; $p=0.038$
Microalbuminuria (mg/L)	7.04±4.96	3.05±1.81	$t=5.363$; $p<0.001$
Blood glucose 120 minutes (mmol/L)	6.93±1.18	6.38±0.93	$t=2.317$; $p=0.023$
Fasting blood insulin ($\mu\text{IU/mL}$)	20.28±7.02	14.95±3.77	$t=4.534$; $p<0.001$
Blood insulin 120 minutes ($\mu\text{IU/mL}$)	140.41±49.98	100.45±39.76	$t=3.979$; $p<0.001$
HOMA	4.25±1.81	2.97±0.95	$t=4.278$; $p<0.001$
QUICKI	0.312±0.013	0.327±0.014	$t=-4.797$; $p<0.001$

The data represent mean ± standard deviation (SD), or n/frequency. Only significant factors are presented for the sake of clarity.

Parent-related risk factors

A detailed analysis of parents' characteristics led to an interesting discovery – the Student's t test showed higher maternal body weight in the group of children and adolescents diagnosed with MetS (81.36 ± 11.85 vs. 77.07 ± 6.81 kg, $p=0.038$), as well as mothers' BMI (29.34 ± 4.33 vs. 27.25 ± 3.42 kg/m², $p=0.018$), and fathers' BMI (32.42 ± 5.99 vs. 30.25 ± 2.62 kg/m², $p=0.023$) (Table 2). The values of fathers' body weight did not differ significantly among the MetS group and the group of obese patients (102.25 ± 16.83 vs. 97.29 ± 7.84 kg, $p>0.05$).

There was also statistically significant difference in the presence of elevated cholesterol/triglyceride levels (abnormal lipid profile values) (82.1% vs. 58.9% , $p=0.033$), and the frequency of patients' parents with type 2 diabetes (67.9% vs. 44.6% , $p=0.045$) among the subjects in the group of patients with MetS and obese control group.

With respect to the family history of obesity (92.9% vs. 78.6%), arterial hypertension (92.9% vs. 80.4%), asthma (25.0% vs. 32.1%), and psychiatric illnesses (7.1% vs. 1.8%), as well as the regularity of meals (42.9% vs. 58.9%), frequency of spicy/fatty foods intake (89.3% vs. 82.1%), carbonated beverage intake (71.4% vs. 55.4%), regularity of fruit and raw vegetables in the diet (35.7% vs. 46.4%), existence of smokers in the family (92.9% vs. 76.8%) and parents' physical activity (7.1% vs. 8.9%), no significant differences were found between the group of children with MetS and the obese group ($p>0.05$).

Review and comparison of mothers' pregnancy-related data for children and adolescents in both study groups with respect to special-care pregnancy and application of tocolytic agents, showed a significantly higher frequency in the group with MetS (53.6% vs. 30.9% , $p=0.045$). Gesta-

tional diabetes was identified as a significant pathology in pregnancy, confirmed by the statistically significant difference within the studied groups (25.0% vs. 8.9% , $p=0.047$). In addition, there was a statistically significant difference regarding certain harmful habits of mothers during pregnancy, such as smoking (57.1% vs. 32.1% , $p=0.028$). In respect to the presence of pregnancy-induced hypertension (28.6% vs. 12.5%), no significant difference in the prevalence of pathophysiological phenomenon in mothers of children and adolescents in the observed groups was found ($p>0.05$).

The existence of a stressogenic family event (divorce of parents, loss of a close person, loss of job, change of residence), a significant risk factor for many diseases, was more prominent in children in the study group versus the control group (53.6% vs. 30.4% , $p=0.039$). In terms of socio-economic, demographic and other relevant factors related to the family setting, neither significant difference regarding rural/urban area of residence (urban - 64.3% vs. 60.7%), adequate, economic living conditions (57.1% vs. 66.1%), university education (at least one) of the parents (17.9% vs. 25.0%), "positive" family attitude toward obesity (50.0% vs. 42.9%) nor frequency of firstbornness (71.4% vs. 55.4%) were found between the observed groups of participants in the study ($p>0.05$).

Child-related risk factors as determined by surveying parents/child

Analyzing both perinatal data and general characteristics of interest related to children and adolescents in the observed groups, a significant difference between the MetS group and the group of obese patients was found regarding breastfeeding (natural food) in the first 6 months of life (32.1% vs. 60.7% , $p=0.014$) (Table 2), while no such difference was determined in body weight at birth (3416.07 ± 270.13 vs. 3335.36 ± 613.98 g) and APGAR scores (8.86 ± 0.59 vs. 9.08 ± 0.57) of children participating in the study ($p>0.05$).

It is interesting to note that between the children and adolescents with MetS and the obese children no difference in physical activity (14.3% vs. 19.6%), regularity of meals (three meals and two snacks) (25.0% vs. 39.3%), diets based on spicy/fatty foods (92.9% vs. 96.4%), i.e. based on the snacks and sweets (96.4% vs. 94.6%), regular presence of fruit and raw vegetables in the diet (28.6% vs. 41.1%), and consumption of soft drinks (64.3% vs. 67.9%) was found ($p>0.05$).

Multivariate analysis (logistic regression)

The results of logistic regression model are shown in Table 3. The multivariate binary logistic regression model, excluding the parameters typical for IDF definition of MetS in children and adolescents, showed a significant association between the development of MetS and microalbuminuria ($OR_{adjusted}$: 1.686; 95%CI: 1.188-2.393; $p=0.003$) and

Table 2. Characteristics of parents, children and families

Risk factors	Metabolic syndrome (n=28)	Obese group (n=56)	Test value; p value
Mother's weight (kg)	81.36 ± 11.85	77.07 ± 6.81	$t=2.105$; $p=0.038$
Mother's BMI (kg/m ²)	29.34 ± 4.33	27.25 ± 3.42	$t=2.414$; $p=0.018$
Father's BMI (kg/m ²)	32.42 ± 5.99	30.25 ± 2.62	$t=2.313$; $p=0.023$
Family history of elevated cholesterol/triglyceride levels	23 (82.1%)	33 (58.9%)	$\chi^2=4.527$; $p=0.033$
Family history of type 2 diabetes mellitus	19 (67.9%)	25 (44.6%)	$\chi^2=4.033$; $p=0.045$
Special-care pregnancy	15 (53.6%)	17 (30.9%)	$\chi^2=4.022$; $p=0.045$
Gestational diabetes	7 (25.0%)	5 (8.9%)	$\chi^2=3.938$; $p=0.047$
Mother smoked during pregnancy	16 (57.1%)	18 (32.1%)	$\chi^2=4.842$; $p=0.028$
Family history of stressogenic event	15 (53.6%)	17 (30.4%)	$\chi^2=4.266$; $p=0.039$
Breastfeeding during first 6 months of life	9 (32.1%)	34 (60.7%)	$\chi^2=6.099$; $p=0.014$

The data represent the mean $\pm$ standard deviation (SD), or n/frequency. Only significant factors are presented for the sake of clarity.

Table 3. Multivariate analysis of risk factors for the development of metabolic syndrome in children and adolescents

Risk factors	B	OR	95% CI		p
			Lower value	Upper value	
Microalbuminuria	0.522	1.686	1.188	2.393	0.003
Gestational diabetes	3.674	39.426	1.822	853.271	0.019
Breastfeeding during the first 6 months of life	-2.537	0.079	0.009	0.716	0.024

Only significant factors are presented for the sake of clarity.

B – coefficient of logistic regression analysis; OR – odds ratio; CI – confidence interval

maternal gestational diabetes (OR_{adjusted}: 39.426; 95%CI: 1.822-853.271; p=0.019), or breastfeeding during the first 6 months of life (OR_{adjusted}: 0.079; 95%CI: 0.009-0.716; p=0.024), while all the other potentially significant predictors/markers after univariate logistic analysis of the study groups as mother's BMI and weight, father's BMI, child/adolescent cortisol levels at 8AM, levels of ALT, GGT, uric acid, LDL, family history of elevated cholesterol/triglyceride levels, family history of type 2 diabetes mellitus, special-care pregnancy, maternal smoking during pregnancy, family history of stressogenic event were not predictive; Hosmer-Lemeshow Goodness-of-Fit Test for the conducted logistic regression model: $\chi^2=2.043$, df=8, p=0.980.

DISCUSSION

Whether a patient meets the criteria for the development of MetS may be adequately determined by observing the patient's medical history, physical examination and laboratory assessments. Globally, obesity in the pediatric population has been one of the major concerns of the modern era, and the increase in MetS prevalence is directly related to the degree of obesity in children and adolescents.

After analysis of risk factors for MetS development in children and adolescents, our study showed that the frequency of gestational diabetes in mothers of children and adolescents with MetS versus mothers of the obese study subjects was significantly higher. Specifically, the presence of maternal gestational diabetes was observed to be one of the factors that may contribute to the increased risk of obesity and type 2 diabetes in children [11], and recent research supports the development of MetS in children born to diabetic mothers as "large for gestational age" [19].

It should be noted that our study demonstrated that breastfeeding during the first months of life was clearly more prevalent in the obese children versus the children with MetS. Opinions on the correlation between the type of diet in the infant period and its repercussions on the development of obesity in later life are controversial. In the past, a dominant hypothesis was that during the first year of life the total number of adipocytes was completed, and that hypercellular obesity developed during this period carried a higher risk of persistent obesity [20]. Today, the assumption that the duration of obesity and not

the age at which it develops represents the crucial factor in determining the number of adipocytes is considered more likely [21, 22]. De Armas et al. [23], in their research which was based on the estimated correlation of breastfeeding and prevalence of obesity, i.e. development of MetS in obese children and adolescents, have demonstrated that breastfeeding longer than three months was associated with a lower degree of obesity, smaller waist circumference and significantly fewer potential complications associated with MetS in childhood and adolescence, and that as many as 64% of children with a complete picture of MetS were fed using formula milk. The assumption that nutrition mode in early childhood may influence the development of obesity in adulthood [24] is not uncommon either. Artificial nutrition, in fact, stimulates postnatal growth and subsequently a more intensive development of obesity in overweight children and adolescents, while in turn, breastfeeding is correlated with a slower pace of growth. Higher protein content in formula milk vs. breast milk is considered a significant factor influencing the rapid growth in the neonatal period. On the other hand, breastfeeding protects children from developing obesity by decreasing plasma insulin, significantly reducing fat reserves, and preventing early development of adipocytes [24].

Although gestational diabetes and maternal diet in the first months of life stand out as the leading risk factors for the development of MetS in the pediatric population, the univariate analysis used in the study showed that factors such as increased maternal body weight, mother's and father's body mass index, increased cholesterol/triglyceride levels, presence of diabetes mellitus type 2 and stressogenic family events, smoking during pregnancy, and special-care pregnancy may be considered the valid predisposing factors, review and analysis of which shall allow for timely and appropriate diagnostic approach to MetS in vulnerable children and adolescents, the attitude further supported by the results of numerous other studies [15, 21, 25, 26, 27].

Cortisol is an adrenal cortex hormone involved in the regulation of many physiological functions of the body. Anagnostis et al. [28] stressed the importance of cortisol in the development of MetS. The increased activity of the hypothalamic-pituitary-adrenal axis was observed in patients with MetS, which may be due to the exposure to chronic stress or low birth weight. In addition, it is well-known that glucocorticoids help adipocyte differentiation and proliferation [29] and that their receptors are more dense in the visceral than in the subcutaneous adipose tissue [30], which in turn leads to the increased cortisol exposure contributing to the increased accumulation of fat in visceral depots. Also, Khani et al. [31] have shown that cortisol significantly influences stimulation of gluconeogenesis. Elevated cortisol levels that may occur within MetS contribute to increased gluconeogenesis in the liver and impaired glucose metabolism.

Even though cortisol levels in our study reached statistical significance in the analytical estimates, this early diagnostic marker for MetS diagnosis cannot be consid-

ered significant, since the confidence interval included the value of one.

The epidemiological study conducted by Sanad and Gharib [32], analyzing only obese children, found the microalbuminuria incidence of 14.7%. These children were found to have a higher waist circumference, increased blood pressure, high triglyceride levels, low HDL levels, insulin resistance and elevated fasting glucose compared to obese children with absence of albumin in urine. Although opinions on microalbuminuria as a component of MetS still differ greatly [33, 34], its significance in the field of MetS is supported by the fact that recent recommendations of WHO suggest that the disorder should be included in the definition of this pathophysiological syndrome [35].

Results of our research also support that microalbuminuria should be a part of this syndrome in obese children and adolescents.

Main limitation of our study was a relatively small study sample, collected from only one study site; therefore, local influences underlying the risk factors could not have been eliminated. Besides, the values of some of the variables were reported by the children and their parents, and could not have been double checked.

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CONCLUSION

Based on our results, we could conclude that the presence of maternal gestational diabetes and/or lack of infant breastfeeding during the first months of life may contribute to the increased risk of developing MetS, while microalbuminuria is frequently associated with MetS in obese children and adolescents. Taking into account these factors, early identification of children and adolescents at risk of developing MetS may be improved, as well as the creation of preventive and timely strategies to prevent the occurrence of the syndrome or the development of potential complications (primarily cardiovascular diseases and diabetes mellitus type 2) in later life.

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Фактори ризика за развој метаболичког синдрома код гојазне деце и адолесцената

Невена Фолић¹, Марко Фолић^{2,3}, Славица Марковић^{1,3}, Марија Анђелковић^{3,4}, Слободан Јанковић^{2,3}

¹Клиника за педијатрију, Клинички центар Крагујевац, Крагујевац, Србија;

²Служба за клиничку фармакологију, Клинички центар Крагујевац, Крагујевац, Србија;

³Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија;

⁴Служба за лабораторијску дијагностику, Клинички центар Крагујевац, Крагујевац, Србија

КРАТАК САДРЖАЈ

Увод Висока преваленција метаболичког синдрома код деце и адолесцената општи је и забрињавајући проблем савременог друштва.

Циљ рада Циљ истраживања је био да се утврди утицај раније испитиваних и потенцијално нових фактора ризика на развој метаболичког синдрома код деце и адолесцената.

Методе рада Урађена је опсервациона клиничка студија испитивања случајева и контрола (енгл. *case-control study*) која је обухватила децу и адолесценте са гојазношћу, односно метаболичким синдромом, која су болнички лечена од јануара 2008. до јануара 2012. године у Педијатријској клиници Клиничког центра у Крагујевцу (Република Србија). Групу „случајева“ чинило је 28 испитаника узраста од 10 до 16 година са дијагнозом метаболичког синдрома сходно критеријумима Међународне федерације за дијабетес (*International Diabetes Federation – IDF*), док је контролну групу

испитаника чинило 56 гојазне деце и адолесцената сличних одлика и коморбидитета као компарирана група.

Резултати Заступљеност гестационог дијабетеса код мајке ($OR_{adjusted}$: 39,426; 95%CI: 1,822–853,271; $p=0,019$) и/или изостанак дојења у првих шест месеци живота детета ($OR_{adjusted}$: 0,079; 95%CI: 0,009–0,716; $p=0,024$) значајни су предиктори за развој метаболичког синдрома. С развојем метаболичког синдрома код гојазне деце и адолесцената удружена је и микроалбуминурија ($OR_{adjusted}$: 1,686; 95%CI: 1,188–2,393; $p=0,003$).

Закључак Гестациони дијабетес мајке и/или изостанак дојења детета у првих шест месеци по његовом рођењу сматрају се релевантним факторима који могу допринети повећаном ризику за развој метаболичког синдрома. Микроалбуминурија је такође веома често удружена с развојем овог синдрома код гојазне деце и адолесцената.

Кључне речи: метаболички синдром; гојазност деце; гојазност адолесцената; фактори ризика

Myocardial Bridges: A Prospective Forensic Autopsy Study

Jelena Micić-Labudović¹, Tatjana Atanasijević¹, Vesna Popović¹, Zoran Mihailović¹, Slobodan Nikolić¹, Dragana Puzović²

¹University of Belgrade, School of Medicine, Institute of Forensic Medicine, Belgrade, Serbia;

²University of Belgrade, School of Dental Medicine, Institute of Forensic Dentistry, Belgrade, Serbia

SUMMARY

Introduction When the coronary artery, located subepicardially, submerges into the myocardium and appears again subepicardially after a short intramural course, it represents an embedded coronary artery, while the part of the myocardium above is a myocardial bridge.

Objective We investigated the frequency of the embedded left coronary artery (LAD) in the autopsy material considering the descending branch of the LAD to be the most important one in the nourishment of the myocardium and myocardial bridges to be the most frequent in its area, as well as clinically important.

Methods A prospective autopsy study of 975 cases was performed, including both, natural (21.33%) and violent (78.67%) deaths. The sample consisted of 74.56% males and 25.44% females. In order to discover myocardial bridges and their characteristics, the hearts were examined by both transverse cuts and longitudinal openings of the LAD.

Results Myocardial bridge was found in 78 cases (8.00%), more commonly in males (9.35%) than females (4.03%). The average length of the myocardial bridge was 21.85 ± 16.10 mm and thickness 3.744 ± 1.48 mm. The common localization of the myocardial bridge was the proximal half of the LAD (89.74%). The upper part of the artery, proximal to the bridge, was a common site of atherosclerotic changes. Myocardial bridge was found in 12.50% of natural deaths, but in 13.38% out of all cases of sudden cardiac deaths.

Conclusion Therefore, the presence of the myocardial bridge by itself is not predominant, but it is certainly a contributing factor to a sudden cardiac death.

Keywords: myocardial bridge; forensic autopsy study; manner of death

INTRODUCTION

Embedded coronary is one of the congenital variations of arterial blood vessels of the heart and represents atavism. The coronary artery is submerged into the myocardium and after a short intramural flow reappears in the subepicardial fat tissue. The section of the myocardium above the embedded coronary is called a myocardial bridge (coronary artery overbridging) [1-4]. The myocardial bridge is situated almost exclusively above the front left descending coronary artery (LAD) and much less (in percentages) on the circumflex – DCA and the right coronary arteries – RCA [5, 6]. The LAD vascularizes the front section of the chamber partition and the lateral wall of the left chamber, however its branches vascularize the bundle of Hiss.

Myocardial bridges are usually small and have no clinical significance. If they become thicker they might show various symptoms: angina pains, tachyarrhythmia; they can also lead to the infarct of the myocardium and a sudden death. It is believed that symptoms associated with a coronary ischemia are the result of either a compression of the coronary artery by the myocardial bridge during a systole or delayed relaxation of the artery during a diastole or both [7, 8]. It is also believed that a change of

the blood flow, characteristic of these anatomic changes of the artery, has a considerable effect.

Bridging of the left coronary artery occurs more often in people with a dominant left coronary artery and with wider myocardial bridges; the artery lies deeper than in cases where the right side is dominant. When the myocardial bridges are present, there might be a certain degree of coronary artery stenosis in the systole; these are places where an arteriosclerotic process is localized more often.

OBJECTIVE

Considering the descending branch of the left coronary artery (LAD) to be the most important one in the nourishment of the myocardium, the myocardial bridges are most frequent in its area and therefore could have forensic importance, we investigated the frequency of the embedded LAD in the autopsy material.

METHODS

A prospective study of 975 autopsy cases was carried out at the Institute of Forensic Medicine, School of Medicine in Belgrade. Different to other similar studies where myocardial

Correspondence to:

Tatjana ATANASIJEVIĆ
Institute of Forensic Medicine
School of Medicine
Deligradska 31a
11000 Belgrade
Serbia
gatanasijevic@sbb.rs



Figure 1. Longitudinal section of the intramural LAD

bridges have been observed in a group of natural coronary deaths, our sample was defined in the way where all samples, regardless of the cause of death, were analyzed.

The frequency of myocardial bridges above the descending branch of the left coronary artery was defined in the overall population in such a way that, regardless of the cause of death, a group was established out of the whole sample, in which myocardial bridges were found.

In order to establish the number of myocardial bridges as well as their exact place and size, during dissections, the LAD was cut open along the whole length (Figure 1) alongside the standard technique (cross sections at 5 mm intervals). The length and the thickest part were measured in every detected myocardial bridge. The type of heart vascularization was established as well as any pathological change in the myocardium. Localization and degree of atherosclerotic changes on the LAD were also determined. The role of the myocardial bridge was analyzed in relation to other predisposed factors (gender, age and circumstances of each individual case).

The following statistical procedures were used: χ^2 test, 2-way analysis of variance (ANOVA), Pearson's product-moment, and Spearman's rank-order correlations. The *p* value smaller than 0.05 from statistical procedures were considered significant, and values ranging from 0.1 to 0.05 as marginally significant.

RESULTS

The analyzed sample of 975 cases of autopsy consisted of 248 women (25.44%) and 727 men (74.56%) thus making men statistically considerably more represented whilst the age distribution was even. Out of 975 cases, the myocardial bridge was found in 8% (78) of the bodies where the post-mortem was carried out – in the group where natural deaths occurred 12.50% and in violent deaths 6.78% ($\chi^2=7.1571$, *df*=1, *p*=0.0075). The existence of the myocardial bridge was noticed to appear significantly more frequently in men (9.35%) than in women (4.03%) ($\chi^2=7.1143$, *df*=1, *p*=0.0076) in middle-aged and older

people. Such differences in the frequency of myocardial bridge presence in different age groups reached the level of a marginal statistical value ($\chi^2=20.9801$, *df*=12, *p*=0.0507). The average age in the group of 78 individuals with the myocardial bridge was 51.88 ± 2.02 years, while the average age in the group of 897 individuals without the myocardial bridge was 50.34 ± 0.65 years.

In relation to the manner of death, in 208 cases death occurred naturally (21.33%) and in 767 cases violently. Proportional representation of the tested individuals, according to their gender in relation to their death, was tested with the χ^2 test ($\chi^2=3.9655$, *df*=1, *p*=0.0464); it showed that men were statistically more represented than women in all post-mortem materials, as well as in both groups of violent and natural deaths. Out of 208 natural deaths, 61.1% or 127 cases were sudden deaths due to heart failure.

The myocardial bridge is most often represented in the upper half (upper and middle third) of the LAD (89.74%), while in the lower half of the artery the myocardial bridge is represented in 10.26% (only isolated myocardial bridges were found).

In our sample a minimal length of the myocardial bridge was 5, maximal 70 mm; the average length was 21.85 ± 16.10 mm without any statistically significant gender differences (male 22.03 ± 16.41 mm, female 20.60 ± 14.56 mm). Minimal thickness of the myocardial bridge was 1 mm, maximal 8 mm and the average thickness was 3.744 ± 1.48 mm without significant gender differences (male 3.72 ± 1.44 mm, females 3.90 ± 1.79 mm).

The analyses of the variants showed that in the lower half of the front descendant branch of the left coronary branch, significantly longer myocardial bridges were found – 34.5 to 20.4 mm ($F=5.85$, *df*=1, *p*=0.0180); the thickness of myocardial bridges in relation to their position, while somewhat thinner myocardial bridges were found in the lower part of the front descending branch of the artery than in the upper half (3.62 to 3.75) without statistically significant differences ($F=0.06$, *df*=1, *p*=0.8128).

Localization of myocardial bridge does not depend on the type of heart vascularization (left 44%, right 28% and mixed 24%, $\chi^2=17.3200$, *df*=15, *p*=0.3001).

The border limit for the heart hypertrophy was the heart mass of 300 g; the heart mass up to 300 g was found in 12.82% and 10%, over in 87.18% – 68 cases.

In relation to the mass of the heart and the length of the myocardial bridge, marginal statistic significance was found (Pearson's correlation quotient $r=0.2$, *p*=0.0791).

Our results show that regardless of the existence of the myocardial bridge in 70% of cases, there was no evidence of a coronary atherosclerotic disease on the descending branch of the left coronary artery. However, some coronary atherosclerotic diseases were found in 30% (23 cases) and were exclusively located above the myocardial bridge. In older individuals (aged over 60), if there was a myocardial bridge, the frequency of atherosclerotic diseases was over 80%.

Presence of the myocardial bridge was established in the analyzed sample of 12.50% of natural deaths (26 out of 208) (Table 1).

Table 1. Manner of death and the presence of myocardial bridge

Myocardial bridge	Natural		Violent		Total	
	N	%	N	%	N	%
With	26	12.5	52	6.8	78	8.0
Without	182	87.5	715	93.2	897	92.0
Total	208	100.0	767	100.0	975	100.0

Out of all deaths, violent deaths occurred in 127 cases (61.05%) and in 17 of these cases (13.38%) the presence of the myocardial bridge was established. However, in 81 cases of natural deaths where the cause of death was not a heart disease, the myocardial bridge was represented in 9 cases (11.11%) whereas there were no statistically significant differences between the representation of the myocardial bridge in violent deaths and other causes of natural deaths ($\chi^2=1.134$, $df=1$, $p=0.287$).

Statistical analysis of the group with a myocardial bridge did not show any significant influence of the myocardial bridge thickness, either in the frequency of arteriosclerosis in the descending artery (Spearman -0.124 , $p=0.280$) or in a more frequent occurrence of natural cardiac death (Spearman $+0.108$, $p=0.346$).

DISCUSSION

Analyzing 1000 post-mortem cases of people who died of natural causes, Di Maio found that 60.9% deaths were caused by a sudden heart failure [9]. Congenital anomalies and variations of coronary blood vessels, amongst which is the embedded coronary, might be the cause of acute ischemic lesion of the myocardium and a sudden death in young people [10]. Depending on the study, whether it is autopsy or a clinical study – the frequency of myocardial bridges ranges from 0.5% to 16% in angiographic studies, up to almost 86% in autopsy studies; in our geographical area a post-mortem pathological study resulted in the frequency of 4.8% [11-16]. The frequency of myocardial bridges in our sample of 8.00% was more in accordance with angiographic findings than with the so far published results based on autopsy studies. It is realistic to expect a greater frequency of a myocardial bridge in clinical studies, because the examined patients already have heart problems. According to this, a recently published high frequency of cases in post-mortem studies can be explained by the choice of deaths caused by heart failures. Significantly higher percentage of myocardial bridges in the group where natural deaths occurred, rather than in the group of violent deaths, showed that the myocardial bridge could be a predisposing factor for the occurrence of a sudden heart failure and death. This is especially relevant for men where a myocardial bridge has been significantly more often noticed (9.35% males) than in women (4.06%).

Myocardial bridges appear on the average 33.8 mm below the beginning of the left coronary artery, while 82.6% of myocardial bridges are localized in the middle third [2, 17] – our study agree with this. In our sample over 13% cases show the so-called ‘tandem myocardial bridge’-

longer than 35 mm that affects both, the top and the middle segments, or the middle and the lower segments of the LAD [2].

The length of myocardial bridges varies from 5 to 50.2 mm [1, 2, 18]. Our study shows that the average length of a myocardial bridge is 22.03, closest to the results of Solte (22.5 mm) [17].

Analyzing the data considering the thickness of myocardial bridges, clinical researches show that the thickness varies from 1.0 to 3.8 mm [2, 17, 18]. Measures on the post-mortem material are from 0.131 to 12 mm [19]. The average thickness of a myocardial bridge of 3.75 mm that was found in our research is in complete agreement with the previous autopsy studies. Both the thickness and the length of the myocardial bridge directly affect the magnitude of the systolic compression of the submerging coronary artery. In publications it is found that the thickness grows with the length of a myocardial bridge [1]. Analyzing the relationship between the thickness and the length of myocardial bridges, we found that with the length the thickness of the myocardial bridge increases with marginally positive correlation ($p=0.0518$). It is interesting that in our sample the thickness of the myocardial bridge does not affect either the more frequent occurrence of proximal atherosclerosis or the more frequent occurrence of a sudden cardiac death.

Our results agree that the occurrence of ischemia has been identified in patients with a myocardial bridge in association with a hypertrophy of the heart [20, 21]. Namely, from 78 established myocardial bridges only in 13% of cases the hypertrophy of the myocardium did not exist. Such results show that the presence of the myocardial bridge may be one of predispositions for myocardial hypertrophy.

Karahan et al. [22] point out the connection between hypertrophy of the left chamber and the existence of a myocardial bridge. Our own results show that the average thickness of the left chamber in the group with a myocardial bridge is 15.286 ± 1.783 mm, whilst in the group without the myocardial bridge it is 16.295 ± 2.146 mm. At first sight, these results are in disagreement with the published ones, but it should be kept in mind that our sample incorporated individuals who died through violence, predominantly young and middle-aged people who did not have enough time to develop a significant hypertrophy of the left chamber. Also, there is a positive correlation between the frequency of a myocardial bridge and the mass of the heart.

One of possible mechanisms by which myocardial bridges cause ischemic diseases of the heart is increased tendency for arteriosclerosis in the segment proximal to the myocardial bridge due to a ‘shear stress’ effect caused by hemodynamic exchanges of the blood flow in the coronary artery and the dysfunction of the endothelium, whilst the endothelium below the myocardial bridge is structurally more resistant to atherosclerosis [2, 23]. Ishikawa et al. [1] have established a protective effect of the myocardial bridge in relation to arteriosclerosis; the greater the thickness and the length of the myocardial bridge, the rarer

is the occurrence of arteriosclerosis on the over-bridging area. This is explained by a difference in the contractile power of the myocardial bridge during the systole; this is in agreement with the previous angiographic studies showing myocardial bridges on the left descending branch together with hypertrophy of the heart, all leading to a much greater compression of the blood vessel and reduction of the blood flow [1, 24]. We found that arteriosclerosis is much more frequent if proximal to the myocardial bridge.

CONCLUSION

It is apparent that in individuals with a myocardial bridge there is no pathological substrate (length and thickness of the myocardial bridge, arteriosclerosis, heart hypertrophy,

etc.) on which the course and final outcome of this anatomical entity could be predicted.

From the forensic aspect, the most important fact is that the existence of the myocardial bridge, considered separately, is not a predominant factor for a sudden cardiac death, but a sufficient one when combined with the clinical history or ischemia confirmed by ECG and followed by the microscopic diagnosis of infarct in the dependent area of vascularization.

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Миокардни мостови – проспективна форензичка аутопсијска студија

Јелена Мицић-Лабудовић¹, Татјана Атанасијевић¹, Весна Поповић¹, Зоран Михаиловић¹, Слободан Николић¹, Драгана Пузовић²

¹Универзитет у Београду, Медицински факултет, Институт за судску медицину, Београд, Србија;

²Универзитет у Београду, Стоматолошки факултет, Институт за форензичку стоматологију, Београд, Србија

КРАТАК САДРЖАЈ

Увод. „Понирућа коронарна артерија“ је појам који се односи на случај када коронарна артерија – иначе локализована субепикардно – понире у миокард и поново се појављује субепикардно, после кратког пута кроз мишић, при чему се мишић изнад ње назива „миокардни мост“.

Циљ рада Истраживали смо учесталост понируће десцендентне гране леве коронарне артерије у аутопсијском материјалу имајући у виду да је она најважнија у исхрани срчаног мишића, да најчешће понире у срчани мишић и да је врло значајна и с клиничког аспекта.

Методе рада Урађена је проспективна аутопсијска студија 975 случајева природних (21,33%) и насилних смрти (78,67%). Узорак је обухватио 74,56% особа мушког и 25,44% женског пола. Ради откривања миокардног моста и анализе његових особености, нисходна грана леве коронарне артерије отварања је уздужним и попречним обдукционим резевима.

Резултати Миокардни мост је утврђен у 78 случајева (8,00%), чешће код мушкараца (9,35%) него код жена (4,03%). Просечна дужина миокардног моста била је $21,85 \pm 16,10$ mm, а дебљина $3,744 \pm 1,48$ mm. Најчешћа локализација миокардног моста била је у пределу проксималне половине десцендентне гране леве коронарне артерије (89,74%), а атеросклеротске промене су најчешће установљене усходно од миокардног моста. Миокардни мост је постојао у 12,50% случајева природних смрти, односно у 13,38% случајева тзв. напрасних срчаних смрти.

Закључак Постојање миокардног моста није преобладајући чинилац за појаву напрасне срчане смрти, али је његово постојање фактор ризика за њен настанак.

Кључне речи: миокардни мост; форензичка аутопсијска студија; порекло смрти

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Comparison of Functional Outcome of Colonic J-Pouch and Latero-Terminal Anastomosis in Low Anterior Resection for Rectal Cancer

Velimir Marković^{1,2}, Ivan Dimitrijević¹, Goran Barišić^{1,2}, Zoran Krivokapić^{1,2}

¹Clinic for Digestive Surgery, First Surgical Clinic, Clinical Center of Serbia, Belgrade, Serbia;

²University of Belgrade, School of Medicine, Belgrade, Serbia

SUMMARY

Introduction Functional results after low anterior resection for rectal cancer are an issue of increasing attention among colorectal surgeons and others interested in this subject. The consensus on ideal reconstruction type has not been achieved to date, although the number of papers on this subject has been published in recent years.

Objective We conducted a prospective, parallel group study comparing latero-terminal with colonic J-pouch anastomosis in terms of defecatory function in patients undergoing stapled low colorectal/coloanal anastomosis.

Methods A total of 80 patients were included in this study with either latero-terminal or colonic J-pouch anastomosis. Defecatory function was evaluated using the modified version of MSKCC questionnaire 6, 12 and 24 months after the operation. Fecal continence was evaluated using the Wexner continence score.

Results In both groups, trend towards improvement was registered in all measured variables in all three control intervals. This can apply to bowel frequency, urgency, night soiling, fragmentation and incomplete evacuation. However, the difference was not statistically significant, and when reviewing the trend of results we can note that in the J-pouch group steady state has not been reached even after 24 month control.

Conclusion This trial did not reveal any significant differences in defecatory function 6, 12 and 24 months after low anterior resection (LAR) between patients with a latero-terminal anastomosis and those with colonic J-pouch anastomosis. Our results did not confirm superiority of colonic J-pouch over the latero-terminal anastomosis

Keywords: low anterior resection; stapled anastomosis; colonic J-pouch; defecatory function; rectal cancer

INTRODUCTION

Functional outcome after low anterior resection (LAR) of the rectum is an issue of great importance for colorectal surgeons as well as for patients with rectal cancer. In order to alleviate the symptoms of "low anterior resection syndrome" a number of technical modalities has been introduced into surgical practice. Most commonly used are a latero-terminal anastomosis and colonic J-pouch – anal anastomosis. Since its introduction in 1986 by Lazorthes et al. [1] and Parc et al. [2] it has been argued that colonic J-pouch anastomosis is better option and a number of studies have demonstrated the advantage of this type of reconstruction [3-13].

OBJECTIVE

In most papers a short term functional outcome was the primary endpoint. In this article we attempted to compare defecatory function in 3 separate time intervals in order to evaluate the "medium" term outcome, and to determine potential advantages or disadvantages of these two most popular reconstruction methods.

METHODS

Between January 2000 and December 2004, a total of 80 patients with middle third or low rectal cancer were enrolled in the study. All operations were performed by the same surgical team. Forty patients were in each arm of the study. Nor pre or postoperative radiotherapy was administered.

Operative technique

After mobilization of the left colon, the inferior mesenteric artery (IMA) was divided just about 1 cm distal from the origin. Much of the sigmoid colon was preserved and used as the neorectum, but in some cases it was necessary to mobilize the splenic flexure. The rectum was mobilized down to the level of the anorectal junction following all the postulates of total mesorectal excision [14]. All vegetative nerves were preserved, except in rare cases of tumor invasion. The anal canal was closed 2-4 cm above the dentate line using a TA 30 linear stapler, and the rectum was transected. In the pouch group, colonic J-pouch, around 70 mm in length, was constructed using the sigmoid

Correspondence to:

Zoran KRIVOKAPIĆ
Clinic for Digestive Surgery
First Surgical Clinic
Clinical Center of Serbia
6 Dr Koste Todorovića Street
11000 Belgrade
Serbia
mbecambeca@yahoo.com

colon with the use of the GIA stapler. When a latero-terminal anastomosis was performed, the anvil of the circular stapling device was placed 3–4 cm from the end of the divided bowel. The end of the divided bowel was closed with a linear stapling device. Low colorectal anastomosis was carried out using the circular stapler No 31 or 33 in both groups. In all patients, a diverting ileostomy was created and closed approximately 2 months after the operation.

Clinical assessment

Tumor and anastomosis height were measured by digital examination and rigid proctoscopy. A questionnaire about defecatory function was completed by patients, with minimum assistance of medical staff, 6, 12 and 24 months following ileostomy closure. The feedback form was a modified version of MSKCC questionnaire asking patients to quantify the frequency of bowel movements, urgency, night soiling and painful evacuations. Also, the degree of incomplete evacuation, constipation and fragmentation was investigated. To quantify the level of fecal continence, the Wexner continence score was used [15].

Statistical analysis

Standard methods of descriptive and inferential statistical analysis were employed as well as functional statistical analysis adapted to the type and nature of analyzed data.

RESULTS

Age, gender, tumor height, anastomotic height, and Dukes' classification did not differ significantly between the two groups (Table 1).

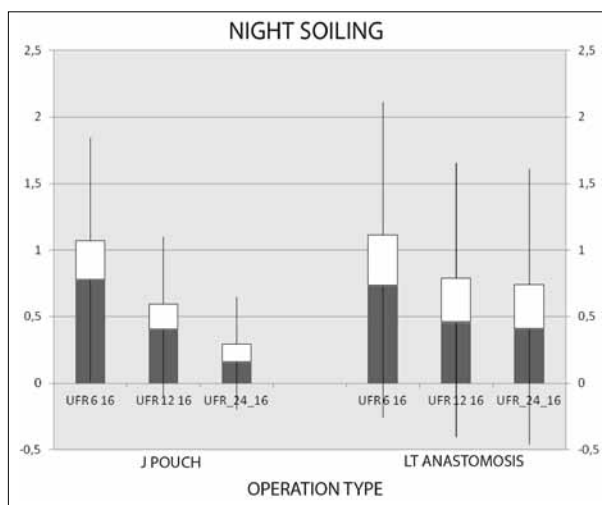
Elderly patients had greater need for additional help and incontinence for gas. In concordance with this, the elderly patients had inferior overall functional outcome, poorer emotional functioning and insomnia. All mentioned observations did not reach statistical significance.

In both groups improvement in measured variables was noted in all three control intervals. This can apply to bowel frequency, urgency, night soiling, fragmentation and incomplete evacuation. The difference was not statistically significant, but we noted that in the J-pouch group results had the trend of improvement even 24 month after the stoma closure while in the LT group they reached a steady state.

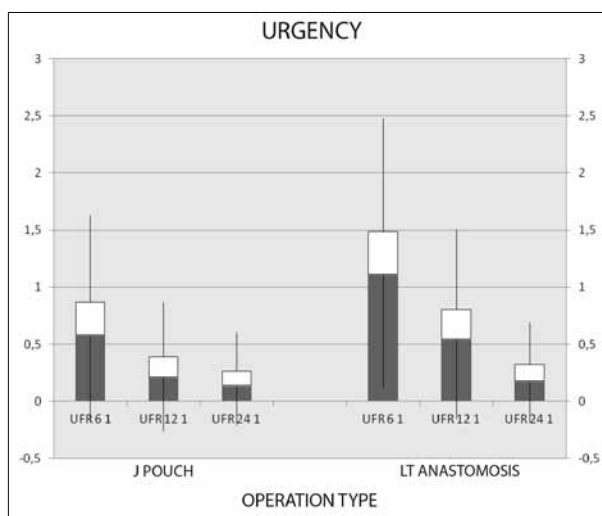
Table 1. Patients' characteristics

Characteristics	J-pouch	LT
Number of patients	40	40
Age, years (range)	55.25 (34–78)	56.4 (35–79)
Sex (female/male)	17/23	10/30
Dukes (A/B1/B2/C1/C2)	2/10/9/12/7	0/14/9/8/9
Level of anastomosis (cm)	2–4	2–4
Diverting stoma	40	40

LT – latero-terminal (anastomosis)



Graph 1. Trends of night soiling in three follow-up intervals



Graph 2. Trends of urgency in three follow-up intervals

Night soiling in the J-pouch group was less dominant compared to the latero-terminal anastomosis and there was a trend of further improvement (Graph 1).

More frequent urgency was noted in the latero-terminal anastomosis group in the first two follow-up intervals, but 24 months after, both groups had similar incidence of urgency (Graph 2).

When measuring constipation, in both groups results were worsened, with slight predominance in the latero-terminal anastomosis group.

Wexner score

According to the Wexner classification, poor result was noted in 3 patients (score 9–20), satisfactory in 7 (score 5–8), good in 11 (score 2–4) and excellent in 59 patients (score 0–1). Incontinence score results were better in the group of patients with J-pouch, but with no statistical significance.

Patients with documented anastomotic complications had significantly worse incontinence scores, probably due to scarring and consequent rigidity of the anal canal.

DISCUSSION

The superiority of colonic J-pouch over the latero-terminal anastomosis was reported by some studies [3-13]. Nevertheless, there are many factors which should be considered when trying to determine the “ideal” method of reconstruction after sphincter saving surgery for rectal cancer.

The number of studies and the difference in methodology confirms the fact that there is no optimal instrument for adequate assessment of postoperative functional results. Many studies dealt with functional outcome up to 2 years after sphincter preserving surgery for rectal cancer in relation to the reconstruction method (termino-terminal, latero-terminal, colonic J-pouch anal anastomosis and transverse coloplasty) [16-19].

Multiple regression analysis of factors that influence postoperative functional result showed that the frequency of defecation 12 months after surgery is directly related to the level of anastomosis and rectal sensation. This suggests that reservoir function of the rectum is essential in control of stool frequency.

It has been established that stool frequency is directly related to the level of anastomosis in patients where termino-terminal anastomosis was performed. In patients with this kind of anastomosis placed below 4-4.5 cm from the anal verge, there is an increased risk for frequent stools. This can be explained by the fact that instead of the rectum, an organ designated to be a stool reservoir is most commonly descendent or sigmoid colon, with a significantly lower compliance, and therefore inferior reservoir function. [20, 21].

Another reason for functional deficit after these operations is transection of the colonic wall, which itself creates discontinuity in the muscle and nerve network and disturbs „massive movements” of the colon [22-25].

The capacity of the neorectum is of paramount importance for good functional outcome. In the early postoperative period it is apparently superior in J pouch, but with time it increases both in J-pouch and latero-terminal anastomosis [8].

Anastomotic complications, narrow male pelvis and the level of anastomosis are generally considered to be the predictors of poor functional outcome [26, 27].

As an instrument for determining the functional outcome after rectal resection we used a modified MSKCC questionnaire [28]. This instrument was capable of identifying patients with a poor functional outcome, but using it we were not able to define the difference in relation to the reconstruction type, the level of anastomosis and the duration of postoperative period [28]. However, this questionnaire proved to be in concordance with other comparable instruments and therefore can be considered to be an adequate measure of defecatory function postoperatively.

Our research revealed complexity in assessing the functional outcome after rectal cancer surgery. All factors are multidimensional in essence influenced by objective physiological factors, as well as subjective ones: the level of education, cognitive status, cultural influence and social environment of the patient.

Both groups of patients, during two years of follow-up, showed improvement irrespective of the reconstruction type. Approximately similar degree of improvement was noted in all investigated factors, with no statistically significant difference between the two groups. It is however very important to stress that for definitive assessment and analysis of investigated factors, the follow-up period of two years was insufficient and further follow-up is needed.

CONCLUSION

Based on available literature data and our experience, all in the context of presented results, we conclude the following: total mesorectal excision is the method of choice in the treatment of rectal cancer. Sphincter preserving procedures directly influence the quality of life. Neorectal formation has the aim to diminish the functional deficit, basically by decreasing stool frequency. Patient selection is one of the essential preconditions for optimal functional outcome.

In this research we demonstrated only a slight functional advantage of colonic J-pouch compared to the latero-terminal anastomosis without significant difference. We believe that follow-up period of two years was insufficient to assess long-term functional results and further research with longer follow-up is warranted.

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Поређење функционалних резултата колонишног „J“ резервоара и латеро-терминалне анастомозе после предње ниске ресекције код карцинома ректума

Велимир Марковић^{1,2}, Иван Димитријевић¹, Горан Баришић^{1,2}, Зоран Кривокапић^{1,2}

¹Клиника за дигестивну хирургију, Прва хируршка клиника, Клинички центар Србије, Београд, Србија;

²Универзитета у Београду, Медицински факултет, Београд, Србија

КРАТАК САДРЖАЈ

Увод Функционални резултати после предње ниске ресекције ректума због карцинома су област која добија на значају и на коју све више пажње обрађују колоректални хирурзи и сви остали заинтересовани за ову проблематику. Не постоји сагласност о идеалном начину реконструкције после ових операција, иако је у последњих неколико година објављен велики број радова који обрађују ову тему.

Циљ рада Урађена је проспективна студија с паралелним групама где су поређени колонишни резервоар и латеро-терминална анастомоза у контексту дефекаторне функције код болесника с ниском колоректалном стаплерском анастомозом.

Методе рада У истраживање је укључено 80 болесника код којих је изведена латеро-терминална или анастомоза с колонишним резервоаром. Функција дефекације је процењена помоћу модификоване верзије упитника *MSKCC* шест месеци, годину дана и две године после операције. Фекална континенција је процењена применом упитника *Wexner Continence Score*.

Резултати У обе групе испитаника забележен је тренд побољшања код свих мерених варијабли у три поменута периода клиничког праћења. Ово се односило на фреквенцију пражњења, ургенцију, ноћно влажење, фрагментацију и осећај непотпуног пражњења. Поменуте разлике, међутим, нису достигле статистичку значајност, а сагледавањем тренда кретања резултата закључили смо да стационарно стање није достигнуто ни после 24 месеца у групи болесника с колонишним резервоаром.

Закључак Ова студија није доказала статистички значајну разлику у функцији дефекације шест месеци, годину дана и две године после предње ниске ресекције ректума због карцинома између две посматране групе болесника. Такође, наши резултати нису доказали предност колонишног резервоара као начина реконструкције после ресекције ректума у односу на латеро-терминалну анастомозу.

Кључне речи: предња ниска ресекција; стаплерска анастомоза; колонишни „J“ резервоар; дефекаторна функција; карцином ректума

Iatrogenic Ureteral Trauma: A 16-Year Single Tertiary Centre Experience

Dragoslav Bašić^{1,2}, Ivan Ignjatović^{1,2}, Milan Potić^{1,2}

¹Clinic of Urology, Clinical Center Niš, Niš, Serbia;

²University of Niš, Faculty of Medicine, Niš, Serbia

SUMMARY

Introduction Iatrogenic ureteral injuries can occur during various abdominopelvic and retroperitoneal surgical procedures including gynecological, urological, colorectal and vascular.

Objective The aim of our study was to examine the incidence and types of iatrogenic ureteral injuries occurred over the period of 16 years, as well as to evaluate the values of applied diagnostic and therapeutic procedures.

Methods A retrospective analysis of clinical data (medical records and operative reports) of 55 patients (11 male and 44 female; mean age 54.5 years) with verified iatrogenic ureteral injury from 1998 to 2014, was performed.

Results Iatrogenic ureteral injuries occurred during gynecological procedures in 55%, urological in 25%, colorectal in 15% and vascular in 5% of cases. Mechanisms of injury were incomplete transection (n=23), complete transection (n=1), ligation (n=7), partial perforation (mucosal abrasion) (n=13) and total perforation (n=1). The most frequent diagnostic procedures for postoperative identification of ureteral injuries were abdominal ultrasonography, excretory urography, antegrade pyeloureterography and retrograde ureteropyelography. Early therapeutic procedures were applied in 35 (64%), while delayed in 20 cases (36%). Early (<30 days) or late (>30 days) postoperative complications were verified in 14 cases (25%).

Conclusion Among different surgeries that may lead to the development of iatrogenic ureteral injury, gynecological procedures represent the most common cause. Rapid diagnosis enables immediate ureteral repair and is associated with low morbidity rates, representing a major factor contributing to the treatment success and ultimately preserving the renal function.

Keywords: iatrogenic ureteral injury; diagnostics; treatment

INTRODUCTION

Injuries to the ureter whether from the external or iatrogenic trauma are very rare and account for 1%-2.5% of all urinary tract traumas [1]. Retroperitoneal anatomic position of the ureter, as well as its mobility and flexibility, enable good protection from external trauma. In the majority of cases (>90%), either a partial or total ureteral injury is due to penetrating trauma, predominantly gunshot wounds and is often associated with collateral damage to other abdominal and retroperitoneal structures. Blunt trauma rarely occurs [2]. Iatrogenic ureteral injuries are more frequent and are usually isolated. The most common causes include complications of abdominopelvic procedures like gynecological, endourological, urological, vascular and colorectal, whether open or laparoscopic [3, 4, 5]. The mechanisms of operative injury to the ureter encompass partial or complete clamping, suture ligation, incomplete or complete transection, ureteral angulations with secondary obstruction, ureteral ischemia due to excessive denudation or electro coagulation, and partial or total perforation. Risk factors include re-do surgery, advanced tumors, inflammation, Ormond's disease, previous irradiation, ureteral duplication, and renal ectopia. The symptoms may appear immediately or after some delay [6, 7, 8].

OBJECTIVE

The aim of our study was to investigate the incidence and types of iatrogenic ureteral injuries over the period of 16 years, as well as to evaluate the value of applied diagnostic and therapeutic procedures.

METHODS

During the period January 1998 – January 2014 a total of 55 patients (11 male and 44 female), mean age 54.5 years (range 19-72 years), were verified with iatrogenic ureteral injury at the Urological Clinic of Clinical Center Niš. In this retrospective study, the medical records and radiographic studies of all patients were reviewed. For the purpose of the study, any adverse or inattentive injury to ureter during any surgical procedure, whether urological, gynecological, colorectal or vascular, was considered iatrogenic ureteral injury. All injuries were identified and verified by the urologist and necessitated some of the following procedures: intraoperative ureteral repair, postoperative endourologic or open urologic procedure. Iatrogenic ureteral injuries were classified by the affected ureteral segment (lumbar, iliac, pelvic), the type of surgical procedure that caused the

Correspondence to:

Dragoslav BAŠIĆ
Clinic of Urology
Clinical Center
Bulevar dr Zorana Djindjića 48
18000 Niš
Serbia
basicdr@gmail.com

injury as well as characteristics and mechanisms of iatrogenic injury by the type of the procedure. Diagnostic and therapeutic procedures were analyzed depending on the time of performance, as early – intraoperative or immediate – postoperative (<24 hours) and delayed procedures. Surgical complications were assessed by the type of the procedure and the time of appearance. Statistical analysis was done using Chi-square and Fisher's exact tests for variables comparison. P values of 0.5 were considered statistically significant.

RESULTS

A total of 55 patients were diagnosed with iatrogenic ureteral injury. In respect of the anatomic localization of the injury, the lumbar ureter was affected in 5 (9%), iliac in 13 (24%) and pelvic in 37 cases (67%).

Iatrogenic ureteral injuries occurred during the following surgical procedures: gynecological, urological, colorectal and vascular. Iatrogenic ureteral injuries by etiology are summarized in Table 1.

Mechanisms of iatrogenic ureteral injuries included: incomplete transection (23 cases) (Figure 1), complete transection (11 cases), ligation (7 cases), partial perforation (mucosal abrasion) (13 cases) and total perforation (1 case). Table 2 shows characteristics and mechanisms of iatrogenic ureteral injury by the type of the procedure.

Intraoperative or immediate postoperative procedures for iatrogenic injuries were applied in 35 cases and are summarized in Table 3.

Table 1. Etiology of iatrogenic ureteral injuries

Surgery	Number of patients	%
Gynecological	30	55
Urological	14	25
Colorectal	8	15
Vascular	3	5
Total	55	100

Table 2. Characteristics and mechanisms of iatrogenic ureteral injury by the type of the procedure

Procedure	Gynecological	Urological	Colorectal	Vascular	Total
Incomplete transection	20	-	2	1	23
Complete transection	7	-	2	2	11
Ligation	7	-	-	-	7
Partial perforation	-	13	-	-	13
Total perforation	-	1	-	-	1
Total	34	14	4	3	55

Table 3. Intraoperative or immediate postoperative procedures

Procedure	Gynecological		Urological		Colorectal		Vascular		Total
	Early	Late	Early	Late	Early	Late	Early	Late	
Incomplete transection	3	17	-	-	2	-	1	-	23
Complete transection	6	-	-	-	2	-	2	1	11
Ligation	5	2	-	-	-	-	-	-	7
Partial perforation	-	-	13	-	-	-	-	-	13
Total perforation	-	-	1	-	-	-	-	-	1
Total	14	19	14	-	4	-	3	1	55



Figure 1. Excretory urogram on the 1st postoperative day shows urinary extravasation due to incomplete ureteral transection

Surgical procedures for ureteral repair were performed in all cases. Depending on the type, extent and localization of the injury, early (<24 h) or delayed treatment were applied.

Early treatment was applied in 35 (64%) (Table 4).

All cases (n=20) with intraoperatively recognized injury underwent primary repair. In 15 cases, during the immediate postoperative period, the diagnosis was established by abdominal ultrasonography, excretory or multislice computer tomography (MSCT) and excretory urography. Additional antegrade pyeloureterography was performed in all cases with percutaneous nephrostomy and retrograde

Table 4. Early treatment

Procedure	Gynecological	Urological	Colorectal	Vascular	Total
Suture+DJ	2	-	1	1	4
UUS	-	1	1	1	3
PCN	5	9	-	-	14
UCN dir.	4	-	2	-	6
Psoas hitch	2	-	-	1	3
Boari	1	-	-	-	1
DJ	-	4	-	-	4
Total	14	14	4	3	35

UUS – ureteroureterostomy; PCN – percutaneous nephrostomy;
UCN dir. – direct ureteroneocystostomy; DJ – double J stent

**Figure 2.** (a) Left-side percutaneous nephrostomy tube due to ureteral ligation; (b) Antegrade pyeloureterogram shows left pelvic ureteral ligation site

ureteropyelography in cases with ureteroscopic ureteral injury (Figure 2a,b).

Ureteral suture (primary closure) with double J stenting was performed in four cases with incomplete ureteral transection (two gynecological, one colorectal and one vascular). Uretero-ureterostomy was performed in three cases after complete ureteral transection (one due to urological, one due to colorectal and one due to vascular surgery). In 14 cases, percutaneous nephrostomy was applied due to ureteral ligation because of gynecological procedure ($n=5$) or partial perforation (mucosal abrasion) due to endoscopic urological interventions ($n=9$). Of these, 5 cases with percutaneous nephrostomy after gynecological ligation underwent further (delayed) treatment. In the remaining 9 urological cases, since ureteral damage had resolved after 2-4 weeks, percutaneous nephrostomy had been extracted. Ureteroneocystostomy was undertaken in 10 cases, seven after gynecological (five with complete and two with incomplete ureteral transection), two after colorectal (one with complete and one with incomplete ureteral transection) and one after vascular surgery (due to complete transection). In one case a complete ureteral transection was overlooked during a colorectal procedure, and during the early postoperative period urinary drainage was the indication for revision and ureteroneocystostomy. By the type of the ureteroneocystostomy procedure, Lich-Gregoire was applied in six, psoas bladder hitch in three and Boari flap in one case. In all cases ureteral stenting by double J stent was performed during the procedure. Double J stenting for 4-6 weeks was used in four cases with a partial ureteral perforation (mucosal abrasion) due

to endoscopic urologic instrumentation. In all of them it was successful treatment option.

In the remaining 25 cases with iatrogenic trauma (including five with temporary percutaneous nephrostomy due to ureteral ligation), delayed operative treatment was applied. Diagnosis was established by radiographic studies, including MSCT urography with additional retrograde ureteropyelography for assessing the length of ureteral stump. Antegrade pyeloureterography was performed in all cases with temporary percutaneous nephrostomy tube.

Delayed procedures included ureteroneocystostomy (Lich-Gregoire, psoas bladder hitch or Boari flap), ureteral reconstruction by ileal segment interposition and nephrectomy (Table 5).

Ureteroneocystostomy was applied in a total of 21 cases (16 with ureterovaginal fistula due to incomplete ureteral transection and five with ligated ureter and temporary percutaneous nephrostomy). Direct ureterovesical anastomosis (Lich Gregoire) was performed in 15 cases (12 with ureterovaginal fistula due to incomplete ureteral transection during gynecological procedures and three with ligated ureter). Psoas bladder hitch technique was applied in three cases (two with incomplete ureteral transection and one with ligated ureter), while the Boari flap in the remaining three cases (two with incomplete ureteral transection and one with ligated ureter). In all cases, intraoperative a double J stent placement was performed. Double J stent was exteriorized at 21st postoperative day. In two cases, since ureteral ligation after gynecological procedure was detected late with grade IV hydronephrosis and severe deterioration of renal function, nephrectomy was done. In one case, nephrectomy was performed due to a complicated post-radiation urinary fistula. In one case, due to a high ureteral position of the fistula after incomplete transection, ileal ureteral reposition was applied (Figure 3).

Table 5. Delayed operative procedures

Procedure	Gynecological	Urological	Total
UCN dir.	15	-	15
Psoas hitch	3	-	3
Boari	3	-	3
Nephrectomy	3	-	3
Ileum	1	-	1
Total	25	-	25

**Figure 3.** Bilateral antegrade pyeloureterography shows good renal drainage after ileal ureteral replacement

A total of 14 cases (25%) were verified with early (<30 days) or late (>30 days) postoperative complications.

After intraoperative or immediate postoperative procedures, of 35 cases surgical complications were verified in four (11%). Of these, there were two cases of gynecological origin (both with direct ureteroneocystostomy Lich-Gregoire), one colorectal (postoperative urinoma) and one vascular (stenosis at the ureteroureterostomy anastomotic site). One gynecological case developed stenosis of ureteroneocystostomy so that a re-do surgery was performed successfully (re-ureteroneocystostomy Lich-Gregoire). Due to early postoperative double J stent migration in the second case, endoscopic replacement of the stent was performed. In the colorectal case with ureteroneocystostomy, urinoma was verified due to double J stent obstruction and the stent was replaced. There was one case with late stenosis at the ureteroureterostomy anastomotic site, following by the loss of ipsilateral renal function. In this case, nephrectomy was performed.

Major late complications were observed in five cases (20%); three with gynecological origin (one stenosis of ureteroneocystostomy and two prolonged drainage due to urinary extravasation) and two with urological origin (one urinoma due to double J stent obstruction and one lumbar ureteral stenosis at the ureteroureterostomy anastomotic site). In a case with neocystostomy (UNC) stenosis, the re-do surgery with reureteroneocystostomy Lich-Gregoire was performed successfully, while in the remaining two cases with gynecological origin of urinary extravasation that ceased after prolonged drainage. Urinoma in the urologic group discontinued after a double J stent replacement. In the case of late lumbar ureteral stenosis following ureteroureterostomy after complete ureteral perforation, a renal autotransplantation was performed.

Compared to early, delayed diagnosis and treatment were associated with higher major surgical complication rate, but the difference is not statistically significant ($\chi^2=0,458$; Fisher = 0.3489).

DISCUSSION

In 1868, Alfred Poland described ureteral avulsion in a young woman and it was the first report on ureteral trauma [9]. Later, in 1904, the first ureteral procedure was described by Henry Morris [10].

Iatrogenic ureteral injuries are usually caused by abdominopelvic surgery including gynecological, urological, colorectal or vascular procedures, with reported incidence between 0.3% and 10% in most series [4, 11, 12]. With regard to the type of surgical procedure, the majority of more than 50% of all ureteral injuries arises from gynecological surgery, with general surgery traditionally accounted as a second frequent cause with the reported incidence of 5-15%. Nevertheless, the latest reports demonstrate that improvements in gynecological and general surgical operative techniques have made it possible to reduce the incidence of ureteral injuries.

However, in recent years a widespread use of minimally invasive endoscopic and laparoscopic, as well as anti-incontinent procedures have increased urologically-induced ureteral trauma. It has been reported that urological procedures share 30% of all iatrogenic ureteral injuries [5, 13-16].

There are three groups of risk factors for iatrogenic ureteral injury: anatomical, anatomo-pathological and technical. Few normal anatomical circumstances complicate intraoperative identification of the ureter including ureteral adherence to the parietal peritoneum and its similarity to adjacent structures such as the lumbo-ovarian ligament and uterine artery. However, the ureter can be easily mistaken and transected or ligated. Moreover, since it is poorly vascularized by terminal arterial branches, it is highly vulnerable to stripping and any vascular periureteral damage can induce avascular necrosis, which usually becomes manifest a few days after surgery. The anatomo-pathological risk factors, as aforementioned, include the presence of congenital anomalies, retroperitoneal or pelvic tumors, uterine prolapse, endometriosis, previous surgery or radiation therapy. Numerous technical factors can increase the risk of ureteral injury. Some of these are associated injuries of abdomen or retroperitoneum, bleeding in the operating field that complicates the identification of ureter, blind clamping for hemostasis, the presence of advanced tumors, and inexperienced surgeons [17].

Iatrogenic ureteral injuries most commonly affect distal one third and pelvic ureter. It is consistent to our experience, since the lumbar ureter was affected in 9%, while in the remaining 91% it was ilio-pelvic segment [3, 6].

In our series, gynecological surgery accounts for 54% of all iatrogenic injuries, followed by urological, colorectal and vascular procedures, which is similar to pooled data from most studies [6, 7, 11]. The overall incidence of ureteral injuries due to gynecological surgery is 1.6 per 1000 procedures [3].

Diagnosis of ureteral injuries depends on the type and the extent of injury. Although the recognition of injury and the diagnostic procedure are typically delayed, the most preferred is early (intraoperative) diagnosis, if possible. Despite some controversies regarding the time of repair, it has been approved by most authors since late identification is commonly associated with high rates of complications including the loss of the renal unit [5, 18, 19].

Dobrowolski et al. [3], reported that only 11.5% of all iatrogenic ureteral injuries are diagnosed and managed intraoperatively. However, 70%-80% of iatrogenic injuries are diagnosed with a delay [20].

During open surgery, urinary extravasation in the operative field represents the most obvious event that enables easy recognition of ureteral injury. If it is not possible to identify the exact site of extravasation, intravenous administration of indigo carmine along with Lasix, or on-table excretory urography could be useful. In case of suspected ureteral ligation, it should be explored and deliberated from the ligature or clip. Afterwards, ureteral viability should be inspected. If it does not provide sufficient information, a retrograde ureteral catheterization through the

cystotomy should be attempted. In cases of partial ureteral transection, a primary repair by direct suture or spatulated anastomosis over the double J stent is recommended.

However, the degree of early iatrogenic injury recognition depends on the type of the procedure. Since the high suspicion index of injury is present in ureteroscopy, this procedure is associated with a high degree of early injury recognition. During the last two decades, the growing experience of urologists performing ureteroscopic procedures along with novel instruments have led to a dramatic decrease of iatrogenic injuries [21, 22, 23]. Nevertheless, most laparoscopy-induced ureteral injuries are still lately recognized [24-28].

Late recognition of injury is often associated with symptoms including fever, flank pain, hematuria, ileus or urinary fistula. If symptoms are present, urinary tract ultrasound should be done as a first choice tool. It can show the presence of hydronephrosis or urinoma. Although rare, bilateral ureteral injuries produce anuria, which can be easily recognized. In our series ultrasound was very useful since it can provide quick and non-invasive diagnosis. Besides, ultrasound-guided percutaneous nephrostomy can be easily performed as a temporary therapeutic solution enabling additional diagnostic procedures. It includes antegrade pyeloureterography (to assess ureteral injury) or ureteral stent placement. In our series, percutaneous nephrostomy was applied in the majority of cases and we strongly support it regarding all aforementioned advantages. The use of percutaneous nephrostomy in the initial diagnosis and/or treatment has been proposed by several authors [3, 6].

In the presence of symptoms, if ultrasound does not provide sufficient data, MSCT urography is preferred, since some authors have reported a low diagnostic value of excretory urography and frequent false-negative results [29]. However, any uncertainties from excretory urography require further investigation. It includes retrograde ureteropyelography. According to our experience which is consistent with several reports, it is a sensitive and specific tool in assessing characteristics of injury, such as the level and degree. Nonetheless, it could have therapeutic effect if the stent is placed safely and appropriate [30, 31, 32].

In our series, early diagnosis and treatment were applied in 35 cases (64%), 17 intraoperatively and 18 immediate postoperatively. Of these, 14 cases underwent percutaneous nephrostomy during the immediate postoperative period (<24 hours). Five of them (gynecological origin) were operated by delayed procedures while the rest of nine cases were with a nephrostomy tube without complications. Early identification of ureteral injury was carried out intraoperatively in 17 cases due to urine leak recognition (incomplete transection of dilated ureter - six cases; complete ureteral transection - 10 cases; total ureteral perforation - one case). In these cases, immediate ureteral repair was performed using the following urologic procedures: ureteral suture in four, end-to-end uretero-ureterostomy in three (with ipsilateral renal mobilization in one), Lich-Gregoire ureteroneocystostomy in six, psoas bladder hitch in three and Boari flap in one case. In all cases, the double J catheter stenting was performed along

with the procedure. As proposed by Koukuras et al. [33], we selected four cases for endourologic treatment of mucosal abrasion with double J stenting and it was a definite and successful treatment option.

In the remaining 18 cases, the diagnosis was established during the immediate postoperative period by renal ultrasound, MSCT urography and/or retrograde ureteropyelography. Intraoperative primary ureteral repair is reported to be in 30% of cases [34]. In a recent report by Papanikolaou et al. [35] more than half ureteral injuries during hysterectomy have been identified intraoperatively with a consequent primary repair.

In our series, a total of 20 (36%) cases were diagnosed with a delay. In all, including five with temporary percutaneous nephrostomy due to ureteral ligation, there were a total of 25 cases who underwent delayed operative treatment. Delayed procedures included ureteroneocystostomy (Lich-Gregoire, psoas bladder hitch or Boari flap), ureteral reconstruction by ileal segment interposition and nephrectomy. Ureteroneocystostomy was applied in a total of 21 cases (16 with ureterovaginal or ureterocutaneous fistula due to incomplete ureteral transection and five with ligated ureter and temporary percutaneous nephrostomy). As aforementioned, in three cases, nephrectomy was done and in one case ileal ureteral reposition was applied. According to our experience, delayed diagnosis and treatment were associated with a higher major surgical complication rate, but the difference is not statistically significant.

It has been reported that maintaining a high index of suspicion along with full recognition of predisposing pathology are of utmost importance for managing ureteral injuries, since urine analysis and imaging studies are often unsafe [3].

Several studies have shown that the majority of lower ureteral iatrogenic injuries are caused by clamping or transection and do not produce extensive ureteral defects [36]. Cormio et al. [37] noted 25 mm (range 5 to 50 mm) as the average length of iatrogenic ureteral injury in their series. Utrie et al. [38] proposed ureteral reimplantation if the length of distal ureteral defect was up to 50 mm from its bladder entry. Nevertheless, several authors proposed end-to-end ureterostomy over the double J stent in all cases with 20-25 mm length of distal ureteral stump. In addition, they consider that at least 60 mm of the ureteral defect can be compensated by renal mobilization, allowing regular tension free anastomosis [39]. In order to assess the distal ureteral stump precisely, ureteropyelography is strongly recommended [36]. It is widely accepted that ureterocystoneostomy procedures, whether direct, psoas hitch or Boari flap, have demonstrated a great potential for the distal ureteral repair, especially if detected late [4, 31]. In our series, it was confirmed with the low rate of ureteral reimplantation-associated complications.

Undoubtedly, the advantages of ureteroureterostomy include preservation of physiologic antireflux mechanism and intact bladder. Anyhow, it has been emphasized that successful ureteroureterostomy requires a precise diagnosis and strict respect of certain surgical principles [30, 40-43].

In all cases in our series, ureteral repair in the acute setting was performed according to the principles proposed

by Brandes et al. [6] in evidence-based analysis Consensus on Genitourinary Trauma. It includes appropriate ureteral debridement and mobilization, implantation of double J ureteral stent and tension-free anastomosis, isolation of the repaired segment, placement of retroperitoneal drain and performing proximal urinary diversion (if necessary) [6, 36]. Based on these principles, primary repair can be successful in most cases.

Otherwise, it has been proposed that prior to difficult abdominopelvic surgical procedures prophylactic placement of double J stent facilitates identification of the ureter and thus decreases the possibility of potential injuries [12].

Other techniques include ileal loop, renal autotransplantation and transureteroureterostomy, but they have been rarely performed as recorded by published series. In our series, the ileal loop was applied in one case due to a long defect of midureter while renal autotransplantation was applied in one case due to a long upper ureteral defect. The rate of nephrectomy, performed in 3/55 cases (5%) from our series is consistent with large published series [5, 12].

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CONCLUSION

Among different surgeries that may lead to the development of iatrogenic ureteral injury, gynecological procedures represent the most common cause. Rapid diagnosis enables immediate ureteral repair and is associated with low morbidity rates, representing a major factor contributing to the treatment success and ultimately preserving the renal function. Regardless of the etiology, iatrogenic ureteral damage is almost always finally addressed to urologist. Hence, it is of utmost importance for surgeons performing procedures within or adjacent to the ureter, to sustain a high index of suspicion, foreseeing potential ureteral injury and therefore facilitate the diagnostic procedure. In cases with delayed diagnosis, urinary leak is commonly managed by percutaneous nephrostomy as a temporary minimally invasive urinary diversion which safely enables further diagnostic and therapeutic approach. Surgical management encompasses a wide range of ureteral reconstructive procedures that can be successfully used depending on the type, extent and localization of the injury.

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Јатрогене повреде уретера: шеснаестогодишње искуство једног центра терцијарног нивоа здравствене заштите

Драгослав Башић^{1,2}, Иван Игњатовић^{1,2}, Милан Поттић^{1,2}

¹Клиника за урологију, Клинички центар Ниш, Ниш, Србија;

²Универзитет у Нишу, Медицински факултет, Ниш, Србија

КРАТАК САДРЖАЈ

Увод Јатрогене повреде уретера могу настати током различитих абдоминално-пелвичних и ретроперитонеалних хируршких захвата, укључујући гинеколошке, уролошке, колоректалне и васкуларне.

Циљ рада Циљ рада је био да се испитају учесталост и врсте јатрогених повреда уретера насталих током 16 година и процени вредност примењених дијагностичких и терапијских поступака.

Методе рада Урађена је ретроспективна анализа клиничких података (историја болести и хируршких извештаја) 55 болесника (11 мушкараца и 44 жена, просечне старости од 54,5 година) с потврђеном јатрогеном повредом уретера током периода 1998–2014. године.

Резултати Јатрогене повреде уретера настале су током гинеколошких захвата код 55% испитаника, уролошких код 25%, колоректалних код 15% и васкуларних код 5% болесника. Механизми повређивања били су: непотпуна трансекција (код 23 испитаника), потпуна трансекција (1), лигату-

ра (7), парцијална перфорација – абразија мукозе (13) и тотална перфорација (1). Најчешћи дијагностички поступци за постоперационо препознавање уретералних повреда били су ултразвучни преглед абдомена, интравенска урографија, антероградна пијелоуретерографија и ретроградна уретеропијелографија. Рани терапијски поступци примењени су код 35 болесника (64%), а одложени код 20 (36%). Ране (до 30 дана) или касне (после више од 30 дана) постоперационе компликације забележене су код 14 испитаника (25%).

Закључак Међу различитим операцијама које могу довести до јатрогених повреда уретера, гинеколошки захвати су најчешћи узрок. Брза и ефикасна дијагностика омогућава непосредну реконструкцију уретера и удружена је с ниским стопама морбидитета, чиме представља главни фактор који доприноси успеху лечења и крајњем очувању функције бубрега.

Кључне речи: јатрогена повреда уретера; дијагностика; лечење

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The Impact of Demographic and Socio-Economic Conditions on the Prevalence of Speech Disorders in Preschool Children in Bitola

Domnika Rajchanovska¹, Beti Zaifirova Ivanovska²

¹University "St. Kliment Ohridski", High Medical School, Bitola, R. Macedonia;

²University "St. Cyril and Methodius", Faculty of Medicine, Skopje, R. Macedonia

SUMMARY

Introduction Speech development in preschool children should be consistent with a child's overall development. However, disorders of speech in childhood are not uncommon.

Objective The purpose of the study was to determine the impact of demographic and socio-economic conditions on the prevalence of speech disorders in preschool children in Bitola.

Methods The study is observational and prospective with two years duration. During the period from May 2009 to June 2011, 1607 children aged 3 and 5 years, who came for regular examinations, were observed. The following research methods were applied: pediatric examination, psychological testing (Test of Chaturik), interviews with parents and a questionnaire for behavior of children (Child Behavior Checklist – CBCL).

Results 1,607 children were analyzed, 772 aged three years, 835 aged five years, 51.65% male and 49.35% female. The prevalence of speech disorders was 37.65%. Statistical analysis showed that these disorders were more frequent in three years old children, males living in rural areas and in larger families. They did not have their own rooms at home, they were using mobile phones and were spending many hours per day watching television, ($p < 0.01$). Also, children whose parents had lower levels of education and were engaged in agriculture, often had significant speech disorders, ($p < 0.01$).

Conclusion Speech disorders in preschool children in Bitola have a high prevalence. Because of their influence on later cognitive development of children, the process requires cooperation among parents, children, speech and the audiologist with the significant role in prevention, early detection and treatment.

Keywords: dyslalia; developmental dysphasia; preschool children; socio-economic conditions

INTRODUCTION

Mental health of children and the prevention of its disorders, takes an important place in the healthcare of preschool children. Their development and maturation occurs under the influence of genetic factors that interact with external factors. The hereditary factors are polygenic and play a significant role in increasing the possibility of developing certain disorders, only in relation to the family, social and cultural factors [1]. Children's behavioral disorders can be regarded as indicators for disorders in general environment [2]. The care and upbringing of children, as well as measures that parents use, are very important [3]. The speech development in preschool children is also highly significant. It is a useful indicator of the development of children's cognitive abilities and is correlated with later school achievement [4]. Most of children show a significant progress in speech during the first 4 years of life. All early deterioration should be therefore disclosed [5]. According to the worldwide literature data, it is emphasized that a large number of children with speech disorders in the preschool period have permanent speech disorders later in school achievement and their life [6, 7]. Primary disorders include

speech delay, speech and receptive problems. Language and spoken slowdown in children are associated with increased difficulties in reading, writing, attention and socialization. Atypical language development may be a secondary characteristic of physical and developmental problems in childhood. Secondary speech and language slowdown are associated with other conditions, such as hearing problems, intellectual disabilities, autism, physical problems, etc. [8, 9]. The speech-language development and social environment are mutually related [10]. The risk factors for speech disorders are: family history of spoken slowdown, masculine and perinatal factors, and less risky factors, i.e. the level of education of parents, birth order of the child and family size [4]. Also, some habits in children, as sucking fingers, can affect the development of speech disorders [11]. The treatment and rehabilitation of children with speech disorders include the child and family and the team of professional speech therapist, psychologist and child psychiatrist, with special attention to parent's education. Such therapy is very effective in these children. Early phonological and metaphonological intervention can help normalize the development of speech and normal acquisition of written skills in children [12].

Correspondence to:

Domnika RAJCHANOVSKA
University "St. Kliment Ohridski"
High Medical School
Kliment Ohridski 25/9
7000 Bitola
R. Macedonia
dr.rajchanovska@gmail.com

OBJECTIVE

The aim of the study was to determine the prevalence of speech disorders in preschool children in Bitola and to quantify its possible connection with certain demographic characteristics of children (age, sex, breastfeeding), family and socio-economic conditions in their families (town, village, having or not having their own room, the number of family members, birth order of the child, education level of parents, family income), as well as the habits of children (using computer, mobile phone or watching television for several hours).

METHODS

The study was conducted at the Health Centre in Bitola, in the office for preventive healthcare for children aged 0-6 years. In the epidemiological, prospective, two-year study, 1607 children aged 3 and 5 years were included. They came for regular medical checkups in the period from May 2009 to June 2011. Children born within the normal perinatal period, without the risk of birth, with normal psychomotor development, were included in the study. Children born with any kind of risk, as well as children in whom the psychological testing was unsuitable for their age, were excluded from the study. Questionnaires that were not properly and completely filled out by parents were not analyzed. During the study the following methods were applied: psychological testing (Test of Chuturik), pediatric examination, method of interview with parents, questionnaire about the behavior of children by Achenbach [13]. The Chuturik test is a standardized test for the psychomotor development of children in the early childhood period, the 5th year. Child Behavior Checklist by Achenbach is a multicentric empirically based

set of statements to evaluate the behavior of children by their parents. There is a list of 113 statements that describe some characteristics of the child, which occur later than the last two months. This questionnaire includes features that characterize internal and external behavior of children. In the study, of all speech disorders in children, only disorders in pronunciation of certain sounds (dyslalia) and disturbances in expressive speech (developmental dysphasia) are analyzed. The conclusion of the existence of these disorders in children was adopted on the basis of analysis of the questionnaires for children's behavior, conversation with parents and clinical examination.

The results were statistically processed, and the following methods were used: the distribution of qualitative data presented in absolute and relative numbers, and for testing the significance of differences in speech disorders occurrence in terms of analyzed parameters non-parametric statistics was used (Pearson chi-squared Yates chi-square test). The significance was determined for the level of $p < 0.05$ and $p < 0.01$. For quantifying the link between certain factors and the presence of disorders in speech, the method of logistic regression analysis was used.

RESULTS

In the analyzed two-year period, in total 1,980 children on regular check-ups were invited to be included in the study. After psychological testing and analysis of the Child Behavior Checklist, the group of respondents consisted of 1,607 children, who had psychomotor development and behavior adequate for their age, 772 of them were three years old and 835 were five years old, 50.65% male and 49.35% female. Six hundred and five (37.65%) had speech disorders, 230 children aged 3 and 102 five-year old chil-

Table 1. Disorders of speech in relation to age and sex of children, breastfeeding, place of residence, having or not having one's own room, using computer, mobile phone and television

Variable		Speech disorders		p-level
		Yes	No	
Age	3 years	377 (48.83%)	395 (51.17%)	0.000*
	5 years	228 (27.31%)	607 (72.69%)	
Sex	Male	370 (45.45%)	444 (54.55%)	0.000*
	Female	235 (29.63%)	558 (70.37%)	
Duration of breastfeeding	>12 months	127 (38.02%)	207 (61.98%)	0.45
	7-12 months	200 (36.36%)	350 (63.64%)	
	Up to 6 months	210 (37.10%)	356 (62.90%)	
	Not breastfed	68 (43.31%)	89 (56.69%)	
Place of residence	Town	330 (31.34%)	723 (68.66%)	0.000*
	Village	275 (49.64%)	279 (50.36%)	
Having own room	Yes	213 (33.97%)	414 (66.03%)	0.015*
	No	392 (40.00%)	588 (60.00%)	
Using computer	Yes	239 (35.41%)	436 (64.59%)	0.11
	No	366 (39.27%)	566 (60.73%)	
Watching TV	Yes	409 (42.05%)	572 (57.95%)	0.000*
	No	196 (31.31%)	430 (68.69%)	
Using mobile phone	Yes	291 (42.05%)	401 (57.95%)	0.001*
	No	314 (34.32%)	601 (65.68%)	

* statistically significant

Table 2. Speech disorders in children, in terms of the number of family members, birth order of the child and education of parents

Variable		Speech disorders		p-level
		Yes	No	
Family members	<3	64 (33.86%)	125 (66.14%)	0.010*
	4	179 (33.52%)	355 (66.48%)	
	>4	362 (40.95%)	522 (59.05%)	
Order of child birth	First	274 (33.95%)	533 (66.05%)	0.009*
	Second	292 (41.36%)	414 (58.64%)	
	Third, fourth, etc.	39 (41.49%)	55 (58.51%)	
Father's education	High	65 (31.71%)	140 (68.29%)	0.007*
	Secondary	383 (36.76%)	659 (63.24%)	
	Primary	155 (44.41%)	194 (55.59%)	
	Without education	2 (18.18%)	9 (81.82%)	
Mother's education	High	95 (29.50%)	227 (70.50%)	0.000*
	Secondary	306 (36.17%)	540 (63.83%)	
	Primary	197 (47.82%)	215 (52.18%)	
	Without education	7 (25.93%)	20 (74.07%)	

* statistically significant

Table 3. Speech disorders in children in relation to parental employment and family income

Variable		Speech disorders		p-level
		Yes	No	
Employment of parents	Father	291 (41.04%)	418 (58.96%)	0.001*
	Mother	33 (34.38%)	63 (65.63%)	
	Both	150 (30.36%)	344 (69.64%)	
	Nobody	47 (39.83%)	71 (60.17%)	
	Farmers	84 (44.21%)	106 (55.79%)	
Material income	Social help	46 (39.32%)	71 (60.68%)	0.39
	Minimal	150 (38.86%)	236 (61.14%)	
	Average	328 (38.27%)	529 (61.73%)	
	Above average	81 (32.79%)	166 (67.21%)	

* statistically significant

dren had dyslalia, while developmental dysphasia was found in 147 three-year old and 126 five-year old children.

Table 1 shows the results of the presence of speech disorders in relation to age and sex of the children, breastfeeding, place of residence, having or not having one's own room, using the computer, mobile phone and television.

The results showed that, of the total number of respondents, speech disorders were significantly more frequently reported in male children aged 3 years, compared to 5-year old girls, ($p < 0.01$). The place of residence had a highly statistically significant impact on the appearance of speech disorders, ($p < 0.01$); 49.64% children in rural areas were faced with such disorders, versus 31.34% children from urban areas. Also, children who did not have room in their homes, significantly more often had disorders in speech as compared to children with their own room, ($p < 0.05$). After testing the differences, the presence of speech disorders in children and using computer, mobile phone and watching TV for many hours, statistical significance was determined with regard to mobile phone usage and TV watching ($p < 0.01$).

The results of the examination for the manifestation of speech disorders in children, in terms of family structure (number of family members, birth order of the child, education of parents) are shown in Table 2.

The distribution in terms of the number of family members, showed that children who were living in larger families often manifested speech disorders, (40.95%) and tested differences were statistically significant, ($p < 0.05$). Speech disorders were significantly more often found in children who were born as a second, third, and other in the family, compared to the firstborn, (41.49% vs. 33.95%, $p < 0.01$), and the children of families whose parents had primary education, $p < 0.01$.

Table 3 shows the results of the presence of speech disorders in children in relation to parental employment and family income.

The displayed distribution for the occurrence of speech disorders indicated that they were mostly registered in subjects whose parents were engaged in agriculture, and at least in children whose parents were employed, (44.21% vs. 30.36%). The tested differences were statistically significant ($p < 0.01$). In terms of material income in families, the results showed that the disorders in speech were insignificantly more frequent in children who lived in families that were users of social welfare, and in families with minimal income (39.32 % and 38.86%, respectively, $p > 0.05$).

Table 4 shows the results of logistic regression analysis for risk factors that have the predictor role or influence on the occurrence of speech disorders in children younger than 5 years.

By using the univariate analysis, for the occurrence of speech disorders in children the following were confirmed as significant risk factors: child's age up to 3 years old, male, living in rural areas, lack of room in one's home, lower level of education of parents, parents - farmers, using a mobile phone and watching TV many for hours per day.

DISCUSSION

The obtained results in the study showed that the prevalence of speech disorders in children was 37.65%, with a significantly higher manifestation on 3-year old male children. In world literature data different results are shown.

Table 4. Logistic binary regression

Variable		Sig.	Exp(B)	OR 95% CI	
				Lower	Upper
Age – 3 years	5 years	0.000*	0.394	0.320	0.484
Sex – male	Female	0.000*	0.505	0.411	0.621
Place of residence	Village	0.000*	2.159	1.748	2.668
Having own room	Does not have	0.015*	1.296	1.051	1.597
Family members – 3 members	4 members	0.932	0.985	0.693	1.399
	>4 members	0.071	1.354	0.974	1.884
Order of childbirth – first	Second	0.003*	1.372	1.113	1.691
	Third, fourth and so on	0.148	1.379	0.892	2.132
Mother's education – high	Secondary	0.032*	1.354	1.026	1.787
	Primary	0.000*	2.189	1.609	2.978
	Without education	0.695	0.836	0.342	2.044
Father's education – high	Secondary	0.169	1.252	0.909	1.724
	Primary	0.003*	1.721	1.198	2.472
	Without education	0.355	0.479	0.101	2.278
Employed parents – both	Father	0.000*	1.597	1.252	2.036
	Mother	0.437	1.201	0.756	1.908
	Farmers	0.001*	1.817	1.288	2.565
	No one	0.049*	1.518	1.002	2.300
Material income above average	Average	0.117	1.271	0.942	1.714
	Minimal	0.122	1.303	0.931	1.822
	Social help	0.223	1.328	0.841	2.095
Not using	Computer	0.115	0.848	0.690	1.041
	Mobile phone	0.002*	1.389	1.133	1.702
	TV	0.000*	1.569	1.270	1.938

* statistically significant

Zubrick et al. [14] analyzed 1,766 children aged 2 years, in 13.4% of children speech disorders (late occurrence) were noted in those who had a significant family history, male gender and early neurobiological growth. In the study, tests for the presence of speech disorders in children concerning breastfeeding showed that children who were not breastfed often manifested speech disorders, compared to the remaining ones. Ferguson and Molfese [15] stated that breastfeeding was found to be a protective factor for the development of speech disorders in children. Fox et al. [16] concluded that speech disorders had a high incidence in children who used a pacifier bottle for a long time. The delayed usage of a bottle during the infant feeding, at least 9 months of age, may also be protective for the development of speech disorders [11]. Andres et al. [17] also found that breastfed children during testing showed advantage in cognitive development (mental, linguistic) compared to those who were fed with milk formula. The obtained results in this study showed that speech disorders were significantly more common among children in rural areas compared to those who had not their own room at home, those who lived in larger families and were born second, third and so on. Nelson et al. [4], on the other hand, found that the number of members in the family, and birth order of the child, were fewer risk factors for the occurrence of disorders in speech. The results in the study also showed that disorders in speech were significantly more common in children whose parents had primary education and were working as farmers and in children of families that were welfare recipients. However, some authors concluded that

the occurrence of speech disorders does not depend on the educational level of parents and social status [14]. Mikelić et al. [18], on the other hand, stated that the rehabilitation of children with speech disorders should normally be in the family environment, monitored by a team of experts (psychiatrist, psychologist, audiologist) during which the educational level of the parents was very significant. The presence of speech disorders among respondents in terms of using a computer, mobile phone and television, was significantly higher in children who used a mobile phone and who were watching TV for a long time.

CONCLUSION

The study showed that the prevalence of speech disorders among preschool children in Bitola was 37.65 %. In the study, the significant correlation between the occurrence of these disorders in children with familiar factors and socio-economic conditions in which children lived was also established. Thus, the reasons for their occurrence should be sought in the family. It is very important that parents should be aware of the existence of these disorders in their children, and they should critically consider the reasons for their appearance, harmful consequences that could arise, and should promptly seek help from the appropriate competent experts. Also, a serious daily involvement of health professionals dealing in preventive health-care is necessary, by working on prevention, and also early detection and treatment of speech disorders in children in

collaboration with the child and hers/his family. Their mutual commitment is to increase their activity to the proper care and education of children, overcoming all factors that are predictors for the occurrence of certain problems, early detection of any changes in children, careful application of reason and involving team action for their improvement.

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Утицај демографских и социјално-економских услова на распрострањеност говорних поремећаја код деце

Домника Рајчановска¹, Бети Заифирова Ивановска²

¹Универзитет „Св. Климент Охридски“, Виша медицинска школа, Битољ, Македонија;

²Универзитет „Св. Кирил и Методиј“, Медицински факултет, Скопље, Македонија

КРАТАК САДРЖАЈ

Увод Развој говора код деце предшколског узраста треба да буде у складу са целокупним развојем детета. Међутим, поремећаји говора код деце нису неуобичајена појава.

Циљ рада Циљ истраживања је био да се одреди утицај демографских и социјално-економских услова на распрострањеност говорних поремећаја код деце предшколског узраста у Битољу, у Македонији.

Методе рада Истраживање је било опсервативно и проспективно, а трајало је од маја 2009. до јуна 2011. године. Током те две године испитивана су деца узраста од три године и пет година која су редовно долазила на прегледе. Примењене су следеће истраживачке методе: педијатријски преглед, психолошко тестирање (Чутуриков тест), разговор с родитељима и упитник за испитивање понашања детета (енгл. *Child Behavior Checklist – CBCL*).

Резултати Испитано је 1.607 деце, и то 772 трогодишњака и 835 петогодишњака. Дечаци су чинили 51,65% испитани-

ка, а девојчице 49,35%. Преваљенција говорних поремећаја била је 37,65%. Статистичка анализа је показала да се ови поремећаји чешће јављају код трогодишњих дечака који живе у руралним областима и у многочланим породицама. Ова деца немају код куће своју засебну собу и свакодневно проводе сате гледајући телевизију ($p < 0,01$). Код деце чији су родитељи нижег степена образовања и баве се пољопривредом такође могу да се јаве значајни поремећаји говора ($p < 0,01$).

Закључак У Битољу је утврђена висока преваљенција деце предшколског узраста са говорним поремећајима. С обзиром на утицај који ови поремећаји имају на каснији когнитивни развој детета, процес превенције, раног откривања и лечења захтева сарадњу родитеља, детета и аудиолога, што у целости игра значајну улогу.

Кључне речи: диспалија; развој дисфазije; деца предшколског узраста; социјално-економски услови

Impact of Educational Intervention on Prescribing Inappropriate Medication to Elderly Nursing Homes Residents

Darko Ilić¹, Zoran Bukumirić², Slobodan Janković³

¹Army of Serbia, Bureau of Preventive Medical Services, Belgrade, Serbia;

²University of Belgrade, School of Medicine, Institute of Medical Statistics and Informatics, Belgrade, Serbia;

³University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

SUMMARY

Introduction Problems with polypharmacy, adverse drug reactions and non-adherence are especially frequent among elderly nursing home residents.

Objective The aim of our study was to evaluate effectiveness of a specific form of staff education on appropriateness of prescribing in a cluster of nursing homes for the elderly.

Methods The study was designed as before-and-after trial of educational intervention on appropriateness of prescribing in nursing homes for the elderly. In total 20 nursing homes located in Belgrade, Serbia were included in the study with 104 elderly residents and 27 caring physicians. Appropriateness of prescribing was checked against Beers, START and STOPP criteria, before and 6 months after the intervention.

Results There were 349 inappropriately prescribed drugs according to Beers criteria before the intervention and 37 drugs six months after the intervention. According to STOPP criteria there were 70 drugs inappropriately prescribed before the intervention, and 20 drugs 6 months after. When both criteria are taken together, there is a significant difference between the average number of inappropriate drugs per patient before (3.4 ± 0.5) and after (0.6 ± 0.7) educational intervention ($t=38.902$; $p<0.001$). Finally, before the intervention 143 appropriate drugs were omitted according to START criteria, while 6 months after the intervention there were only 67 omissions.

Conclusion Simple, but well targeted educational interventions may improve polypharmacy and decrease inappropriate prescribing rate, contributing to a better care of elderly patients in nursing homes.

Keywords: elderly; nursing homes; inappropriate prescribing; education; polypharmacy

INTRODUCTION

Aging is actually the accumulation of progressive and irreversible molecular changes in cells and tissues of human organism [1]. Therefore, more specificity of elderly people exists in regard to pharmacokinetics and pharmacodynamics of drugs that are used for their numerous functional problems and disorders (1-5 on average). Majority of elderly people are chronically taking several drugs, and it is not rare that even 20 or more drugs are prescribed to one person [2, 3], or that drugs are prescribed without obvious reason or diagnosis [4]. Recent studies among elderly nursing home residents showed that even 48% of patients in Italy [5] and 21.9% of patients in Germany [6] were prescribed inappropriate medication, which led to the increased risk of their hospitalization (hazard ratio 1.73). At least some of inappropriate prescriptions were associated with doctors who did not know well the residents or did not have important information about their patients when prescribing [7].

Polypharmacy in the elderly is always associated with increased occurrence rate of adverse drug reactions and clinically significant interactions. If the elderly are left without appropriate guidance, they are prone to non-adherence and avoidance of drugs for which

they believe that have caused their unpleasant symptoms. With such behaviour, the elderly are exposed to significant risks of under-treatment and/or complications caused by drugs with a narrow therapeutic window [8]. Besides, physicians in charge of elderly patients often cannot recognize whether a certain symptom or sign is caused by the disease itself, or by a certain drug taken by the patient [9].

Problems with polypharmacy, adverse drug reactions and non-adherence are especially frequent among elderly nursing home residents, and there are certain risk factors for their occurrence: age over 75, length of stay more than 2 years and feeding tube versus normal feeding [10]. Recent systematic review [11] analyzed interventions aimed at optimizing prescribing in nursing homes for the elderly, as staff education, multi-disciplinary team meetings, pharmacist medication reviews and computerized clinical decision support systems. Education has shown to be most promising, but its effectiveness and optimal forms are not yet established [12].

OBJECTIVE

The aim of our study was to evaluate the effectiveness of a specific form of staff education on

Correspondence to:

Slobodan M. JANKOVIĆ
Faculty of Medical Sciences
University of Kragujevac
Svetozara Markovića 69
34000 Kragujevac
Serbia

slobodan.jankovic@medf.kg.ac.rs

the appropriateness of prescribing in a cluster of nursing homes for the elderly.

METHODS

The study was designed as before-and-after trial of educational intervention on the appropriateness of prescribing in nursing homes for the elderly. In total 20 nursing homes located in Belgrade, Serbia were included in the study, with 104 elderly residents that fulfilled inclusion and exclusion criteria, and 27 caring physicians. In the beginning, all 47 existing nursing homes in Belgrade were contacted with a request for the study, but managers of only 20 of them were willing to participate in the study. The inclusion criteria were age over 65 and at least two chronic health disorders; the exclusion criteria were major psychiatric diseases, dementia and refusal of the residents to participate in the study.

The study was conducted during 2012 and 2013 in three phases: in the first, three-month phase prescribing practices were recorded and analyzed; the second, one-month phase was education of both physicians and nursing homes residents, and the third, three-month phase was carried out 6 months after completion of the second phase consisting of repeated recording and analyzing of prescribing practices.

The data about the prescribed medication and diagnosis were recorded from the residents' medical files. Appropriateness of prescribing was judged according to Beers, START and STOPP criteria [13, 14]. The Beers criteria were developed by a geriatrician Mark Beers in 1991, and they listed drugs which should not be used in elderly persons due to their propensity to cause adverse effects thanks to pharmacological properties or to changes in physiological functions of elderly persons. The START criteria (Screening Tool to Alert doctors to the Right Treatment) consist of 22 indicators which may reveal omissions in prescribing drugs that are actually needed by elderly persons [15]. The STOPP criteria (Screening Tool of Older People's potentially inappropriate Prescriptions) consist of 65 frequent examples of potentially inappropriate prescribing in the elderly including drug-drug and drug-disease interactions, drugs which increased the risk of falls in the elderly and duplicate prescriptions of drugs from the same pharmacological group [16]. These criteria were chosen because they are most used and cited in studies on inappropriate drug prescribing in elderly patients [13-16]. Besides, the residents were interviewed about adverse drug reactions and over-the-counter drugs they use, including money they spent for such drugs.

The intervention was two-faceted: (1) one-hour lectures about specificities of pharmacokinetics and pharmacodynamics of drugs in the elderly, the Beers, START and STOPP criteria, screening tool to alert physicians to right treatment, together with the brochure with identical content; (2) one-hour lectures given to the nursing homes residents about adherence, adverse drug reactions and drug-drug interactions, together with the brochure with the same content. The lectures were structured, with the

following subheadings: introduction, changes of intestinal absorption of drugs with increasing age, distribution of drugs in elderly patients, excretory function of kidneys in the elderly, excretory function of liver in the elderly, changes in the responsiveness of the elderly to centrally acting drugs, compliance of elderly patients, rationale, composition and utilization of the Beers criteria for inappropriate prescribing, composition and utilization of the START criteria for inappropriate prescribing and composition and utilization of the STOPP criteria for inappropriate prescribing. The lectures were held by one of the investigators (medical doctor, Master of Science in pharmacology), using audio/visual aids (video beam presentation). The brochures were written by another investigator (medical doctor, clinical pharmacology specialist), with the same subheadings as in the video presentation. The brochure for the residents was written using layperson's language, with short sentences, and was pilot-tested for clarity prior to printing in a small sample of 5 residents.

The data were primarily statistically described, using central tendency measures (median or mean) and standard deviation as a measure of dispersion for continuous variables; the percentages were used for categorical variables. Correlation between continuous variables was tested by the Pearson correlation coefficient. Differences in the values of categorical variables before and after educational intervention were tested by the Chi-square test, and differences in the values of continuous variables were tested by the Wilcoxon's test. The differences were considered significant if probability of null hypothesis was less than 0.05.

RESULTS

A total of 104 nursing home residents participated in the study, with average age of 82.6 ± 2.1 years. There were 62 (59.6%) females and 42 (40.4%) males. The average length of stay in a nursing home was 4.3 ± 1.4 years. Eighty-three (79.9%) participants were suffering from chronic diseases for more than 10 years, and the average number of diagnosis per participant was 7.5 ± 1.6 (median 8, range 5-16) (Table 1). The participants were taking on the average 14.1 ± 2.5 drugs (median 14, range 8-21) chronically. Among the medication used, 10.2 ± 2.3 drugs were prescribed (median 10, range 6-16), while 3.2 ± 1.5 drugs were bought over-the-counter (median 3, range 1-6).

Eighty-five participants (81.7%) experienced at least two adverse drug reactions during the last year, and they spent on the average 2828.8 ± 1128.6 RSD (Republic of Serbia Dinars) monthly for over-the-counter (OTC) drugs. Sixty-four (61.5%) nursing home residents spent more than 2000 RSD monthly for the OTC drugs. While there were no significant correlations between the duration of stay in a nursing home and the number of drugs taken by participants ($r = -0.133$; $p = 0.183$) or money spent on the OTC drugs ($r = -0.001$; $p = 0.995$), a weak correlation was detected between the total number of drugs taken by the residents and money they spent on the OTC drugs ($r = 0.230$; $p = 0.019$).

Table 1. Diagnoses recorded among the nursing homes residents

Diagnosis	N	%
Essential hypertension	49	13.8
Diabetes mellitus type II	43	12.1
Insomnia	41	11.5
Depression	37	10.4
Rheumatism (not specified)	30	8.4
Angina pectoris	29	8.1
Urinary incontinence	26	7.3
Anxiety	15	4.2
Cardiac arrhythmias	13	3.7
Breast cancer	12	3.4
Epilepsy	12	3.4
COPD	11	3.1
Cerebrovascular insufficiency	8	2.2
Supraventricular tachycardia	8	2.2
Parkinson's disease	7	2.0
Chronic heart failure	7	2.0
Edema	3	0.8
Stroke	2	0.6
Lumbar syndrome	1	0.3
Fracture of thoracic vertebral body	1	0.3
Ischemic cardiomyopathy	1	0.3
Total	356	100.0

N – number of patients; COPD – chronic obstructive pulmonary disease

Table 2. Inappropriately prescribed drugs to the nursing home residents according to the Beers criteria before and after intervention

Drug	Before intervention		After intervention	
	N	%	N	%
Glibenclamide	43	12.3	1	2.7
Nifedipine	32	9.2	1	2.7
Zolpidem	33	9.5	2	5.4
Amitriptyline	20	5.7	1	2.7
Nifedipine, slow-release	15	4.3	1	2.7
Verapamil	14	4.0	2	5.4
Alprazolam	14	4.0	1	2.7
Diltiazem, slow-release	13	3.7	1	2.7
Tolterodine	13	3.7	1	2.7
Megestrol	12	3.4	2	5.4
Naproxen	12	3.4	2	5.4
Carbamazepine	12	3.4	1	2.7
Lorazepam	11	3.2	1	2.7
Digoxine	11	3.2	2	5.4
Clomipramine	11	3.2	1	2.7
Theophylline	11	3.2	1	2.7
Diclofenac	10	2.9	1	2.7
Darifenacin	10	2.9	1	2.7
Ticlopidine	9	2.6	1	2.7
Ibuprofen	7	2.0	2	5.4
Amiodarone	7	2.0	2	5.4
Maprotiline	7	2.0	2	5.4
Trihexyphenidyl	6	1.7	1	2.7
Spironolactone	5	1.4	1	2.7
Trospium chloride	3	0.9	1	2.7
Propafenone	3	0.9	1	2.7
Methyldopa	2	0.6	1	2.7
Sotalol	2	0.6	1	2.7
Terazosine	1	0.3	1	2.7
Total	349	100.0	37	100.0

N – number of patients

Table 3. Inappropriately prescribed drugs to the nursing home residents according to STOPP criteria before and after intervention

Drug	Before intervention		After intervention	
	N	%	N	%
Acetylsalicylic acid	50	71.5	13	65.0
Diazepam	4	5.7	2	10.0
Bromazepam	4	5.7	2	10.0
Lorazepam	3	4.3	1	5.0
Loperamide	2	2.9	1	5.0
Thiotropium	3	4.3	1	5.0
Aminophylline	3	4.3	0	0.0
Glibenclamide	1	1.4	0	0.0
Total	70	100.0	20	100.0

Table 4. Inappropriately omitted drugs to nursing home residents according to START criteria before and after intervention

Drug	Before intervention		After intervention	
	N	%	N	%
Ranitidine	35	24.5	16	23.8
Famotidine	16	11.2	7	10.4
Ipratropium + fenoterol	16	11.2	7	10.4
Acenokumarol	13	9.1	6	9.0
Heparin	10	6.9	5	7.5
Salbutamol	10	6.9	5	7.5
Trihexyphenidyl	9	6.3	4	6.0
Hydrotalcitum	7	4.9	5	7.5
Antacide 1	7	4.9	4	6.0
Biperiden	6	4.2	3	4.5
Antacide 2	4	2.8	2	2.9
Bromocriptine	4	2.8	1	1.5
Progesterone depo	3	2.1	1	1.5
Progesterone + estradiol	3	2.1	1	1.5
Total	143	100.0	67	100.0

There were 349 inappropriately prescribed drugs according to the Beers criteria before the intervention and only 37 drugs six months after the intervention (Table 2). The median number of inappropriately prescribed drugs according to the Beers criteria before education was 11.0 (range 1.0–43.0), and the median number after education was 1.0 (range 1.0–2.0); the difference was significant ($Z=4.629$; $p<0.001$). According to the STOPP criteria there were 70 drugs inappropriately prescribed before the intervention, and 20 drugs after 6 months (Table 3). The median number of inappropriately prescribed drugs according to the STOPP criteria before education was 3.5 (range 1.0–20.0) and the median number after education was 1.5 (range 0.0–6.0); the difference was significant ($Z=2.823$; $p<0.005$). When both criteria were taken together, there was significant difference between the average number of inappropriate drugs per patient before (3.4 ± 0.5) and after (0.6 ± 0.7) the educative intervention ($t=38.902$; $p<0.001$). Finally, before the intervention 143 appropriate drugs were omitted according to the START criteria, while 6 months after the intervention there were only 67 omissions (Table 4). The median number of omitted drugs according to the START criteria before education was 9.0 (range 3.0–18.0), and the median number after education was 5.0 (range 1.0–8.0); the difference was significant ($Z=3.423$; $p<0.001$).

DISCUSSION

Polypharmacy and inappropriate prescribing have been already described in nursing homes worldwide, and the necessity for more careful prescribing for this vulnerable population has been stressed-out [12, 13]. The average number of prescribed drugs per elderly person is constantly growing [14]; at the same time, prescribing for the elderly becomes increasingly complex, since the prolongation of life is associated with increase in the number of co-morbidities, and more drugs means more drug-drug and drug-disease interactions and more possible adverse effects [15, 16].

Inappropriate prescribing to the elderly is a serious public health problem, since increased rates of interactions and adverse effects lead to increased morbidity and mortality [17]. Prescription drugs that may have especially harmful consequences for elderly persons if prescribed in high doses are antihypertensives and diuretics, due to the decreased perfusion to vital organs and electrolyte abnormalities, and cardiac glycosides due to a narrow therapeutic window and arrhythmogenic potential [18].

According to a study of Linjakumpu et al. [19], even 64.6% of elderly persons regularly use two or more non-steroid anti-inflammatory analgesics (NSAIDs). In our study, 28% of the nursing homes residents were taking at least one drug from this group. In the elderly, NSAIDs decrease renal perfusion which leads to hypertension and initiate gastritis; patients are then prescribed antihypertensives and antisecretory drugs in the attempt to ameliorate adverse effects of NSAIDs. This can cause polypharmacy and further complicate the care of the elderly. On the other hand, appropriately chosen and carefully titrated antihypertensive therapy considerably reduces morbidity and mortality of the elderly [20].

We noted prescription of amitriptyline in 20 patients (19%), the drug which is considered inappropriate for the elderly due to its strong anticholinergic properties [21]. Besides, even 41% of all study participants were prescribed glibenclamide, an oral antidiabetic drug from the sulphonylurea group. This type of long-acting oral antidiabetics should be avoided in the elderly due to a very high risk of hypoglycemia, as explicitly stated in the Beers criteria.

Although there are drugs which have very positive influence on health of elderly patients, like statins, ACE inhibitors, beta-adrenergic receptor blockers [22] and especially aspirin, which successfully reduces cardiovascular events [23], therapeutic regimens of the elderly should be regularly reviewed and adjusted according to major organs function and co-morbidities of patients [24]. Physicians should be familiar with specificities of prescribing to the elderly, and this could be ensured with a targeted, high-quality education. On the other hand, elderly patients are mostly aware of polypharmacy, and almost 70% of them require from their care-givers to eliminate at least one of the prescribed drugs [25]. It has been already shown that co-medication with two drugs bears 6% chances of drug-drug interactions, while co-medication with 8 drugs increases the chance of interactions to almost 100% [10]. Besides, polypharmacy in nursing homes also increases pressure to

their residents to buy the OTC drugs, creating them a considerable financial burden, as demonstrated in our study.

Although various kinds of educational interventions have been tested in the past for their ability to improve prescribing to elderly nursing homes residents, the results are inconsistent and the quality of published studies is moderate [26, 27, 28]. Interventions that were shown to be at least partially effective were on-site education as a solitary measure or as a segment of intervention package and medication review performed by hospital pharmacist [27]. However, the majority of studies implemented a multifaceted educational intervention, and some of them demonstrated improvement. Good example of such an intervention was shown in a study from Sweden, where the combination of small group educational sessions with nurses and physicians, feedback on prescribing, presentation of guidelines and written materials used in 46 nursing homes led to a decrease in the unnecessary utilization of antibiotics for 12.4% [29]. In spite of promising results from certain studies, the overall picture is still unclear, and specific recommendations cannot be offered [26, 27, 28]. Our study was designed to shed some more light on this problem by educating physician about specific criteria for appropriate prescribing to elderly nursing homes residents.

Educating caring physicians of elderly patients about the Beers and STOPP/START criteria of appropriate prescribing is a very important measure, since experienced doctors are sometimes skeptical towards guidelines in general and doubt their practical usefulness [30]. Duration of stay in a nursing home and the number of prescribed drugs are usually correlated with the number of inappropriately prescribed drugs [31, 32], although in our study we could not demonstrate this correlation (probably due to a relatively small number of study participants, which is the main limitation of our study). Regular educational sessions with physicians in charge of medical care of nursing homes' residents could change some obsolete prescribing habits and reduce risks associated with polypharmacy. Our undertaken educational intervention was simple, cheap and easy to perform, and it resulted in a significant improvement according to all three criteria.

CONCLUSION

Our study has confirmed that elderly patients in nursing homes are exposed to polypharmacy, which increases the risk of inappropriate prescribing, adverse drug reactions and higher treatment costs. Simple, but well-targeted educational interventions may improve such a situation, contributing to a better care of elderly patients in nursing homes.

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Утицај образовне интервенције на преписивање неодговарајућих лекова штићеницима установа за збрињавање старих лица

Дарко Илић¹, Зоран Букумирић², Слободан Јанковић³

¹Војска Србије, Служба за превентивне медицинске услуге, Београд, Србија;

²Универзитет у Београду, Медицински факултет, Институт за медицинску статистику и информатику, Београд, Србија;

³Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија

КРАТАК САДРЖАЈ

Увод Проблеми с политерапијом, нежељене реакције на лекове и непридржавање режима лечења су нарочито чести код старијих штићеника старачких домова.

Циљ рада Циљ истраживања је био да се процени ефикасност специфичног облика образовања кадрова на целисходност преписивања лекова штићеницима домова за стара лица.

Методе рада Током студије испитана је целисходност преписивања лекова у домовима за збрињавање старих лица пре извођења образовне интервенције и после ње. Из укупно 20 београдских старачких домова у студију су укључене 104 старе особе и 27 ординирајућих лекара. Адекватност преписивања лекова је проверена на основу критеријума *Beers*, *START* и *STOPP* пре едукације, као и шест месеци након интервенције.

Резултати Укупно је било 349 непримерено преписаних лекова према критеријумима *Beers* пре интервенције и 37

лекова шест месеци после интервенције. Према критеријумима *STOPP*, било је 70 лекова непримерено преписаних пре интервенције и 20 лекова шест месеци након ње. Када су оба критеријума узета заједно, утврђена је значајна разлика између просечних бројева неодговарајућих лекова по болеснику пре ($3,4 \pm 0,5$) и после ($0,6 \pm 0,7$) образовне интервенције ($t=38,902$; $p<0,001$). Коначно, пре интервенције 143 одговарајућа лека изостављена су према критеријумима *START*, док је шест месеци након интервенције било само 67 пропуста.

Закључак Једноставна, али добро циљана образовна интервенција може побољшати политерапију и смањити стопу неприкладног преписивања лекова, те допринети бољој бризи о старијим штићеницима у домовима.

Кључне речи: старе особе; домови за негу; неприкладно преписивање; образовање; политерапија

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Social Support, Self-Perceived Health and Mental Status of General Population of Republic of Srpska

Jelena Niškanović, Sladjana Šiljak

Public Health Institute, Republic of Srpska, Banja Luka, Bosnia and Herzegovina

SUMMARY

Introduction Social support is defined as perception of how other people take care of us, how they understand our needs and give us support. Social support has positive influence on health, adoption of healthy lifestyles and recovery from illness.

Objective The aim of this paper is to detect the level of social support across different socio-demographic groups and to analyze relationship between social support, self-perceived health and mental well-being.

Methods Data from the 2010 Household Survey (National Health Survey) for the Republic of Srpska were used. A specially designed questionnaire was used, developed on the basis of internationally recognized and accepted instruments. Representative sample of 4,178 persons aged 18 and older were interviewed.

Results The obtained results showed that the level of social support was the lowest among the oldest population, persons with the lowest level of education unemployed and unmarried. There was present relationship between social support, self-perceived health and mental health (distress/stress and vitality). It was detected that males mostly lived alone relying on help from neighbors, while females mostly lived with other household members and relied more on persons close to them.

Conclusion Social support appears to be related to mental status and self-perceived health. The results are intertwined with different age groups and they can provide baseline for further analysis of causal relationship between social support and mental and physical health among different age categories. Detecting a link among social support, mental and physical health could provide insight into the mechanisms of social support influencing health status and behaviour.

Keywords: social support; health assessment; mental well-being

INTRODUCTION

Social support can be defined as the perception of how other people take care of us, understand our needs and respond to them [1, 2]. Such information can be obtained from a spouse, children, friends or other social contacts in the community, social clubs, etc. [1]. House and Kahn defined several types of social support depending on its primary functions; emotional support (showing concern, empathy and love, as well as the presence of someone with whom we can talk to), instrumental support (knowing there is someone who can help us in case of need) and assessment support (feedback that is useful for self-perception; someone whose opinion can be relied upon) [3]. According to Cohen and Wills [4], there are basically two ways in which social support can affect mental and physical health. First, social support may encourage people to take better care of themselves. For example, people important to us may persuade us to live a healthier life, simply because they care. Positive experience in stable social relationships also facilitate people to develop healthier life habits [1], although pressure of social peer networks can facilitate development of risk behavior (smoking, alcohol and drug use) [3]. Second, social support may positively affect health, because it buffers stress, and stress is directly associated with individual health. People better cope with stress knowing

they have someone who can rely on, get advice or even solution for problems [1, 2, 5].

Social support is associated with mortality and morbidity [6, 7, 8], precisely, people who have more social relationships are in a lower risk of dying compared with those with little social connections [1]. According to surveys, people who have close, supporting relationships more successfully cope with life's problems, have better health [2], express healthier lifestyles, and they recover faster from disease [9]. Examining the impact of social support on health amongst patients who face stressful health problems (cancer, coronary disease etc.), the researchers have found that persons who enjoy more social support through self-help groups or by spouses recover faster from disease, and have greater emotional satisfaction, in comparison with the control group [1, 2, 10]. Most studies, however, show a positive effect of social support on the course of mental health, either as a direct or buffer effect [11].

OBJECTIVE

This paper focused on the level of social support amongst different socio-demographic groups so that the vulnerable groups of population with the lowest level of social support could be detected. Considering previous surveys of the effect of social support on health

Correspondence to:

Jelena NIŠKANović
Public Health Institute
Jovana Dučića 1
78000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina
jelena.niskanovic@gmail.com

and healthy lifestyles, this survey examined the relationship between social support, self-perceived health and mental status amongst adult population of Republic of Srpska.

METHODS

Data presented in this paper were a part of the Household Survey (National Health Survey) conducted among adult population in the Republic of Srpska during 2010 [12]. The target population was people ≥ 18 years old that were present in the country minimally for one year and longer. A stratified two-stage representative sample of the population of Republic of Srpska was used. The units of the first stage were enumeration districts, the sampling units of the second stage were households. The total number of households selected for the survey was 1,866. The total of 4,178 adults was interviewed.

Instrument and variables

Specially designed questionnaire was used for the survey which was developed on the basis of internationally recognized and accepted instruments. Information was obtained through a face-to-face interview carried out at home. From the original instrument, 18 questions were used for the purpose of this paper from sections related with socio-demographic characteristic, social support, mental health and self-perceived health.

From the section related with socio-demographic characteristics five questions were used; gender (females and males), age (categorized in 10 years age groups: 25 to 34 years, 35 to 44 years etc.), education level (low, middle, high), marital status (married, living with partner, not married/divorced/widowed), employment (employed, unemployed and inactive).

Three questions were identified for assessing social support (National Health Survey – recommendation from: Finbalt, SF 36 questionnaire, WHO Health Survey, ECHI – Child Project, CDC National Health Interview Survey); assessment of possibility of getting support from neighbors when it was needed estimated by using Likert scale (1 – very difficult to 5 – very easy), assessments of the number of people that could be counted on in the event of serious personal problems assessed by a four degree scale (1 – no one to 4 – more than 5 persons) and the question related to whether a person lives alone or with other household members (yes/live alone; if yes, then with a specified number of household members).

European Health Interview (EUROHIS) and European Community Health Indicators Monitoring (ECHIM) considered psychological distress and positive mental health as important measures of mental health on the population level [13, 14]. Form on the instrument SF-36 (Mental Health Indicator 5 or MHI5) was used for measuring mental distress and they were a part of survey instrument. MHI5 consisted of five items that measured the level of

negative/positive emotional states through the Likert scale with possible scores ranging from 0 to 100 in which the higher score indicated better mental health and vice versa. Positive mental health (vitality) was measured by the vitality scale of SF-36. The mentioned scale was used to measure the level of positive mental health with four items, i.e. the presence of energy levels, agility and vitality through the Likert scale. Scores ranged from 0 to 100, with a higher score indicating a greater vitality and vice versa. One question on the Likert scale was used for measuring self-perceived health (1 – very bad to 5 – very good).

Data collection

Field work was conducted by teams of interviewers from primary health centers. One team consisted of two interviewers; two medical workers who had always worked together. All members of households who met the criteria of target population were interviewed.

Statistical analysis

Frequencies of social support measures among different socio-demographic groups were examined and differences were calculated using the χ^2 test. In order to estimate the association of variables of social support and age with self-perceived health and mental status (distress and vitality), multivariate logistic regression models were used (one model for each dependent variables; self-perceived health, mental stress and vitality). All selected independent variables (age, number of household members, help from neighbors, and the number of people that one can rely on) were included in the final models and all analyses were carried out separately for males and females. The probability, $p < 0.05$ was used as the minimal level of significance. The analyses were conducted using the statistical software package SPSS version 16.

RESULTS

Since the study included a variety number of general population (≥ 18), first we focused on the presence of social support among different socio-demographic groups. There are statistically significant differences in the number of household members among different population categories. Males (71.7%) and persons older than 55 (85.3%) mostly live alone. The same situation was found to be present among population with a lower level of education (68.1%) and inactive persons (retired, housewives of disabled). A significantly higher percentage of persons who are not married, divorced or who are widowed (97.8%) live alone in comparison with others who live in marriage or with a partner who mostly live with other household members (70.5%) (Table 1).

Percentage of person who can rely on others in case of serious personal problem is slightly higher among females

Table 1. Number of household members among different socio-demographic groups of adult population

Variable		Households with more than one member				p (χ² test)
		Yes		No (live alone)		
		N	%	N	%	
Gender	Male	2048	52.6	200	71.7	0.000
	Female	1842	47.4	79	28.3	
	Total	3890	100.0	279	100.0	
Age (years)	18–24	378	9.7	0	0.0	0.000
	25–34	556	14.3	7	2.5	
	35–44	639	16.4	12	4.3	
	45–54	812	20.9	22	7.9	
	55–64	685	17.6	68	24.4	
	≥65	820	21.1	170	60.9	
	Total	3890	100.0	279	100.0	
Education	Low	1507	38.8	190	68.1	0.000
	Middle	2005	51.6	70	25.1	
	High	374	9.6	19	6.8	
	Total	3886	100.0	279	100.0	
Employment	Employed	1210	31.1	24	8.6	0.000
	Unemployed	956	24.6	37	13.3	
	Inactive	1722	44.3	217	78.1	
	Total	3888	100.0	278	100.0	
Marital status	Married or living with partner	2734	70.5	6	2.2	0.000
	Not married, divorced, widowed	1145	29.5	273	97.8	
	Total	3879	100.0	279	100.0	

than males ($p=0.011$). Comparing variables of social support among different age categories we noticed that the number of person and neighbors that one could rely on or seek for help statistically significantly decreased among older population (≥ 55) in comparison with younger ones. The presence of social support was significantly lower among persons with a low level of education in comparison with persons with middle education (3 or 4 year high school). It is evident that persons with a high level of education perceive more availability of help from persons that one can rely on (11.7%) than from neighbors (8.1%). Unemployed and inactive persons perceive more that they do not have anybody to rely on than persons who are employed ($p=0.007$). Persons who are single, divorced or widow/widower have significantly less persons who they can rely on in case of serious personal problems (29.9% have more than 5 persons) than others who live in marriage or with partner (70.1% have more than 5 persons) (Table 2).

For the evaluation of the possibility of age and social support indicators (number of household members, ability to rely on help of neighbors and the number of people we can count on in case of a serious problem) to provide relationship with self-perceived health, level of distress and positive mental health (vitality) multiple regression was applied. The model as a whole explained 33.6% of the total variance of global health assessment, 12.5% of the total variance of levels of distress and 20.5% of the total variance vitality. This model is a significant predictor of self-perceived health ($F=528.686$; $p<0.001$), distress ($F=149.938$; $p<0.001$) and vitality ($F=269.519$; $p<0.001$).

All variables in the model give a statistically significant and unique contribution to the prediction of dependent variables. The largest negative association is present be-

tween self-perceived health and age ($p<0.001$). The same variable (age) is most negatively associated with distress ($p<0.001$) and vitality ($p<0.001$), while help from the neighbors is positively associated with mental distress (Table 3). Next, by comparing males and females, a negative association was found between self-perceived health and age ($p<0.001$) in both groups, while among males a positive association between self-perceived health and help from neighbors was present ($p<0.001$). Among males a negative association between age and distress ($p<0.001$) and a positive association between help from neighbors and mental distress were present ($p<0.001$). However, among females a negative association between distress and age ($p<0.001$) and a positive association between distress and persons that they can rely on were present ($p<0.001$). A negative association of age on mental vitality was large for males and females, although the association of vitality and help from neighbors was more present among males (Table 3).

DISCUSSION

The level of social support varies across different categories of population. Reduced number of people and neighbors from whom one can seek help is present among older categories of population. A low presence of social support is evident among inactive (retired, housewives and disabled) persons, persons with the lowest level of education and those who live alone (divorced, widowed, unmarried). Also, males, more than females, live alone and rely on a smaller number of persons in case of serious problems. The presented groups of persons were more vulner-

Table 2. Level of social support among different socio-demographic groups of adult population

Variable		Can get help form neighbour when it is needed – N (%)			p	No. of persons one can rely on when there is a serious personal problem – N (%)			p (χ^2 test)
		Hard	Possible	Easy		No one	1–5	> 5	
Gender	Male	42 (50.6)	1177 (54.4)	762 (54.9)	0.747	36 (46.2)	1726 (55.2)	492 (50.4)	0.011
	Female	41 (49.4)	985 (45.6)	627 (45.1)		42 (53.8)	1398 (44.8)	484 (49.6)	
	Total	83 (100.0)	2162 (100.0)	1389 (100.)		78 (100.0)	3124 (100.0)	976 (100.0)	
Age (years)	18–24	4 (4.8)	183 (8.5)	137 (9.9)	0.046	1 (1.3)	272 (8.7)	108 (11.1)	0.001
	25–34	7 (8.4)	283 (13.1)	175 (12.6)		7 (9.0)	409 (13.1)	147 (15.1)	
	35–44	11 (13.3)	306 (14.2)	242 (17.4)		8 (10.3)	488 (15.6)	159 (16.3)	
	45–54	22 (26.5)	433 (20.0)	284 (20.4)		20 (25.6)	613 (19.6)	203 (20.8)	
	55–64	16 (19.3)	398 (18.4)	246 (17.7)		16 (20.5)	563 (18.0)	174 (17.8)	
	≥65	23 (27.7)	559 (25.9)	305 (22.0)		26 (33.3)	779 (24.9)	185 (19.0)	
	Total	83 (100.0)	2162 (100.0)	1389 (100.0)		78 (100.0)	3124 (100.0)	976 (100.0)	
Education	Low	47 (56.6)	920 (42.6)	538 (38.8)	0.001	48 (61.5)	1330 (42.6)	319 (32.7)	0.000
	Middle	27 (32.5)	1035 (47.9)	736 (53.1)		25 (32.1)	1514 (48.5)	542 (55.6)	
	High	9 (10.8)	204 (9.4)	113 (8.1)		5 (6.4)	276 (8.8)	114 (11.7)	
	Total	83 (100.0)	2159 (100.0)	1387 (100.0)		78 (100.0)	3120 (100.0)	975 (100.0)	
Employment	Employed	13 (15.7)	622 (28.8)	406 (29.3)	0.073	10 (12.8)	916 (29.3)	311 (31.9)	0.007
	Unemployed	28 (33.7)	517 (23.9)	331 (23.8)		26 (33.3)	737 (23.6)	231 (23.7)	
	Inactive	42 (50.6)	1020 (47.2)	651 (46.9)		42 (53.8)	1468 (47.0)	433 (44.4)	
	Total	83 (100)	2159 (100.0)	1388 (100.0)		78 (100.0)	3121 (100.0)	975 (100.0)	
Marital status	Married or living with partner	53 (63.9)	1387 (64.4)	940 (67.8)	0.108	47 (60.3)	2014 (64.7)	683 (70.1)	0.004
	Not married, divorced, widowed	30 (36.1)	766 (35.6)	446 (32.2)		31 (39.7)	1100 (35.3)	291 (29.9)	
	Total	83 (100.0)	2153 (100.0)	1386 (100.0)		78 (100.0)	3114 (100.0)	974 (100.0)	

Table 3. Association of self-perceived health, mental distress and mental vitality with age and variables of social support in the total sample and according to gender: results of multivariate logistic regression

Variables		β (p)		
		Total	Males	Females
Model for self-perceived health*	Age	-0.550 (<0.001)	-0.493 (<0.001)	-0.602 (<0.001)
	No. of household members	-0.018 (0.171)	-0.031 (0.109)	-0.010 (0.585)
	Help from neighbors	0.075 (<0.001)	0.104 (<0.001)	0.055 (0.003)
	No. of people who can be relied on	0.060 (<0.001)	0.051 (0.022)	0.059 (0.002)
	Adjusted R ²	0.336	0.282	0.379
Model for mental distress**	Age	-0.198 (<0.001)	-0.170 (<0.001)	-0.223 (<0.001)
	No. of household members	-0.091 (<0.001)	-0.113 (<0.001)	-0.065 (0.002)
	Help from neighbors	0.163 (<0.001)	0.220 (<0.001)	0.127 (<0.001)
	No. of people who can be relied on	0.109 (<0.001)	0.047 (0.056)	0.147 (<0.001)
	Adjusted R ²	0.125	0.118	0.129
Model for mental vitality***	Age	-0.392 (<0.001)	-0.356 (<0.001)	-0.425 (<0.001)
	No. of household members	-0.059 (<0.001)	-0.063 (0.003)	-0.040 (0.043)
	Help from neighbors	0.134 (<0.001)	0.197 (<0.001)	0.091 (<0.001)
	No. of people who can be relied on	0.031 (0.050)	-0.019 (0.427)	0.058 (0.005)
	Adjusted R ²	0.205	0.184	0.220

* males: F=189.681; p=0.000; females: F=344.355; p=0.000

** males: F=64.924; p=0.000; females: F=84.419; p=0.000

*** males: F=109.300; p=0.000; females: F=159.300; p=0.000

able since the lack of social support could deteriorate their health, especially with aging. Therefore, integrated social networks provide more social support to seniors and have a positive impact on mental and physical health, while loneliness and social isolation are associated with health problems and chronic conditions in older population [15]. Effects of reduced social support on health and life satisfaction among older population groups become more important since aging population is a growing problem.

The influence of social support is significant but small in terms of self-perceived health, while it is slightly higher in terms of distress and vitality (mental status). The influence of age on self-perceived health and mental status is much greater, so we can conclude that the level of health status satisfaction and mental health decreases with aging. Also, the impact of social support on the level of distress and vitality confirms the influence of social support on mental health [16, 17]. Researchers confirm that perceived

social support has a positive effect on mental health, i.e. reduces psychological distress, depression and anxiety [3, 4]. Previous research suggests that one's perception of having social support when it is needed is associated with a better mental status (distress and vitality). Self-reported or perceived low social support is indeed the risk factor for a poorer health status [18]. When it comes to gender differences, the impact of connections with neighbors on mental distress is higher among males while for female aging is more related to mental distress. According to our results, ageing is also an important risk factor for mental and self-perceived health which can be partially explained with living conditions and a small income of retired persons. More accurate measures of the life-span perspective of social capital and perceived social support [6] are important for revealing gender and age differences.

The presented results partially confirm theoretical hypothesis about the buffering effects of social support. Persons who live in the community, who feel that they can rely on a wider range of people have positive mental health and greater satisfaction with life. Capacity to cope with stress is higher due to the increased level of self-control mechanism that supports overcoming stressful events [19]. By comparing males and females we can notice that the impact of ageing on self-perceived health and mental status is important for both groups, but the social support impact of perceived help from neighbors on mental stress and vitality is more present among males than females. Females are more relied on persons who they can count on if some serious problem emerges. This difference can be partially explained by the fact that males live alone more often than females so they mostly rely on close neighbors while females have more household members that they can rely on.

Since the presented results are a part of a much bigger population survey, there are some dilemmas which we have to stress out. Social support and different age categories are overlapping and leave uncertainties in the interpretation of results, so that a more detailed analysis (based on a comparison of different socio-demographic groups in the population) could provide insight into the processes that mediate the effects of social support on health status. Also, some parts of applied instrument are not so sensitive measures

of social support, so that there is an open question of the appropriateness of social support indicators. Further linking of these results with objective parameters of health status would provide a more accurate relation of social support with mental health and health status between the different age categories of population. Comparing the impact of social support on mental and physical health across different socio-demographic groups (unemployed, unmarried etc.) will certainly reveal all factors which together with social support have a great impact on health. Further analyses could reveal mediating factors which have impact, together with social support, on health status and mental state of older population.

CONCLUSION

The study suggests differences in the level of social support between different age categories and socio-demographic groups. The level of social support is the lowest among the oldest population, persons with low education who are unemployed and single. With aging there is the presence of the lower level of self-perceived health and mental stress and vitality. Males mostly rely on help from neighbors while females mostly expect support from important persons whom they can rely on. These variables are mostly associated with mental health. The presented indicators limit the capacity of fine distinction of the structural and functional aspect of social support. However, the present study is nationally representative and contains a comprehensive set of demographic variables which reveal relationship among social support, self-perceived health and mental status. Wise socio-psychological support measures are urgently needed with a primary focus on the most socially disadvantaged socio-demographic groups.

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Социјална подршка, самопроцена здравља и ментално здравље становништва Републике Српске

Јелена Нишкановић, Слађана Шиљак

ЈЗУ Институт за јавно здравство, Република Српска, Бања Лука, Босна и Херцеговина

КРАТАК САДРЖАЈ

Увод Социјална подршка значи процену онога колико се други људи брину за нас, прихватају наше потребе и пружају нам подршку. Њен значај се огледа у позитивном утицају на здравље, усвајању здравих стилова живота и опоравку од болести.

Циљ рада Циљ рада је био да се утврде заступљеност социјалне подршке међу различитим групама становништва и њен утицај на ментално благостање и процену општег здравља.

Методе рада Истраживање је урађено као студија пресека међу одраслим становништвом на територији Републике Српске. У истраживању је коришћен посебно дизајниран упитник осмишљен на основу међународно потврђених и прихваћених инструмената са посебно издвојеним питањима у области социјалне подршке, самопроцене здравља и менталног здравља. Укупно 1.866 домаћинстава је обухваћено истраживањем, а анкетирано је 4.178 лица.

Резултати Добијени резултати су показали да је ниво социјалне подршке, изражен кроз број чланова домаћинства, суседе од којих особа може тражити помоћ, те особе на ко-

је се неко може ослонити, нижи код најстаријих категорија становништва, особа с најнижим нивоом образовања, незапослених и оних који не живе у брачној заједници. Заступљен је утицај социјалне подршке на процену општег здравља и ментално здравље (дистрес/стрес и виталност). Поредећи мушкарце и жене, може се уочити да мушкарци у већем проценту живе сами, те више очекују помоћ од суседа у случају потребе, док жене живе са другим члановима породице и више се ослањају на помоћ супруга.

Закључак Очигледан је утицај социјалне подршке на процену здравља и ментално благостање. Добијени резултати се преплићу с различитим старосним категоријама, те представљају основу за дубље анализе и утврђивање узрочних односа између социјалне подршке и менталног здравља становништва. Утврђивање процеса који посредују између утицаја социјалне подршке и физичког и менталног здравља пружило би увид у механизме њеног утицаја на здравствено стање и понашање.

Кључне речи: социјална подршка; процена здравља; ментално благостање

Giant Destructive Sinonasal Polyposis

Milovan V. Dimitrijević^{1,2}, Nenad A. Arsović^{1,2}, Zoran R. Dudvarski^{1,2}, Ivan V. Boričić^{1,3}

¹University of Belgrade, School of Medicine, Belgrade, Serbia;

²Clinic for Otorhinolaryngology and Maxillofacial Surgery, Clinical Center of Serbia, Belgrade, Serbia;

³University of Belgrade, School of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY

Introduction Authors report their clinical experience in managing a 46-year-old male patient with long lasting nose breathing difficulties caused by nasal obstruction due to a large bilateral tumor masses in both nasal cavities.

Case Outline Physical examination, laboratory and biochemistry analyses, as well as computed tomography showed an inhomogeneous soft-tissue tumor mass completely filling both nasal cavities, maxillary, ethmoidal, sphenoidal, and frontal sinuses on both sides, accompanied by destruction of bony walls of all sinuses. Preoperative histopathology analysis showed a polyp with squamous metaplasia. The gigantic polypoid mass was removed by bicoronal approach to the frontal and ethmoidal sinuses and by direct approach to the maxillary sinuses and nasal cavity. Definite histopathology analysis confirmed the initial diagnosis, but the presence of fungal hyphae in allergic mucus was also observed.

Conclusion Polypoid growth in the nose rarely grow to such gigantic dimensions that it causes destruction of all walls of paranasal sinuses. Considering so far published reports from the literature, the presented case is among the biggest nasal polyps reported until now.

Keywords: giant sinonasal polyp; squamous metaplasia; surgical treatment

INTRODUCTION

Nasal polyposis is a chronic, inflammatory disorder of mucous membranes of the nose and paranasal sinuses, presenting with soft, smooth, pedunculated, tumor-like masses in the nasal cavity. According to the data from the literature, the prevalence of nasal polyposis in general population is 1-4% [1, 2, 3], while the prevalence is much higher in persons with comorbidities such as asthma, aspirin intolerance or cystic fibrosis. In cases of allergic fungal rhinosinusitis, nasal polyposis can be seen in 66-100% of cases [4]. Etiopathogenesis of sinonasal polyposis yet remains unclear, but it has been shown that inflammation plays the major role in the development and progression of the disease [5-10]. The most common symptoms of nasal polyps include nasal obstruction, nasal secretion and hyposmia. Others signs and symptoms such as severe headaches and eyelid proptosis may suggest imminent complications, especially in patients with diabetes mellitus who are more susceptible to fungal infections. Furthermore, appearances of diplopia or VI cranial nerve paralysis are signs of intracranial irritation.

Although in general sinonasal polyposis does not belong to the group of life-threatening conditions, cases of eosinophilic pansinusitis with polyposis and destruction of bony walls of the middle and posterior cranial fossa have been described in the literature. Aspergilosis of sinuses can have a complicated clinical course with destruction of the skull base [11] and in some cases eosinophilic fungal sinusitis can

cause destruction of frontal sinuses and compression of the dura of the middle cranial fossa in young adults [12].

We report a case of a massive, gigantic nasal polyposis with destruction of bony structures (medial and anterior walls of maxillary sinuses, anterior and posterior walls of frontal sinuses) in an adult patient who was successfully treated surgically. The Ethic Committee of the Clinical Centre of Serbia approved this case report.

CASE REPORT

A 46-year-old male patient was admitted at the Clinic due to nasal obstruction and impaired nasal breathing lasting for several years. Six months before admission, the patient noticed a left-sided edema of the face, diplopia and inability to feel odors. Physical examination of the patient revealed massive polypoid masses completely filling both nasal cavities (Figure 1). The patient had divergent strabismus. Computed tomography (CT) of the brain and paranasal sinuses showed an inhomogeneous soft-tissue mass, which completely filled both nasal passages, maxillary and frontal sinus on both sides, accompanied by destruction of bony walls, medial and anterior walls of maxillary sinuses, both medial orbital walls, ethmoidal cells, sphenoid sinus and anterior and posterior walls of frontal sinuses (Figure 2). The mass was in contact with the dura.

Routine laboratory and biochemistry analyses were within the normal range, except el-

Correspondence to:

Milovan V. DIMITRIJEVIĆ
Clinic for Otorhinolaryngology
and Maxillofacial Surgery
Clinical Center of Serbia
Pasterova 2, 11000 Belgrade
Serbia
drmilovan@yahoo.com
milovan.dimitrijevic@kcs.ac.rs



Figure 1. Massive polypoid masses completely filling both nasal cavities

evated total serum levels of IgE. Cutaneous PRICK test for standard inhalation allergens was negative.

The tissue sample was obtained and histopathology analysis showed a polyp displaying combination of stromal edema and containing a mild infiltrate of eosinophils, plasma cells and lymphocytes. The surface epithelium was of the respiratory type, with areas of squamous metaplasia (Figure 3). Allergic mucus was observed with sporadic fungal hyphae.

After a thorough preoperative preparation, the patient was treated surgically by bicoronal approach. During surgery a defect of bony anterior wall of the frontal sinus was found measuring 10×10 mm on the right and 8×5 mm on the left side. Both frontal sinuses were filled with polyps, mucosa with chronic changes and with thick, mucous secretion. The defect of the posterior wall of the sinus was almost $\frac{3}{4}$ of the area, with no signs of lesion of the dura and cerebrospinal fluid leakage. Defect of both superior orbital walls was noted. Bilateral ethmoidectomy was also performed and polyps from ethmoidal cells and sphenoid sinus were removed. The maxillary sinus was accessed using Caldwell-Luc approach, and destruction of both anterior walls was observed. Medial walls were also completely missing. In the end, the polyps were removed from the nasal cavity and endoscopic examination was performed. Defect of the posterior wall of frontal sinus was reconstructed with a pericranial flap and sealed with Beriplast®, and the defect of orbital roof was reconstructed with aliphatic polyester urethane (Neuro-Patch®) and also sealed with fibrin sealant (Beriplast®). Repositioning of the anterior wall of the frontal sinus and its fixation was done with two titanium microplates.

Antibiotic and corticosteroid treatment was administered immediately after surgery. Moreover, antimycotic

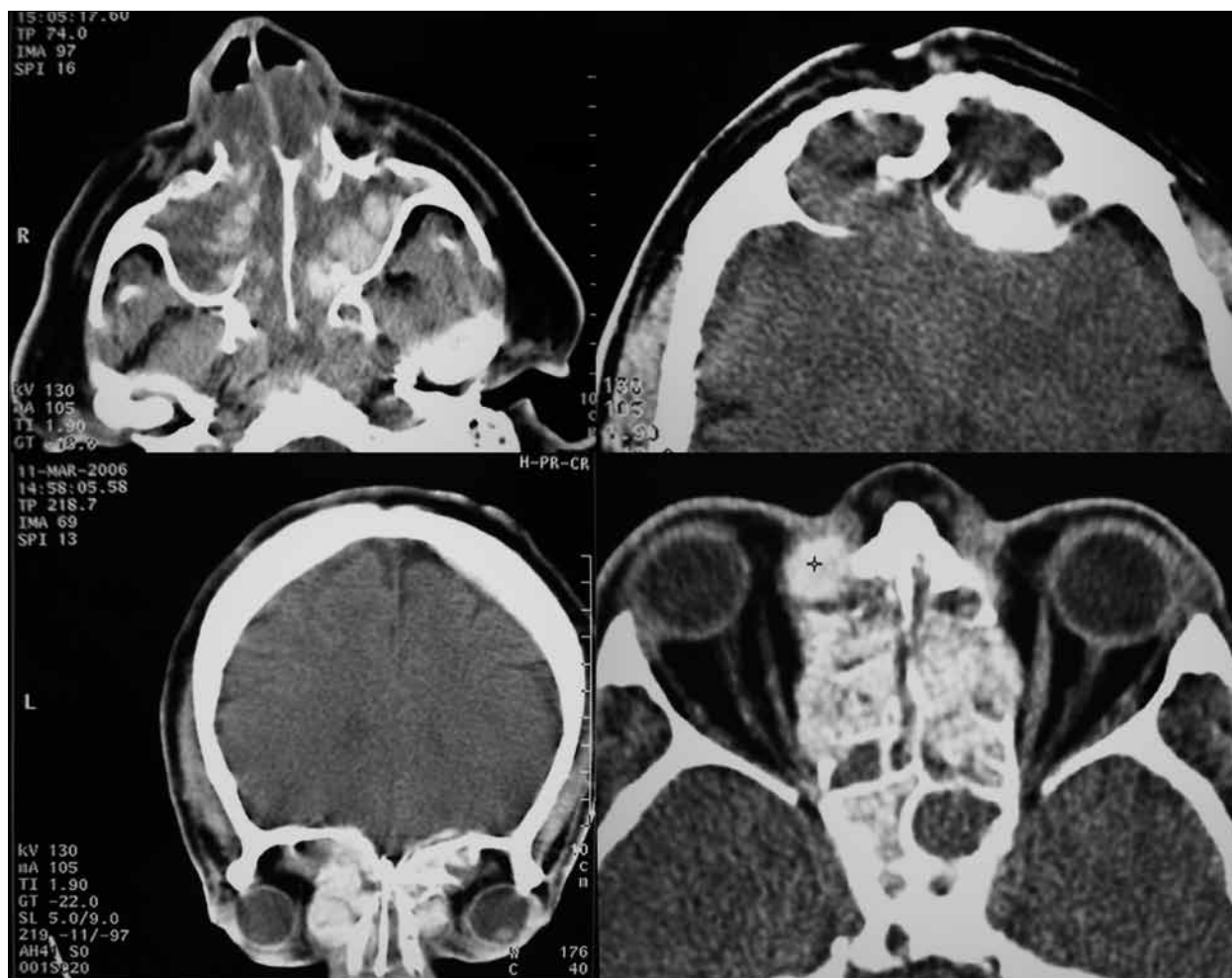


Figure 2. Computed tomography (CT) of the brain and paranasal sinuses showed a soft-tissue mass completely filling both nasal passages, maxillary and frontal sinuses, ethmoidal cells, sphenoid sinus, accompanied by destruction of bony walls



Figure 3. Polyp displays combinations of stromal edema and contains a mild infiltrate of eosinophils, plasma cells and lymphocytes (HE, 40x). The surface epithelium is of the respiratory type (lower part of the figure), with areas of squamous metaplasia (upper part of the figure).

drug ketoconazole (daily 200 mg) and topical nasal steroid mometasone furonate (Nasonex®) was used during two weeks and 6 months after surgery, respectively. Intensive saline solutions irrigations were applied.

Histopathology analysis of material obtained during surgery confirmed the findings of preoperative biopsy and specific Grocott staining for mycotic infection was applied.

The patient was under regular follow-up regularly and 7 years after surgery. There are no signs or symptoms of relapse.

DISCUSSION

Sinonasal polyposis is a chronic, inflammatory disease of mucosal membranes of the nose and paranasal sinuses. Apart from the patient's history, clinical and endoscopic examination, CT scans of paranasal sinuses are the golden diagnostic standard for accurate diagnosis. If there is suspicion regarding the development of intracranial complications, magnetic resonance imaging has higher sensitivity and specificity than CT scan.

Clinicians must always maintain a high level of suspicion in patients with nasal polyps, because allergic fungal sinusitis is commonly seen in these patients and it usually exhibits recurrent and intractable course of the disease. It was reported that in 20% of patients with allergic fungal sinusitis the propagation of pathologic process in the paranasal sinuses and erosion of bony structures was observed [13].

In polyposis with squamous metaplasia, the destruction of bony walls is rarely seen. If such destruction is present, a potential malignancy should be excluded. The necrosis of bone may appear due to the compression of polypoid tissue and can cause serious morbidity such as seen in our patient. Use of radiotherapy in such cases is proved to be inefficient and there is always the risk of neoplastic proliferation. The standard in treating patients with this condition is surgery [11].

With the development of functional endoscopic sinus surgery (FESS), the indications for classical surgical procedures are much narrowed. Endoscopic frontal sinusotomy is used even in cases of refractory chronic sinusitis with erosion of the posterior wall of the frontal sinus [14] and there are cases of endoscopic sphenoidectomy with removal of extensive allergic mucus and destruction of the clivus and parasellar region reported in the literature [13]. In diagnostically challenging cases with fungal coinfection even today, the conventional surgery of sinuses is justified [11].

Reported relapse in cases of sinonasal polyposis after endoscopic surgery is even more than 60% [15, 16, 17], and patients with this condition may be an important group of patients in whom conventional surgery provides a better control of the disease over a prolonged period of time [15, 18]. Postoperative administration of systemic or topical antifungal treatment in these patients is still controversial, but it has been shown that oral corticosteroid drugs are justified in preventing immunological response of the host on residual fungi and to minimize the need for further surgical interventions [19, 20].

Due to the elevation of total serum levels of IgE and histopathologic confirmation of fungal infection, we decided to perform the classical surgical intervention with reconstruction of eroded bony walls. We also avoided the need for revision of surgical interventions, which are very common in patients with this condition.

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Џиновска деструктивна синоназална полипоза

Милован В. Димитријевић^{1,2}, Ненад А. Арсовић^{1,2}, Зоран Р. Дудварски^{1,2}, Иван В. Борић^{1,3}

¹Универзитет у Београду, Медицински факултет, Београд, Србија;

²Клиника за оториноларингологију и максиларно-фацијалну хирургију, Клинички центар Србије, Београд, Србија;

³Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

КРАТАК САДРЖАЈ

Увод Аутори приказују своје клиничко искуство у лечењу 46-годишњег мушкарца са дуготрајним сметњама у дисању на нос услед великих туморских промена у обе носне шупљине.

Приказ болесника Физикални преглед, лабораторијске и биохемијске анализе и налаз компјутеризоване томографије параназалних синуса указали су на нехомогену, мекоткивну туморску масу, која потпуно испуњава обе носне шупљине, максиларне, етмоидалне, сфеноидалне и фронталне синусе с обе стране уз оштећење коштаног зида свих синуса. Преоперациона хистопатолошка анализа указала је на полип са сквамозном метаплазијом. Џиновска полипоидна

маса је уклоњена бикоронарним приступом фронталним и етмоидалним синусима и директним приступом максиларним синусима и носној шупљини. Коначна хистопатолошка анализа је потврдила почетну дијагнозу, уз присуство гљивичних хифа у алергијској слузи.

Закључак Полипоидни израштаји у носу ретко достижу овакве велике димензије које узрокују уништавање свих зидова параназалних синуса. Имајући у виду досад објављене радове у литератури, приказани случај синоназалне полипозе је међу највећим пријављеним до данас.

Кључне речи: џиновска синоназална полипоза; сквамозна метаплазија; хируршко лечење

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Ameloblastic Fibroma: A Rare Case Report with 7-Year Follow-Up

Leonardo de Araújo Melo¹, Adna Conceição Barros¹, Sandra de Cássia Santana Sardinha², Arlei Cerqueira², Jean Nunes dos Santos³

¹School of Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil;

²Division of Oral and Maxillofacial Surgery, School of Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil;

³Laboratory of Oral Surgical Pathology, School of Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil

SUMMARY

Introduction Ameloblastic fibroma (AF) is a rare benign odontogenic tumor that usually occurs in the first two decades of life. It affects adolescents and young adults and is found in the mandible and with a higher frequency in the posterior region of this segment. There are rare case reports with a long-term follow-up.

Case Outline We report the case of a 6-year-old boy with extensive ameloblastic fibroma in the mandible. Treatment consisted of enucleation and bone curettage, with the preservation of permanent teeth adjacent to the tumor. Clinical and radiographic follow-up of the patient over a period of 7 years showed no signs of recurrence or malignant transformation.

Conclusion Patients with AF should be under follow-up for prolonged periods of time, even in cases exhibiting a low proliferation index, because of the potential for recurrence and malignant transformation of this tumor.

Keywords: ameloblastic fibroma; odontogenic tumors; jaws; follow-up

INTRODUCTION

Ameloblastic fibroma (AF) is a rare tumor which accounts for 0.9 to 2.4% of all odontogenic tumors involving the jaw bones [1-4]. AF mainly affects adolescents and young adults and has a slight male predominance. Most tumors are found in the mandible, while a higher incidence is observed in the posterior region. Patients usually seek treatment because of a swelling in the jaw bones and delayed tooth eruption, although some cases are diagnosed incidentally during routine radiographic examination [5]. Radiographically, AF appears as a unilocular lesion with well-defined margins. Multilocular lesions are occasionally observed in more extensive cases. The lesions are frequently associated with impacted teeth [6, 7].

Histologically, AF is characterized by epithelial islands and cords whose center resembles the stellate reticulum of the enamel organ. The islands and cords are immersed in ectomesenchyme that mimics the dental papilla. The presence of a capsule is considered an uncommon feature of AF [8].

AF shows a high rate of recurrence [5], while malignant transformation is observed in some cases [9, 10]. These findings highlight the importance of the study of this tumor and the need for long-term follow-up. This study reports a case of extensive AF in the mandible of a child. No signs of recurrence were observed after 7 years of follow-up.

CASE REPORT

A 6-year-old boy was referred to a private clinic in Salvador, Bahia, Brazil, for evaluation of a swelling on the right side of the face. The parents reported no eating difficulties. The medical history revealed that the patient had thalassemia minor, but no clinical signs or symptoms were observed.

Extraoral physical examination showed a hard swelling in the mandibular body and angle on the right side, which caused a mild facial asymmetry. Intraoral examination revealed a swelling of the alveolar ridge in the right posteroinferior region and the absence of teeth in the same region, which led the patient to seek treatment (Figure 1A). Panoramic radiography showed the presence of a well-defined multilocular radiolucent area extending from the right deciduous first molar to the mandibular angle on the same side, causing the retention of teeth 85 and 46 (Figure 1B). The clinical suspicions included dentigerous cysts, keratocystic odontogenic tumor, and ameloblastoma. An incisional biopsy was performed and anatomopathological analysis showed odontogenic epithelial islands and cords amidst a cellular and embryonic stroma resembling the dental papilla. These findings were consistent with the diagnosis of AF. Two weeks later, the patient was submitted to general anesthesia for enucleation of the lesion, extraction of tooth 85, and bone curettage (Figure 1C). Macroscopic inspection of the tu-

Correspondence to:

Jean Nunes DOS SANTOS
Avenida Araújo Pinho, 62
Canela, Salvador-BA
Brazil 40110-150
jeanunes@ufba.br

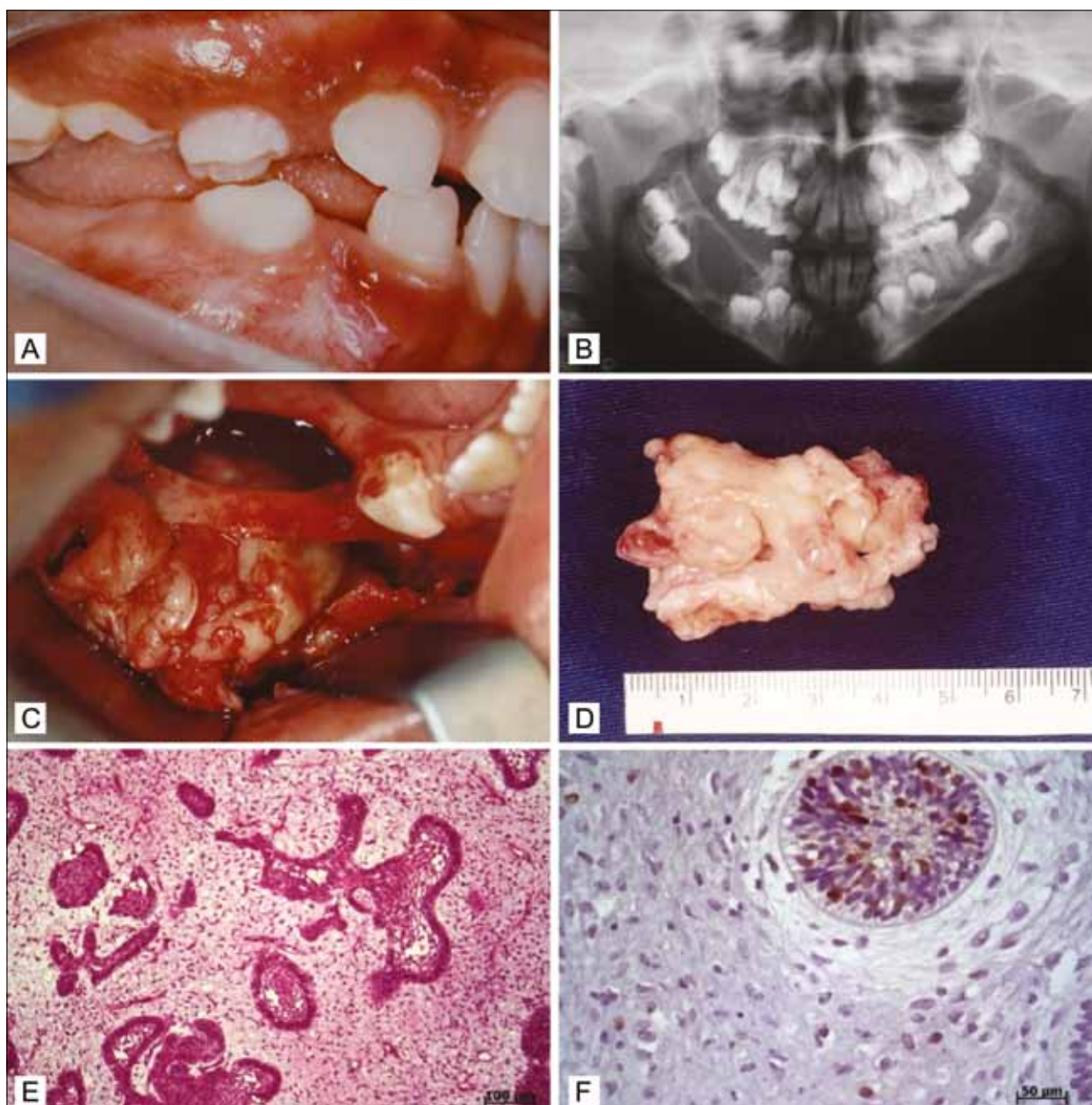


Figure 1. **A.** Intraoral view. Swelling of the alveolar ridge in the right posteroinferior region and absence of teeth. **B.** Panoramic radiograph showing a well-defined multilocular radiolucent lesion at the right side of the mandible. **C.** Intraoperative image obtained during surgical removal of the tumor. **D.** Macroscopic inspection of the tumor specimen measuring 45×40×10 mm. **E.** Presence of odontogenic epithelial islands and cords amidst a cellular and embryonic stroma resembling the dental papilla (HE, 10×). **F.** Immunohistochemical analysis showing the presence of few Ki-67-positive nuclei in the epithelial parenchyma.

mor specimen, which measured 45×40×10 mm, revealed an irregular surface and fibroelastic consistency (Figure 1D). Histopathological analysis confirmed the diagnosis of AF (Figure 1E). Immunohistochemistry detected few Ki-67-positive nuclei, especially in the epithelial parenchyma, indicating a low proliferation index of the tumor (Figure 1F).

No complications were observed during the postoperative period. The patient was followed up over a period of 7 years and no clinical or radiographic signs of recurrence were observed. Control panoramic radiographs, after 2 months, 1 and 5 years, showed the formation of new bone in the right posterior region of the mandibular body and complete eruption of teeth 46 and 47 (Figure 2). Com-

puted tomography scans obtained after 7 years revealed cortical bone integrity, complete formation of medullary bone, and complete eruption of tooth 46 which had been preserved during surgery. In addition, the bone architecture in the right posteroinferior region was preserved and no radiolucency was observed (Figure 3).

DISCUSSION

This study reported a case of AF involving the body and angle of the mandible in a 6-year-old child. Philipsen et al. [11] and Tomich [6] suggested that AF corresponds to a stage of maturation of ameloblastic fibro-odontoma and

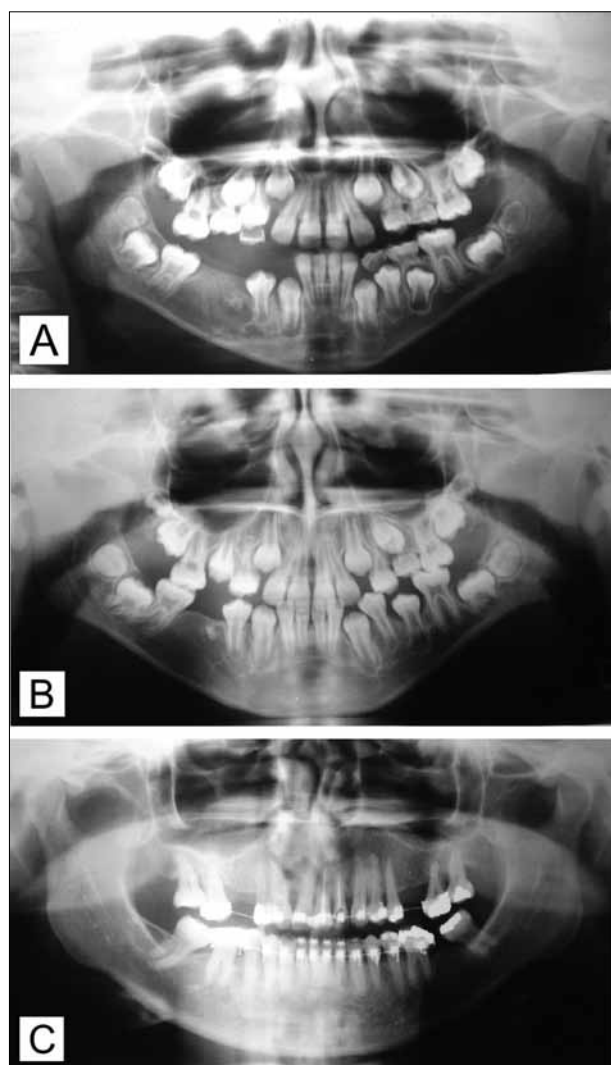


Figure 2. Control panoramic radiographs, after 2 months (A), 1 year (B) and 5 years (C), respectively, showing the formation of new bone in the right posterior region of the mandibular body and complete eruption of teeth 46 and 47.



Figure 3. Control computed tomograph scans obtained after 7 years. Note the integrity of cortical bone, absence of radiolucency, and preservation of bone architecture in the region.

odontoma. This hypothesis has been refuted since recurrent AFs show no evidence of maturation to ameloblastic fibro-odontoma or odontoma. In addition, AFs usually affect patients in the third decade of life when the process of odontogenesis is already completed [12].

Clinically, the patient presented with a mandibular swelling extending from the right deciduous first molar to the mandibular angle on the same side, causing a delay in tooth eruption. According to Kim and Jang [8], this swelling is caused by gradual expansion of the cortical plate during growth of the tumor. In addition, these authors have reported that AF shows slower growth than other odontogenic tumors, such as ameloblastoma, and does not tend to infiltrate bone. However, Pereira et al. [13] reported a case of rapidly growing AF in an 11-month-old infant, which was attributed to the small size of the jaw.

The patient had thalassemia minor, the heterozygous state of a hereditary genetic disease characterized by a reduction in beta globin chain synthesis, causing mild and silent microcytic and hypochromic anemia [14, 15]. There are no reports in the literature correlating this hereditary disease with AF, but this odontogenic tumor has been diagnosed in other diseases such as Goldenhar syndrome [16].

The histopathological features of the present case met the criteria for AF [12, 17]. The lesion consisted of odontogenic epithelial islands and cords amidst a cellular and embryonic stroma resembling the dental papilla. Usubutun et al. [18] also found extensive cystic formation as a result of a degenerative process, but this was not observed in the present case.

According to Cernelio and Vij [19] and Rao et al. [20], AF exhibits a low proliferation rate. This was confirmed in the present study by sparse immunostaining for Ki-67, especially in the parenchymal compartment. Evaluation of the proliferative potential of AF using immunohistochemical markers contributes to the understanding of tumor aggressiveness and to adequate surgical planning [8], as in the present case.

The initial diagnosis of the case included a dentigerous cyst, odontogenic keratocystic tumor and ameloblastoma due to the clinical and radiographic similarities between these lesions. The differential diagnosis of AF should include odontogenic lesions such as the dentigerous cyst, ameloblastoma, myxoma, and other mixed tumors [21, 22]. According to Nelson and Folk [23], despite many similarities, it is essential to differentiate AF from other mixed odontogenic tumors in view of its true neoplastic potential, possibility of recurrence and malignant transformation potential.

The present patient was submitted to conservative treatment considering that the lesion was a primary tumor and to avoid possible esthetic deformities. Consensus exists regarding the preference of conservative treatment of AFs, including enucleation of the tumor and removal of all teeth involving bone curettage [13, 24, 25]. According to these authors, en bloc resection results in significant morbidity and esthetic deformity and should be reserved for extensive tumors invading soft tissue and for recurrent cases.

The present patient was followed up for 7 years and no clinical or radiographic signs of recurrence or malignant transformation were observed after this period, demonstrating the success of treatment. Long-term follow-up of AF as done in the present study is important due to the possibility of recurrence and malignant transformation.

Follow-up of cases for up to 12 years has been reported [8, 13, 21, 25, 26].

In conclusion, patients with AF should be followed up for prolonged periods of time, even cases exhibiting a low proliferation index, because of the potential for recurrence and malignant transformation of this tumor.

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Амелобластни фибром: приказ ретког случаја са седмогодишњим периодом клиничког праћења

Леонардо де Араужо Мело¹, Адна Консеисао Барос¹, Сандра де Касиа Сантана Сардиња², Арлеи Серквеира², Жеан Нунес дос Сантос³

¹Стоматолошки факултет, Државни универзитет Баије, Салвадор, Баија, Бразил;

²Катедра за оралну и максилофацијалну хирургију, Стоматолошки факултет, Државни универзитет Баије, Салвадор, Баија, Бразил;

³Лабораторија за оралну патологију, Стоматолошки факултет, Државни универзитет Баије, Салвадор, Баија, Бразил

КРАТАК САДРЖАЈ

Увод Амелобластни фибром је редак, бенигни, одонтогени тумор који се обично јавља до двадесете године живота. Обољење погађа адолесценте и младе одрасле особе, а захвата доњу вилицу, и то чешће постериорну регију овог сегмента. Прикази болесника са дугорочним клиничким праћењем су ретки.

Приказ болесника Приказујемо шестогодишњег дечака са екстензивним амелобластним фибромом доње вилице. Болесник је лечен применом хируршке ресекције и киретаже

кости, уз очување сталних зуба у близини тумора. Клиничко и радиолошко испитивање болесника током седмогодишњег периода није показало знаке рецидива или малигне трансформације.

Закључак Болеснике оболеле од амелобластног фиброма потребно је дугорочно надгледати, чак и у случајевима с ниским индексом пролиферације, с обзиром на могућу појаву рецидива и малигну трансформацију овог тумора.

Кључне речи: амелобластни фибром; одонтогени тумори; вилица; клиничко праћење

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Laparoscopic Distal Pancreatectomy for Intrapancreatic Accessory Spleen: Case Report

Slavko Matic^{1,2}, Djordje Knežević^{1,2}, Igor Ignjatović², Nikola Grubor², Vladimir Dugalić^{1,2}, Marjan Micev², Srbislav Knežević^{1,2}

¹University of Belgrade, School of Medicine, Belgrade, Serbia;

²Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade, Serbia

SUMMARY

Introduction Accessory spleens can be found in up to 10% of the population, and their intrapancreatic occurrence is considered uncommon. When present, the intrapancreatic accessory spleen is usually found in the tail of the pancreas in about 1.7% of adult individuals. The infrequent presence of the accessory spleen in the pancreatic tissue could lead to inappropriate diagnosis and hence therapeutic approach, as they are commonly presented as a hypervascular node in the tail of the pancreas on abdominal CT and MRI, mimicking a well differentiated tumor of the pancreas or non-functioning pancreatic neuroendocrine tumor.

Case Outline We present a 70-year-old female in whom a preoperative evaluation finding was highly suggestive of a non-functioning neuroendocrine tumor of the pancreatic tail. We performed spleen preserving laparoscopic distal pancreatectomy, and histopathological examination revealed the intrapancreatic accessory spleen.

Conclusion Although infrequent, the presence of the intrapancreatic accessory spleen must be considered in the differential diagnosis of pancreatic tail tumors.

Keywords: intrapancreatic spleen; accessory spleen; pancreas; pancreatic neuroendocrine tumor; laparoscopic distal pancreatectomy

INTRODUCTION

Accessory spleen is a congenital anomaly in which splenic tissue is found outside the spleen. This anomaly usually occurs in the fifth week of intrauterine fetal development [1]. Accessory spleens occur in about 10% of normal population and can be found practically anywhere in the abdominal cavity. In the majority of cases they are localized in the splenic hilum, gastro-splenic ligament and greater omentum [2]. Less frequent localizations include gastric wall, small intestine, mesenterium, pancreas, even ovary and testicle [3]. Accessory spleens are in fact ectopic splenic tissue. They are usually asymptomatic and almost never require specific treatment, except in some hematologic disorders such as idiopathic thrombocytopenic purpura (ITP). Intrapancreatic accessory spleens (IPAS) are found in about 1.7% of the population and their intrapancreatic localization can be misleading in diagnostic procedures as well as in choosing the proper therapeutic approach. These lesions are usually present in CT/MRI findings as hypervascular, well-delimited lesions which can be easily misdiagnosed for a well differentiated pancreatic tumor, pancreatic neuroendocrine tumor (PNET), solid pseudo-papillary pancreatic neoplasm or even metastatic pancreatic tumor [4]. Therefore, the diagnosis is usually obtained only after histopathologic examination of the resected specimen since these pa-

tients frequently undergo pancreatic resection due to impossibility of excluding pancreatic neoplasm [5]. Although uncommon, intrapancreatic accessory spleen should be taken into consideration in the diagnostic algorithm for pancreatic lesions, especially since new and adequate diagnostic procedures can be of use in obtaining the right diagnosis and avoiding the unnecessary surgical intervention with all potential complications [6].

CASE REPORT

A 70-year-old female was admitted to hospital for non-specific, dull epigastric pain and upper abdominal discomfort. Laboratory findings and tumor-marker serum levels (CA 19-9, CEA, CA 72-4) were within the reference range. Chromogranin A (CgA) serum level was slightly elevated. Abdominal ultrasound and multi-detector computed tomography (MDCT) revealed a well-delimited, hypervascular tumor-like lesion, 20×18 mm in size, located in the tail of the pancreas (Figures 1, 2 and 3). According to the imaging characteristics of the lesion and elevated serum CgA level, the lesion was interpreted as a non-functioning PNET and the decision for surgical procedure was made.

The patient was operated by the laparoscopic approach in the right lateral supine position (hanging spleen technique) which eases

Correspondence to:

Slavko MATIĆ
Clinic for Digestive Surgery
Clinical Center of Serbia
Dr Koste Todorovića 6
11000 Belgrade
Serbia
slavko.matic@med.bg.ac.rs
calematic@gmail.com

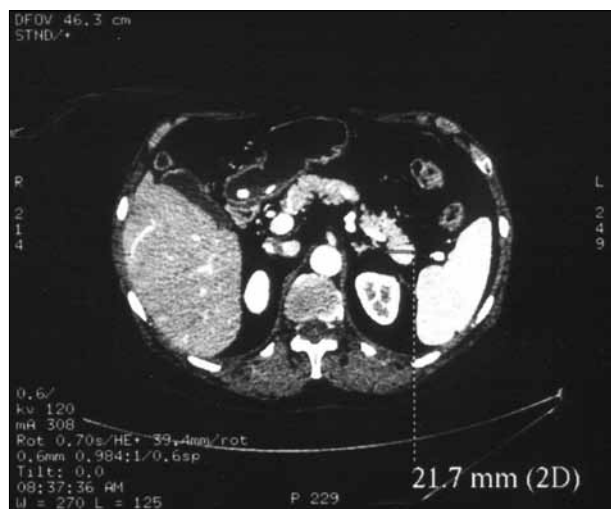


Figure 1. Upper abdominal MDCT showing pancreatic tail tumor

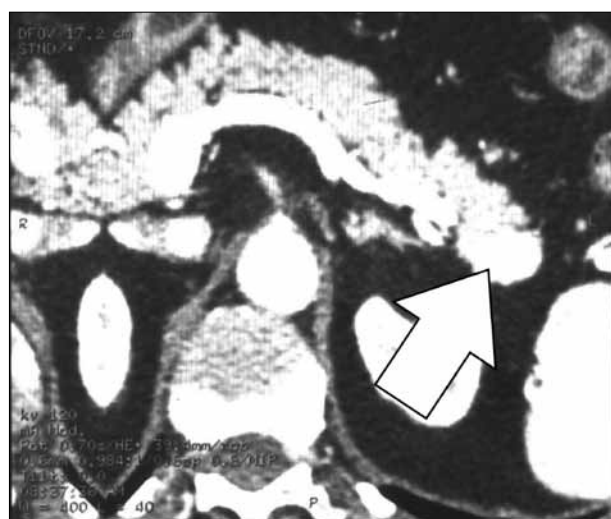


Figure 2. Enlarged view of the pancreatic tail; IPAS marked by an arrow



Figure 3. MDCT showing hypervascular pancreatic tail node

the access to the colon splenic flexure, spleen and tail of the pancreas. After complete mobilization of the colon, splenic flexure and entering the greater sac (omental bursa) through the gastro-colic ligament, anterior surface of the

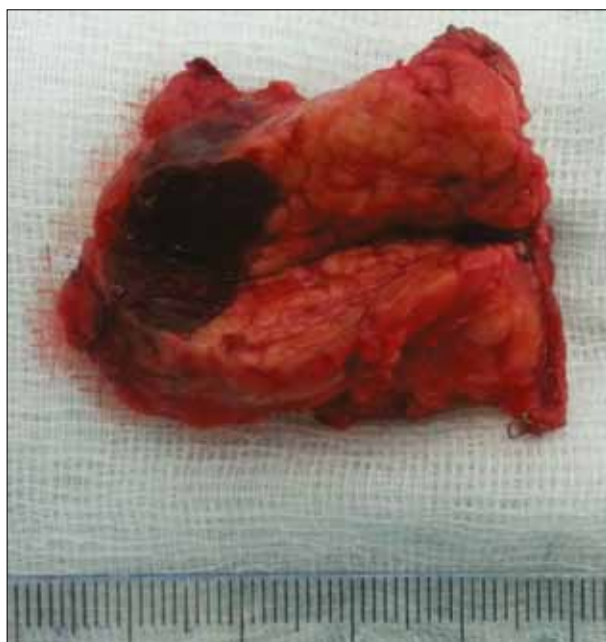


Figure 4. Operative specimen of resected pancreas

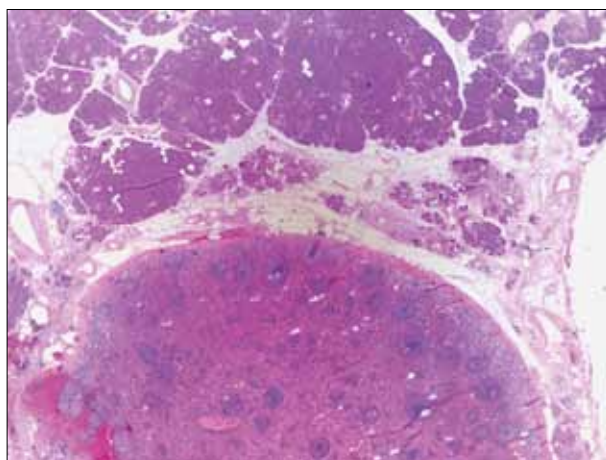


Figure 5. Histopathology showing the typical encapsulated splenic parenchyma as an accessory spleen surrounded by pancreatic tissue (HE, 2.5x)

pancreatic body and tail was completely exposed. A dark reddish-brown in color tumorous lesion on the posterior side of the pancreatic tail was detected. The pancreatic tail was divided from blood vessels for splenic inferior pole and from splenic vein by cutting short pancreatic vein branches with an ultrasound harmonic knife. The tail of the pancreas was further mobilized toward the medial axis to the left lateral side of the superior mesenteric vein. Pancreatic transection was then performed at the level of the neck of the pancreas using an endoscopic stapling device (Endo GIA). No major bleeding from the resected surface of the pancreas or pancreatic juice leakage was observed. Laparoscopic distal pancreatectomy with preservation of the spleen was then completed. This was, in fact, the first ever laparoscopic pancreatic resection performed in the Clinical Centre of Serbia. The resected pancreas was placed in the endoscopic bag and removed through one of the ports on the anterior abdominal wall. The specimen was then sent to the pathologist for histopathologic examination (Figure 4).

Macroscopically, the lesion was oval, encapsulated, node-like, dark reddish-brown in color, 20 mm in size and resembling that of splenic tissue. Histopathologic analysis revealed the true nature of the lesion and the diagnosis of intrapancreatic accessory spleen was established (Figure 5). Postoperative course was uneventful and the patient was discharged from hospital after six days. One year after surgery, the patient is well and disease-free.

DISCUSSION

Although the intrapancreatic accessory spleen is considered as uncommon, Halpert and Gyorkey [3] have found 364 cases on 3,000 autopsies with 17% of them localized in the tail of the pancreas. Considering the benign nature of the lesion and frequent performance of unnecessary surgical procedures, it is important to obtain the correct diagnosis [7].

There are less than 40 cases of IPAS published in the English literature to date. Vast majority of these patients underwent pancreatic resection as IPAS were misdiagnosed for pancreatic tumor, or PNET as in our case. Uchiyama et al. [8] published a case report and review of the literature in 2008 showing 11 patients with IPAS treated with pancreatic resections. In 9 cases IPAS was interpreted as non-functioning PNET, in 1 case as exocrine pancreatic tumor while only 1 patient had indication for surgery since the ITP was present along with IPAS. Lehtinen et al. [9] found, analyzed and published a report on 25 patients with IPAS in 2013 including those who were not treated with surgery. Beside the ITP, other spleen conditions and disorders may rise as well in the accessory spleen. There are several published cases of epidermoid cysts in resected IPAS and they were interpreted preoperatively as pancreatic cystadenomas [10, 11].

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Лапароскопска дистална панкреатектомија због интрапанкреасне акцесорне слезине – приказ болесника

Славко Матић^{1,2}, Ђорђе Кнежевић^{1,2}, Игор Игњатовић², Никола Грубор², Владимир Дугалић^{1,2},
Марјан Мицев², Србислав Кнежевић^{1,2}

¹Универзитет у Београду, Медицински факултет, Београд, Србија;

²Клиника за дигестивну хирургију, Прва хируршка клиника, Клинички центар Србије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Акцесорне слезине се јављају код око 10% популације, а једно од ређих места њихове појаве је ткиво панкреаса. Интрапанкреасне акцесорне слезине најчешће настају у пределу репа панкреаса, а срећу се код 1,7% здравих људи. Постојање акцесорне слезине на овом нетипичном месту може довести до дијагностичке и терапијске недоумице с обзиром на то да је промена најчешће хиперваскуларна и стога, на основу налаза компјутеризоване томографије и магнетне резонанције абдомена, може бити протумачена као тумор панкреаса.

Приказ болесника Код жене старе 70 година је након

свеобухватне дијагностике постављена дијагноза нефункционалног неуроендокриног тумора репа панкреаса. Болесница је оперисана применом лапароскопске дисталне панкреатектомије с очувањем слезине, а хистопатолошким анализом је утврђено да је туморска промена интрапанкреасна акцесорна слезина.

Закључак Иако је ово изузетно ретка аномалија, треба је узети у обзир у диференцијалној дијагнози тумора репа панкреаса.

Кључне речи: интрапанкреасна слезина; акцесорна слезина; панкреас; панкреасни неуроендокрини тумор; лапароскопска дистална панкреатектомија

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Extragenital Malignant Mixed Mullerian Tumor in the Incisional Hernia – Primary Carcinosarcoma in the Abdominal Wall: Case Report

Marinko Žuvela^{1,2}, Marjan Micev^{1,2}, Milan Terzić^{2,3}, Djordjije Šaranović^{1,2}, Danijel Galun^{1,2}, Miroslav Miličević^{1,2}

¹Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade, Serbia;

²University of Belgrade, School of Medicine, Belgrade, Serbia;

³Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

SUMMARY

Introduction This report presents a primary Mullerian carcinosarcoma localized in the incisional hernia i.e. anterior abdominal wall. There is no data in the literature about this localization of extragenital Mullerian carcinosarcoma.

Case Outline The patient had previous medical history of right-sided ovarian cystadenocarcinoma managed by hysterectomy, bilateral ovariectomy and chemotherapy. An incisional hernia occurred 1 year after the operation and Mullerian carcinosarcoma at the right border of the incisional hernia 16 years later. There was no tumor spreading into the abdominal cavity and pelvis. Full thickness of the abdominal wall resection and coexisting incisional hernia resulted in a large 25x20 cm abdominal wall defect managed by the modified components separation technique and implanting meshes.

Conclusion Major abdominal wall resection and abdominal wall reconstruction using the modified components separation technique reinforced with meshes could be one of possible solutions in the surgical treatment of primary malignant mixed Mullerian tumor localized in the abdominal wall.

Keywords: Müllerian carcinosarcoma; components separation technique; abdominal wall; incisional hernia

INTRODUCTION

Mullerian carcinosarcoma or malignant mixed Mullerian tumor (MMMT) is a very aggressive, malignant, female genital neoplasm composed of malignant epithelial and mesenchymal elements [1, 2]. Tumor stage, tumor type, grade of carcinomatous component and genital or extragenital tumor localization are prognostic factors influencing the overall survival [3, 4].

Primary extragenital Mullerian carcinosarcoma is a very rare disease and its localization in the anterior abdominal wall has not been reported in the literature. Due to different clinical presentations, small number of reported cases associated with limited surgical experience and absence of standardized treatment extragenital tumors have dismal prognosis. The aim of this report is to present a case of primary Mullerian tumor in the incisional hernia of the anterior abdominal wall.

CASE REPORT

A 70-year-old woman was admitted to the hospital with a huge palpable mass in an incisional abdominal wall hernia. Her medical history included midline laparotomy, total hysterectomy and bilateral adnexectomy, performed for a right ovarian tumor and myomatous uterus 18

years ago. Histopathological analysis demonstrated a well differentiated cystic endometriod ovarian adenocarcinoma and intrauterine leiomyoma. Chemotherapy with Alceran was administered and the patient had a regular post-operative course. The asymptomatic midline incisional hernia occurred one year after the operation. A small tumor in the incisional hernia was diagnosed by clinical and ultrasound examination in January 2011. Abdominal CT was performed in May 2011 and confirmed a 62x50x38 cm right rectus muscle tumor next to the hernia sac. In October 2012 the patient was referred to a specialist for abdominal wall surgery. Clinical examination demonstrated a huge tumor in the incisional abdominal wall hernia. Three-phase contrast-enhanced MDCT detected a large inhomogeneous tumor mass in the anterior abdominal wall with infiltration of the rectus muscle, fascia and peritoneum. There were no signs of bowel infiltration. MDCT arterial phase demonstrated a tumor feeding artery arising from the right common iliac artery (Figure 1). Tumor markers: CA₁₉₋₉ (353 U/mL) and CA₁₂₅ (287 U/mL) were significantly elevated. The patient was estimated as ASA II (diabetes type II and chronic diabetic nephropathy).

The patient was operated for the abdominal wall tumor and incisional hernia in December 2012. Intraoperative findings showed

Correspondence to:

Danijel GALUN
Clinic for Digestive Surgery
Clinical Center of Serbia
Dr Koste Todorovića 6
11000 Belgrade
Serbia
galun95@gmail.com

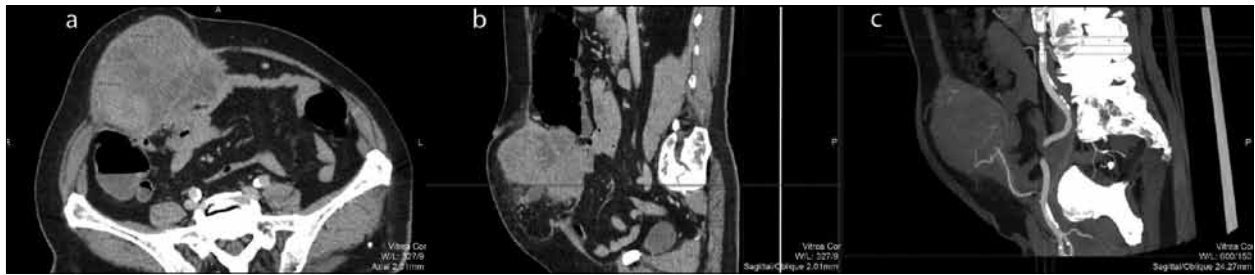


Figure 1. Three-phase contrast-enhanced MDCT (a) transversal plane; bulky tumor mass is presented in the right antero-lateral abdominal wall predominantly with soft tissue density. A central part of tumor mass demonstrates necrosis. There are no signs of bowel infiltration (b) multi planar reconstruction in sagittal plane; tumor mass is partly located in the incisional hernia. Hernia sac contains part of anterior abdominal wall tumor and part of the omentum majus (c) arterial phase with multi planar reconstruction and maximum intensity projection in the sagittal plane; there is a feeding artery arising from the right common iliac artery.

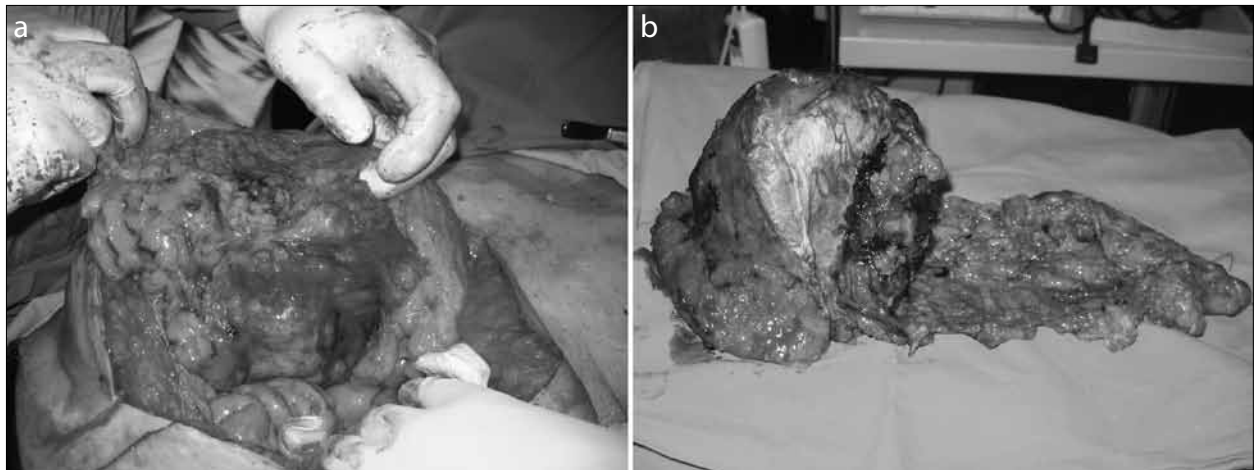


Figure 2. (a) Abdominal wall tumor in the right border of the incisional hernia involved all myofascial layers of the anterior abdominal wall at the right side; part of the omentum is attached to the tumor mass; (b) Resected full thickness of the right anterior abdominal wall with tumor and part of the omentum.

a sharply demarcated and partly incapsulated 12×10×10 cm abdominal wall tumor at the right border of the incisional hernia infiltrating the full thickness of the anterior abdominal wall. The skin and part of subcutaneous tissue were tumor-free. There was no tumor spreading in the abdominal cavity and pelvis, although a part of the omentum was attached to the tumor mass. Block resection of the full thickness of the right anterior abdominal wall with tumor (skin, subcutaneous tissue, 2/3 of the rectus muscle, parts of obliques and transverse muscles, and peritoneum), and partial omentectomy was performed (Figure 2). The size of the resected abdominal wall was 22×13 cm, however the size of abdominal wall defect was 25×20 cm due to the midline incisional hernia.

The abdominal wall defect was managed by the modified components separation technique as follows: a) dissection of the external from internal oblique muscle without skin dissection was performed at the right abdominal side; b) skin and subcutaneous tissue dissection from the anterior fascial layer in the direction from midline to the left spigelian line was followed by a left external oblique muscle aponeurosis longitudinal incision 1 cm lateral to the spigelian line and its dissection from the internal oblique muscle to the level of posterior axilar line; c) right internal oblique and transverse muscles were sutured to the left rectus muscle with its anterior and posterior sheaths

using interrupted mattress non-resorbable sutures (suture line of the left and right myofascial flaps was localized at the level of the right mammillary line); d) herniorrhaphy was reinforced with 2 meshes in the onlay position, 1 non-resorbable (Parietene standard polypropylene mesh 30×10 cm, Covidien-Sofradim, Trevoux, France) and 1 resorbable (Vycril mesh 26×21 cm, Johnson-Johnson, Ethicon); e) nonresorbable mesh was sutured to the right external oblique muscle aponeurosis and lateral border of the left anterior rectus muscle sheath with running suture (the mesh protected myofascial flaps suture line and potential weakness in the region of the remaining right internal oblique muscle); f) resorbable mesh was sutured to the left external oblique muscle aponeurosis and the lateral border of the left anterior rectus muscle sheath with running suture (the mesh protected potential weakness in the region of the left internal oblique muscle); g) skin and subcutaneous tissue were sutured over meshes (Figure 3).

Histopathology confirmed malignant mixed mesodermal Mullerian tumor (carcinosarcoma) composed of moderately differentiated endometrioid adenocarcinoma (type I) with focal squamous differentiation and abundant homologues type sarcoma which was consistent with a low grade endometrial stromal sarcoma. Mitotic index of sarcomatous component and proliferation status based on the labeling index of Ki-67 protein were estimated as 9/10 HPF

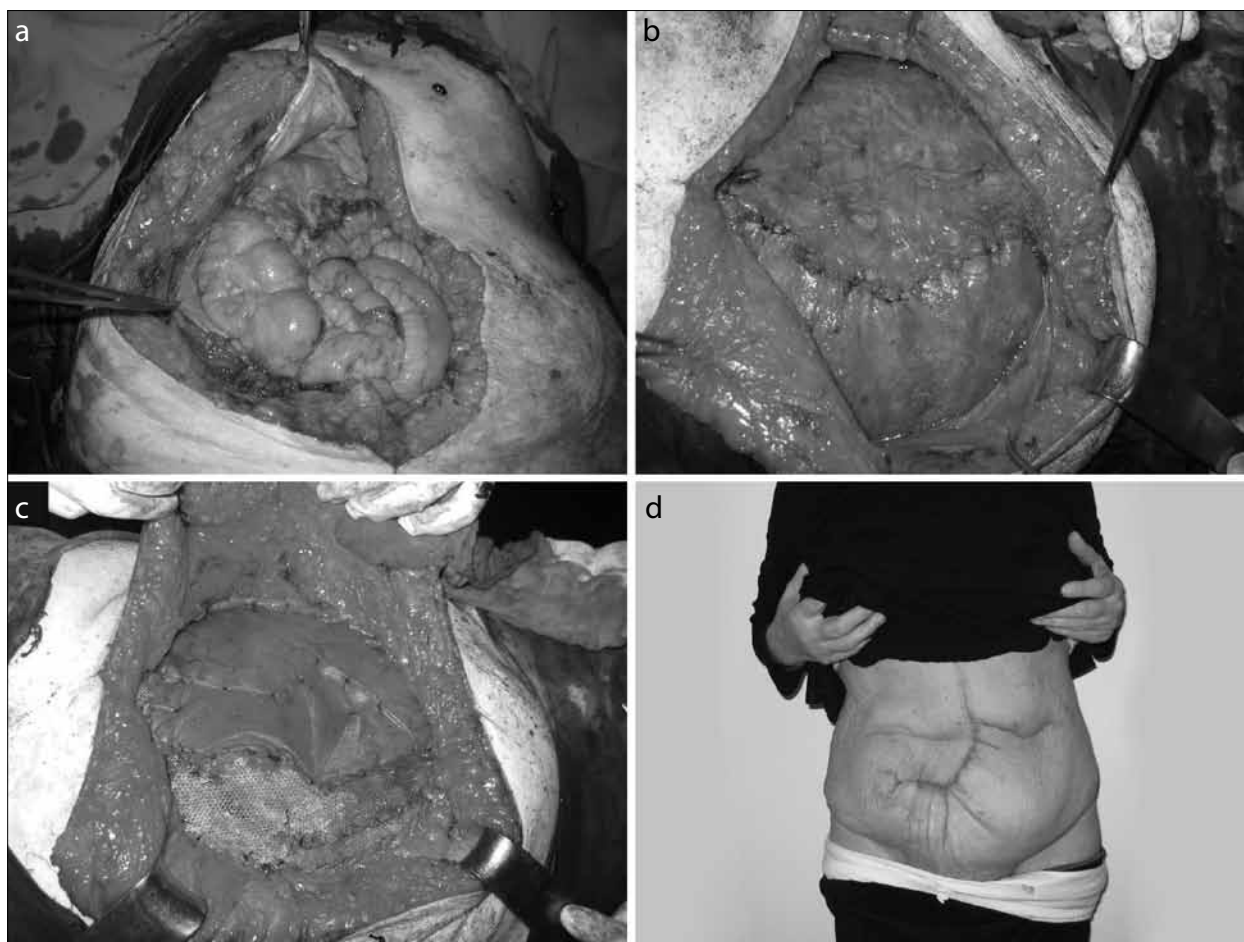


Figure 3. (a) Abdominal wall defect measuring 25×20 cm in diameter; (b) Abdominal wall defect was managed by the modified components separation technique; (c) Modified components separation technique reinforced with onlay nonresorbable and resorbable meshes; (d) Post-operative findings.

and 45%, respectively. Immunohistochemistry of carcinomatous component showed CK7+/CK20 immune profile, often strong vimentin immunoreactivity and strong nuclear estrogen receptor as well as progesteron receptor immunostainings, as well as focal CK5 and p63 immunoreexpression corresponding to squamoid differentiated carcinomatous areas. The sarcomatous component showed strong diffuse vimentin and CD10 immunoreexpression, but no immunostainings to desmin, smooth muscle actin, caldesmon, CD34 and S-100 protein (Figure 4).

Tumor marker levels decreased after the operation (CA_{19-9} 29 U/mL and Ca 59 U/mL). There were no post-operative complications and the patient was discharged 7 days after the operation. Chemotherapy with paclitaxel (Taxol) and carboplatin (CBDCA) was given. There was no tumor or incisional hernia recurrence during the 7-month follow-up period.

DISCUSSION

Malignant mixed Müllerian tumor (MMMT), also called malignant mixed mesodermal tumor or Mullerian carcinosarcoma, occurs in less than 1% of elderly menopausal females. This complex tumor usually occurs in the uterus,

rather than in the ovaries, fallopian tubes and the upper portion of the vagina, and consists of carcinomatous and sarcomatous components [4].

According to the sarcomatous components, MMMT is divided into homologous type arising from tissues which are present in the uterus (endometrium and myometrium) and heterologous type arising from tissues absent in the uterus (bone, cartilage and skeletal muscle) [1, 4]. Histogenesis of MMMT might be closely related to the so-called secondary Mullerian system, composed of the pelvic and lower abdominal mesothelium and the subjacent mesenchyme. MMMT can be associated with extragenital endometriosis, synchronous or metachronous gynecological malignancies, colon cancer and primary peritoneal serous carcinoma [5, 6, 7]. There are reported cases of MMMT occurring after tamoxifen therapy in breast cancer [8]. The most common sites of metastasis are lungs and the abdominal cavity.

Extragenital primary Mullerian carcinosarcoma is extremely rare. Ober and Black [9] in 1955 reported the first extragenital MMMT, however there have been less than 50 reports in the English literature about this entity. The majority of reported extragenital MMMT are located in the peritoneum and almost half of cases in the pelvic peritoneum [6, 10, 11, 12]. There are only few reports of primary

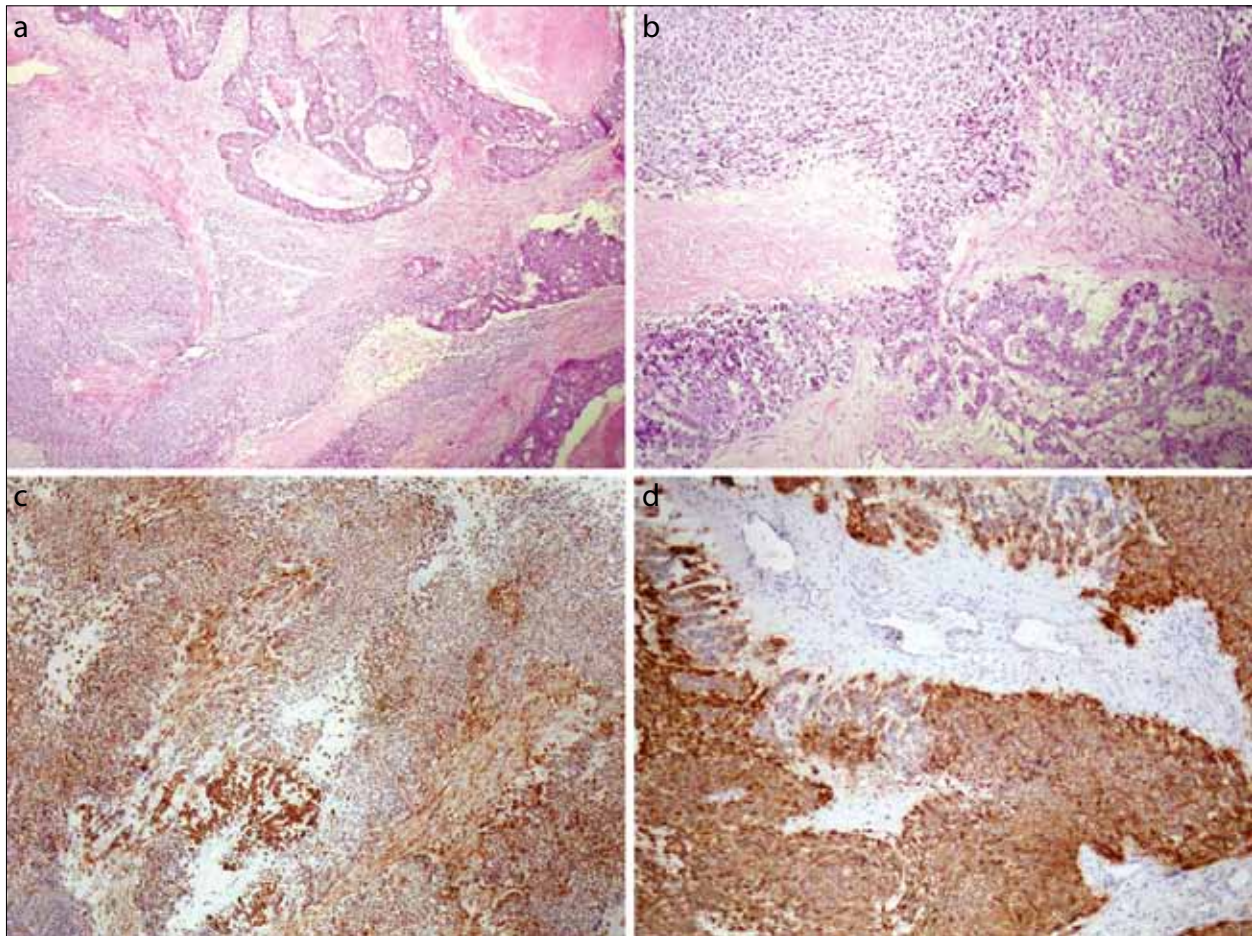


Figure 4. Histological examination (a) biphasic malignant neoplasm with coexistent carcinomatous and sarcomatous areas (H&E, original magnification 5×), (b) close admixture of both cell populations (H&E, original magnification 20×), (c) immunohistochemical stainings demonstrated vimentin immunoreactivity (original magnification 20×) in sarcomatous as well as in endometrioid carcinomatous components and (d) strong CD10 immunoreactivity (original magnification 20×) predominantly in the mesenchymal portion of the tumor.

extragenital Mullerian tumor arising from the mesentery, omentum, spleen, urinary bladder, and retroperitoneum [3, 13-17].

This report presents a primary MMMT localized in the incisional hernia i.e. anterior abdominal wall. There is no data in the literature about this localization of extragenital MMMT. The patient had previous medical history of right-sided ovarian cystadenocarcinoma managed by hysterectomy, bilateral ovariectomy and chemotherapy. An incisional hernia occurred 1 year after the operation and MMMT at the right border of the incisional hernia 16 years later. There was no clear evidence of a histological relationship between the ovarian neoplasm and extragenital MMMT in the abdominal wall. Similar to this case, Garde et al. [18] reported extragenital MMMT occurrence after operation for ovarian malignancy, while Huang et al. [3] and Arora et al. [6] reported synchronous extragenital MMMT and ovarian carcinoma. In the present patient, primary extragenital MMMT involved all myofascial layers of the right anterior abdominal wall including parietal peritoneum and a part of the major omentum, while skin and subcutaneous tissue were tumor-free. It should be noted that the parietal peritoneum and a part of the adhered major omentum were involved only in the region of the abdominal wall tumor. There was no tumor spread-

ing into the abdominal cavity and pelvis, and there was no peritoneal dissemination or ascites. The largest tumor in-growth was at the myofascial layers of the abdominal wall and not into the abdominal cavity.

It could be assumed that the development of the incisional hernia in the abdominal wall after the first operation might be related to implantation of previous undetected or unrecognized peritoneal endometriosis. This assumption is based on the morphological aspect and strong diffuse CD10 immunoreactivity of abundant sarcomatous component of MMMT consistent with a low grade stromal sarcoma. Not surprisingly, one could also consider very late recurrence of previously operated ovarian carcinoma in the abdominal wall [19]. However, on detailed revision of histology samples of the well differentiated ovarian endometrioid carcinoma neither elements of associated stromal proliferation nor previous endometriosis or endosalpingiosis in resection specimen could be detected. Furthermore, one can speculate the possibility of metastatic dormant carcinoma cells stimulating the adjacent peritoneal stroma to develop the mesenchymal component of the tumor and in-growth into the abdominal wall, according to the so-called “combination” histogenetic theory of these tumors [20]. The metaplastic conversion of poorly differentiated carcinomatous components to sarcomatous differentiated

areas is highly unlikely as both malignant components are not dominantly poorly differentiated. In the absence of evidence to support such possibilities, the strong Mullerian metaplastic potential of the inserted peritoneum in the incisional hernia could give rise to *de novo* MMMT.

Full thickness of the abdominal wall resection and coexisting incisional hernia resulted in a large 25×20 cm abdominal wall defect managed by the modified components separation technique and by implanting meshes. The abdominal wall reconstruction was based on the Ramirez "rectus-sharing" modification of the components separation technique for the management of abdominal wall defects following transverse rectus abdominus myocutaneous (TRAM) flap breast reconstruction [21, 22]. Unlike the Ramirez modified technique for TRAM a flap of external oblique was released from the internal oblique muscle at the side of the resected abdominal wall. Releasing the left and right rectus-internal-transverse muscles complex achieved myofascial flaps that were sutured at the level of the right mammary line. Myofascial flaps movement in this case was much greater than in the Ramirez "rectus-sharing" modification. In order to achieve the best results in the abdominal wall reconstruction (obtained by combination of components separation technique and mesh hernioplasty) [23, 24] we reinforced our herniorraphy with 2 meshes: a nonresorbable mesh which protected the right internal oblique/transverse muscle and left rectus muscle suture line, as well as the area of the remaining right internal oblique muscle (parts of the right internal oblique

and transverse muscle were resected with the tumor); and a resorbable mesh which protected the released internal oblique muscle at the left side. Using autologous tissue in combination with meshes a dynamic abdominal wall support was achieved.

Chemotherapy with Taxol/CBDCA protocol was administered and six months after the operation there are no signs of the disease and incisional hernia recurrence.

Surgical experience in the management of extragenital MMMT is limited due to the small number of reported cases and the fact that the majority of cases have been in the advanced tumor stage. The standardization of surgical treatment for extragenital MMMT is not possible and therapy should be adapted to each individual patient. In all patients with extragenital MMMT chemotherapy should be applied.

In conclusion, this is the first reported case of MMMT in the abdominal wall. Major abdominal wall resection and abdominal wall reconstruction using modified components separation technique reinforced with meshes could be one of possible solutions in the surgical treatment of primary MMMT localized in the abdominal wall.

ACKNOWLEDGMENT

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Екстрагенитални малигни мешовити Милеров тумор у инцизионој хернији – примарни карциносарком у трбушном зиду: приказ болесника

Маринко Жуvela^{1,2}, Марјан Мицев^{1,2}, Милан Терзић^{2,3}, Ђорђије Шарановић^{1,2}, Данијел Галун^{1,2}, Мирослав Милићевић^{1,2}

¹Клиника за дигестивну хирургију, Клинички центар Србије, Београд, Србија;

²Универзитет у Београду, Медицински факултет, Београд, Србија;

³Клиника за гинекологију и акушерство, Клинички центар Србије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Овај приказ представља примарни Милеров (*Müller*) карциносарком локализован у инцизионој хернији предњег трбушног зида. У литератури нема података о овој локализацији екстрагениталног Милеровог карциносаркома.

Приказ болесника Болесница је претходно оперисана због цистаденосаркома на десном јајнику, када су примењене хистеректомија, обострана оваријектомија и постоперацио-на хемиотерапија. Инцизиона хернија се јавила годину дана после операције, а Милеров карциносарком у инцизионој хернији се развио 16 година касније. Није било ширења тумора у трбушну дупљу, нити у малу карлицу. Комплетна

ресекција тумором захваћеног трбушног зида и инцизиона кила оставиле су оштећен предњи трбушни зид величине 25×20 cm који је решен модификованом техником компонентне сепарације и имплантацијом мрежице.

Закључак Потпуно одстрањивање трбушног зида захваћеног тумором с реконструкцијом применом модификоване технике компонентне сепарације уз уградњу мрежице може бити једна од опција хирушког лечења болесника с Милеровим карциносаркомом локализованог у трбушном зиду.

Кључне речи: Милеров карциносарком; техника компонентне сепарације; трбушни зид; инцизиона хернија

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Management of Brain Metastasis in a Patient with Advanced Epithelial Ovarian Carcinoma by Gamma-Knife Radiosurgery

Marinos Nikolaou¹, Srdjan Stamenković², Christos Stergiou³, Christos Skarleas³, Michael Torrens³

¹Department of Obstetrics and Gynecology, General Hospital of Agios Nikolaos, Lasithi, Crete, Greece;

²Department of Obstetrics and Gynecology, University Women's Hospital in Neuenheimer Feld, Heidelberg, Germany;

³Gamma Knife Department, Hygeia Hospital, Marousi, Athens, Greece

SUMMARY

Introduction Brain metastases from epithelial ovarian cancer (EOC) are rare events. We present a rare case of single ovarian cancer metastasis to the brain treated with gamma-knife radiosurgery (GKRS).

Case Outline A 65-year-old woman with advanced EOC presented with severe neurologic symptoms. A single brain metastasis of 3.2 cm with surrounding edema in the left parietal lobe was detected by brain magnetic resonance imaging (MRI) scan during the work-up. The decision to perform GKRS was due to a surgical inaccessibility of intracranial lesion. Twelve weeks after the procedure, the MRI scan showed reduction in the diameter of brain metastasis and surrounding edema and the patient returned to good mental and motor performance. The patient survived for 22 months following treatment and died from a progressive intra-abdominal disease. Prognosis of ovarian cancer patients with brain metastases is generally poor regardless of treatment.

Conclusion Our case shows that GKRS as primary treatment modality for the control of ovarian cancer metastases to the brain was effective and can be considered as a treatment of choice if international selection criteria are followed.

Keywords: gamma-knife stereotactic radiosurgery; solitary brain metastasis; ovarian carcinoma

INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of mortality among gynecologic malignancies in the developed countries [1]. In recent decades, the natural course of the disease has changed as a result of better primary control of intra-abdominal disease with platinum-based chemotherapy. The patients with ovarian carcinoma have longer survival and develop recurrences in rare sites after initial treatment [2].

Brain is an unusual site for metastases from a primary EOC, with an estimated range of incidence of 1-3% [3]. In an autopsy study, Mayer et al. [4] reported an incidence of 0.87% in 576 autopsies of patients with EOC. However, some recent reports suggest an increased incidence of ovarian cancer metastases to the brain in patients with prolonged survival as a late manifestation of disease [5]. Most of the patients with ovarian cancer metastases to the brain have advanced stage disease at the time of diagnosis and poor long-term prognosis regardless of treatment [6, 7].

Due to the rarity of this entity, published guidelines are based on evidence from case reports and small clinical series [3]. Therefore issues concerning management and follow-up of these patients require specific consideration due to limited data that exist in the literature. During the last years, more aggressive treat-

ments for ovarian cancer metastases to the brain have been promoted, including surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) and chemotherapy alone or in combination [8]. This therapeutic approach may produce prolongation of patient survival and in some cases long-term remissions.

Gamma-knife radiosurgery (GKRS) is an alternative treatment option in selected cases without symptoms of brain compression [9]. It is particularly useful in surgically inaccessible lesions or where surgical resection is contraindicated due to co-morbidities. However, very few studies in the literature have investigated the role of GKRS in the management of ovarian cancer metastases to the brain [10-17].

We report a rare case of a patient with advanced stage EOC treated with GKRS for solitary ovarian cancer metastasis to the brain. The aim of this report is to record the therapeutic impact of GKRS on the patient's quality of life and survival.

CASE REPORT

A 65-year-old woman with advanced EOC disease (stage IIIC according to the International Federation of Gynecology and Obstetrics-FIGO) presented to our institution with severe neurologic symptoms. Eight years earlier, she

Correspondence to:

Marinos NIKOLAOU
Dept. of Obstetrics and Gynecology
General Hospital of Agios Nikolaos
Lasithi, Crete 72100
Greece
nikolaoumarinos@yahoo.gr

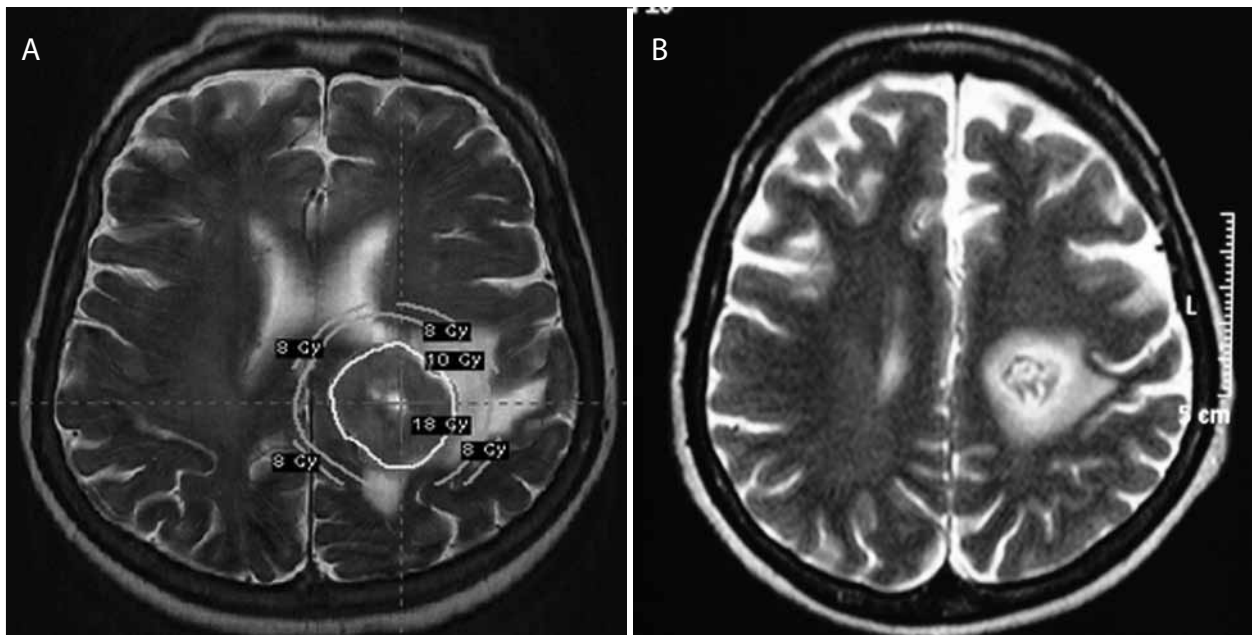


Figure 1. Axial T2-weighted brain MRI scan shows a solitary metastatic lesion in the left parietal lobe at the time of GKRS, with the treatment isodoses superimposed (A), and three months later with significant shrinkage of the tumor and reduction of edema (B)

had been treated with optimal cytoreductive surgery after detection of an endometrioid adenocarcinoma of low differentiation in the left ovary. A 6-course multi-agent chemotherapy was followed, with paclitaxel 280 mg and carboplatin 600 mg every 21 days with good response. Afterwards, hormonal therapy started, due to elevated levels of the tumor marker CA-125 (>90 IU/ml), with oral tamoxifen once a day.

Three years later a hard mass was found in her inguinal area and the lymph nodes surgically removed were positive for metastasis. New 6-course chemotherapy with paclitaxel 280 mg and carboplatin 600 mg every 21 days was started. At the end of this treatment, the patient had a complete resolution of the disease and was followed up regularly. Two years later, a left para-aortic lymphatic block was found by the abdominal computerized tomography (CT) scan, which proved to be metastatic on positron emission tomography (PET) scan and 6-course chemotherapy with cisplatin 130 mg and docetaxel 129 mg every 3 weeks was followed. Six months later, due to an increase in the diameter of the lymphatic block, a new course of chemotherapy with liposomal doxorubicin 600 mg (1st and 29th day) and gemcitabine 1500 mg IV (1st and 8th day) was given.

In February 2009, at the end of the above therapy, she started to have difficulty in walking and limitation in the movement of the right leg. The brain CT and MRI-examination revealed a 3.2-cm mass with surrounding edema in the left parietal region (Figures 1A and 2A).

Immediately, high-doses of intravenous corticosteroids (dexamethasone 32 mg daily) and prophylactic anticonvulsant medications were used for the palliation of mass effect and seizures, respectively. Surgical resection was relatively contraindicated due to the position of the lesion in the dominant hemisphere, and therefore it was decided to perform GKRS with a Leksell Gamma Knife (Electra AB[®], Stockholm, Sweden). Before the procedure

stereotactic MRI was performed using a double dose of Gadolinium contrast agent and T1 slices (1.5 mm) were used for target coordinate determination and image directed dose planning.

The target was outlined without margins using Leksell GammaPlan and treated with a prescription dose of 18 Gy in one fraction prescribed to the 50% isodose with 93% coverage. The target volume was 18.8 cc, maximum dose 36 Gy, mean dose 23.5 Gy, Paddick conformity index 0.84 and gradient index 3.2. The procedure was well tolerated by the patient and there were no complications.

Three months after the procedure, the MRI showed reduction in the diameter of ovarian cancer metastasis to the brain (2.0 cm) and surrounding edema and the patient returned to good mental and motor performance (Figures 1B and 2B).

Twelve months after GKRS, chemotherapy for coexistent intra-abdominal recurrence of the disease with paclitaxel was initiated once a week for 12 weeks. This was discontinued because of the disease progressive course and was followed with oral etoposide for 3 months. The patient was followed up and died 22 months after the initial manifestation of the brain metastasis without any sign of cerebral involvement or any other neurological symptoms due to disseminated intravascular coagulation from the ileus.

DISCUSSION

Ovarian cancer metastases to the brain are rarely observed in comparison to other primary tumors [3]. Clinical manifestations are highly variable depending on the location of brain metastases. Patients usually complain of various neurological symptoms such as headache, neurologic deficits, altered mental status, confusion and seizures [3]. In our case, right lower extremity motor weakness was the

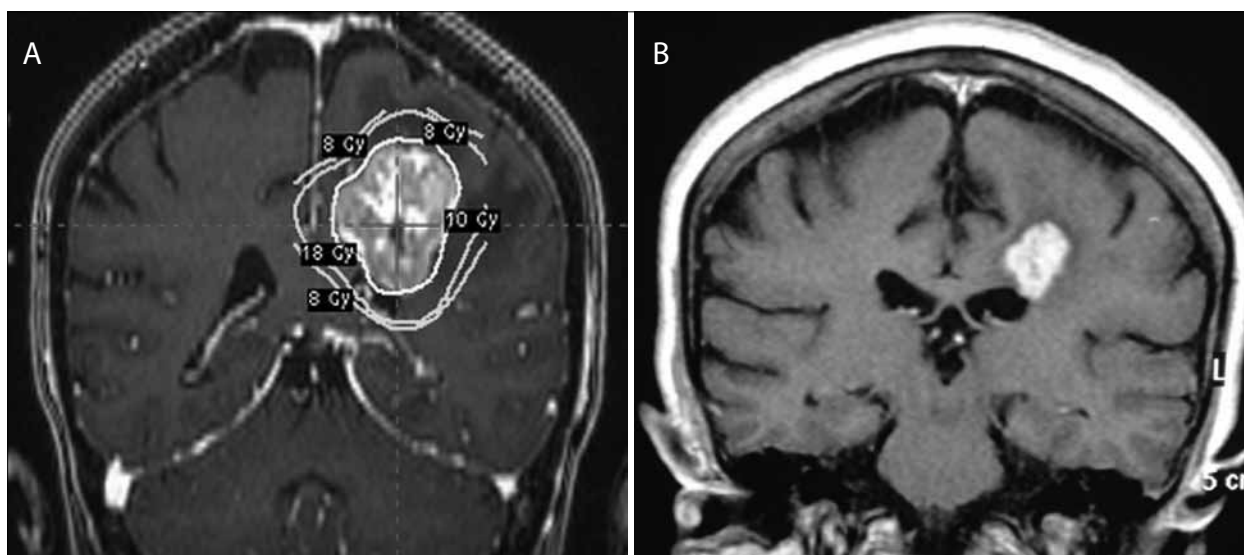


Figure 2. Coronal contrast-enhanced T1-weighted brain MRI scan shows the metastatic lesion at the time of treatment (A) and with decreased size at 3 months after GKRS (B)

main presenting sign, followed rapidly by altered mental status and confusion.

Routine brain imaging studies are not recommended in the follow-up procedures after primary treatment. So, a high level of clinical suspicion is required by clinicians in EOC patients presenting with neurological symptoms.

Management of ovarian cancer metastases to the brain has evolved over years from WBRT and corticosteroids to multimodal therapy achieving median survival of more than 20 months [3, 8, 11]. The treatment modality is dependent on several factors, including the number and location of metastases, the general status of the patient, the presence of active intra-abdominal disease and the history of previous treatments [7]. In our patient, surgical resection was contraindicated due to inaccessibility and we decided to perform GKRS.

Selection criteria for patients with ovarian cancer metastases to the brain who will benefit from GKRS help to guide treatment decisions and evaluate prognostic factors [15]. GKRS is especially useful for patients with single ovarian cancer metastases to the brain who are unable to tolerate surgery and for those with surgical inaccessible lesions [6]. However, a recent prospective observational study showed that GKRS might be a suitable alternative for patients with up to ten cancer metastases to the brain for initial treatment as it was not inferior to that for patients with two to four cancer metastases to the brain in terms of overall survival [18, 19]. So, selection criteria for patients with cancer metastases to the brain who will undergo GKRS are up to 10 brain metastases, maximum diameter of tumor <4 cm, minimal mass effect, inaccessible lesions and total tumor volume of <15 cm³. On the contrary, the exclusion criteria are a poor medical condition and/or the presence of carcinomatous meningitis [16, 19].

However, limited data in the literature are available on the management of ovarian cancer metastases to the brain using GKRS. The first report by Kawana et al. [10] described a patient with multiple ovarian cancer metas-

tases to the brain treated by a multimodality approach including GKRS which produced complete remission for 21 months with good quality of life. In the case of Anupol et al. [11], a patient treated with GKRS and chemotherapy for the second brain recurrence after 22 months of initial multimodal therapy had survival prolonged for another 27 months. Another case report by Shiohara et al. [12] recorded a survival of greater than 38 months from radiosurgery treatment but Monaco et al. [13] in a series of 27 patients (22 ovarian and 6 endometrial) found a much poorer mean survival of only 5 months despite effective control of all brain lesions. It is evident that survival is not the best index for the evaluation of radiosurgery since it depends mostly on extracranial disease status. Local brain control is a better index. Brown et al. [14] achieved local control of ovarian cancer metastases to the brain and prolongation of survival in three ovarian cancer patients with multimodality therapy including GKRS. In a small clinical series of 13 patients with ovarian cancer metastases to the brain, the multivariate analysis showed that including GKRS was the most important prognostic factor affecting the survival time [15]. Furthermore, seven patients with ovarian cancer metastases to the brain treated with GKRS achieved a longer median survival period than those treated with WBRT, 29 months versus 6 months, respectively [16]. In addition, a recent study by Navaro-Martin et al. [17] reported that GKRS provided excellent local control of solitary ovarian cancer metastasis to the brain and mean survival of 23.6 months in three EOC patients. In the present case, GKRS resulted in the local control of a solitary ovarian cancer metastasis to the brain, good quality of life and survival of 22 months.

GKRS has a number of advantages in the management of metastatic disease of the brain which have been enumerated by Linskey et al. [20] in a recent evidence-based clinical practice guideline. Combining radiosurgery (RS) with WBRT improves survival but RS is superior to WBRT for up to 3 metastases. RS+WBRT provide equal survival

to surgery+WBRT and indeed RS alone may be equivalent to surgery+WBRT. Since RS is quicker and easier for the patient and had fewer complications than surgery it would seem to be the method of choice in most cases. RS has been shown to be more cost-effective than surgery with approximately half the average cost per week of survival [21, 22]. RS is also less likely to cause cognitive defects than WBRT [23]. Accordingly, the method has been approved for routine funding by the National Health System in the UK provided certain criteria are met [24].

This combination of clinical and cost effectiveness, together with the high level of local control reported for GKRS in ovarian cancer metastases to the brain, as summarized in this paper, indicate that the method is likely to become the method of choice in cases where the intervention is indicated. The indication for treatment implies

a reasonable prognosis for the systemic disease such as potential survival greater than 6 months that is usually judged based on prognostic criteria such as the Brussels score for brain metastases [25].

As overall survival has increased due to improvements in the management of primary disease, more EOC patients will present with ovarian cancer metastases to the brain in the future. Currently, there is relatively less experience with GKRS as the treatment modality because of the clinical rarity of ovarian cancer metastases to the brain but the initial results are encouraging in terms of palliation of symptoms and improved prognosis. Further studies with multicenter participation are needed to confirm its efficacy in the management of ovarian cancer metastases to the brain but, in the meantime the results from other diagnoses suggest that GKRS should be the method of choice in most cases.

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Лечење метастазе у мозгу код жене са узнапредовалим епителним карциномом јајника радиохируршки гама-ножом

Маринос Николау¹, Срђан Стаменковић², Христос Стерију³, Христос Скарлеас³, Мајкл Торенс³

¹Одсек за гинекологију и акушерство, Општа болница „Свети Никола“, Ласити, Крит, Грчка;

²Одсек за гинекологију и акушерство, Универзитетска болница за лечење жена у Нојенхајмер Фелду, Хајделберг, Немачка;

³Одсек за гама-нож, Болница Хигија, Маруси, Атина, Грчка

КРАТАК САДРЖАЈ

Увод Метастазе у мозгу код жена с епителним карциномом јајника су веома ретке. Представљамо редак случај болеснице с метастазом на мозгу пореклом од епителног карцинома јајника која је лечена радиохируршки гама-ножом (енгл. *gamma-knife radiosurgery – GKRS*).

Приказ болесника Приказана је жена стара 65 година са узнапредовалим епителним карциномом јајника и тешким неуролошким симптомима. На снимку магнетне резонанције (*MRI*) уочени су солитарна метастаза пречника 3,2 *cm* и едем околног можданог ткива, локализовани у паријеталном режњу. Одлука о примени *GKRS* била је условљена неприступачношћу интракранијалној лезији. Дванаест недеља касније применом *MRI* утврђено је значајно смањење мета-

стазе у мозгу и околног едема, као и побољшање менталног стања и моторике болеснице. Болесница је преживела још 22 месеца, а смртни исход је наступио услед прогресије тумора у абдомену. Прогноза код жена с карциномом јајника и метастазама у мозгу је веома лоша без обзира на врсту лечења којем су подвргнуте.

Закључак У приказаном случају се види да је *GKRS*, као терапија избора код можданих метастаза у оквиру карцинома јајника, била успешна и може се прихватити као терапија избора код добро одабраних болесница поштујући међународне критеријуме.

Кључне речи: стереотаксична радиотерапија гама-ножом; солитарна мождана метастаза; карцином јајника

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First Successful Pregnancy Outcome after Intrauterine Insemination in a Woman with Primary Infertility and Essential Thrombocythemia Treated with Interferon-Alpha and Aspirin

Danijela Leković¹, Mirjana Gotić^{1,2}, Aleksandar Ljubić^{2,3}

¹Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia;

²University of Belgrade, School of Medicine, Belgrade, Serbia;

³Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

SUMMARY

Introduction The management of pregnancy in young women with essential thrombocythemia is complex and may present a difficult problem. An adverse pregnancy outcome due to thrombosis or bleeding is a common complication. In addition, little is known about fertility in these women prior to the disease.

Case Outline We present the first case of a young woman with primary infertility and essential thrombocythemia who had uneventfully delivered a healthy boy in the fortieth week of pregnancy. Her platelet count was normalized during treatment with interferon-alfa. The patient failed to become pregnant in the natural way and after three attempts of programmed intercourse. She conceived only following intrauterine insemination. During pregnancy, the patient was carefully controlled by a hematologist and gynecologist.

Conclusion Natural course and prognosis of essential thrombocythemia is not adversely affected by pregnancy. In these women, the pregnancy should be planned only after normalization of platelet count. The interferon-alpha should be administered before the pregnancy to regulate and maintain the platelet count within the normal range. Intrauterine insemination with minimal hormonal stimulation due to the risk of thrombosis could be recommended as the safest treatment option of infertility in women with essential thrombocythemia.

Keywords: essential thrombocythemia; pregnancy; interferon-alpha; intrauterine insemination

INTRODUCTION

Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by an elevated platelet (Plt) count in the peripheral blood and the increased risk of vascular complications [1]. Patients with ET are predominantly women and 15% to 20% of them are diagnosed during the childbearing age [2]. Maternal and fetal complications during pregnancy in patients with ET are well documented [3, 4]. The causes of these complications are thrombosis of placental vessels leading to chronic blood flow insufficiency and placental infarctions [5]. However, little is known about the fertility in these patients before the onset of ET. Decision-making on pregnancy is therefore a frequent issue in the clinical management of young women with ET imposing on physicians difficulties in relation to treatment.

To the best of our knowledge, we report the first case of a young woman with ET who normalized the Plt count during treatment with interferon-alpha (INF- α) but failed to conceive in the natural way. The successful intrauterine insemination (IUI) was carefully followed up by a hematologist and gynecologist and she uneventfully delivered a healthy male newborn in the fortieth week of pregnancy.

CASE REPORT

A 23-year-old woman was referred to the Clinic for Hematology, Clinical Center of Serbia in April 2005 because of a high Plt count. She has already experienced episodes of gingivorragia when tooth brushing over previous few years. Her physical examination revealed a mild splenomegaly (+1 cm below the left costal margin) which was later confirmed by abdominal ultrasonography. The initial complete blood cell count (CBC) showed white blood cells of $10.7 \times 10^9/L$, with normal cell differentiation, hemoglobin value of 132 g/L, and Plt count of $1748 \times 10^9/L$. Serum iron (24.5 $\mu\text{mol/L}$), total binding capacity (49.3 $\mu\text{mol/L}$), ferritin (53.5 $\mu\text{g/L}$) and other biochemical analyses were normal. A bone marrow (BM) aspirate showed numerous sheets of megakaryocytes and normal iron stores. A BM trephine biopsy revealed megakaryocytic hyperplasia without signs of fibrosis. Most megakaryocytes had abundant cytoplasm and showed hyperlobulation with a tendency to form clusters. In vitro culture of hematopoietic progenitors from the BM disclosed spontaneous CFU-E and spontaneous BFU-E growth. Conventional cytogenetic analyses showed a normal female karyotype 46, XX. Mutation of JAK2V617F was not de-

Correspondence to:

Danijela LEKOVIĆ
Clinic for Hematology
Clinical Center of Serbia
Dr Koste Todorovića 2
11000 Belgrade
Serbia
danijela.lekovic@yahoo.com

tected in the granulocytes of peripheral blood. Based on these findings, the diagnosis of ET was made following the World Health Organization criteria.

The treatment with anagrelide was started 3 months after the diagnosis was made, within a multicentre clinical study when her Plt count was $1866 \times 10^9/L$ [6]. A complete hematological response was achieved after 3 weeks. Thereafter, her Plt count was maintained within the normal range (from 265 to $457 \times 10^9/L$), without any thrombotic or hemorrhagic complications. The patient was on initial and continuous anagrelide treatment with 1.5 mg per day for 6 years.

During the first 3 years of anagrelide treatment in clinical study, the patient was advised to use contraception during intercourse with her fiancé. After the multicentre clinical study was ended, and over the next 3 years of treatment with anagrelide, the patient did not enforce any contraception with expectation if she became pregnant to immediately stop with anagrelide. However, the pregnancy did not occur. She decided to discontinue anagrelide treatment after 6 years. In the next three months, she was taking only aspirin 100 mg daily. Assessment of fertility in both spouses was conducted after two years of primary infertility. Routine infertility investigations (serum FSH and LH concentrations, hysterosalpingography and semen analysis) detected no signs of perturbation, except for unilateral tubal obstruction. Basal body temperature was biphasic. Ureaplasma infection was treated in the male partner with an epididymal cyst. He was found to have normozoospermia.

Intercourse programming was attempted for three times. Afterwards, treatment with INF- α was started in the patient, at a dose of 3 MU s. c. three times per week, when the patient's Plt count was $1060 \times 10^9/L$. A month later her Plt count was still increased ($922 \times 10^9/L$) and the dose of INF- α was intensified to 3 MU s. c. four times per week. Thereafter, her Plt count was normalized but the patient still could not get pregnant spontaneously. After four months of INF- α treatment and almost one year of conservative gynecological medical treatment, the gynecologist decided to conduct intrauterine insemination (IUI) with a minimal hormonal stimulation of the patient in the attempt to conceive. The ovarian stimulation was done by administration of clomiphene citrate tablets, 50 mg twice a day, starting day 2, for five days. The follicle was 18 mm on day 11 and endometrium was 9 mm, with adequate morphology. Ovulation triggering with human chorionic-gonadotrophin (hCG) 5000 IU was administered on the same day. Fallopian sperm perfusion (FSP) was performed 34 hours later. The "swim-up" method was used for sperm preparation. After swim-up, there were $110 \times 10^6/ml$ of spermatozoa, which were used with 15 ml of Medicult media for FSP. Two weeks later the beta hCG test was positive (130 IU/L). Four weeks after FSP, intrauterine 18 mm gestational sac was identified, with 3 mm embryoblast. Fetal heart activity was confirmed one week later. The hematologist continued to monitor patient's Plt count once monthly. Following the normalization of her Plt count, the dose of INF- α was continued thrice weekly until delivery. During further pregnancy

monitoring regular laboratory analyses were performed. A double test for chromosome abnormalities screening was performed at 12th gestational week. Fetal morphology, fetal and utero-placental circulations and dynamics were assessed on monthly basis, continuously showing normal fetal growth and unaffected uteroplacental circulation. At 22nd week, there was an episode of abdominal pain with diarrhea, so that micronized progesterone was administered vaginally, 200 mg twice a day. At 27th gestational week, a 75 gr. OGTT revealed glucose intolerance, so that she was recommended diet with a low carbohydrate intake. At 40th week of gestations the Bishop score was 3, and Misgav Ladach Cesarean section was performed, with normal operative and postoperative outcome. A healthy baby boy was born, weighting 3.4 kg with a normal blood count. Starting from the delivery, the patient was given danaparoid sodium over the next seven days for the prevention of thrombosis, and INF- α was continued. The boy is now two and a half year old, with normal growth and development.

DISCUSSION

Available data about pregnancy in women with ET are mainly related to the complications arising during gestation, without evidence about their premorbid fertility. The most frequent complication is the fetal loss in the first trimester occurring in 31-35% women with ET. Estimated prevalence of the fetal loss in the general population is approximately 15 and 20% [4]. Moreover, the overall risk of fetal loss in women with ET is 3.4-fold higher than expected for an age-matched healthy population [7]. Live birth rate recorded in ET pregnancies was 63%, while full-term normal delivery was in 51%. [8]. Fetal complications occurred in 40% of ET pregnancies, whereas maternal complications, such as pre-eclampsia and arterial hypertension, developed in 9% of them.

Regarding the data from large patient series, the predictive risk factors for pregnancy outcome have not been identified in patients with ET [4, 9]. The presence of the JAK2 mutation in patients with ET was not clearly defined as a predictor of pregnancy complications. Other possible risk factors, such as age >35 years, Plt count or leukocytosis did not significantly influence the pregnancy outcome.

However, irrespective of the treatment modalities, the proportion of live births was higher (74%) in treated pregnancies than in untreated ones (43%) [10]. In respect to this finding it could be assumed that control of Plts may correlate positively with a successful pregnancy outcome. Thrombophilia is also known to play an important role in the development of complications in pregnancy in general population, but there is not enough data that could indicate the impact of thrombophilia in pregnant women with ET [11].

There is limited information concerning the fertility of women with ET. So far as we know, only a single case was reported of a 37-year-old woman with ET who developed massive intra-abdominal bleeding after transvaginal oocyte retrieval during in vitro fertilization [12].

Infertility is defined as a failure to achieve pregnancy during a year or more without use of contraception during the childbearing period and commonly affects 10–15% of the couples [13]. In our case, few factors influenced fertility. The patient had clogged Fallopian tube and myeloproliferative neoplasm with increased Plt count (ET) while the male partner had ureaplasma infection and epididymal cyst. An additional factor could be the psychological effect on fertility in both spouses. Oddens et al. [14] reported that infertile women had symptoms of depression and anxiety four times more frequently than fertile ones, which may negatively affect the outcome of treatment for infertility.

Currently, the IUI is the recommended method for the treatment of moderate male infertility and unexplained infertility [15]. The therapeutic procedure involves placing washed spermatozoa transcervically into the uterine cavity. The pregnancy rate after the IUI is 10–20% [16]. The known limitations of IUI are the potential risk of infection, ectopic pregnancies and miscarriages which arise at the same frequency as in application of other infertility treatment modalities. In our case, the IUI was the safest method of assisted fertilization, since it could be applied with minimal hormonal stimulation due to the risk of thrombosis since ET and its prothrombotic influence. Due to failure of prior therapy, our patient received selective estrogen receptor modulator, clomiphene citrate, which by binding to estrogen receptors increases endogenous production of pituitary gonadotropins. Ovulation triggering was achieved giving highly purified human chorionic gonadotropin (hCG). This is significantly less aggressive method of ovulation stimulation than the usually used combination of recombinant follicle-stimulating hormone

(FSH) and luteinizing hormone (LH) with recombinant hCG, which is the standard way of ovarian stimulation for the complex infertility treatment.

Our patient was treated before the conception and during the pregnancy with INF- α . According to the data from literature and also from our experience, INF- α is highly effective in normalization of the Plt count, and produce favorable response in 90% of pregnant woman with myeloproliferative neoplasms associated with thrombocytosis [17, 18]. It has been shown that INF- α lowers the Plt count by a direct effect on megakaryocytopoiesis. Based on results from the in vitro studies, INF- α neither crosses the placental barrier or affects fertility [19]. It also does not increase the risk of maternal and fetal complications during treatment.

It is important to provide young women with ET an opportunity to become mothers since the pregnancy itself does not adversely affect the natural course and prognosis of ET. The presented case also highlights the need for the assessment of fertility in this group of patients. The IUI can be recommended as the safest treatment option for infertility in women with ET. The INF- α should be applied before the pregnancy in order to achieve a favorable response and to maintain a normal Plt count. The pregnancy should be planned only after the Plt count has been normalized. Doppler ultrasonography of uteroplacental circulation in pregnancy should be conducted at monthly basis. Disease control achieved in this way provides a good opportunity for a normal course and a favorable outcome of pregnancy for both mother and child. In these women multidisciplinary approach is needed in order to achieve the most optimal treatment results.

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Прва успешна трудноћа након интраутерине инсеминације код болеснице с примарним инфертилитетом и есенцијалном тромбоцитемијом лечене алфа-интерфероном и аспирином

Данијела Лековић¹, Мирјана Готић^{1,2}, Александар Љубић^{2,3}

¹Клиника за хематологију, Клинички центар Србије, Београд, Србија;

²Универзитет у Београду, Медицински факултет, Београд, Србија;

³Клиника за гинекологију и акушерство, Клинички центар Србије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Лечење младих жена с есенцијалном тромбоцитемијом током трудноће је комплексно. Проблем представљају могуће тромбоембологичке компликације које могу утицати на неповољан исход трудноће. Поред тога, мало се зна о плодности ових жена пре болести.

Приказ болесника Приказујемо први случај младе болеснице с примарним инфертилитетом и есенцијалном тромбоцитемијом која је успешно порођена у 40. недељи трудноће, при чему је родила здравог дечака. Код болеснице је нормализован број тромбоцита применом алфа-интерферона. Болесница није могла да затрудни природним путем, као ни након три покушаја програмираног односа. Она је остала трудна тек након интраутерине инсеминације.

Детаљне и учестале контроле од стране хематолога и гинеколога током трудноће су биле неопходне.

Закључак Трудноћа нема негативан утицај на природни ток и прогнозу есенцијалне тромбоцитемије. Код ових болесница трудноћу треба планирати само након нормализације броја тромбоцита. Лечење алфа-интерфероном треба започети пре трудноће до нормализације броја тромбоцита, и наставити током трудноће уз одржавање броја тромбоцита у референтном опсегу. Интраутерина инсеминација с минималном хормонском стимулацијом због ризика од тромбозе може се препоручити као најсигурнија метода за лечење неплодности код жена с есенцијалном тромбоцитемијом.

Кључне речи: есенцијална тромбоцитемија; трудноћа; алфа-интерферон; интраутерина инсеминација

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Синдром потпуне неосетљивости на андрогене

Милина Танчић Гајић^{1,2}, Светлана Вујовић^{1,2}, Миомира Ивовић^{1,2}, Љиљана В. Марина^{1,2},
Зорана Аризановић^{1,2}, Драгана Раковић^{1,2}, Драган Мицић^{1,2}

¹Универзитет у Београду, Медицински факултет, Београд, Србија;

²Клиника за ендокринологију, дијабетес и болести метаболизма, Клинички центар Србије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Синдром неосетљивости на андрогене (енгл. *androgen insensitivity syndrome*) припада групи поремећаја сексуалног развоја који настаје као резултат делимичне или потпуне неосетљивости на биолошко дејство андрогена код особа које су генетски мушкарци (XY) с нормално развијеним тестисима и концентрацијом тестостерона у серуму која одговара узрасту за мушку популацију.

Приказ болесника Двадесетједногодишња девојка упућена је у Клинику за ендокринологију, дијабетес и болести метаболизма Клиничког центра Србије ради ендокринолошког тестирања и лечења због тестисне феминизације која је дијагностикована у 16. години. Болесница је имала примарну аменореју и развијене дојке, али није имала пубичну и аксиларну маљавост. Спољашње гениталије су биле женског типа. Кариотип је био 46XY. Вредности полних хормона су биле као код одрасле особе мушког пола. На вишеслојној компјутеризованој томографији (MSCT) абдомена и мале карлице обострано пелвично су биле уочене творевине с особинама тестиса. Урађена је билатерална орхиектомија. После операције је уведена хормонска супституциона терапија, а због диспареуније саветована је вагинална дилатација.

Закључак Дијагноза синдрома потпуне неосетљивости на андрогене се поставља на основу клиничке слике, хормонских анализа, кариотипа, визуелизационих метода и генетских анализа. Због могуће малигне алтерације тестиса у одраслом добу, саветује се билатерална орхиектомија непосредно након пубертета. Могућа је диспареунија, а због кратке вагине врши се вагинална дилатација, која је обично и довољна, а у изузетним случајевима и хируршка елонгација вагине.

Кључне речи: синдром неосетљивости на андрогене; 46XY; андрогени рецептор; примарна аменореја

УВОД

Поремећаји сексуалног развоја обухватају групу наследних болести анатомije репродуктивних органа као резултат хромозомских поремећаја и нетипичног развоја гонада. Споразумом из 2006. године, према новој номенклатури, „поремећаји сексуалног развоја“ обухватају све раније термине – хермафродитизам, псеудохермафродитизам, *inter-sex*, неодређен пол, уз објашњење да су сви претходни називи пежоративни за болеснике [1].

Синдром неосетљивости на андрогене (енгл. *androgen insensitivity syndrome* – AIS), типичан облик некада тзв. мушког псеудохермафродитизма, припада групи поремећаја сексуалног развоја који настаје као резултат делимичне или потпуне неосетљивости на биолошко дејство андрогена код особа које су генетски мушкарци (XY) с нормално развијеним тестисима и концентрацијом тестостерона у серуму која одговара узрасту за мушку популацију [1, 2]. Овај феномен први пут је описао амерички гинеколог Џон Морис (John Morris) [3] 1953. године анализом 82 дотада у литератури приказана болесника (укључујући и своја два). С обзиром на то да су сви болесници имали тестисе, а били су женског фенотипа, овом синдрому

је дао назив „тестисна феминизација“ (енгл. *testicular feminization syndrome*).

Генетска испитивања су показала да је узрок тестисне феминизације мутација гена за андрогени рецептор (AR). Ген за AR се налази на дугом краку X-хромозома (*Xq11-13*). Састоји се од осам егзона и кодира четири функционална домена AR: NH2-терминални домен (NTD), који кодира највећи, тј. 1. егзон; DNK-везујући домен (DBD), који кодирају 2. и 3. егзон; лиганд-везујући домен (LBD), који кодирају 4–8. егзон; и зглобни регион, који везује LBD и DBD. У AIS мутације су углавном локализоване у DBD и LBD. Досад је описано више од 1.000 мутација гена за AR чији је резултат смањење или потпуни губитак функције AR, што за крајњи резултат има смањен или потпуно изостављен пострецепторски ефекат на циљна ткива и поред нормалне концентрације андрогена [2, 4].

ПРИКАЗ БОЛЕСНИКА

Двадесетједногодишња девојка упућена је у Клинику за ендокринологију, дијабетес и болести метаболизма Клиничког центра Србије ради ендокринолошког испитивања и лечења због тестисне феминизације.

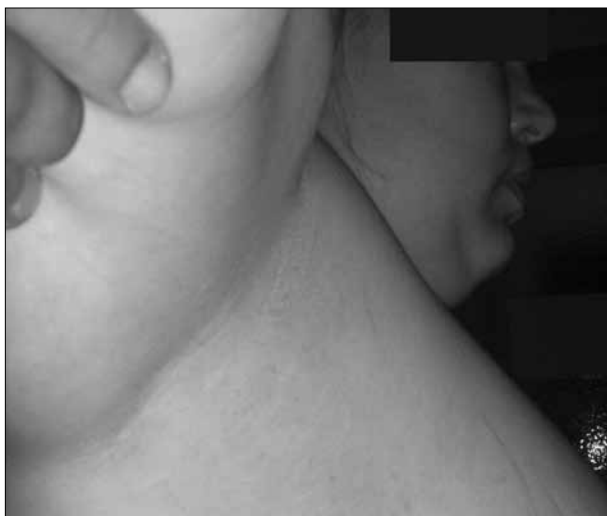
Correspondence to:

Milina TANČIĆ GAJIĆ
Klinika za endokrinologiju,
dijabetes i bolesti metabolizma
Klinički centar Srbije
Dr Subotića 13, 11000 Beograd
Srbija
mtancicgajic@yahoo.com



Слика 1. Гиноидни тип гојазности, развијене дојке, изостанак пубичне маљавости

Figure 1. Gynoid obesity, developed breasts, absent pubic hair



Слика 2. Изостанак пазушне маљавости

Figure 2. Absent axillary hair

Анамнезом и хетероанамнезом се сазнало да је болесница дете из друге трудноће, која је протекла нормално. Рани психомоторни развој болеснице је био без особености. Од своје седме године постепено је добијала на телесној тежини. Дојке су почеле да се развијају са 12 година. Са 15 година обратила се гинекологу јер није добила менструацију. Упућена је у Клинику за гинекологију и акушерство Клиничког центра у Београду, где јој је у 16. години постављена дијагноза тестисне феминизације типичног облика. Отада је нико није медицински надгледао до њене 21. године.

У 21. години се због хипертензије јавила ендокринологу у регионалној болници, који јој је преписао ан-

Табела 1. Хормонске анализе и туморски маркери болеснице пре орхијектомије

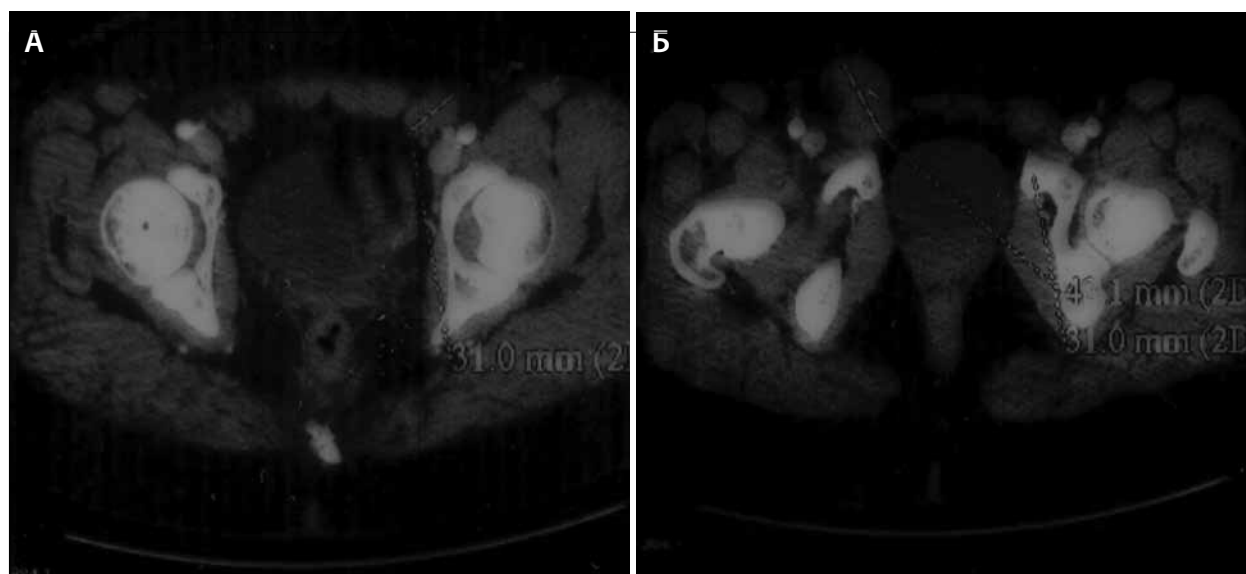
Table 1. Hormonal analysis and patient's tumor markers before gonadectomy

Хормонски и туморски маркери Hormonal and tumor markers	Резултати болеснице Patient's results	Референтне вредности Reference range
FSH на 15 мин. FSH at 15 min.	4.8/4.9/4.6 /3.9 IU/l	2.5–15 IU/l
LH на 15 мин. LH at 15 min.	9.9/11.2/9.9 /11.9 IU/l	2.5–16 IU/l
E2 на 15 мин. E2 at 15 min.	223/247/253.9 /380.9 pmol/l	34–226 pmol/l
T на 15 мин. T at 15 min.	20.4;17.5;18.1; 18.9 nmol/l	8.2–34.8 nmol/l
17-OHPg	0.73 nmol/l	0.94–6.57 nmol/l
SHBG	17 nmol/l	9–54 nmol/l
DHEAS	5.4 μmol/l	5.4–9.1 μmol/l
Андростенедион Androstenedione	2.2 ng/ml	0.26–2.34 ng/ml
Пролактин Prolactin	368.5 mIU/l	121–545 mIU/l
Прогестерон Progesterone	0.33 nmol/l	0.3–1.9 nmol/l
ACTH	43.5 ng/l	10–90 ng/l
Кортизол Cortisol	435 nmol/l	131–642 nmol/l
TSH	2.1 mIU/l	0.3–5.5 mIU/l
ft4	17.3 ng/l	7–18 ng/l
DST (1 mg), кортизол DST (1 mg), cortisol	25.9 nmol/l	<50 nmol/l
CEA	0.72 ng/ml	3.8 ng/ml
AFP	1.06 IU/ml	<5.8 IU/ml
betaHCG	1.32 IU/l	<2 IU/ml
Ca-125	7.76 U/ml	<35 U/ml
Ca 19-9	5.57 U/ml	<39 U/ml
Ca 15-3	15.86 U/ml	<25 U/ml

FSH – фоликулостимулишући хормон; LH – лутеинизирајући хормон; E2 – естрадиол; T – тестостерон; 17-OHPg – 17-хидроксипрогестерон; SHBG – глобулин који везује полне хормоне; DHEAS – дехидроепиандростерон; ACTH – аденокортикотропни хормон; TSH – тироестимулишући хормон; ft4 – слободни тироксин; DST – преконоћни дексаметазонски супресиони тест; CEA – карцино-ембрионални антиген; AFP – алфа фетопротеин; betaHCG – хумани хорионски гонадотропин; Ca-125 – канцер-антиген Ca-125; Ca 19-9 – канцер-антиген Ca 19-9; Ca 15-3 – канцер-антиген Ca 15-3

FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; T – testosterone; 17-OHPg – 17-hydroxyprogesterone; SHBG – sex hormone binding globulin; DHEAS – dehydroepiandrosterone; ACTH – adrenocorticotrophic hormone; TSH – thyroid-stimulating hormone; ft4 – free thyroxine; DST – overnight dexametasone suppression test; CEA – carcinoembryonic antigen; AFP – alpha fetoprotein; betaHCG – human chorionic gonadotropin; Ca-125 – cancer antigen Ca-125; Ca 19-9 – cancer antigen Ca 19-9; Ca 15-3 – cancer antigen Ca 15-3

тихипертензивну терапију, а након увида у дијагнозу тестисне феминизације упутио ју је на нашу клинику ради даљег испитивања и лечења. Њена рођена старија сестра је имала редовне менструације до 15. године и лечења карцинома епифаринкса. Нико у породици од женских рођака није имао примарну аменореју. На пријему болесница је била екстремно гојазна по гиноидном типу (телесна тежина 127,5 kg; телесна висина 170 cm; индекс телесне масе 42,2 kg/m²; обим струка 112 cm; обим кукова 131 cm), са седефастим и ружичастим стријама на грудима и трбуху. Пубичне и аксиларне маљавости није било. Дојке су биле развијене (Слике 1 и 2). Спољашње гениталије су биле женског



Слика 3. Налаз компјутеризоване томографије абдомена и мале карлице (MSCT) приказује обострано пелвично творевине карактеристика тестиса

Figure 3. Multi-sliced computed tomography (MSCT) shows structures on both sides of the pelvic region, suggestive of testicles

типа, без клиторомегалије. Кариотип је био 46XY. Вредности полних хормона су биле као код одрасле особе мушког пола (Табела 1). На ултразвуку мале карлице нису били уочени ни материца, ни јајници. На вишеслојној компјутеризованој томографији (MSCT) абдомена и мале карлице обострано пелвично уочене су промене карактеристика тестиса, десно готово у субкутису, а лево у дисталном параилијачном простору и трбушном зиду (Слика 3). Материца и јајници се нису видели, а вагина је била скраћена.

Будући да је болесница била женске сексуалне оријентације, уз личну и сагласност породице упућена је у Клинику за гинекологију и акушерство ради обостране орхиектомије. По пријему на ову клинику, одлуком конзилијума лекара, болесница је премештена на Хируршку клинику, где је 2012. године подвргнута лапароскопској експлорацији, горњој и доњој медијалној лапаротомiji и билатералној орхиектомији десног тестиса (величине 50×20×28 mm) и левог тестиса (величине 40×20×22 mm), са пластиком десног ингвиналног канала. Патохистолошки налаз је гласио: *Scleroatrophia testis bilateralis, Leydig cell hyperplasia*, без елемената тумора.

Након операције примењена јој је терапија трансдермалним естрадиолским фластерима, а након шест месеци и орална терапија прогестероном (200 mg током седам дана у месецу), уз смањење телесне тежине и наставак лечења антихипертензивним лековима. Годину дана после операције први пут је имала сексуалне односе, који су били болни. Због болне диспареуније саветоване су јој вагинална дилатација и примена естрадиолског крема локално вагинално два пута недељно.

ДИСКУСИЈА

Током ембрионалног развоја постоји сексуално индиферентна фаза у којој ембрион има потенцијал да

развије било мушке било женске репродуктивне органе. Непосредно уз примитивне индиферентне гонаде налазе се два примитивна канала: Волфов канал, који може да доведе до развоја мушког репродуктивног тракта, и Милеров канал, који може да доведе до развоја женског репродуктивног тракта.

Андрогени су суштински значајни за мушку сексуалну диференцијацију током развоја фетуса, за разлику од женског феталног развоја, који не захтева постојање естрогена. Сексуална диференцијација почиње сексуалном детерминацијом гонада или као тестиса или као јајника, која зависи од полних хромозома X и Y. Ако је ембрион XY, присуство гена *SRY* (регион Y-хромозома који одређује пол јединке) усмериће развој гонада у тестисе, а у супротном, гонаде се развијају као јајници. Лајдигове ћелије тестиса у деветој недељи гестације почињу да стварају тестостерон, који подстиче развој Волфових канала, из којих се стварају епидидимис, *vas deferens*, семене кесице и ејакулаторни каналићи. Сертолијеве ћелије производе анти-Милеров хормон (AMH), који изазива регресију Милерових канала.

Гонаде које се развијају у AIS су тестиси. AMH изазива регресију Милерових канала и изостанак развоја материце, јајовода и горњих делова вагине. Лајдигове ћелије тестиса стварају тестостерон, али због мутације андрогеног рецептора (AR), он не остварује своје биолошко дејство и нема развоја Волфових канала у еферентне органе. AR припада породици нуклеарних рецептора и експримује се у феталном ткиву у осмој недељи гестације, пре почетка лучења тестостерона. Ендогени андрогени, тестостерон и потентнији дихидротестостерон (DHT) (5α-редуктаза тип 2 конвертује тестостерон у DHT) могу да остваре своју биолошку активност само након везивања за AR у циљним ткивима. Развој простате из урогениталног синуса и маскулинизација примордијалних спољашњих гениталија у пенис и скротум захтева активност DHT [5].

Синдром неосетљивости на андрогене (AIS) се традиционално класификује на основу гениталног фенотипа у три подгрупе: комплетан АИС (CAIS), парцијалан (PAIS) и благ или минималан (MAIS). MAIS је најблажа генетска аномалија AIS у 46XY, а фенотипски најдаља од CAIS. Особе имају мушки фенотип, обично азооспермију, а описани су и ретки случајеви фертилних мушкараца с овим поремећајем. PAIS је резултат делимичне неосетљивости на андрогене у 46XY и представља широку палету фенотипске презентације са различитим степеном вирилизације. Преваленција CAIS је један оболели на 20.400–99.100 особа које су генетски мушког пола. На рођењу CAIS се може презентовати као ингвинална хернија или оток велике усне вагине код наизглед женског новорођенчета. Билатерална ингвинална хернија је ретка код женске новорођенчади и у таквом случају инциденција CAIS је 1–2%. Дијагноза CAIS се најчешће поставља у пубертету, као и код описане болеснице, када због примарне аменореје особе с нормалним спољним женским гениталијама траже медицинску помоћ. Одрасле жене са CAIS су вишег раста, што се објашњава генетским утицајем региона на дугом краку Y-хромозома, који је одговоран за контролу раста. Жене са CAIS и одложеном гонадектомијом су вишег раста због релативног недостатка естрогена. Имају развијене дојке, као резултат ароматизације андрогена. Немају знаке адренархе, тј. не постоји пубична и аксиларна маљавост и немају акне, а као резултат неосетљивости на андрогене уместо јајника имају тестисе, немају материцу, нити проксимални део вагине која се слепо завршава и најчешће је скраћена, као код описане болеснице [2].

Описани су спорадични случајеви где не долази до потпуне регресије Милерових канала, те се развија један или оба јајовода, а изузетно ретко и материца. Могућа објашњења су: 1) неодговарајућа синтеза или активност АМН; 2) интраутерусно излагање диетил-стилбестролу, које смањује осетљивост Милерових канала за АМН; 3) поремећај пролаза андроген–АР на нуклеарном нивоу; или 4) рано спуштање тестиса, тако да је Милеров канал ван домаћаја АМН [6].

Особе са CAIS немају простату, нити се Волфови канали развијају током развоја фетуса, па се не стварају епидидимис, *vas deferens*, семене кесице и ејакулаторни каналићи. Клиничка слика која побуђује сумњу на CAIS захтева одређивање и потврду XY кариотипа [4]. Код одраслих особа са CAIS концентрација тестостерона обично је нормална или повишена у односу на одрасле особе мушког пола, који као супстрат за ароматазну активност доводи до повећане концентрације естрогена. Ниво FSH је у оквиру нормалних вредности, а ниво LH обично благо повишен услед хипоталамо-хипофизне резистенције на андрогене. Повишене вредности LH подстичу Лајдигове ћелије, синтеза и лучење тестостерона се појачавају, а последично и концентрација естрадиола. Ако функција и структура Сертолијевих ћелија није оштећена, концентрација АМН је нормална. Код приказане болесни-

це забележена је нормална концентрација тестостерона, док је концентрација LH била је на горњој граници нормале, као што је приказано у табели 1. Објашњење зашто у случају наше болеснице ниво LH није виши би било постојање одређеног степена хипоталамо-хипофизне осетљивости на андрогене, што је мало вероватно и досад није описано. Вероватнији разлог је екстремна гојазност болеснице и повећана количина масног ткива, а самим тим и повећана расположивост ензима ароматазе, који се примарно налазе у масном ткиву, па је могућа повећана конверзија тестостерона у естрогене. Естрогени преко негативне повратне спреге на нивоу хипоталамуса и хипофизе доводе до смањене концентрације гонадотропина, пре свега LH, и смањене стимулације лучења тестостерона, чему у прилог говоре нормална (у односу на мушкарце), а не повишена концентрација тестостерона и повишена концентрација естрадиола код приказане болеснице (Табела 1) [7].

Дијагноза CAIS се, као у нашем случају, поставља на основу клиничке слике и хормонских анализа (Табела 1) код особа са XY кариотипом. Потврда дијагнозе CAIS добија се генетском анализом и налазом мутације гена за АР, за шта није било техничких могућности.

Диференцијално дијагностички у обзир долазе: комплетна, тј. „права“, XY гонадна дисгенеза позната као Свајеров (Swyer) синдром, Мајер–Рокитански–Кустер–Хаустеров (Mayer-Rokitansky-Kuster-Hauser) синдром, недостатак 17 β -хидроксистероид-дехидрогеназе тип III, 5 α -редуктаза тип 2 дефицит (5-ARD) и KAH због дефицита 17-хидроксиллазе (17-OH) или због дефицита 17,20-лиазе [1]. 46XY особе са CAIS имају женске спољне гениталије, одрастају и васпитавају се као девојчице и немају дилему о женској сексуалној оријентацији. По постављању дијагнозе CAIS, саветује се психолошко саветовање и за болесника и за породицу. Гонадектомија се саветује након пубертета, по завршеној феминизацији, с обзиром на то да је феминизација делом последица тестикуларне, а делом периферне конверзије тестостерона у естрогене. Ако се гонадектомија уради пре пубертета, саветује се индукција пубертета естрогенима. Ризик за малигну алтерацију тестиса пре пубертета је мали, а у одраслој доби је до 30%, па се као идеално време за гонадектомију предлаже рани одрасли период, непосредно након пубертета. После гонадектомије саветује се примена хормонске супституционе терапије (HRT) само естрогенима, пошто болеснице немају материцу, а неки аутори саветују комплетну супституцију естропрогестагенима, уз образложење да се рецептори за прогестерон не налазе само у материци, него у целом телу, а посебно су значајни у мозгу. Након гонадектомије, ми смо болесници преписали терапију естрадиолом трансдермално током шест месеци, а затим је додата терапија природним прогестероном, који за разлику од прогестагена нема ефекат ретенције течности и има најповољнији кардиометаболички профил [8, 9]. Изостанак менструације током примене комбиноване HRT је искључило

постојање материце код наше болеснице, што је иначе редак ентитет код особа са CAIS.

Код особа са CAIS, као и код приказане болеснице, могућа је диспареунија због кратке вагине, за шта је обично довољна вагинална дилатација, а у изузетним случајевима и хируршка елонгација вагине. Највећи проблем ових жена је то што, уколико желе, не могу да имају своје потомство [4].

Дијагнозу CAIS је неопходно поставити у 16. години, а затим урадити орхиектомију рано након пубертета, због могуће малигне алтерације тестиса, и увести

супституцију естропрогестагенима до периода очекиваног уласка жене у менопаузу, а по процени и дуже.

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Complete Androgen Insensitivity Syndrome

Milina Tančić Gajić^{1,2}, Svetlana Vujović^{1,2}, Miomira Ivović^{1,2}, Ljiljana V. Marina^{1,2}, Zorana Arizanović^{1,2}, Dragana Raković^{1,2}, Dragan Micić^{1,2}

¹University of Belgrade, School of medicine, Belgrade, Serbia;

²Clinic for Endocrinology, Diabetes and Metabolism Diseases, Clinical Center of Serbia, Belgrade, Serbia

SUMMARY

Introduction Androgen insensitivity syndrome (AIS) belongs to disorders of sex development, resulting from complete or partial resistance to the biological actions of androgens in persons who are genetically males (XY) with normally developed testes and age-appropriate for males of serum testosterone concentration.

Case Outline A 21-year-old female patient was admitted at our Clinic further evaluation and treatment of testicular feminization syndrome, which was diagnosed at the age of 16 years. The patient had never menstruated. On physical examination, her external genitalia and breast development appeared as completely normal feminine structures but pubic and axillary hair was absent. Cytogenetic analysis showed a 46 XY karyotype. The values of sex hormones were as in adult males. The multi-

sliced computed tomography (MSCT) showed structures on both sides of the pelvic region, suggestive of testes. Bilateral orchiectomy was performed. Hormone replacement therapy was prescribed after gonadectomy. Vaginal dilatation was advised to avoid dyspareunia.

Conclusion The diagnosis of complete androgen insensitivity is based on clinical findings, hormonal analysis karyotype, visualization methods and genetic analysis. Bilateral gonadectomy is generally recommended in early adulthood to avoid the risk of testicular malignancy. Vaginal length may be short requiring dilatation in an effort to avoid dyspareunia. Vaginal surgery is rarely indicated for the creation of a functional vagina.

Keywords: androgen insensitivity syndrome; 46 XY; androgen receptor; primary amenorrhea

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Развој доњег мокраћног тракта и његови функционални поремећаји

Амира Пецо-Антић, Гордана Милошевић-Ломић

Универзитетска деčја клиника, Београд, Србија

КРАТАК САДРЖАЈ

Нормалан развој контролне функције доњег уринарног тракта је процес током којег се прогресивно усавршава начин мокрења, од незрелог, невољног пражњења мокраћне бешике (инконтиненције) до успешне контроле мокрења у току дана и ноћи, што се најчешће постиже до пете, односно седме године живота. Овај постепени процес зависи, пре свега, од прогресивног сазревања нервне регулације доњег уринарног тракта, али је и под утицајем бихевиоралног тренинга који се одвија кроз процес социјалне подршке. Функционални поремећаји мокрења су чести проблеми у детињству. Јављају се код 5–15% деце, односно код петине деце школског узраста или код више од трећине пацијената деçјег уролога или нефролога. Код више од половине деце с функционалним поремећајем мокрења бележи се везикоуретерни рефлукс, а више од две трећине има понављане уринарне инфекције. Честа је удруженост поремећаја мокрења с опстипацијом и енкопрезом, позната под називом „дисфункционални елиминациони синдром“. Функционални поремећаји мокрења могу изазвати трајно оштећење горњих мокраћних путева и бубрега. Поред тога, инконтиненција мокраће, као најчешћа манифестација поремећаја мокрења, може бити узрок великог психолошког стреса код детета школског узраста и неповољно утицати на осећај самопоштовања детета. Због тога су важни благовремено откривање и лечење ове групе поремећаја код деце.

Кључне речи: инконтиненција урина; ноћно умокравање; уринарне инфекције; дисфункционално мокрење

УВОД

Доњи мокраћни тракт је функционална јединица мокраћног система која обезбеђује привремени резервоар мокраће и омогућава интермитентно, потпуно пражњење бешике у социјално прихватљивим околностима. Чине га мокраћна бешика, врат мокраћне бешике са сфинктерима и уретра. Зид мокраћне бешике се састоји од три слоја: унутрашњи – мукозни, средњи – састављен од мишића детрузора, и спољни – од адвентиције. Мишићне ћелије детрузора су међусобно повезане у јединствену функционалну целину и имају способност да развију максималну тензију при различитим дужинама својих влакана.

Захваљујући растегљивости детрузора, мокраћа се акумулира у бешици под ниским интравезикалним притиском (мање од 30 *cm* воде при пуном капацитету), а сфинктерни механизам, који чине врат мокраћне бешике, проксимална уретра и попречно-пругасти мишићи пелвичног дна, спречава истицање мокраће до социјално прихватљивих прилика за вољно мокрење. Обично се говори о унутрашњем и спољашњем уретралном сфинктеру. Спољни уретрални сфинктер се пружа од апекса простате дуж мембранозне уретре код мушкараца и од врата мокраћне бешике до средње уретре код жена. Чине га глатка мишићна влакна с унутрашње стране и попречно-пругасти

мишићи са спољне стране, који су распоређени у виду цилиндричне структуре која је дебља спреда, а истањена позади, што на пресеку даје изглед потковице. Унутрашњи сфинктер чине глатка мишићна влакна која полазе од базе мокраћне бешике и тригонула, пружају се преко врата мокраћне бешике до проксималне уретре.

Уринарна континенција зависи од сложене, међусобно условљене активности аутономног нервног система и соматских нерава који се интегришу на нивоу кичмене мождине, можданог стабла и виших кортикалних структура. Нормална координација омогућује пуњење мокраћне бешике под ниским притиском и високим отпором на излазном делу, односно мокрење с ујединаченом контракцијом детрузора и ниским отпором на излазном делу.

У фази пуњења мокраћне бешике, активација бета рецептора симпатичког нервног система у фундусу мокраћне бешике изазива релаксацију детрузора, а активација алфа рецептора унутрашњег сфинктера уретре његову контракцију. Стимулација пудендалног нерва контрахује спољашњи сфинктер уретре, што заједно с контракцијом врата мокраћне бешике обезбеђује континенцију. Дакле, у нормалној фази пуњења мокраћне бешике детрузор је релаксиран, а уретрални сфинктер контрахован. Када је мокраћна бешика пуна, активирају се механорецептори од којих полази узлазни

Correspondence to:

Amira PECO-ANTIĆ
Univerzitetska deçja klinika
Tiršova 10, 11000 Beograd
Srbija
amirapecoantic@yahoo.com

сигнал кроз кичмену мождину према центру мокрења у понсу. Одатле полази десцендентни сигнал који инхибира пудендалне моторне неуроне с резултирајућом релаксацијом спољнег уретралног сфинктера, стимулацијом парасимпатичких влакана у пелвичним спланхичним нервима и инхибицијом симпатичких нервних влакана у хипогастричним нервима. Као резултат активације парасимпатичких влакана настаје контракција детрузора, а услед инхибиције симпатичких влакана релаксира се врат мокраћне бешике. Дакле, са успостављањем вољне контроле мокрења, у социјално прихватљивим околностима, мокрење започиње вољном релаксацијом мишића пелвичног дна, што рефлексно изазива контракцију мокраћне бешике и релаксацију сфинктера.

Мокраћна бешика је у непосредној близини утеруса и ректума код жена, односно простате и ректума код мушкараца. Блиски анатомски односи мокраћне бешике и уретре с ректумом, као и њихова слична инервација, утичу на удруженост патофизиолошких збивања доњег мокраћног тракта и црева. То означава термин „дисфункционални елиминациони синдром“ (ДЕС), под којим се подразумева удруженост дисфункције доњег мокраћног тракта и опстипације, које најчешће прате понављане уринарне инфекције (УТИ) [1].

Дисфункција доњег мокраћног тракта је релативно честа код деце и ако се на време не излечи, може довести до оштећења горњег дела мокраћног система с развојем ожиљне нефропатије и њених последица [2-6].

Циљ овог рада био је да пружи преглед савремених сазнања о развоју доњег мокраћног тракта и најчешћим облицима његове дисфункције код деце.

ФЕТАЛНИ РАЗВОЈ ДОЊЕГ УРИНАРНОГ ТРАКТА

Развој мокраћне бешике почиње рано, већ у 4–6. гестационој недељи. Мокраћна бешика се развија из урогениталног синуса, који настаје из клоаке. Уретер и везикоуретерна ушћа се формирају из уретралног пупољка, који полази из Волфовог канала (енгл. *Wolffian duct*). Уретерални пупољак се грана у мезенхимном ткиву, метанефросу, формирајући заједно с њим ткиво бубрега.

Ненормална позиција уретералног пупољка с латерализацијом његових ушћа у бешици одговорна је за настанак примарног везикоуретерног рефлукса (ВУР), који је неретко удружен са дисплазијом бубрега [7, 8].

Испитивања на људском фетусу су показала да се мишићне ћелије налазе у бешици већ око девете гестационе недеље, а у дванаестој недељи већ је формиран трослојни зид бешике, чија се дебљина повећава током даљег феталног развоја [9]. Попречно-пругасти мишићи спољнег уретралног сфинктера се уочавају тек око двадесете недеље гестације. Унутрашњи уретрални сфинктер се развија као кружна мишићна структура у пределу врата мокраћне бешике, која код мушког фетуса хипертрофише пред крај трудноће, чиме се барем делимично може разјаснити разлика у функцији

мокраћне бешике између дечака и девојчица у првом месецу по рођењу [10].

У експерименталним испитивањима је показано да се растегљивост мокраћне бешике повећава у другој половини феталног периода, када долази до замене колагена III колагеном I [10, 11] и смањења унутарћелијских комуникација између мишићних ћелија детрузора. Показано је да неонатални детрузор, у односу на адултни, различито реагује на надражаје. Тако се зна да холинергични агонисти изазивају мултифазичну контракцију у новорођеначком добу, а у одраслом добу исти агонисти доводе до једнофазичне контракције детрузора. Из овога се може претпоставити да хиперактивност детрузора у каснијем периоду има сличности с његовом раном функцијом и вероватно одражава успорену матурацију [12].

ФУНКЦИЈА МОКРАЋНЕ БЕШИКЕ У ПРВОЈ ГОДИНИ ЖИВОТА

Функција мокраћне бешике код одојчета се разликује од оне код одраслих. Цистометријска испитивања у првој години по рођењу су ретка. Ипак, она су показала да се хиперактивност детрузора налази код мање од 10% здраве новорођенчади и одојчади [13, 14], али је екситабилност на надражаје детрузора већа него у каснијем животном добу [15], што објашњава мањи капацитет мокраћне бешике при цистометријском прегледу у односу на волумен спонтано измочреног урина. Овај период такође одликује често мокрење, на сваких сат времена у првој недељи по рођењу, 10–15 пута дневно у првих 6–12 месеци. Код око 40% новорођенчади се бележи испрекидано мокрење као резултат дискоординације детрузора и сфинктера, и сматра се нормалним налазом у првој години. Знак је незрелости јер се налази код око 60% превремено рођене деце, а ишчезава с узрастом и успостављањем вољне контроле мокрења [16].

Пражњење мокраћне бешике је непотпуно током прве године и доводи се у везу са испрекиданим мокрењем, односно са феноменом незрелости мокраћне бешике, односно њене незреле нервне регулације. Мокрење мушке одојчади се разликује у односу на женску одојчад. Дечаци мокре са високим интравезикалним притиском (просек 120 *cm* воде код дечака и 75 *cm* воде код девојчица), који се вероватно ствара услед дуге уретре и функционалне опструкције на нивоу хипертрофисаног врата мокраћне бешике. Класично становиште да новорођенчад и мала деца мокре уз активност спиналног рефлексног лука уз никакву или незнатну активност виших центара је кориговано новијим сазнањима која су показала да се микција, чак и интраутерино, одвија само у будном стању [17]. Данас је прихваћено становиште да здрава новорођенчад и одојчад мокре у фази будности или бар током краткотрајног прекида сна [18, 19]. То индиректно показује да и у најранијем животном добу рефлекс мокрења укључује активност и виших можданих структура.

ИНЕРВАЦИЈА

Инервацију детрузора мокраћне бешике и сфинктера обезбеђују сакрални парасимпатички, тораколумбални симпатички и сакрални соматски нерви. Парасимпатичка нервна влакна која полазе од C2–C4 сегмента кичме чине пелвични нерв и везикални плексус пре уласка у мокраћну бешику. Парасимпатичке ганглије се налазе унутар плексуса и у зиду мокраћне бешике. Симпатичка нервна влакна полазе из торакалног и лумбалног дела кичме (T10–L2), иду према доњем мезентеричном ганглиону и онда улазе у пелвични плексус и мокраћну бешику као хипогастрични нерви. Соматска нервна влакна чине пудендални нерв који полази из C2–C4 сегмента кичме и инервише периуретрално пелвично мишићно дно.

Неуролошка контрола нормалне микције се одвија координисано на различитим нивоима, од сакралног микционог центра у кичменој мождини преко понтиног микционог центра унутар можданог стабла и малог мозга, затим у базалним ганглијама, лимбичком систему, таламусу и хипоталамусу, и на крају у церебралном кортексу. Парасимпатичке и соматске нерве чине холинергична нервна влакна, а симпатичке нерве адренергична нервна влакна. Поред адренергичних (норадреналин) и холинергичних (ацетилхолин) трансмитера, различити други неуротрансмитери такође учествују у нервној регулацији доњег уринарног тракта, укључујући простагландинску супстанцу P, опиоидне пептиде, вазоактивни интестинални пептид и неуропептид Y. Присуство нехолинергичних и неадренергичних неуротрансмитера објашњава непотпуну ефикасност фармаколошке блокаде адренергичних и холинергичних рецептора.

РАЗВОЈ КОНТРОЛЕ МОКРЕЊА

Вољна контрола мокрења се нормално успоставља до пет године. То је постепен процес током којег се прогресивно усавршава начин мокрења, од инфантилног, невољног до адолтног обрасца мокрења, који подразумева вољну микцију у социјално прихватљивим околностима. У овом процесу пресудан је процес матурације, али су важни и бихејвиорални тренинг и процес социјалне потпоре.

Прво се, у просеку око 18. месеца, јавља свест код детета да је мокрило. После тога се развија свест о потреби мокрења, а затим се мокрење може на захтев одложити. Тада је дете спремно за тренинг контроле мокрења који треба да буде пажљив и без кажњавања детета.

У једној студији, која је обухватила 1.192 деце у Америци, просечно доба успостављања контроле дневног мокрења било је $2,4 \pm 0,6$ година (распон од 0,75 до 5 година) [20]. Контрола ноћног мокрења се обично постиже касније од дневне.

Током успостављања контроле мокрења повећава се капацитет мокраћне бешике и смањује учесталост мокрења.

Током трећег триместра трудноће фетус мокри приближно 30 пута у току 24 часа. Одмах по рођењу учесталост мокрења се смањује, да би се поново повећала после прве недеље, с највећом учесталошћу од друге до четврте недеље, када дете мокри у просеку једном сваких сат времена. Касније се учесталост мокрења смањује на 10 до 15 пута дневно у узрасту 6–12 месеци, односно на осам до десет пута дневно у узрасту од две до три године. Око 12. године учесталост мокрења је слична учесталости мокрења код одраслих особа, и износи 4–6 пута током 24 часа.

Капацитет мокраћне бешике се прогресивно повећава са узрастом детета. За процену очекиваног капацитета служе различите формуле. Тако се очекивани капацитет мокраћне бешике одојчета израчунава на основу следеће формуле: капацитет мокраћне бешике ($y \text{ ml}$) = $38 + 2,5 \times \text{узраст у месецима}$ [19]. За старију децу користи се Кофова (*Koff*) формула, према којој је капацитет мокраћне бешике ($y \text{ ml}$) = (узраст у годинама) + 2) $\times 30$ [21], или Хјалмасова (*Hjalmas*) формула: капацитет мокраћне бешике ($y \text{ ml}$) = $30 + (\text{узраст у годинама} \times 30)$ [22, 23].

Испрекидано мокрење услед пролазне дискоординације детрузора и сфинктера се обично повлачи у време успостављене контроле мокрења, када је пражњење мокраћне бешике потпуно. За разлику од одојчета, код детета са успостављеном контролом мокрења цистометријски капацитет је већи од волумена вољно измочреног урина, притисак детрузора током мокрења је у нивоу адолтног и током мокрења нема дискоординације између детрузора и сфинктера уретре. Могуће је да се упорним вежбањем успостави контрола мокрења раније, јер матурациони предуслови за то постоје већ пред крај прве године живота [23, 24].

ФУНКЦИОНАЛНИ ПОРЕМЕЋАЈИ МОКРЕЊА

Одступања од нормалног пуњења и пражњења мокраћне бешике која нису последица неуролошких, морфолошких или других медицинских узрока називају се функционални поремећаји мокрења. Мада по дефиницији ови поремећаји искључују неуролошку лезију, она се у свим случајевима, попут Хинмановог или Очоа (*Ochoa*) синдрома не може искључити. Функционални поремећаји мокрења се најчешће испољавају као невољно испуштање урина у виду дневне инконтиненције урина или ноћне енурезе. Ургентна инконтиненција означава дневну инконтиненцију која је праћена осећајем хитности. Често су дневна инконтиненција и ноћна енуреза удружене, што упућује на сличне патогенетске механизме [25].

Функционални поремећаји мокрења су чести проблеми у детињству [2-5, 26-29]. Срећу се код 5–15% целокупне педијатријске популације, односно код 21,8% деце школског узраста, или код више од 40% пацијената дечјег нефролога, односно уролога. У око 54% случајева удружени су с мањим степеном ВУР, а у 70% са дилатирајућим степеном ВУР (ВУР III–V степе-

на). Узрок су понављане инфекције уринарног тракта (65–85%) [26, 27], због којих се често примењују антибактеријска терапија и продужена антибактеријска профилакса. То свакако доприноси повећању антибактеријске резистенције [30].

Терминологију поремећаја мокрења усвојило је Међународно удружење за континенцију код деце 1997. године, са допунама 2005. и 2006. године [31, 32].

Дневна инконтиненција

Дневна инконтиненција се дефинише као влажење или умокравање најмање једном сваке две недеље и она се смањује са узрастом, од 10%, колико се бележи у узрасту од пет до шест година, до 4% у узрасту од 12 до 18 година. Фактори ризика за дневну инконтиненцију су женски пол, уринарне инфекције или енкопреза. Може бити оскудна, у капима, или нешто обилнија, али најчешће не долази до потпуног умокравања. Настаје услед структурних промена на доњем уринарном тракту (попут ектопичног ушћа уретера испод уретралног сфинктера), неурогене мокраћне бешике или је функционалне природе, што је и најчешће. Функционална дневна инконтиненција је чешћа код девојчица него код дечака. Верује се да је последица успореног развоја рефлекса мокрења [33, 34, 35].

Дневна инконтиненција може бити удружена са одлагањем мокрења и опстипацијом, када дистендирано црево врши притисак на мокраћну бешику и ремети нормалан инхибиторни ефекат пелвичне и уретралне контракције на микцију [36, 37].

Дневна инконтиненција се чешће јавља у неким породицама, што упућује и на њено наследно порекло [38].

Хиперактивна мокраћна бешика

Хиперактивна мокраћна бешика је најчешћи узрок дневне инконтиненције која је праћена ургенцијом и учесталим мокрењем. Учесталост је највећа пред полазак у школу (21% девојчица и 18% дечака) и у адолесценцији (6% девојака и 1% младића) [37]. Цистометријски налаз показује неинхибиране контракције детрузора у фази пуњења, нормалну фазу пражњења и смањен капацитет мокраћне бешике. Неинхибиране контракције детрузора се дефинишу као пораст притиска детрузора више од 15 *cm* воде изнад базалног, који настаје спонтано или је изазван променом положаја тела, кашљањем, скакањем и другим надражајима. Деца с овим поремећајем обично избегавају унос течности да би смањила опасност од инконтиненције. Осим тога, да би спречила умокравање у фази неинхибираних контракција, контрахују мускулатуру пелвичног дна, услед чега спречавају не само умокравање, него и одлажу пражњење црева с последичном опстипацијом [36].

Стресна инконтиненција

Стресна инконтиненција је дневна инконтиненција која се дешава када повишен интравезикални притисак и без мерљиве контракције детрузора превазиђе отпор на нивоу сфинктера уретре. За разлику од одраслих (већином старијих жена), код неуролошки нормалне деце је права стресна инконтиненција ретка и уопште се одликује нормалним уродинамским налазом. За разлику од одраслих, код деце се као главни разлог не може навести некомпетентност излазног дела уринарног тракта услед смањене резистенције на нивоу уретралних сфинктера. Инконтиненција је обично врло оскудна, тако да се често занемарује, због чега недостаје прави увид у учесталост овог поремећаја код деце.

Инконтиненција услед смејања (енгл. *giggle incontinence*)

Овај облик инконтиненције је редак и обично се описује код девојчица код којих се током или одмах после кикотања или смејања невољно и непредвиђено дешава истицање урина које је често обилно, до потпуног умокравања. Слично као и код стресне инконтиненције, уродинамски налаз када се дете не смеје је типично нормалан.

Инконтиненција после мокрења (енгл. *postvoid dribbling*)

Дневна инконтиненција може бити и последица истицања урина непосредно после мокрења. Ово се типично јавља код девојчица које су иначе без других уринарних симптома као последица лабијалних адхезија (конгениталних или стечених) или везиковагиналног рефлукса, услед којег урин током мокрења доспева у вагину, из које се излива када дете по завршетку мокрења устане. Може се потврдити микцијом цистграфијом или форсирањем инконтиненције заузимањем положаја с раширеним ногама при мокрењу. Међутим, ово је стање без опасности по здравље и обично ишчезава са одрастањем.

Дисфункционално мокрење

Дисфункционално мокрење је уродинамски ентитет који се одликује непотпуном релаксацијом или невољном контракцијом мишића пелвичног дна током мокрења код неуролошки здраве деце. Типично се испољава као различит интензитет млаза урина при микцији (енгл. *staccato voiding*) или испрекидалим млазом урина, што се лепо може документовати урофлуометријом.

Стакато мокрење се испољава као млаз урина различите јачине, а проузроковано је периодичним кон-

тракцијама пелвичне мускулатуре у току којих се смањују интензитет или прекида излазак урина. Истицање урина је обично продужено и често непотпуно.

Испрекидано (фракционисано) мокрење је, као што и само име каже, мокрење с прекидима, а последица је слабих контракција детрузора. Заправо, мокрење се одвија помоћу контракција трбушне мускулатуре, која је често парадоксално удружена и са контракцијама пелвичне мускулатуре. Стога се мокрење одвија с повишеним интравезикалним притиском, неефикасно је и у мањим количинама. Капацитет мокраћне бешике је увећан на рачун великог резидуалног урина.

Ретко мокрење и неактивна мокраћна бешика (синдром лење бешике)

Ова два стања су последица хроничне функционалне опструкције излазног тракта, која доводи до слабости детрузора (декомпензација детрузора), његове слабе контрактилности и услед тога слабог и непотпуног пражњења бешике. Осећај потребе за мокрењем је врло ослабљен, тако да деца ретко мокре, на 8–10 сати, или мокре само на подсећање. Мокраћна бешика је увећана. На уродинамском испитивању се могу доказати ослабљен до угашен осећај за мокрење, велики капацитет мокраћне бешике, ослабљене или одсутне контракције детрузора у фази микције која се форсира контракцијама абдомена. Растегљивост мокраћне бешике је увећана, а електромиографија бележи активност пелвичне мускулатуре која се јавља истовремено с контракцијама трбушних мишића. Резидуални урин је веома увећан. Врло су честе уринарне инфекције и опстипација.

Хинманов синдром и окултна неуропатска мокраћна бешика

Хинман (*Hinman*) и Бауман (*Baumann*) [39], Ален (*Allen*) [40] и Дорфман (*Dorfman*) и сарадници [41] су први описали поремећај мокрења који има све одлике неурогене мокраћне бешике код деце код које се неуролошки дефект расположивим методама прегледа не може доказати. Стога је овај поремећај назван неуро-гена-неурогена мокраћна бешика или Хинманов синдром, односно окултна неуропатска мокраћна бешика. Клиничке манифестације овог синдрома одражавају декомпензацију мокраћне бешике и укључују инконтиненцију урина, слабо и непотпуно пражњење мокраћне бешике и честе уринарне инфекције. Већина деце има и опстипацију и енкопрезу. И даље се са сигурношћу не зна узрок овог поремећаја. Раније мишљење да је реч о поремећају понашања и вољно изазваној дискоординацији између детрузора и мишића пелвичног дна/ спољнег сфинктера уретре данас је напуштено и сумња се да је у основи суштински или окултни спинални поремећај који се не може доказати чак ни магнетном резонанцијом. Уродинамска испитивања често показују наглашену активност сфинктера и изненадне контрак-

ције мишића пелвичног дна којима дете покушава да исконтролише неинхибиране контракције бешике. На крају се види потпуна декомпензација мокраћне бешике са дневном и ноћном инконтиненцијом, ретенцијом урина, честим уринарним инфекцијама и хроничним пијелонефритисом. Терапијске мере су сличне онима које се примењују код неурогене мокраћне бешике.

Урофацијални синдром припада такође групи не-неурогених-неурогених поремећаја мокрења. Назива се још Охоа синдром, по аутору који га је први описао [42]. Има сличне манифестације Хинмановом синдрому, с тим што га додатно одликује парадоксална, плачна мимика лица при смејању. Наслеђује се аутозомно рецесивно, а одговоран ген је лоциран на хромозому 10. Уродинамска испитивања показују дискоординацију детрузора и сфинктера која временом изазива декомпензацију детрузора са свим последицама. У студији Охое и сарадника [42] на 66 деце, код 33% забележена је слаба функција бубрега, код 26% хипертензија, а код 24% терминална инсуфицијенција бубрега, због које је петоро деце трансплантирано, док је 17 умрло. Претпоставља се да је за овај поремећај одговорно генетско оштећење у нервним ганглијама које контролишу мишиће лица, а смештене су близу центра за мокрење у понсу [43].

Ноћна енуреза

Ноћна енуреза је неконтролисано ноћно умокравање после пете године. Чешћа је код дечака него код девојчица. Може бити примарна, што значи да јој није претходио сув период дужи од шест месеци, или секундарна, која се јавља после успостављене ноћне контроле мокрења у интервалу дужем од шест месеци. Три су главна патогенетска механизма примарне ноћне енурезе: први је повећан праг буђења, други је ноћна полиурија, док је трећи хиперактивност детрузора. Ноћна полиурија се процењује на основу волумена ноћног урина (волумен измокреног урина у току ноћи плус волумен јутарњег урина) који је већи него што је нормално, тј. када је волумен ноћног урина већи од 130% израчунатог капацитета за узраст, односно однос дневног и ноћног урина мањи од 3, јавља се ноћна полиурија [21, 22]. Ноћна полиурија се објашњава поремећајем циркадијалног ритма антидиуретског хормона, који се смањено лучи ноћу [44]. Хиперактивност детрузора може бити узрок ноћне енурезе нарочито када је она удружена с повишеним прагом буђења.

Најновија сазнања упућују на уску повезаност ноћне полиурије, хиперактивности детрузора и повећаног прага буђења. Има доказа да основни узрок лежи у горњем делу понса (*locus coeruleus*), где се налази центар за буђење [44], који се анатомски и функционално поклапа са центром за мокрење у понсу [45] и главни је нуклеус симпатичког нервног система, са директним и индиректним аксоналним везама са супраоптичким једрима хипоталамуса у којима се лучи вазопресин [46].

ЗАКЉУЧАК

Функционални поремећаји мокрења су проблеми који се често јављају у детињству. Чести су код понављајућих инфекција мокраћног тракта и често су удружени

са опстипацијом. Могу довести до оштећења горњих мокраћних путева и бубрега. Лоше утичу на самопоуздање деце и на квалитет њиховог живота; стога је потребно да се рано открију и лече.

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Development of the Lower Urinary Tract and Its Functional Disorders

Amira Peco-Antić, Gordana Miloševski-Lomić

University Children's Hospital, Belgrade, Serbia

SUMMARY

A normal development of lower urinary tract function control evolves from involuntary bladder emptying (incontinence) during infancy to daytime urinary continence, and finally a successful day and night continence that is generally achieved by the 5th to 7th year of age. This gradual process primarily depends on the progressive maturation of the neural control of the lower urinary tract, but it is also influenced by behavioral training that evolves through social support. Functional voiding disorders (bladder dysfunction) are common problems during childhood. They are present in 5-15 % of general pediatric population, and in one-fifth of school-age children or in over one-third of patients of the pediatric urologist or nephrologist. More than half

of children with bladder dysfunction have vesicoureteral reflux, and more than two-thirds have recurrent urinary tract infections. There is also a frequent association of bladder dysfunction with constipation and encopresis (dysfunctional elimination syndrome). Bladder dysfunction may cause a permanent damage to the upper urinary tract and kidneys. In addition, urinary incontinence, as the most common manifestation of bladder dysfunction can be the cause of major stress in school-age children and have a negative effect on the child's feeling of self-esteem. Thus, a timely detection and treatment of this group of disorders in children is highly significant.

Keywords: urine incontinence; nocturnal enuresis; urinary tract infections; dysfunctional voiding

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Висок проценат нативних артериовенских фистула – како достићи тај циљ?

Тамара Јемцов¹, Марија Милинковић¹, Игор Кончар^{2,3}, Илија Кузмановић²,
Ненад Јаковљевић², Марко Драгаш^{2,3}, Никола Илић^{2,3}, Предраг Ђорић^{2,3}, Андреја Димић^{2,3},
Игор Банзић², Милица Крављача¹, Видосава Нешић^{1,3}, Лазар Давидовић^{2,3}

¹Клиника за нефрологију, Клинички центар Србије, Београд, Србија;

²Клиника за васкуларну и ендоваскуларну хирургију, Клинички центар Србије, Београд, Србија;

³Универзитет у Београду, Медицински факултет, Београд, Србија

КРАТАК САДРЖАЈ

Васкуларни приступи за хемодијализу су: нативна артериовенска фистула (АВФ), артериовенски графт (АВГ) и централни венски катетери (ЦВК). Правилно сазрела нативна АВФ је примарни избор за лечење хемодијализом, а висок проценат њене учесталости је циљ сваког нефролога и васкуларног хирурга. У овом раду анализирани су број и врста урађених васкуларних приступа за хемодијализу током десетогодишњег периода у Клиничком центру Србије и приказани фактори значајни за креирање високог броја успешних нативних АВФ (више од 80%). Овакав резултат, између осталог, последица је именовања координатора за васкуларне приступе, чији је задатак био да побољша квалитет бриге и неге крвних судова у преддијализном периоду и васкуларних приступа у функцији, те да унапреди сарадњу између професионалаца различитих специјалности из ове области. Васкуларни приступ је тзв. линија живота болесника на хемодијализи, па су његово успешно планирање, креирање и праћење континуиран процес, који захтева сарадњу болесника, нефролога, васкуларног хирурга, радиолога и медицинског особља.

Кључне речи: артериовенска фистула; хемодијализа; координатор за васкуларне приступе; колор доплер ултрасонографија; васкуларни приступ

УВОД

Све већи број болесника у терминалној фази хроничне слабости бубрега и повећање броја старих људи на хемодијализи, са све већим бројем коморбидних стања, намеће потребу за системским приступом, како у планираном креирању васкуларних приступа, тако и у њиховом праћењу и решавању компликација [1, 2]. Нативна артериовенска фистула (АВФ) је васкуларни приступ са најдужим преживљавањем и најнижом стопом компликација у односу на друге опције [3, 4, 5]. Међутим, њено креирање захтева постојање адекватних артеријских и венских крвних судова. Артериовенски графтови (АВГ) се користе када не постоји адекватан нативни венски крвни суд. Могу се користити биолошки материјали (аутовенски графтови – велика сафенска вена, умбиликална вена, говеђи уретер) или различити синтетски материјали, а најбоље резултате су показали политетрафлуороетилен (PTFE) и полиуретан. Трошкови њихове уградње и одржавања су значајно виши у поређењу с трошковима одржавања АВФ, а компликације (инфекције и тромбозе) значајно чешће [3, 4, 5].

Централни венски катетери (ЦВК) се, према својим особинама и индикацијама у којима се користе, могу поделити на привремене (ригидне, краткотрајне) и трајне (тунелизоване). Привремени ЦВК се користе уколико дође до развоја акутне слабости

бубрега и код пролазне потребе за хемодијализом, али и код болесника у терминалној фази слабости бубрега, да би се премостио период од креирања до почетка коришћења трајног васкуларног приступа. Могу бити постављени у унутрашњу југуларну вену, поткључну или феморалну вену, а постављају се транскутаном пункцијом. ЦВК је васкуларни приступ с великим ризиком за настанак неке компликације у поређењу с претходне две опције [4, 5, 6]. Трајни ЦВК (ТЦВК) су нешто компликованији за постављање, уграђују се хируршки и од флексибилног (мекшег) су материјала, а излазним делом се провлаче кроз формирани поткожни тунел. Ови катетери су предвиђени и као трајно решење за болеснике код којих су исцрпљене могућности креирања АВФ и АВГ, као и код болесника са слабошћу срца или код оних с очекиваним кратким временом преживљавања.

ПРЕДУСЛОВИ И ПОСТУПЦИ ЗА ПРАВОВРЕМЕНО КРЕИРАЊЕ ВАСКУЛАРНОГ ПРИСТУПА

Имајући у виду бројне предности нативних АВФ у односу на друге врсте васкуларних приступа, званични водичи саветују започињање хемодијализе преко правилно сазреле примарне нативне АВФ [7, 8]. Међутим, упркос препорукама и сазнању о

Correspondence to:

Tamara JEMCOV
Klinika za nefrologiju
Klinički centar Srbije
Pasterova 2, 11000 Beograd
Srbija
tjemcov@gmail.com

предностима АВФ у односу на АВГ и ТЦВК, њихову високу инциденцију и преваленцију код тих болесника у пракси није лако постићи. Препреке су бројне и подразумевају рад на: 1) планирању креирања васкуларног приступа у предиајализном периоду; 2) примени дијагностичких поступака који олакшавају доношење одлуке о врсти васкуларног приступа; 3) предиајализној бризи о крвним судовима, што повећава могућност креирања нативне АВФ; 4) сарадњи нефролога, васкуларног хирурга, здравствених радника у јединицама хемодијализе и болесника.

Европски водич за хемодијализе (*EBPG*) и водич Америчке фондације за бубрег (*NKF/DOQI*) саветују упућивање болесника нефрологу и васкуларном хирургу у четвртој стадијуму хроничне слабости бубрега, када је јачина гломерулске филтрације мања од $30 \text{ ml/min/1.73 m}^2$ [7, 8]. Оваквим приступом се благовремено планира прављење васкуларног приступа, смањује стопа морбидитета и морталитета болесника у терминалној фази слабости бубрега и смањују трошкови лечења [9, 10].

Васкуларни хирург ће обавити преглед крвних судова ових болесника који, према препорукама Удружења за васкуларне приступе (*Vascular Access Society*), подразумева: 1) процену фактора значајних за креацију фистуле и њено функционисање: старост и пол болесника, основно обољење бубрега, придружене болести (кардиоваскуларне, цереброваскуларне, деформације коштаног-зглобног система), раније регионалне хируршке интервенције и зрачна терапија; и 2) клинички преглед који се састоји од прегледа коже (инспекције и палпације), прегледа венског система (инспекције и палпације) и прегледа артеријског система (инспекције, палпације, аускултације и посебних тестова) [11]. Уколико је реч о млађим, негојазним болесницима мушког пола, често је овај преглед довољан. Међутим, болесници који су гојазни, старије животне доби, оболели од дијабетеса или су већ имали неку компликацију захтевају додатну дијагностику, а то је, пре свега, преглед ултразвуком.

КОЛОР ДОПЛЕР УЛТРАСОНОГРАФИЈА

Color Doppler ултрасонографија (*CDU*) је поуздана метода за стицање потпунијег увида у стање крвних судова екстремитета. Доступна, лако изводљива и неинвазивна, представља незаобилазан преглед у изради, планирању, праћењу и дијагностици компликација васкуларних приступа [12, 13]. Користећи упоредо Б-мод (сива скала) и колорни Доплеров мод, добијају се на истој слици анатомски приказ крвних судова и проток крви кроз њих. *CDU* преглед артерија је поуздана метода у одређивању: унутрашњег пречника артерија, дебљине зида, постојања калцификација и мерења индекса резистенције (*RI*), као функционалне одлике артерија. Сензитивност ове методе у откривању опструктивних болести артерија је 90%, док је специфичност 99% [14]. *CDU* преглед вена подразумева мерење

унутрашњег пречника вена, приказ тока пружања вена, приказ постојања колатералних вена и валвула и оцену функционалних особина зида вена (компресибилност и дистензибилитет). Дистензибилитет (растегљивост) је могућност вене да се прошири при повећаном приливу крви након споја с артеријом. Мерење дистензибилитета вена се врши пре и након проксималне компресије надлактице повеском и пружа нам значајну информацију о томе како ће се вена понашати након креирања АВФ. На функционалне одлике вена значајно утичу претходни упални процеси, најчешће узроковани понављаним пункцијама и постављањем каниле у вене. Зато су веома важне предиајализна брига и нега вена код болесника са слабошћу бубрега.

Подаци из литературе показују да мерење пречника крвних судова коришћењем *CDU* добро корелира с хируршким налазом [15, 16], док преоперациони *CDU* са мерењем морфолошких и функционалних одлика значајно утиче на позитиван исход нативних АВФ [17-20].

БРИГА И НЕГА КРВНИХ СУДОВА

Као што је већ поменуто, упални процеси вена условљени понављаним пункцијама и постављеним браунилама доводе до трајних оштећења. Овакве вене су тврде, ригидне и представљају места будућих сужења и разлог неуспеха васкуларних приступа. Да бисмо спречили ове нежељене последице, потребно је правилно обучити болеснике и медицинско особље о бризи и нези крвних судова. Болесницима треба скренути пажњу на то да не дозволе пункције у кубиталној регији, нити подлакти. Медицинском особљу треба указати на то да не постављају брауниле у кубиталној регији, већ на венама надлактице. Уколико је болесницима потребна продужена парентерална терапија, боље је пласирати терапијски ЦВК у унутрашњу југуларну вену него браунилу на подлактици.

ИСКУСТВО КЛИНИЧКОГ ЦЕНТРА СРБИЈЕ У КРЕИРАЊУ ВАСКУЛАРНИХ ПРИСТУПА

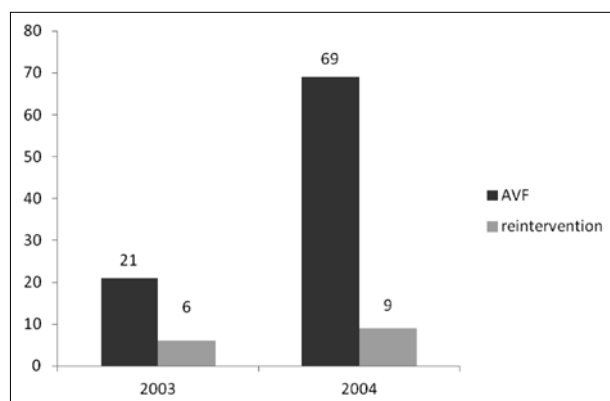
У Клиничком центру Србије (КЦС) годишње се уради 100–150 операција васкуларних приступа за хемодијализу. До 2003. године број креираних васкуларних приступа током једне године није прелазео 100, док су 35–40% тих приступа чинили васкуларни графтови. Највећи број васкуларних приступа креирали су васкуларни хирург и поједини уролози из тима за трансплантацију бубрега Клинике за урологију КЦС. Од 2003. године долази до успостављања сарадње између Клинике за нефрологију и Клинике за васкуларну и ендоваскуларну хирургију са другачијим приступом решавању ове проблематике. Именован је координатор за васкуларне приступе, нефролог, са задатком да анализира актуелну ситуацију, дефинише постојеће проблеме и предложи могућности њиховог решавања. Од координатора се очекивало да укључи све заинте-

ресоване стране (нефролога, васкуларног хирурга, радиолога, медицинске техничаре и болеснике) у програм планирања и креирања васкуларних приступа. Након обављених консултација координатора са директорима клиника, успостављен је заједнички протокол припреме болесника за хронични програм хемодијализе који је подразумевао рад на унапређењу неколико сегмената:

- увођења *CDU* прегледа крвних судова екстремитета у рутинску, свакодневну праксу;
- благовремено упућивање болесника васкуларном хирургу од стране нефролога ради планирања будућег васкуларног приступа;
- едукацији болесника и медицинског особља запосленог у Клиници за нефрологију о бризи и начину чувања крвних судова;
- успостављању континуиране комуникације између нефролога, васкуларних хирурга и радиолога с међусобном разменом мишљења и доношењем заједничке одлуке о оптималном месту креирања и врсти васкуларног приступа. Компликовани и проблематични случајеви су решавани конзилијарно.

Од 2004. године у Клиници за нефрологију је обавезан *CDU* преглед крвних судова код сваког болесника коме се планира васкуларни приступ. Након клиничког и *CDU* прегледа добија се увид у стање артеријског и венског крвног система и у договору између нефролога и васкуларног хирурга доноси одлука о оптималном месту и врсти будућег васкуларног приступа. Преоперациони *CDU* преглед крвних судова је допринео смањењу броја поновних интервенција приликом израде примарне АВФ, као и свеукупном броју креираних АВФ. Поређењем броја поновних интервенција на примарним АВФ током 2003. године, када се није изводио преоперациони *CDU* крвних судова, и 2004. године, с обавезним преоперационим *CDU*, показује њихово двоструко смањење (Графикон 1).

Током десетогодишњег периода клиничког праћења у Клиничком центру Србије број урађених васкуларних приступа се повећао (Табела 1). Управо захваљујући до-



Графикон 1. Број артериовенских фистула и поновних интервенција урађених 2003. године без преоперационог колор доплер ултразвучног прегледа (28,5%) и 2004. године, када је он постао обавезан (14,5%) ($\chi^2=1,11$; $p=0,29$)

Graph 1. The number of arteriovenous fistulas and reinterventions without preoperative color Doppler ultrasonography – *CDU* (28.5%) in 2003 and with required preoperative *CDU* (14.5%) ($\chi^2=1.11$; $p=0.29$) in 2004

Табела 1. Врста и број креираних васкуларних приступа током десетогодишњег периода у Клиничком центру Србије

Table 1. The number and types of vascular accesses created during ten-year period at the Clinical Center of Serbia

Година Year	АВФ AVF	АВГ AVG	ТЦВК TCVC	Укупно Total
2003	38 (88%)	3 (7%)	2 (5%)	43
2004	99 (86%)	12 (10%)	4 (3%)	115
2005	76 (91%)	3 (4%)	4 (5%)	83
2006	81 (90%)	4 (4%)	6 (7%)	90
2007	73 (81%)	10 (10%)	7 (7%)	90
2008	56 (85%)	3 (4%)	7 (10%)	66
2009	61 (87%)	1 (1%)	8 (11%)	71
2010	81 (81%)	3 (3%)	16 (16%)	100
2011	145 (84%)	5 (3%)	22 (13%)	172
2012	93 (87%)	2 (2%)	12 (11%)	107

АВФ – артериовенска фистула; АВГ – артериовенски графт; ТЦВК – трајни централни венски катетер

AVF – arteriovenous fistula; AVG – arteriovenous graft; TCVC – central venous catheter (perm-cath)

број сарадњи нефролога и васкуларних хирурга проценат нативних АВФ одржавао се изнад 80%, док је број уграђених АВГ сведен на најмању могућу меру. У првих пет година урађено је 367 АВФ и уграђена су 32 АВГ, а у следећих пет година 336 АВФ и само 14 АВГ; разлика је била статистички значајна ($\chi^2=4,55$; $p=0,0329$). Подаци из националног регистра за 2010. годину указују на чешћи висок проценат нативних АВФ код превалентних болесника на хемодијализи у Србији (91,9%), а нативне АВФ предњаче по броју и када су у питању новокреирани васкуларни приступи (89%) у поређењу са бројем уграђених АВГ (3,3%) или ТЦВК (7,7%) [21]. Имајући у виду значајно нижу учесталост нативних АВФ међу болесницима на хемодијализи у земљама Европе, САД и Канади [22], српски нефролози и васкуларни хирурзи би свакако требало да буду задовољни.

Табела 1 приказује повећање броја уграђених ТЦВК у периоду 2003–2010. године. Ово се може објаснити продужењем животног века болесника на хемодијализи праћеним развојем бројних коморбидитета (дијабетес мелитус, периферна васкуларна болест), као и повећањем броја геријатријских болесника који започињу лечење хемодијализом. С овим проблемом ћемо се тек суочавати у годинама које долазе.

ЗАКЉУЧАК

Васкуларни приступи су „линија живота“ болесника на хемодијализи и Ахилова пета целог процеса дијализе. Искуство Клиничког центра Србије потврђује да су планирање, креирање и праћење континуирани процес који захтева тесну сарадњу нефролога, васкуларног хирурга, радиолога, медицинских техничара и болесника. Њихова координисана сарадња омогућила је да се код највећег процента болесника креира нативна АВФ, да се значајно смањи број поновних интервенција после израде примарне АВФ, те да се проценат уграђених АВГ у последњих пет година сведе на мање од 5%.

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High Rate of Native Arteriovenous Fistulas: How to Reach This Goal?

Tamara Jemcov¹, Marija Milinković¹, Igor Končar^{2,3}, Ilija Kuzmanović², Nenad Jakovljević², Marko Dragaš^{2,3}, Nikola Ilić^{2,3}, Predrag Djorić^{2,3}, Andreja Dimić^{2,3}, Igor Banzić², Milica Kravljča¹, Vidosava Nešić^{1,3}, Lazar Davidović^{2,3}

¹Clinic for Nephrology, Clinical Center of Serbia, Belgrade, Serbia;

²Clinic for Vascular and Endovascular Surgery, Clinical Center of Serbia, Belgrade, Serbia;

³University of Belgrade, School of Medicine, Belgrade, Serbia

SUMMARY

The types of vascular accesses for hemodialysis (HD) include the native arteriovenous fistula (AVF), arteriovenous graft (AVG) and central venous catheter (CVC). Adequately matured native AVF is the best choice for HD patients and a high percentage of its presence is the goal of every nephrologist and vascular surgeon. This paper analyses the number and type of vascular accesses for HD performed over a 10-year period at the Clinical Center of Serbia, and presents the factors of importance for the creation of such a high number of successful native AVF (over 80%). Such a result is, inter alia, the consequence of the

appointment of the Vascular Access Coordinator, whose task was to improve the quality of care of blood vessels in the pre-dialysis period as well as of functional vascular accesses, and to promote the cooperation among different specialists within the field. Vascular access is the "lifeline" for HD patients. Thus, its successful planning, creation and monitoring of vascular access is a continuous process that requires the collaboration and cooperation of the patient, nephrologist, vascular surgeon, radiologist and medical personnel.

Keywords: arteriovenous fistula; hemodialysis; vascular access coordinator; Color Doppler ultrasonography; vascular access

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Допринос нових антикоагулантних лекова фондапаринукса и дабигатрана у превенцији венског тромбоемболизма

Небојша Антонијевић^{1,2}, Владимир Кањућ^{1,3}, Ивана Живковић², Љубица Јовановић², Миодраг Вукчевић^{1,4}, Милан Апостоловић^{1,5}

¹Универзитета у Београду, Медицински факултет, Београд, Србија;

²Клиника за кардиологију, Клинички центар Србије, Београд, Србија;

³Српска академија наука и уметности, Одбор за кардиоваскуларну патологију, Београд, Србија;

⁴Клиничко-болнички центар „Бежанијска коса“, Београд, Србија;

⁵Институт за ортопедско-хируршке болести „Бањица“, Београд, Србија

КРАТАК САДРЖАЈ

Податак да се код знатног процента болесника при примени стандардних антикоагулантних лекова у превенцији венског тромбоемболизма (ВТЕ) нефракционисаним и нискомолекуларним хепаринима и инхибиторима витамина К бележе епизоде и секвеле ВТЕ, као и чињеница да ови лекови имају значајних ограничења и да њихова примена у појединим случајевима може изазвати настанак тешких нежељених дејстава, указују на потребу за применом нових антикоагулантних лекова. Фондапаринукс, селективни инхибитор фактора Ха, примењен током великих ортопедских операција високоризичних за настанак ВТЕ, ефикаснији је од еноксапарина примењеног у европским и северноамеричким дозама. Повећана инциденција значајних, али не и фаталних, крварења изазваних фондапаринуксом евентуално би се могла смањити смањењем дозе код болесника с умерено сниженим клиренсом креатинина. Дабигатран, перорални, реверзибилни директни тромбински инхибитор, примењен у профилакси ВТЕ у селективним операцијама кука и колена, у досадашњим студијама показао је дејство компарабилно (дабигатран примењиван у оба дозна режима од 150 *mg* и 220 *mg* дневно) или супериорно (ако се дабигатран примењује у дози од 220 *mg* дневно) у односу на еноксапарин примењен у европским дозама, али су северноамеричке дозе еноксапарина биле делотворније у редукцији ВТЕ. Нису утврђене значајне разлике у степену крварења ни у једној испитиваној групи. Сматрамо да ће увођење нових антикоагулантних лекова, међу којима су и фондапаринукс и дабигатран, допринети успостављању бољег сигурносног профила и ефикасности и омогућити адекватну индивидуализацију терапије код сваког болесника зависно од његових клиничких одлика. Увођење нових пероралних антикоагулантних лекова, између осталог, знатно утиче на унапређење квалитета живота, ослобађа од бројних ограничења у исхрани, интеракција и честог лабораторијског испитивања, те значајно поправља предвиђање исхода лечења.

Кључне речи: превенција; венски тромбоемболизам; фондапаринукс; дабигатран

УВОД

Венски тромбоемболизам (ВТЕ), као заједнички именитељ тромбоза дубоких вена и/или плућне емболије, трећи је по реду узрок васкуларног морталитета у савременом свету, одмах после инфаркта миокарда и цереброваскуларног инсульта [1-4]. У Европској унији број умирања као последица ВТЕ износи 543.454 годишње, што је бројка која више него дупло премашује смртност од карцинома дојке, простате, синдрома стечене имунодефицијенције и саобраћајног трауматизма. У Сједињеним Америчким Државама (САД) и Европској унији од ВТЕ сваких 37 секунди умре једна особа [5]. Пре увођења тромбопрофилактике после операција тоталне артропластике кука и тоталне артропластике колена, тромбозе дубоких вена – често и асимптоматске – настајале су код 40–60% болесника, емболије плућа код 5–10% болесника, а фатални плућни емболизам настајао је код 1–2% болесника [6].

Примена нефракционисаних хепарина (UFH), првих фармаколошких агенаса који су се користили у тромбопрофилактици, смањила је преваленцију фаталних плућних емболија са 0,8% на 0,3%, симптоматских плућних емболија са 2% на 1,3%, а тромбозе дубоких вена са 22% на 9% [7]. Оваква клиничка корист била је праћена повећањем степена крварења са 3,8% на 5,9% [7]. Попут UFH, нискомолекуларни хепарини (LMWH) смањују ризик од ВТЕ најмање за 60% у поређењу са групом болесника која није користила тромбопрофилактику [7]. Податак да LMWH смањују ризик од ВТЕ за приближно половину у односу на плацебо, остављајући значајан проценат болесника у ризику од настанка ВТЕ, намеће потребу за применом ефикаснијих антикоагулантних лекова [7]. Процењује се да је инциденција хепаринске тромбоцитопеније типа II чак 3–5% код болесника лечених применом UFH у ортопедској хирургији, а 0–0,9% код болесника лечених са LMWH [8-14].

Correspondence to:

Nebojša ANTONIJEVIĆ
Klinika za kardiologiju
Klinički centar Srbije
Dr Koste Todorovića 8
11000 Beograd
Srbija
drantoni@gmail.com

Неуспех у превенцији ВТЕ доводи до наведених компликација које угрожавају живот, али и дуготрајног морбидитета у виду хипертензије плућа, рекурентних тромбоза, хроничне инсуфицијенције вена, односно посттромбофлебитског синдрома и венских улкуса, те последично има велику социоекономску тежину у сваком друштву [1, 15].

Без обзира на доказану ефикасност у превенцији ВТЕ, перорална антикоагулантна терапија антагонистима витамина К (VKA) има доста ограничења, као што су: непредвиђена дејства, узак терапијски прозор, спор почетак дејства, одложено дејство после обуставе терапије, бројне интеракције са храном и другим лековима, варирање терапијског дејства, релативно мали проценат болесника у предвиђеном терапијском опсегу, настанак кожных некроза код болесника с недостатком протеина Ц и С код примене VKA, ризик настанка остеопорозе код дуже примене [16].

Примена хепаринских антикоагуланса ограничена је: неопходношћу парентералне примене, ризиком од настанка хепаринске тромбоцитопеније с могућим тромбозама опасним по живот, остеопорозом и сл. [14].

Од свих узрока морталитета, ВТЕ, односно емболија плућа, сматрају се најпревентабилнијим узроцима смрти, па је усавршавање мера превенције ВТЕ у највећој могућој мери посебно важно [7].

ФОНДАПАРИНУКС

Фондапаринукс је, према механизму дејства, синтетски парентерални селективни инхибитор фактора Ха, без интерреакције с фактором II. Фармакокинетика овог пентасахарида одликују брз почетак дејства, висока биорасположивост (100% два сата након поткожне примене), доминантно излучивање преко бубрега и релативно дуг полуживот елиминације (17–21 сат), што омогућава дозирање једном дневно (Табела 1) [5, 17, 18, 19]. Нису доказане интерреакције фондапаринукса с аспирином, варфарином и дигоксином, као ни инхибиција изoenзима цитохром P450 [17, 18, 19].

Табела 1. Фармакокинетске одлике нових антикоагулантних лекова [19, 34]

Table 1. Pharmacokinetic characteristics of new anticoagulant drugs [19, 34]

Одлике Characteristics	Фондапаринукс Fondaparinux	Дабигатран Dabigatran
Апсорпција Absorption	Висока (100%) биорасположивост High (100%) bioavailability	Ниска (<10%) биорасположивост Low (<10%) bioavailability
Полуживот Half-life	17 h*/21 h**	11 h*/12–14 h**/ 13.4–27.2 h***
Ренална елиминација Renal elimination	64–75%	85%

* генерално код здравих младих особа; ** генерално код старијих особа;

+ код здравих старијих особа; ** полувреме након вишеструких доза; *** код оштећене функције бубрега полувреме је продужено

* generally in young healthy individuals; ** generally in the elderly; + in healthy elderly subjects; ** terminal half-life after multiple doses; *** half-life is prolonged in renal impairment

Када је реч о клиничкој ефикасности и сигурности примене овога лека, у студији ARTEMIS (ARixtra for ThromboEmbolism Prevention in a Medical Indications Study), која је укључила 425 особа оболелих од нехируршких – акутних медицинских стања, установљено је да је ризик од ВТЕ доказан обостраном асцендентном венографијом, сцинтиграфијом плућа, плућном ангиографијом или аутопсијски редукован за 46,7%; прецизније речено, ризик од ВТЕ је смањен са 10,5% у плацебо групи на 5,6% у групи болесника који су примали 2,5 mg фондапаринукса током 14 дана ($p=0,029$), без пораста значајних (major) хеморагијских догађаја [5, 20]. Фондапаринукс је ефикасан у превенцији асимптоматских и симптоматских ВТЕ догађаја код особа оболелих од нехируршких – акутних медицинских стања старијих од 60 година (конгестивна слабост срца, акутна респираторна болест у оквиру хроничне болести плућа, или инфламаторна болест када се очекује везаност за постељу најмање четири дана) [20].

Рандомизирана дупло слепа студија EPHEUS (European Pentasaccharide Elective Surgery Study), у којој је учествовало 2.309 болесника подвргнутих елективној операцији кука, показала је да је фондапаринукс у дози од 2,5 mg ефикаснији од еноксапарина примењеног у европским профилактичким дозама (40 mg) у превенцији ВТЕ доказаног венографијом између 5. и 11. дана. Током шест недеља клиничког праћења ВТЕ је утврђен код 4% болесника лечених са 2,5 mg фондапаринукса, чија је примена започета шест сати након операције, у односу на 9% болесника лечених са 40 mg еноксапарина започетим 12 сати пре хируршког лечења са следећом дозом 12–24 сата после операције ($p<0,0001$), што је представљало релативну редукацију ризика за 55,9%, уз напомену да између ове две групе нису постојале разлике у фреквенцији умирања или степену клинички релевантних крварења. Истичемо да се корисни ефекат фондапаринукса посебно испољава у смањењу броја венографски испољених проксималних тромбоза дубоких вена (посебно склоних емболизацији) за 74% [15].

Метаанализа четири мултицентричне рандомизираних двоструко слепа студије које су испитале 7.344 болесника подвргнутих великим ортопедским хируршким интервенцијама (елективна операција кука и колена, операција прелома кука) утврдила је значајно смањење инциденције венографски потврђеног тромбоемболизма за више од 50% у поређењу с еноксапарином примењеним два пута у дози од 30 mg дневно или 40 mg једном дневно без повећања инциденције клинички значајних крварења између 5. и 9. дана (6,8% према 13,7%; $p<0,01$). Но, број епизода значајних крварења био је чешћи у групи болесника лечених фондапаринуксом, уз напомену да се инциденција клинички релевантних крварења која доводе до умирања или поновне операције, или се дешавају у критичном органу, није разликовала међу испитиваним групама [20, 21]. Дупло слепа рандомизирана студија PENTATHLON (PENTAsaccharide in Total Hip replacement, or Low-mo-

lecular-weight heparin) установила је да је код 2.275 болесника с елективном операцијом кука смањење ВТЕ фондапаринуксом у дози од 2,5 mg (6%) било статистички безначајно ниже у односу на установљених 8% ВТЕ догађаја у групи болесника који су примали еноксапарин у дози од 30 mg два пута дневно без пораста клинички значајних крварења [21].

Истраживачи студије PENTHIFRA (PENTasaccharide in Hip-FRActure surgery study) потврдили су предност продужене профилаксе фондапаринуксом код болесника с преломом кука [22]. Примена фондапаринукса током четворонедељног режима довела је до смањења инциденције ВТЕ после операције прелома кука за 90%, у поређењу с једнонедељним режимом фондапаринукса праћеним тронедељном применом плацеба [23].

Код елективне операције колена фондапаринукс у дневној дози од 2,5 mg довео је до ефикаснијег смањења инциденције асимптоматских и симптоматских ВТЕ догађаја у поређењу с еноксапарином у дози од 30 mg два пута дневно (12,5% према 27,8%; $p < 0,001$), али на уштрб повећања значајних хеморагијских догађаја (2,1% према 0,2%; $p = 0,006$) [24, 25]. Међутим, резултати дупло слепо студије PENTAMAKS (PENTasaccharide in MAjor Knee Surgery study), која је обухватила 1.049 болесника након елективне операције колена, показали су значајно нижу инциденцију венских тромбоза (12,5%) у групи испитаника лечених фондапаринуксом у дози од 2,5 mg у односу на групу лечену еноксапарином у дози од 2×30 mg (27,8%). Дакле, смањење је било 55,2% ($p < 0,001$), али уз напомену да је било више значајних крварења, али не и оних који су доводили до смртног исхода или поновне операције [25].

Код операција прелома кука, применом фондапаринукса у дози од 2,5 mg једном дневно, у поређењу с еноксапарином у дози од 40 mg једном дневно, умањен је степен ВТЕ (8,3% према 19,1%; $p < 0,001$) без значајног повећања у главним хеморагијским догађајима [24, 26]. Према Клиничким водичима за профилаксу ВТЕ код болесника с преломом кука *Thrombosis Interest Group of Canada (2009)* [6], фондапаринукс се препоручује код ових болесника на основу резултата неколико студија које су поредиле његову ефикасност са нискомолекуларним хепаринима, а која се огледала у смањењу процента проксималних тромбоза дубоких вена за 79% и дисталних тромбоза дубоких вена за 55%. У великој ретроспективној кохортној студији са 144.806 болесника с великим ортопедским интервенцијама (операције прелома кука или замене кука и колена) из 500 болница, забележено је значајно мање ВТЕ догађаја са фондапаринуксом (1,5%) у поређењу са еноксапарином (2,3%), далтепарином (2,1%) и UFH (4,2%) [27].

У метаанализи четири студије коју су објавили Турпи (Turpie) и сарадници [23], у великој ортопедској хирургији инциденција симптоматског или асимптоматског ВТЕ са фондапаринуксом била је нижа него са еноксапарином (6,8% према 13,7%; $p < 0,001$), али је била праћена повећањем броја значајних хеморагијских манифестација (2,7% према 1,7%; $p = 0,008$).

У клиничкој студији PEGASUS (*Postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery*), фондапаринукс у дози од 2,5 mg једном дневно, шест сати после ушивања хируршког реза, показује сличан ефекат далтепарину у дози од 5000 и.ј. једном дневно (уз прве две дозе од 2500 и.ј. два сата пре операције и 12 сати након ње) у смањење настанка ВТЕ (4,6% према 6,1%; $p = 0,144$, смањење релативног ризика од ВТЕ за 24,6%) [28]. Такође, инциденција значајних крварења у овој студији се није статистички разликовала [28]. Фондапаринукс примењен уз механичку профилаксу интермитентном пнеуматском компресијом смањује појаву ВТЕ за 69,8% у односу на болеснике који су имали само механичку профилаксу ВТЕ интермитентном пнеуматском компресијом, уз очекивано повећање нефаталних значајних крварења [29].

Захваљујући својим предностима, фондапаринукс има шире индикације за профилаксу ВТЕ у односу на друге нове антикоагулансе. FDA (*Food and Drug Administration*) и EMA (*European Medical Agency*) одобрили су га за профилаксу ВТЕ код болесника после операције абдомена, код особа оболелих од нехируршких – акутних медицинских стања, као и после операције кука и колена и током хируршког лечења прелома кука [9, 24, 30].

Многи аутори сматрају да је фондапаринукс делотворнији од еноксапарина у превенцији тромбозе дубоких вена после ортопедских интервенција, али су и главна крварења значајно чешћа код болесника лечених фондапариноксом, мада су се у пракси могла умањити применом фондапаринукса шест сати после операције, као и смањењем дозе лека на 1,5 mg код болесника са инсуфицијенцијом бубрега тежег степена [1].

Контраиндиковано је примењивати фондапаринукс код болесника с клиренсом креатинина мањим од 30 ml/min, а налаже се посебан опрез нарочито код болесника с клиренсом креатинина 30–50 ml/min [19]. EMA препоручује употребу мањих доза овога лека, од 1,5 mg, код болесника са сниженим клиренсом креатинина (20–50 ml/min) уместо уобичајене дозе од 2,5 mg [19].

Фондапаринукс и тромбоцитопенија изазвана хепарином

Антитела на тромбоцитни фактор 4 (TF4)/фондапаринукс јавља се у сличном степену као и антитела на TF4/LMWH, али су антитела на TF4/фондапаринукс мање реактивна и имуногена, тако да већи број аутора сматра да нема релевантних имуногених интерреакција између TF4/хепарин антитела и TF4/фондапаринукс [9, 18], односно да фондапаринукс није способан да активира тромбоците у серуму болесника оболелих од тромбоцитопеније изазване хепарином (тј. хепарином индуковане тромбоцитопеније – ХИТ). И поред податка да неки еминентни стручњаци у пракси успешно користе фондапаринукс у лечењу болесника са ХИТ, такав приступ засад не саветују ни произвођачи, а ни

много стручњаци посвећени овој проблематици [14, 18]. Ова резерва приликом терапијске примене фондапаринукса код болесника са ХИТ проиходи из неколико објављених контроверзних случајева удружене примене фондапаринукса и настанка ХИТ. С обзиром на то да се у неким од ових случајева вероватно радило о тзв. касно насталој ХИТ услед раније примене хепаринских деривата или инсуфицијентном искључењу других узрока тромбцитопеније, ХИТ узрокована фондапаринуксом се и даље сматра стручном и научном енигмом [14, 18]. Једна од предности примене нових антикоагулантних лекова свакако лежи у мањем ризику од настанка тромбоза изазваних ХИТ-ом и других животноугрожавајућих компликација [9-14].

ДАБИГАТРАН

Дабигатран-етексилат је, према механизму дејства, селективни орални реверзибилни директни инхибитор тромбина који компетитивно и зависно од концентрације инхибира активисани тромбин, као и генерацију тромбина индуковану ткивним фактором и тромбцитну агрегацију индуковану тромбином [31]. Фармакокинетичку дабигатрана одликују ниска биорасположивост, полуживот у плазми 12–17 сати и примарно ослобађање преко бубрега (Табела 1). Због тога је потребно дневну дозу смањити са 220 mg на 150 mg код болесника с умереном инсуфицијенцијом бубрега (клиренс креатинина 30–50 ml/min), код болесника старијих од 75 година и оних који узимају амјодарон, верапамил и кинидин [30]. Употреба дабигатрана је контраиндикована код болесника с клиренсом креатинина мањим од 30 ml/min [1, 31].

Предности дабигатрана су могућност оралне примене, предвиђање антикоагулантног ефекта (без потребе за рутинским праћењем коагулације), непостојање интеракција с храном, значајно мањи број интеракција с лековима, изостанак ризика од ХИТ [8, 32].

Ограничења примене дабигатрана су посебан режим током припреме за спиналну анестезију и релативно виша цена лека. Засада не постоји јасно утврђен режим лабораторијског испитивања, као ни директни антидот [16, 32].

Дабигатран је индикован и за лечење ВТЕ. Осећај мучнине је каткад разлог за обуставу терапије [8].

Забележене су интеракције дабигатрана са другим лековима. Истовремена примена *P-gp* инхибитора доводи до повећања концентрације дабигатрана у плазми. Употреба јаких *P-gp* инхибитора кетоконазола, итраконазола, такролимуса, циклоспорина и дронедарона је контраиндикована при истовременој употреби дабигатрана [33, 34]. Посебан опрез се саветује при преписивању слабијих или умерених *P-gp* инхибитора амјодарона, кларитромицина, кинидина, верапамила и тикагрелора. Примена амјодарона повећава биорасположивост дабигатрана за 50–60%, тако да се у тим случајевима препоручује смањење дозе дабигатрана. Насупрот томе, сматра се да примена пантопрозола

смањује биорасположивост дабигатрана за 20–30%, као и употреба *P-gp* индуктора рифампицина, кантариона и карбамазепина [31, 33, 34].

Када је реч о клиничкој ефикасности и сигурности примене, дабигатран је одобрен за тромбопрофилактику болесника после елективне тоталне артропластике кука и тоталне артропластике колена у Европи, САД и многим другим земљама света [31]. У студији *RE-NOVATE (Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement)*, која је обухватила 3.494 болесника, након елективне тоталне артропластике кука примарни исход ефикасности (венографски доказана или симптоматска ВТЕ и укупни морталитет током лечења) забележен је код 8,6% болесника лечених дабигатраном у дози од 150 mg и 6% оних који су лечени дабигатраном у дози од 220 mg, у односу на 6,7% болесника лечених европским дозама еноксапарина од 40 mg једном дневно, што је потврдило неинфериорност обе дозе дабигатрана. Инциденција значајних крварења била је 1,3% код болесника лечених дабигатраном у дози од 150 mg, односно 2% оних који су лечени истим леком у дози од 220 mg, а 1,6% у групи испитаника којима је примењен еноксапарин [16, 31].

Студија *RE-MODEL (Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement)* упоређивала је ефикасност обе горепоменуте дозе дабигатрана у односу на европске дозе еноксапарина од 40 mg једном дневно код 2.100 болесника с тоталном артропластиком колена. Примарни и секундарни исход ефикасности је забележен са сличном инциденцијом код болесника лечених применом обе дозе дабигатрана, као и код оних лечених еноксапарином, уз напомену да се инциденција значајних крварења није разликовала међу испитиваним групама [31, 35].

У студији *RE-MOBILISE (Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery)*, за разлику од утврђене неинфериорности дабигатрана у другим два европских студијама, исте дозе дабигатрана су се показале инфериорним у односу на еноксапарин примењен у северноамеричким дозама од 2×30 mg у студији *RE-MOBILISE*, урађеној у САД, која је обухватила 2.615 болесника после тоталне артропластике колена. Инциденција свих ВТЕ и свих узрока морталитета као примарног исхода ефикасности била је значајно виша код испитаника лечених дабигатраном применом обе дозе, него код оних из групе која је примала еноксапарин. И у њој је као активни компаратор употребљен еноксапарин у укупној дневној дози од 60 mg. Још једна разлика била је и у томе да је у студији *RE-MOBILISE* дабигатран примењен 6–12 сати после операције, а еноксапарин 12–24 сата после хируршког лечења, за разлику од студија *RE-NOVATE* и *RE-MODEL*, у којима је дабигатран даван 1–4 сата после операције, док је еноксапарин примењен болесницима вече уочи хируршког захвата. Инциденција крварења је била слична у свим испитиваним групама [31, 35].

У обе студије, *RE-NOVATE* и *RE-MODEL*, примарно изведене у европским земљама, употреба дабигатрана је започињана сат-два после хируршког лечења, док је еноксапарин у дози од 40 mg једном дневно примењиван вече пре операције. У студији *RE-MOBILISE* примена дабигатрана је започета 6–12 сати после операције, док је еноксапарин уведен 12–24 сати после ње у дози од 2×30 mg. У све три студије прва доза дабигатрана чинила је половину стандардне дневне дозе, тј. 75 mg дневно, што је препоручено у складу с резултатима студије *BISTRO 2* ради смањења учесталости крварења.

Дужина профилаксе у студији *RE-NOVATE* после артропластике кука била је 28–35 дана, а после артропластике колена у студијама *RE-MODEL* и *RE-MOBILISE* до 15 дана.

У студији *RE-NOVATE II* испитиване су ефикасност и сигурност оралних доза дабигатрана у дози од 220 mg једном дневно (започињање с половином дозе 1–4 сата после операције) у односу на поткожно примењене дозе еноксапарина од 40 mg једном дневно (увођење вече пре хируршког захвата) у продуженој профилакси након елективне операције замене кука код 2.055 болесника током 28–35 дана. Примарни исход ефикасности (збир укупног ВТЕ и морталитета свих узрока) забележен је код 7,7% болесника у групи која је примала дабигатран, наспрам 8,8% оних који су примали еноксапарин ($p < 0,0001$), а главни секундарни циљ ефикасности (главне ВТЕ – проксималне тромбозе дубоких вена и нефатални емболизам плућа, заједно са морталитетом везаним за ВТЕ) забележен је код 2,2% испитаника који су примали дабигатран, односно код 4,2% испитаника лечених еноксапарином ($p = 0,03$). Значајна крварења су утврђена код 1,4% особа лечених дабигатраном, наспрам 0,9% лечених еноксапарином ($p = 0,4$), што није било статистички значајно. Дал (*Dahl*) сматра да је студија *RE-NOVATE II* потврдила неинфериорност дабигатрана у односу на еноксапарин и да се дабигатран показао супериорним у односу на еноксапарин у клинички релевантном исходу (*major* ВТЕ и умирање због ВТЕ) [32]. Такође, метаанализа је установила да дабигатран у дози од 220 mg није инфериоран у односу на еноксапарин, али да је у дози од 150 mg значајно инфериоран у односу на еноксапарин [36].

Антагонизовање дејства дабигатрана и фондапаринукса

За дабигатран не постоји специфични антидот који би извршио евентуалну неутрализацију његовог дејства, али се у случајевима животнутогрожвајућих крварења може применити рекомбиновани активирани фактор VII или активирани концентрат протромбинског комплекса (*FEIBA*) [33]. Чињеница је да се око 60% дабигатрана може уклонити из крви хемодијализама (захваљујући релативно ниском везивању за протеине плазме и могућности убрзавања плазматског клиренса

код особа са значајном инсуфицијенцијом бубрега) [16, 32]. Антидот за фондапаринукс такође не постоји. При хемодијализама клиренс фондапаринукса се увећава за 20%, а симптоматска стратегија слична горенаведеној (рекомбинантни активирани фактор VIIa, транексамична киселина) примењује се код предозирања и настанка компликација крварења [37]. И поред чињенице да се ови лекови за профилаксу ВТЕ примењују у мањим профилактичким, а не терапијским дозама, при примени ових лекова потребно је обезбедити стратегију лечења евентуалних компликација крварења.

МЕСТО НОВИХ АНТИКОАГУЛАНТНИХ ЛЕКОВА СА ФОКУСОМ НА ФОНДАПАРИНУКС И ДАБИГАТРАН У ПРАКТИЧНОЈ ПРИМЕНИ У СВЕТЛУ НАЈНОВИЈИХ ПРЕПОРУКА

Код болесника којима је урађена артропластика кука и колена препоручује се, према смерницама АССП (*American College of Chest Physicians*) из 2012. године, да поред одраније познатих лекова (*VKA, LMWH*), узимају дабигатран и фондапаринукс уз ривароксабан и аликсабан током најмање 10–14 дана за елективну артропластику колена, односно оптимално 35 дана за елективну артропластику кука [27]. Препоруке АССП из 2008. године су се децидно изјасниле против употребе аспирина, *UFH*, градуисаних компресионих чарапа и венских пумпи за стопало, као једине мере профилаксе [30].

Према препорукама *NICE (National Institute For Health and Clinical Excellence)*, за тромбопрофилаксу после тоталне артропластике кука и тоталне артропластике колена, поред стандардних, раније примењиваних мера тромбопрофилаксе, саветује се и примена дабигатран-етексилата 1–4 сата после хируршке интервенције и фондапаринукса започетог шест сати после ушивања хируршке ране и обезбеђења хемостазе [38].

Према смерницама Клиничких водича за профилаксу ВТЕ у великим ортопедским операцијама *Thrombosis Interest Group of Canada (2009)* [6], поред стандардних мера тромбопрофилаксе код болесника с тоталном артропластиком кука и колена, саветује се примена пентасахарида фондапаринукса у дози од 2,5 mg 4–8 сати после операције, дабигатран-етексилата у дози од 110 mg или 75 mg 1–4 сата после операције, а у даљем току 220 mg перорално, односно код болесника с умереном дисфункцијом бубрега 30–50 ml/min и болесника старијих од 75 година у дози од 150 mg једном дневно. Када је реч о примени фондапаринукса, лека са дужим полуживотом, канадске препоруке не саветују његову употребу код болесника с имплантираним епидуралним катетером, што се односи и на примену дабигатрана. Дабигатран се не сме давати два сата од уклањања епидуралног катетера [6].

Код болесника с преломом кука, препоруке АССП из 2012. године, поред досад предложених *VKA*, нискомолекуларних хепарина, залажу се за примену фондапаринукса [27].

Према препорукама *NICE* из 2010. године, за тромбoproфилаксу после прелома кука, поред стандардних, раније примењиваних мера тромбoproфилактике, саветује се примена фондапаринукса започетог шест сати после затварања хируршке ране и обезбеђења хемостазе код болесника без ризика од крварења, уз напомену да се не користи пре операције, али уколико се ипак користи пре хируршког лечења, мора се прекинути 24 сата пре захвата и поново применити шест сати по хируршкој интервенцији (прим. аут. уз назнаку да је неопходан посебан режим ако постоји инсуфицијенција бубрега). Указује се на потребу да фармаколошка профилакса траје од 28 до 35 дана за све модалитете терапије код болесника после операције прелома кука [38].

Према Клиничким водичима за профилаксу ВТЕ код болесника с преломом кука *Thrombosis Interest Group of Canada* (2009), препоручује се примена фондапаринукса 4–8 сати после операције, док се нискомолекуларни хепарини дају 12–24 сата после операције до 35 дана после хируршке операције прелома кука [6].

ЗАКЉУЧАК

Поред несумњивих предности нових антикоагулантних лекова, међу којима се код оралних антикоагулантних лекова, као што је дабигатран, истичу једноставност примене, недостатак интерреакција с храном, не-

упоредиво мањи број интерреакција с лековима, боље предвиђање дејства, општа могућност примене која не изискује нужно рутинско лабораторијско испитивање, неопходно је нагласити да за нове антикоагулантне лекове нема директног антидота [32]. Због доказане ефикасности у профилакси ВТЕ, фондапаринукс би имао предност код високоризичних ортопедских болесника с малим ризиком од крварења [20, 21, 23, 26]. Свакако, прецизнија потврда ефикасности нових антикоагулантних лекова и њихова сигурност у профилакси венског тромбоемболизма, као једног од горућих проблема савремене медицине, предмет је клиничке праксе и будућих студија, чији резултати треба да омогуће пуну примену њихових потенцијала у свакодневној употреби и у саврше постојећу профилаксу ВТЕ.

НАПОМЕНА

Рад је интегрални део пројекта под називом „Истраживање патолошко-морфолошких лезија: урођених и стечених срчаних мана (и њихове плућне циркулације), миокарда и коронарних крвних судова“, Одељења медицинских наука Српске академије наука и уметности и пројекта бр. 173008 од 2011. године „Комплексне болести као модел систем за проучавање модулације фенотипа – структурна и функционална анализа молекуларних биомаркера“ под окриљем Министарства просвете, науке и технолошког развоја Републике Србије.

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Contribution of Novel Anticoagulants Fondaparinux and Dabigatran to Venous Thromboembolism Prevention

Nebojša Antonijević^{1,2}, Vladimir Kanjuh^{1,3}, Ivana Živković², Ljubica Jovanović², Miodrag Vukčević^{1,4}, Milan Apostolović^{1,5}

¹University of Belgrade, School of Medicine, Belgrade, Serbia;

²Clinic for Cardiology, Clinical Center of Serbia, Belgrade, Serbia;

³Serbian Academy of Sciences and Arts, Committee of Cardiovascular Pathology, Belgrade, Serbia;

⁴Medical Center "Bežanijska kosa", Belgrade, Serbia;

⁵Institute for Orthopedic Surgery "Banjica", Belgrade, Serbia

SUMMARY

The data that episodes and sequels of venous thromboembolism (VTE) are recorded in a significant percentage of patients receiving standard anticoagulants as VTE prophylaxis (unfractionated, low-molecular-weight heparin and vitamin K inhibitors) as well as the fact that these drugs have significant limitations and that they may cause serious side-effects in some patients indicate the need for the introduction of new anticoagulant drugs. Fondaparinux, a selective inhibitor of Factor Xa, administered following major orthopedic surgeries having a high risk for the development of VTE, is more efficient than enoxaparin sodium used in European and North-American approved doses. The increased incidence of major bleeding (excluding fatal) due to fondaparinux could be perhaps lowered by dosage reduction in patients with a mildly decreased creatinine clearance. Dabigatran, a peroral direct thrombin inhibitor, administered for VTE prophylaxis in elective hip and knee surgery, showed in to date studies the efficacy comparable (if dabigatran

is given in both dosage regimes of 150 mg and 220 mg daily) or superior (if dabigatran is given at a dose of 220 mg daily) to enoxaparin administered in European-approved doses, while North American-approved doses of enoxaparin were superior than dabigatran in VTE reduction. No significant differences in bleeding rates were determined in any of the study groups. We consider that the introduction of new anticoagulants, including fondaparinux and dabigatran, will contribute to the establishment of a better safety profile and efficacy, and will also enable adequate therapy individualization for each patient depending on his/hers clinical characteristics. The introduction of novel peroral anticoagulants will, inter alia, significantly contribute to improvement in the quality of life, release the patient from numerous limitations in nutrition, interreaction, frequent laboratory monitoring, and also significantly improve therapeutic predictability.

Keywords: prevention; venous thromboembolism; fondaparinux; dabigatran

Learning Medical English: A Prerequisite for Successful Academic and Professional Education

Nataša Milosavljević¹, Aleksandar Vuletić², Ljiljana Jovković³

¹University of Niš, Faculty of Medicine, Niš, Serbia;

²Union University "Nikola Tesla", Faculty of Sports, Belgrade, Serbia;

³Union University, Belgrade, Serbia

SUMMARY

The aim of this paper is to present specificities of the English language teaching necessary for successful education and professional training of medical students. In contemporary globalized world the English language has become the basic language of communication in all scientific fields including the field of medical science. It is well established that Medical English teaching should primarily focus on stable linguistic competence in English that is created by means of content and context based curriculum, thus preparing students for active use of English upon graduation. In order to achieve this it is very important that English language teaching be based on specific real situations in which the language is to be used. In addition, students should be encouraged to adapt practical skills applicable in specific future professional setting. Medical English teaching represents constant challenge for teachers because they need to be flexible, open to new approaches and methods, make decisions and adapt themselves to constant changes. In addition, long-term learning is at the core of higher education, and being equal partners, both students and teachers should be aware that education is a two-way process.

Keywords: English language teaching; medical students; linguistic competence; professional setting; long-term learning

BASIC PRINCIPLES OF ENGLISH FOR SPECIFIC PURPOSES

In the last few decades English for specific purposes (ESP) has become one of the most prevalent forms of teaching English as a foreign language (EFL). The concept underlying the term *language for specific purposes* (LSP) is closely associated with the teaching of language for professional purposes where students need to learn how to use language in their future professional setting. In this context, specific linguistic features of the language used in different specialized fields are emphasized.

The basic principle of teaching languages for specific purposes has been created to meet specific academic and professional needs of learners, whereby each pedagogical situation and each group of learners is considered to be new and different from the previous one. The language courses for specific purposes are based on particular vocabulary set and unique language skills that will be indispensable to learners in a specialized field. There is no single approach for all pedagogical situations; there is no curriculum and set of activities that are applicable in all contexts. Therefore, it is of crucial importance in ESP teaching to determine the unique features of teaching and learning and apply them in the development of the curriculum, syllabus and assessment [1].

The goal of ESP teaching is to achieve successful professional and educational goals. Such form of teaching is based on a serious analysis of the needs of students and should be specially

designed. It includes a special selection of skills, topics, contents and functions. What is important in designing special programmes is to take into account the level of students' knowledge of the English language. Some students are beginners, some have an intermediate level of English, while others have a high level of English and strive to improve their knowledge. For this reason it is very important to begin the process of designing an adequate programme by performing adequate needs analysis. Such an analysis may provide two important pieces of information: the first relates to the current level of knowledge, motivation and previous learning methods; the latter relates to students' aspirations. Therefore, this information will be of great help to the teacher to adequately perform his role [2].

BASIC PRINCIPLES OF ENGLISH FOR MEDICAL PURPOSES

Nowadays English is *the lingua franca* of communication in the field of medical science. It is used as the primary means of communication in correspondence, at conferences, in the process of writing scientific articles, which leads to globalization and homogenization of science and scientific language. It is characterized by specific linguistic features and requires special study which can be realized only by using specifically designed programmes.

Designing a curriculum in which the student is in the centre of attention is the basis of

Correspondence to:

Nataša MILOSAVLJEVIĆ
Faculty of Medicine
University of Niš
81, Dr Zoran Djindjić Blvd.
18000 Niš
Serbia
natasaselmilosavljevic@gmail.com

foreign language teaching in most universities worldwide and is becoming more and more prevailing. It is based on the needs of students and reflects their motivation and success, consequently affecting the creation of adequate curriculum and syllabus [3].

English for medical purposes (EMP) belongs to the category of discipline-specific language learning. It should primarily focus on stable linguistic competence in English created by means of content and context based curriculum preparing students for active use of English upon graduation. In order to achieve this, it is very important that the English language teaching be based on specific target situations, that is, real situations in which the language is to be used. In addition, students should be encouraged to adapt practical skills applicable in specific future professional setting [4].

EMP is primarily taught from the perspective of the real situation. Teaching is focused on language in context and acquiring specific vocabulary, as well as on grammar and structures. The aim of such a course is to prepare students for further education or training in specific fields, where the knowledge of English would greatly facilitate this process. The goal is to instruct future medical professionals to actively communicate in English, primarily through specific situations that closely reflect the real world of professional setting. This approach combines the core medical courses and an English language course. Having already oriented their education towards a specific area, medical students are generally aware of the purpose of learning English and finding it complementary in that orientation. Moreover, the knowledge of the basic field of interest allows them to identify the real context of vocabulary and language structures presented to them [5].

THE IMPACT OF ENGLISH LANGUAGE KNOWLEDGE ON MEDICAL EDUCATION

Numerous studies have investigated the influence of the English language knowledge on students' medical education. The aim of an Australian study was to assess students' level of EFL prior to enrolling in Medical School. The results of the study indicated that students lacked the speaking skill and the authors of the study offered recommendations for improving oral communication skills thus enabling them to successfully communicate in professional setting [6].

In addition, the study carried out in Italian medical schools aimed at the assessment of English language knowledge of medical students. The authors of the study came to the conclusion that the goals of EMP teaching and minimum level of specific skills were not strictly defined. They pointed to the fact that there should be greater collaboration between universities and believed that it would contribute to higher teaching quality, and students' academic performance. Furthermore, they proposed taking mandatory Medical English language exam upon graduation [7].

According to Brown [8] from the United States of America, the ESP curriculum should be based on content leading to students' successful academic performance. It also

pointed the fact that traditional methods of language learning were out of context and lack adequate linguistic competence needed in everyday, real-world situations. Thus it was suggested that the content of all academic core courses should be incorporated into the curriculum of a foreign language. As a result, the solid base for acquisition of specialized communicative skills, both professional and academic, could be established [8].

Hull [3] believes that the priority of Medical English teaching should be adequate linguistic competence achieved by involving healthcare professionals in the process of creating the English language curriculum. At the centre of the approach he advocates is the content and context based programme preparing students for active language use after graduation.

According to O'Dowd [9] from Hamamatzu University, Medical English teaching should not only focus on vocabulary acquisition and text analysis but also on developing communication skills, problem solving, as well as decision making. ESP teachers should recognize the necessity of implementing and developing the so called *higher-order thinking skills* in their students so that they would be able to satisfy both professional and social requirements.

STRATEGIES FOR ACCELERATING LEARNING AND BOOSTING STUDENTS' PERFORMANCE

It is generally agreed that ESP teaching should be directed towards the needs of individuals learning the language. Regarding EMP teaching, basic needs of medical students include understanding of referent texts about the latest developments in the field of medical science, practicing and improving the speaking skill with an emphasis on acquiring medical terminology through role play, pair and team work, projects. In addition, practicing writing skill in terms of presenting case reports, case studies, and completing medical documentation is also beneficial. Furthermore, medical students should be able to follow relevant literature, write research papers, as well as participate in student exchanges and international student congresses. Such activities provide firm base allowing them to share their knowledge and experience with colleagues from abroad, as well as to publish scientific articles in prestigious international journals [10].

Small group work based on the skillfulness of each individual student is considered to be one of the important components of ESP teaching. The main activities that are to be used in class include *brainstorming*, the process designed to obtain the broadest range of ideas relating to a specific subject, *circle of knowledge*, the strategy providing a framework for developing effective group discussions, and *metaphorical expression*, where direct analogies and personal analogies are used to teach new concept or to deepen students' understanding of already known concepts. The objectives of teaching in small groups are encouraging students to think and discuss openly, participate actively, develop communication skills consisting of listening, explaining, asking and answering questions [9].

Advantages of small group work include enhanced identification of the needs of the students and development of responsibility and interpersonal skills. According to this approach, teachers need to demonstrate positive attitude, confidence and respect of their students, as well as express understanding of students' way of learning. Teachers cannot teach students the thinking process, but they can increase the awareness of their own inner potential through practice of the so-called sub-skills. These sub-skills include analytical thinking, problem solving, deduction, and use of imagination. In order for these skills to be improved, teachers are expected to adopt the attitudes and approaches of students in various activities in class [9].

The task of the ESP/EMP teacher is to provide balanced practicing of all these skills in the teaching process. This is a very demanding task if one considers the huge amount of necessary research and at the same time very limited duration of lectures and classes. It should be emphasized that designing an academic course is very dynamic process, primarily due to the development of both medical science and methods of teaching English. Since students usually transfer their knowledge of core courses to English classes, they can participate in planning the content

of the course, which enables introduction of autonomy in the English language course [11]. Some of the strategies include improving the constructive dialogue between teachers and students, collaboration with teachers of core courses, as well as continuous evaluation in order to create adequate curriculum specially designed for medical profession. The special relationship between teachers and students has great impact on teaching methodology and is student initiated. In addition, long-term learning is at the core of higher education, and being equal partners, both students and teachers should be aware that education is a two-way process [12].

CONCLUSION

Medical English teaching represents constant challenge for teachers because they need to be flexible, open to new approaches and methods, make decisions and adapt themselves to constant changes. In this context, they should take on the role of organizers whose job is to create the conditions and opportunities for learning, and provide assistance to students in the acquisition of knowledge and skills necessary to achieve their professional and academic goals.

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Учење енглеског језика за потребе медицине – предуслов за успешно образовање и стручно усавршавање

Наташа Милосављевић¹, Александар Вулетић², Љиљана Јовковић³

¹Универзитет у Нишу, Медицински факултет, Ниш, Србија;

²Универзитет Унион-Никола Тесла, Факултет за спорт, Београд, Србија;

³Универзитет Унион, Београд, Србија

КРАТАК САДРЖАЈ

Циљ овог рада је да представи специфичности наставе енглеског језика неопходне за успешно образовање и усавршавање студената медицинске струке. У савременом глобализованом свету енглески језик је постао основно средство комуникације у свим научним областима, укључујући и медицину. Опште је познато да би настава енглеског језика за потребе медицинске струке требало да се заснива на чврстој језичкој компетенцији, коју је најбоље постићи кроз наставни план базиран на садржају и контексту, чиме се студенти припремају за активно коришћење енглеског језика након дипломирања. Да би се ово постигло, веома је важно да настава енглеског језика буде заснована на одређеним реалним ситуацијама у којима ће се језик користити.

Поред тога, студенте би требало охрабрити да усвоје језичке вештине које су применљиве у будућем професионалном окружењу. Настава медицинског енглеског језика је стални изазов за наставнике због тога што је потребно да буду флексибилни, отворени за нове приступе и методе, доносе одлуке и прилагођавају се сталним променама. Поред тога, дугорочно учење је у основи високог образовања, а наставници и студенти би требало да су свесни да је образовање двосмеран процес с обзиром на то да су у том процесу једнаки партнери.

Кључне речи: настава енглеског језика; студенти медицинске струке; језичка компетенција; професионално окружење; дугорочно учење

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Professor Yukio Fukuyama (1928–2014)



It is with great sadness that we have received the news that Prof. Yukio Fukuyama passed away in his Tokyo home on 17th July 2014. He was a true pioneer and one of the greatest child neurologists in the world, who established international relations and cooperation, taught and mentored young doctors all around the world, including Serbia, where he had always been a dear guest and a great friend. He will be sorely missed.

Prof. Fukuyama was born in Miyazaki, Japan, in 1928. He completed his medical training at the Faculty of Medicine, University of Tokyo, 1948–1952; his internship was at the University of Tokyo Hospital, Tokyo, 1952–1953 and he finished a postgraduate course at the Faculty of Medicine, University of Tokyo, where he also obtained his PhD in 1957. He was promoted to Assistant Professor in 1960 and Associate Professor in 1964 and was appointed Chairman of the Department of Pediatrics in 1967, at the age of 39. In 1994 he received the title of Emeritus Professor at Tokyo Women's Medical University and became Director of Child Neurology Institute, Tokyo. Amongst other involvements, he pursued the international goal by serving as the 4th president of the International Child Neurology Association (ICNA) from 1982 to 1986. His major fields of interest were in child neurology, with emphasis on pediatric epileptology, pediatric neuro-muscular disorders, clinical neurogenetics, and international relations.

Prof. Fukuyama was the first to identify a peculiar type of congenital cerebromuscular dystrophy in 1960 which is now widely known as Fukuyama congenital muscular dystrophy. The causal gene was mapped at 9q31 and gene product called *fukutin* was cloned later (1998) by Toda et al. Furthermore, he made a major contribution in the field of convulsive disorders, especially in very early stages, delineating the concepts of various epileptic syndromes. Thus he described the clinical features and courses of 53 cases of benign infantile convulsions in 1963 and became the first advocator of their basic concepts almost 30 years before Vigeveno's findings. Fukuyama contributed pioneering work in the fields of febrile seizures, paroxysmal kinesigenic choreoathetosis, reflex epilepsies and so on. In his doctorate thesis regarding West syndrome he described a significant number of important findings – explained ictal and interictal symptomatology, demonstrated the etiologic heterogeneity of West syndrome, and indicated a particularly high occurrence of the brain stem involve-

ment, especially of the tegmentum. These studies clearly showed that subcortical mechanism may play a crucial role in the expression of this peculiar age-specific syndrome, which had a major impact on the investigation in this area.

Apart from the above stated, Prof. Fukuyama also made a significant contribution to other areas of child neurology by means of writing numerous papers (up to 1984 he had published 433 papers) and books. Naturally, he continued working prolifically even after retirement.

He was the first author or editor of the following books: *Child Neurology* (1982), *Epilepsies in Childhood* (2nd edition, 1984), *Child Neurology Atlas* (1986), *Neurological Examinations in Children* (1987), *EEG and Evoked Potentials in Children* (1990), *Modern Perspectives of Child Neurology* (1991), *Febrile Seizures – Modern Concept* (1991), *Fetal and Neonatal Neurology* (1992), *Crossroads of Child Neurology* (1995), *Congenital Muscular Dystrophies* (1997), *Epilepsy Bibliography – Books and Monographs, 1945–2003* (8th print edition, 2004), *Biology of Seizure Susceptibility in Developing Brain* (2008), *Epilepsy Bibliography – Books and Monographs, 1945–2009* (10th edition, online, 2009).

He was awarded honorary positions in many academic societies: Japanese Society of Child Neurology (Honorary Chairman of the Board of Trustees since 1993), Asian & Oceanian Child Neurology Association (Honorary President since 1992), and Infantile Seizure Society (Honorary Chairman since 2013). He was the honorary member of the following societies: American Academy of Neurology (since 1990), American Neurological Association (since 2006), Canadian Child Neurology Society (since 1985), Child Neurology Society (US) (since 1986), European Paediatric Neurology Society (since 2005), International Child Neurology Association (since 2010), numerous Japanese societies (for epilepsy, pediatrics, clinical neurophysiology, human genetics and teratology).

He was also an active member of the American Association for the Advancement of Science, American Epilepsy Society, American Society of Human Genetics, Société Européenne de Neurologie Pédiatrique (corresponding member since 2002), International Child Neurology Association (4th president, 1982–1986) and Infantile Seizure Society (president, 1998–2001, 2005–2012). In addition, he presided over the Joint Meeting of the 5th International Child Neurology Congress and the 3rd Asian & Oceanian Congress of Child Neurology (Tokyo, November 1990).

Due to his outstanding contributions to neurology, Prof. Fukuyama was repeatedly awarded by the most prominent associations in the world: Frank Ford Lectureship Award (International Child Neurology Association, 1992), Lifetime Achievement Award (World Federation of Neurology, 2002), The William G. Lennox Award (American Epilepsy Society, 2004), Ambassador for Epilepsy Award (ILAE/IBE, 2007), Achievement Grand Award (Japan Pediatric Society, 2008), Special Recognition Award (Japanese Society of Child Neurology, 2008), The Order of the Sacred Treasure, Gold Rays with Neck Ribbon (The Cabinet Office, Japanese Government, 2008), The First Japan Epilepsy Society Outstanding Achievement Award (2010).

Prof. Fukuyama was an enthusiastic visitor of Serbia, mostly before or after being a guest of another European association, where he was regularly invited. I had the pleasure and honor of meeting him in the early 1980s. As a member of International Association of Child Neurology, I used this opportunity to inform the Professor of the state of affairs in our child neurology. He was particularly interested in the development of child neurology in our country so that he could include our results in his publications in *Brain & Development*. Although the world-renowned authority, he was a very pleasant, simple man. We soon established a close connection and I humbly invited him and his wife Ayako to be my guests and to visit our clinic on that occasion. In 1985, I also suggested that he should come to the School of Medicine, University of Belgrade, as the invited Visiting Professor. The topic was naturally Fukuyama type congenital muscular dystrophy and the turnout at the lecture was impressive and the lecture room was completely full. A significant number of doctors interested in child neurology attended. The following day we organized a clinical seminar with the demonstration of rare or unresolved cases at our Clinic for Child Neurology and Psychiatry, Belgrade. The doctors in the audience were thrilled, and the Professor's visit represented a great event. However what really showed his partiality toward Serbia was the fact that he accepted our invitation to come here in 1995 (during the imposed economic sanctions against Serbia) when we organized a symposium on child neurology at the "Sava Centre" in Belgrade. His acceptance facilitated visits by other esteemed neurologists such as Marvin Fishman and Charles Swisher (USA) and others. The symposium was a great success and proved to be extremely morale-boosting for us during those hard times.

On his visits to Belgrade special clinical seminars were organized and the turnout was exceptional. After having demonstrated cases or rare diseases a discussion and questions section would commence. The Professor listened to everything carefully and did his best to express his opinion and suggestions. After the seminar he would stay at the Clinic and continue with tutorials. His opinion was sought in regard to various issues. It is difficult to state all the problems discussed, but we can certainly say that he was a really attentive listener who provided a lot of assistance and valuable advice. The Professor was regularly asked to answer numerous questions or provide second opinions and advice, and he continuously strove to provide assistance

and supply his explanation or suggestion. He always gave clear opinions about where a doctor could ideally continue further professional development and at all times was ready to recommend an institution. A doctor who was uncertain whether to accept the offer to be a regular consultant at the Maternity Ward of the Gynecology and Obstetrics Clinic received his explanation regarding the significance and possibilities of early diagnosis of disorders and diseases at that stage, which stimulated her to accept the offer, and has been a consultant for 20 years now, with numerous early diagnosed disorders and diseases in the course of her career.

Having learnt that there were six cases of familial MS diagnosed at the Clinic, he immediately advised us to submit that for the first ICNA Congress, and soon afterwards informed a famous German clinic dealing with MS, and asked them to contact us with the aim to establish further cooperation in the research, which quickly materialized. Talking to the President of the Union of Serbian and Montenegrin Leagues against Epilepsy, he promptly suggested that our country should be included in this presentation of epileptology publications. He also asked to be given a list of books by our authors in this field. That list was sent to him and as previously discussed he included it in electronic bibliographic epilepsy registry which was widely available to professional public as a project carried out by the International League against Epilepsy (ILAE). In this way he made a significant contribution to the promotion of our authors and our country. He also enabled our doctors who work on West syndrome to become foreign members of the Japanese society for this disorder free of charge.

The immensely impressive diversity of Prof. Fukuyama's achievements and contributions to medicine left a testament of his commitment to patients, their families, the university, his co-workers and advances in pediatric neurology worldwide. By leaving some medical dilemmas unresolved when lecturing, he was able to come up with thought-provoking questions and promote lively and informative discussions at conferences and scientific meetings. He had a mountain of literature in his home, which he managed with the help of his wife Ayako. His famous library was very impressive to many people who visited his home (I personally witnessed this during my visit of Tokyo in 1990). He and Ayako loved dogs, and they gave the name Fukutin (the designation of the Fukuyama type congenital muscular dystrophy gene) to one of their dogs. Not only was Prof. Fukuyama a life-long teacher and mentor, he was also a leader in the field of Pediatric Neurology throughout the world.

In this text I have used the information provided by Professor Makiko Osawa, MD, PhD (President, Japan Epilepsy Society; Chairperson, Infantile Seizure Society; Professor Emeritus, Chairperson of Alumni Association, Department of Pediatrics, Tokyo Women's Medical University) in a farewell article about Prof. Yukio Fukuyama, details from a retrospective article which the Professor himself wrote about his own achievements (*Brain & Development* 26, 2004), as well as the data by the author of the text regarding 30 years of friendship with the Professor.

Prof. Dr. Dušan Vranješević

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Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ 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 може одложити објављивање рада или чак одбити његово публиковање. Стога се ауторима и потенцијалним сарадницима саветује да пажљиво прочитају ово упутство пре него што приступе припреми рукописа за штампу у „Српском архиву за целокупно лекарство“.

ОПШТА УПУТСТВА. Оригинални и стручни радови се у целини достављају на енглеском језику са сажетком на енглеском и српском. 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. ⁹⁹Tc, IL-6, O₂, B₁₂, CD8).

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.

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања која се односе на једну здравствену интервенцију или на више њих, а ради испитивања утицаја на здравствени исход. Регистарски број истраживања треба да се наведе у последњем реду Кратког садржаја.

ЕТИЧКА САГЛАСНОСТ. Рукописи о хуманим медицинским истраживањима или историјама болести пацијената 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 локалним 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 рада, наравно, уз писани пристанак.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установе 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.

КРАТАК САДРЖАЈ. Уз оригинални рад, саопштење, преглед литературе, приказ болесника, рад из историје медицине, рад за рубрику „Језик медицине“ и рад за праксу, на другој по реду страници документа треба приложити кратак садржај рада обима 100–250 речи. За оригинале радова кратак садржај 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. За приказе болесника кратак садржај треба да има следеће делове: Увод, Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Кратког садржаја 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 установе у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити кратак садржај (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан кратак садржај 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 (нпр. рад из историје медицине, језика медицине и др.), потребно је превести називе прилога (табела, графикана, 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 обавезно треба да има следеће поднаслове: Увод, Циљ рада, Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (референце у којима је био први аутор или коаутор рада) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ болесника чине: Увод, Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од седам аутора.

Прилоге (табеле, графиконе, слике итд.) сместити на крај рукописа, а у самом телу текста назначити место које се односи на дати прилог. Крајња позиција прилога пре штампања рада зависиће од прелома текста.

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 кратком садржају, али ако су неопходне, сваку скраћеницу поново 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. $12,5 \pm 3,8$). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм – *kg*, литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса ($^{\circ}\text{C}$), 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 РУКОПИСА. Целокупни рукопис рада – који чине насловна страна, кратак садржај, 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, саопштење, рад из историје медицине и преглед литературе до 5.000 речи, а за 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.

Провера броја речи у документу може се извршити у програму *Word* кроз подмени *Tools-Word Count* или *File-Properties-Statistics*.

ТАБЕЛЕ. 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. Сlike се означавају арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолюције 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 као *Grayscale* (или у боји) у резолуцији 300 dpi и снимити их у оригиналној величини.

Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Сlike се у свесци могу штампати у боји, али додатне трошкове штампе сноси аутори.

ГРАФИКОНИ. 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 графикана.

Уколико је рукопис на српском језику, приложити називе графикана и легенду на оба језика.

СХЕМЕ (ЦРТЕЖИ). Схеме цртати 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 индексан 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. 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 публикације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не треба да буде старија од пет година. Избежавати коришћење апстракта као референце, а апстракте старије од две године не цитирати. 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, не-објављеног 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.srp-arh.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 И ПРЕТПЛАТА. Да би рад био објављен у часопису Српски архив за целокупно лекарство, сви аутори морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва), док први аутор мора бити и претплатник на часопис, за годину у којој се рад предаје Уредништву. 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, као доказ о уплатама. Аутори из иностранства нису дужни да буду чланови Српског лекарског друштва, нити претплатници на часопис за текућу годину. Додатне информације о чланарини и претплати могу се добити на телефоне 011/3245-149 и 011/3346-963, односно имејлом ([srparhiv@bvcom.net](mailto:srp-arh@bvcom.net)) и на интернет-страници часописа (<http://www.srp-arh.rs>).

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Србија

ТЕЛЕФОН: 011/3245-149

E-MAIL: [srparhiv@bvcom.net](mailto:srp-arh@bvcom.net)

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11000 Beograd
Serbia

PHONE: +381 11 3245 149

E-MAIL: srparhiv@bvcom.net

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1872- (Београд : Службени гласник). - 29 cm

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