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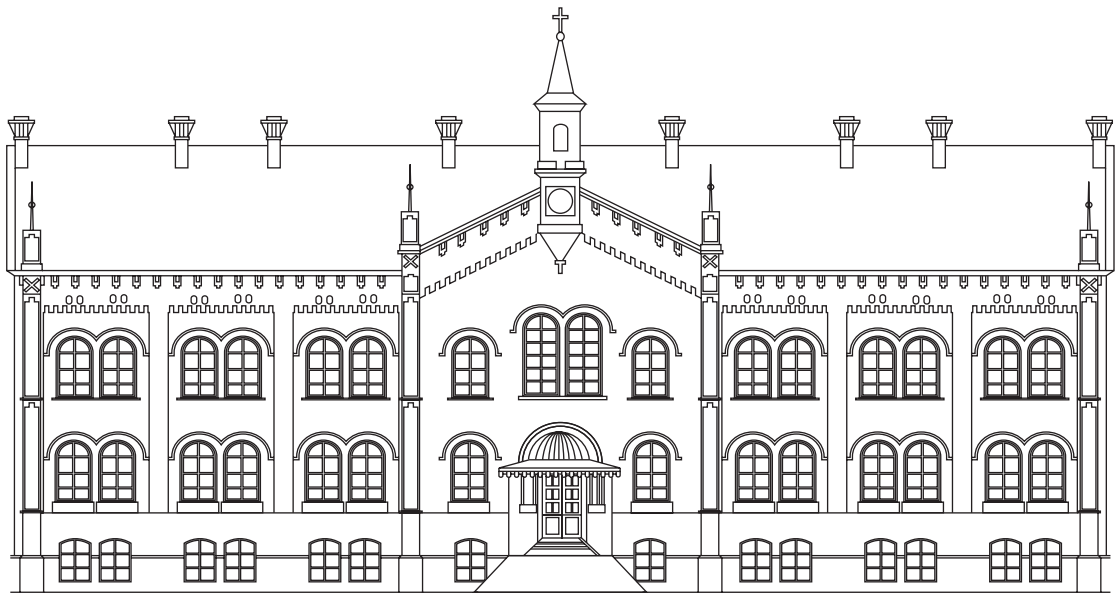

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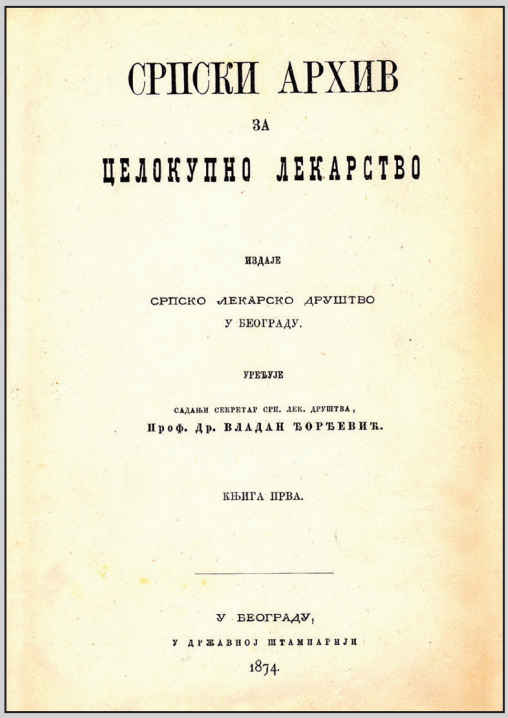

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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1874.

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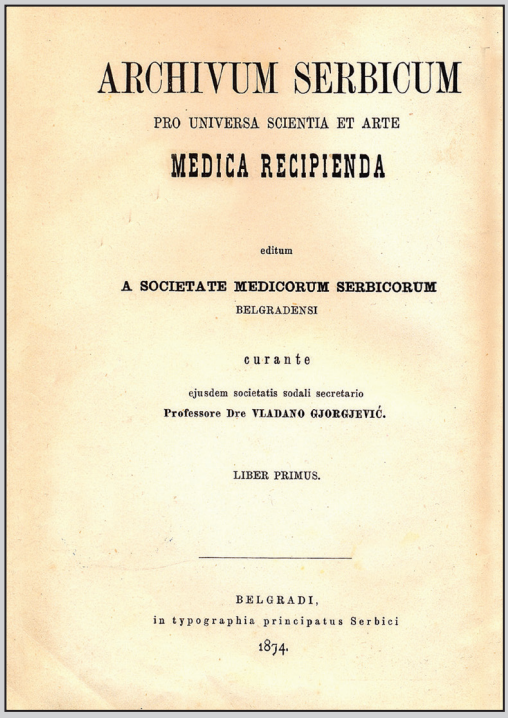

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1874.

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Краљице Наталије 1, 11000 Београд, Србија
Телефон: +381 (0)11 409 27 76
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Kraljice Natalije 1, 11000 Belgrade, Serbia
Phone: +381 (0)11 409 27 76
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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Upper airway sagittal dimensions in children with hyper-divergent class II/1 malocclusion

Stojan Ivić[1,2], Predrag Vučinić[1,2], Đorđe Petrović[1,2], Nataša Puškar[1], Danijela Radumilo[1,3], Ana Tadić[1,2], Stefan Kulić[4]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Dentistry Clinic of Vojvodina, Novi Sad, Serbia;
[3]Community Health Centre of Novi Sad, Novi Sad, Serbia;
[4]Clinical Centre of Vojvodina, Clinic for Ear, Nose and Throat, Novi Sad, Serbia

SUMMARY

Introduction/Objective Upper air dimensions are associated with morphological facial features. The objective of study is to test the hypothesis that the sagittal size of the upper respiratory pathways in children aged 8–12 years with hyperdivergent class II/1 malocclusion is smaller compared to the general population of the same age. This may be associated with an increased risk of developing obstructive sleep apnea syndrome in these individuals later in life.

Methods Using profile teleradiograms of 31 children average age being 9.02 ± 1 years with hyperdivergent class II/1 malocclusion, sagittal dimensions of the pharyngeal respiratory pathway at the levels of naso-, oro-, and hypopharynx were measured. These dimensions were compared with measurements from 35 children with an average age of 8.97 ± 0.6 years with other types of malocclusions.

Results Statistically significant smaller sagittal dimensions of the upper respiratory pathways were found in children with hyperdivergent class II/1 malocclusion compared to the general population of the same age at all three measured levels.

Conclusion The hypothesis was confirmed that in children with hyperdivergent class II/1 malocclusion, the dimensions of the pharyngeal respiratory pathways are significantly smaller compared to the general population of the same age. The width of the oropharynx contributes most to this difference, followed by the width of the nasopharynx, with the least contribution from the hypopharynx.

Keywords: upper airway size; pharynx; distal occlusion; malocclusion

INTRODUCTION

The pharynx represents the intersection of the aerodigestive tracts. Diverse morphological types and their corresponding growth patterns can be identified within the pharynx, similar to the face. The posterior cranial base occupies a diagonal position within the cranium and constitutes the posterior wall of the bony nasopharynx. Consequently, its growth will influence the pharynx's horizontal and vertical dimensions [1]. Individuals with dolichocephalic growth patterns are commonly associated with an inclination to develop a more acute cranial base angle and posterior position of the tongue, thus reducing sagittal dimensions of the upper respiratory tracts [2, 3].

In nasal-breathing participants the sagittal breadth of the nasopharynx appears to be largely independent of anterior dentofacial dimensions [1]. Higher correlations found in mouth breathers suggest that limited patency of the upper airways has physiological implications linked to changes in dentofacial morphology [4, 5].

Factors contributing to the narrowing of the upper airways are believed to be both reduced pharyngeal muscle tone and unfavorable anatomical relations in the pharynx and surrounding structures, as airway constrictions [6].

El and Palomo's [7] three-dimensional analysis of pharyngeal airways finds a significantly narrower oropharyngeal airway in class II participants compared to those in classes I and III. A more constricted nasopharyngeal passage is observed in class II participants relative to those in class I [7, 8]. All authors concur that pharyngeal dimensions are diminished in class II skeletal patterns, irrespective of the patient's position during examination (upright or supine) and regardless of the imaging technique employed [6, 9, 10].

In examination of the regions of the upper respiratory tract susceptible to collapse based on craniofacial morphology, Alhammadi et al. [11] build on established views that retrognathism, micrognathism, and elongated face, along with a shortened length and angle of the anterior cranial base, increased ANB angle, influence pharyngeal airway constrictions. Nevertheless, they contend that constriction sites depend on specific craniofacial morphology parameters or their combinations, and that multi-site collapses are not uncommon [11, 12].

In Caucasian individuals with narrowed upper respiratory tracts, a retrognathic face is observed. The maxilla and an underdeveloped mandible are retrusive, anterior facial height is increased, occlusal and mandibular plane angles

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Correspondence to:
Stojan IVIĆ
Dentistry Clinic of Vojvodina
Hajduk Veljkova 12
21000 Novi Sad, Serbia
stojan.ivic@mf.uns.ac.rs

are augmented, upper and lower molars are hypererupted, incisors proclined, and incisal overbite reduced [13, 14].

Vučinić et al. [15], analyzing morphological features of the upper jaw in mouth-breathing children, identified peculiarities that also exist in individuals with manifesting obstructive sleep apnea syndrome (OSA), such as narrow maxilla, underdeveloped apical bases, and a reduced inclination of the upper jaw plane to the anterior cranial base. OSA represents a broad spectrum of disorders primarily manifested by snoring, witnessed apnea, and daytime sleepiness [16]. This underscores the need for early detection of factors that can contribute to morphofunctional narrowing of the airways to potentially influence them during growth [17]. Tangugsorn and colleagues recommend lateral cephalogram analysis in assessing areas of pharyngeal airway constriction [18].

This study aims to ascertain the dimensions of orofacial structures in the upper respiratory tract region during growth and development, and potential deviations which, in later life stages, could contribute to respiratory disturbances and OSA. Furthermore, it aims to assess opportunities for early intervention using functional orthodontics.

Research hypothesis: the upper respiratory tracts are significantly narrower in at least one sagittal dimension in children with hyperdivergent skeletal class II/1 compared to children with normative skeletal relationships or the remainder of the population.

METHODS

The study was conducted at the Department of Orthodontics, Clinic of Dentistry of Vojvodina, involving 66 children. They were divided into two primary groups based on facial morphology. The research entailed examining and comparing the sagittal dimensions of the upper respiratory pathways in children with a distal position of the lower jaw and children without this malocclusion from the general population.

Selection of participants

The subjects were children aged 8-12 years with a retrognathic face of class II and protrusion and proclination of the upper incisors (class II/1). This was routinely determined for each patient through the analysis of lateral cephalometric radiographs as part of the diagnostic methods employed to determine the type and severity of stomatognathic development disorders.

Only those participants whose parents gave informed consent were included in the study. Given that a narrow upper respiratory pathway is associated with an increased vertical dimension of the lower part of the face, an additional criterion for patient selection was vertical growth of orofacial structures (Björk polygon greater than 396° and Jaraback index less than 62%). From the patient database of the Department of Orthodontics, 31 patients with characteristics corresponding to the research topic were identified, who were either undergoing or about to undergo treatment with functional devices.

The experimental group consisted of 16 girls (51.61%) and 15 boys (48.39%), with an average age of 9.02 ± 1 years (range 8–11.3 years).

The control group, consisted of 35 children with an average age similar to the experimental sample (8.97 ± 0.6 years). They were randomly selected among patients of the Department of Orthodontics at the Clinic of Dentistry of Vojvodina to closely represent the cranio-facio-cervical morphological characteristics of the general population of the corresponding age and growth stage.

Patients with facial morphology matching the experimental group could not be part of the control group.

Exclusion criteria for both groups included reduced airway patency due to hypertrophic adenoid vegetation, cleft lip and palate, hypo- and hyperdontia, severe congenital syndromes like Pierre Robin, Crouzon, Apert, and Treacher Collins syndromes.

Methodology

The study utilized cephalometric radiographic examination of patient profile images, employing standard analyses developed for orthodontic diagnostics, supplemented by measurements of upper respiratory pathways.

Lateral cephalometric radiographs were taken at the Radiology Department of the Clinic of Dentistry of Vojvodina using the standard technique under uniform conditions on the Orthophos XG5 device (Sirona Dental GmbH, Wals bei Salzburg, Austria). Analyses of the obtained cephalometric radiographs were performed using the OnyxCeph software (Image Instruments GmbH, Chemnitz, Germany). Data were entered into tables adapted to the research topic using MS Office Excel 2007 software (Microsoft Corporation, Redmond, WA, USA).

In addition to standard cephalometric parameters – angles of maxillary prognathism (SNA), mandibular prognathism (SNB), and the angle of skeletal jaw relationship in the sagittal dimension (ANB) – the dimensions of the upper respiratory pathways were determined.

Sagittal diameter dimensions of the upper respiratory pathways were determined by measuring the following distances:

1. Distance between the posterior nasal spine and the intersection point of the line from the posterior nasal spine to the basion with the posterior pharyngeal wall, representing the width of the nasopharynx.
2. Distance between the uvula's tip and the nearest point on the pharyngeal posterior wall, representing the width of the oropharynx.
3. Distance between the vallecula and the nearest point on the pharyngeal posterior wall, representing the width of the hypopharynx (adopted from Tangugsorn et al. [17]) (Figure 1).

Reliability

Duplicate measurements were undertaken for all variables. These measurements were taken two weeks apart by the same examiner on a random sample of 20 cephalograms.

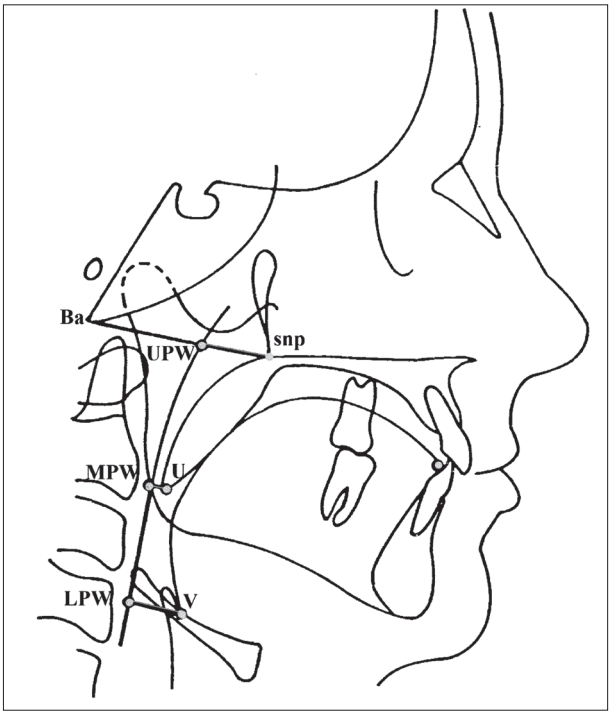

Figure 1. Sagittal diameter dimensions of the upper respiratory pathways

Systematic errors between the two measurements were assessed using a paired t-test for $p < 0.05$. No significant differences were identified for any hard or soft tissue variables between the two datasets. The error variance was calculated according to Dahlberg's formula.

Statistical methods

This paper presents descriptive parameters: mean, standard deviation, minimum and maximum of all values, coefficient of variation, confidence interval, and the Kolmogorov–Smirnov test value.

Multivariate procedures MANOVA and discriminant analysis were used. Univariate procedures applied included ANOVA and the t-test.

The application of procedures that provide a contribution measure gives a new dimension to this research. By calculating the discrimination coefficient, we can identify the features that determine the specificity of the subsamples and the features that need to be excluded from further processing, i.e., a reduction of the observed space is performed. The representation of subsample homogeneity estimates, the distance between them, and cluster analysis aim to study the observed phenomenon thoroughly.

Data are presented in tabular form.

Research was approved by the Ethics Committee of the Dental Clinic of Vojvodina (01-107/8-2012).

RESULTS

Basic characteristics of the sample (experimental and control group)

The experimental group included 31 participants [16 girls (51.61%) and 15 boys (48.39%)], with an average age of 9.02 ± 1 years (range 8–11.3 years).

In the experimental group, no sex-based differences were observed in age ($p = 0.1381$), nor in the parameters used as inclusion criteria: Björk's polygon ($p = 0.1771$), the lower face index ($p = 0.3423$), and the size of the ANB angle ($p = 0.3790$). Thus, participant data were processed regardless of the sex.

The control group consisted of 35 patients [21 girls (60%) and 14 boys (40%)], with an average age of 8.97 ± 0.6 years (range 8–9.9 years).

In the control group, no sex-based differences were observed in age ($p = 0.2148$) or in the parameters used as inclusion criteria: Björk's polygon ($p = 0.7408$), the lower face index ($p = 0.9132$), and the size of the ANB angle ($p = 0.9426$). Thus, participant data were processed regardless of the sex.

Basic parameters of the upper respiratory pathway dimensions relative to the groups

Central and dispersion parameters for the dimensions of the upper airways of the experimental group of 31 participants and the control group of 35 participants are shown in Table 1 and Table 2, respectively.

Table 1. Central and dispersion parameters for the dimensions of the upper airways, the experimental group of 31 participants.

Airway segments	Mean value	Standard deviation	Minimal value	Maximal value	Coefficient of variation	Confidence interval		p
Nasopharynx	16.26	3.72	6	23	22.9	14.89	17.62	0.998
Oropharynx	8.19	2.3	3	13	28.08	7.35	9.04	0.884
Hypopharynx	12.03	3.01	6	18	24.98	10.93	13.14	0.976

Table 2. Central and dispersion parameters for the dimensions of the upper airways, the control group of 35 participants

Airway segments	Mean value	Standard deviation	Minimal value	Maximal value	Coefficient of variation	Confidence interval		p
Nasopharynx	19.27	4.18	8.0	29	21.7	17.83	20.71	0.996
Oropharynx	10.33	2.03	6.5	15	19.68	9.63	11.03	0.933
Hypopharynx	13.97	3.27	6.0	24	23.43	12.85	15.1	0.195

Differences between the experimental and control groups concerning the dimensions of the upper respiratory pathways

The test of the assertion if there is a significant difference between participant groups concerning the dimensions of the upper respiratory pathways was done. Group differences are shown in Table 3, whereas individual differences are shown in Table 4.

Table 3. Significance of differences between participant groups concerning the dimensions of the upper airways (group differences)

Analysis	n	F	p
MANOVA	3	9.085	0.000
Discriminative	3	9.085	0.000

F-value – the significance of the difference in variance between the means of two samples

Table 4. Significance of differences between groups concerning the dimensions of the upper airways (individual differences)

Airway segments	F	p	Discriminant coefficient
Nasopharynx	9.453	0.003	0.176
Oropharynx	16.023	0.000	0.180
Hypopharynx	6.226	0.015	0.017

F-value – the significance of the difference in variance between the means of samples

The discrimination coefficient suggests that the most significant contribution to discrimination between participant groups concerning the dimensions of the upper respiratory pathways is, namely, the difference in the following:

1. oropharynx width (0.180),
2. nasopharynx width (0.176), and
3. hypopharynx width (0.017).

Characteristics and homogeneity of participant groups concerning the dimensions of the upper respiratory pathways

Based on previous considerations and sample analysis of 66 participants, in accordance with the applied methodology, the next step in the research is determining the characteristics and homogeneity of each participant group and the distance between them.

The fact that $p = 0.000$ of the discriminant analysis indicates there's a clear boundary between participant groups, i.e., it's possible to determine the characteristics of each group concerning the dimensions of the upper airways. Characteristics and homogeneity of participant groups concerning the dimensions of the upper airways are shown in Table 5, whereas distance (Mahalanobis) between participant groups concerning the dimensions of the upper respiratory pathways is shown in Table 6.

Table 5. Characteristics and homogeneity of groups concerning the dimensions of the upper airways

Characteristics	Experimental (31)	Control (35)	Contribution (%)
Oropharynx	smaller	larger	48.257
Nasopharynx	smaller	larger	47.185
Hypopharynx	smaller	larger	4.558
SSHE	22/31	28/35	
homogeneity (%)	70.97	80	

SSHE – subsample homogeneity estimates (number of participants with group characteristics compared to total number of group participants)

Table 6. Distance (Mahalanobis) between the groups concerning the dimensions of the upper airways

Group	Experimental	Control
Experimental	0	1.31
Control	1.31	0

DISCUSSION

The average values of the sagittal diameter of the nasopharynx in the experimental group (16.26 ± 3.72 mm) and the control group (19.27 ± 4.18 mm), as well as the oropharynx (8.19 ± 2.3 mm and 10.33 ± 2.03 mm, respectively) and hypopharynx (12.03 ± 3.01 mm and 13.97 ± 3.27 mm, respectively), were statistically compared.

The results of this study, based on the values of $p = 0.000$ (MANOVA analysis) and $p = 0.000$ (discriminant analysis), indicate a difference and a clearly defined boundary between the groups of participants.

The statistically determined $p < 0.05$ shows that there is a significant difference between the groups of participants in the width of the nasopharynx (0.003), the width of the oropharynx (0.000), and the width of the hypopharynx (0.015). This is consistent with previous studies by de Oliveira et al. [14] on a sample of adolescents, as well as Alhammadi et al. [11] on an adult sample.

Based on the previous results, it can be said that the pharyngeal airways are statistically significantly narrower at all three measured levels.

The values of the upper respiratory tract widths were statistically significantly different, and there is a clearly defined boundary between the experimental and control groups if the diameters of the upper respiratory pathways are viewed as a group of statistical features, i.e., collectively approaching the diameters of the nasopharynx, oropharynx, and hypopharynx.

The largest individual contribution to the difference was found at the level of the oropharynx, followed by the nasopharynx, and then the hypopharynx.

When viewed separately, the values of the widths of the nasopharynx, oropharynx, and hypopharynx also show a statistically significant difference and a clear boundary between the experimental and the control group. With the presence of a boundary, it is possible to determine the characteristics of each group concerning the dimensions of the upper respiratory pathways at the initial measurement. The characteristic of each subsample group is most defined by the width of the oropharynx because its contribution to the characteristics is 48.26%, followed by the width of the nasopharynx (47.18%), and the width of the hypopharynx (4.56%).

Based on the measured values and their statistical processing, it can be said for the experimental group that the

dimensions of the upper respiratory pathways at all three levels are smaller, while for the control group they are larger at all three levels. The finding that the pharyngeal respiratory pathways in retrognathic participants of class II malocclusion are narrower compared to the respiratory pathways in the general population is consistent with previous research referenced in this paper.

Similar findings were also observed by El and Palomo [7] when measuring the volume of the upper respiratory pathways in skeletal classes I, II, and III. There was a significant difference in the size of the respiratory pathways in class II, while in class III these differences were not statistically significant [7].

In contrast, Lowe et al. [13] did not find significant differences between people with obstructive sleep apnea, during sleep, concerning the malocclusion class.

Pirilä-Parkkinen et al. [19], in a sample of children with an average age of 7.3 ± 1.43 years, found that the greatest narrowness is at the level of the nasopharynx. It should be noted that Taylor et al. [20] found that at this age, there has not yet been an involution of adenoid tissue that can affect the apparent narrowing in that part.

For correct dimensions of the upper airways of children with yet uncompleted growth, there is scant data, further complicated by a large number of etiological factors that can contribute to the occurrence of the narrowing, as well as different places where the narrowing can occur. In their research on the connection between facial morphology growth and chronological age in preschool children with obstructive sleep apnea, Kawashima et al. [21] indicate that adenoid tissue begins to regress between the ages of eight and 10.

Oh et al. [22], in a sample of 60 healthy children, found that children with class II have a more posterior orientation and a smaller volume of pharyngeal airways than healthy children with malocclusions of classes I and III. The key factor in determining the shape of the pharyngeal respiratory pathway is its inclination and head position.

The homogeneity of the experimental group is 70.97%, and that of the control group is 80%.

The characteristics of the experimental group are held by 22 out of 31 participants, with a homogeneity of 70.97% (expressed), and the characteristics of the control group are present in 28 out of 35 participants, with a homogeneity of 80% (expressed).

In addition to the inclination and size of the pharynx, adjacent structures are related to the reduction of available space for the accommodation of soft tissue structures of the orofacial system, especially the tongue, due to the distal position of the mandible and preventing its action on the proper development of the jaws [14]. Vučinić et al. [15] found that narrowed pharyngeal dimensions are associated with the maxillary narrowness, underdevelopment of the apical bases, and a reduced basal inclination to the anterior cranial base.

By comparing the homogeneity of the experimental and control groups, it can be said that these dimensions in the general population are more homogeneous than in the population with hyperdivergent malocclusion class II/1. This again suggests the possibility that a combination of various morphofunctional craniofacial features affects the narrowness of the upper respiratory pathways at least at one level, which is consistent with literary findings, both in studies of the adult and child populations [4, 11, 19, 20, 21].

Another indicator of similarity or differences is obtained by calculating the Mahalanobis distance between the groups of participants. Distances of different spaces can be compared. The distances from the table indicate that the distance between the groups of participants of the experimental group and the control group is greater, and the existing difference is expressed.

In this study, special attention is paid to the impact of inter-jaw relations in the sagittal and vertical dimension (posterior relationship of the lower jaw structures with hyperdivergence of the jaw bases) in children who have not finished growing and can still be therapeutically affected. This, in turn, affects the sagittal narrowness of the upper respiratory pathways. To even consider the connection of these phenomena, it is necessary to define a normal finding.

For skeletal inter-jaw relations, there is an accepted classification of anteroposterior positions (skeletal classes I, II, and III), which is determined by analyzing a standard cephalogram.

Skeletal class II is a disorder of craniofacial development that is treated in children. Correction of morphological abnormalities in children is corrected by properly directing growth, and normalizing the functions of the orofacial muscles, which is achieved by using functional orthodontic devices [23].

Good indicators of the position, both skeletal and soft tissue cranio-cervico-facial structures, are the standard lateral cephalogram, which has been routinely used for many years in the diagnosis of dentofacial anomalies. Researchers like Johal et al. [24], Bitar et al. [25], who examined the reliability of this technique in examining the dimensions of the upper airways, agree that it is competitive as it reveals the most characteristics with the least costs, while Pirilä-Parkkinen et al. [26] believe that the precision of measurement with a cephalogram is highest in the region of the nasopharynx and retropalatinal area. However, cone beam computed tomography is being used in computing the functional space of the tongue and surrounding structures. Thus, Shi et al. [27] found that adults with different OSA types have similar anatomical balance and shape of their upper airway in the supine position. Slowik et al. [28] note that OSA has significant implications for cardiovascular health, mental illness, quality of life, and driving safety.

Given the measured dimensions in the experimental group, both with collectively smaller mean sizes and with significantly smaller mean values for the nasopharynx, oropharynx, and hypopharynx, the hypothesis of this study has been confirmed.

In the adults with developed OSA syndrome, Degraeve et al. [29] found that mandibular advancement devices may be effective for OSA regardless of whether or not the obstruction site is in the velopharynx or oropharynx.

This cross-sectional study is part of a larger longitudinal study in which the effect of orthodontic treatment

of hyperdivergent malocclusion of skeletal class II on the dimensions of the upper respiratory pathways was observed.

CONCLUSION

The study showed that the experimental group's upper airways were statistically significantly smaller mean values for the nasopharynx, oropharynx, and hypopharynx, thus confirming the hypothesis of this study.

The measured sagittal dimensions of the upper respiratory pathways in children with hyperdivergent malocclusion class II/1 are significantly smaller than in the general population, at all three observed levels – at the level of the nasopharynx, the level of the oropharynx, and the level of the hypopharynx.

The findings indicate that the upper respiratory pathways in children with hyperdivergent class II/1 are narrower than in the rest of the population, with the greatest difference contributed by narrowness at the level of the oropharynx, less at the level of the nasopharynx, with the smallest contribution at the level of the hypopharynx.

The greater homogeneity of the general population by the value of the widths of the upper respiratory pathways compared to the experimental group indicates the existence of a wide range of possibilities for the adverse effects of morphofunctional disorders of the craniofacial system on the dimensions of the pharyngeal part of the airways.

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Сагиталне димензије горњих дисајних путева код деце са хипердивергентном малоклузијом класе II/1

Стојан Ивић[1,2], Предраг Вучинић[1,2], Ђорђе Петровић[1,2], Наташа Пушкар[1], Данијела Радумило[1,3], Ана Тадић[1,2], Стефан Кулић[4]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Клиника за стоматологију Војводине, Нови Сад, Србија;
[3]Дом здравља „Нови Сад", Нови Сад, Србија;
[4]Универзитетски клинички центар Војводине, Клиника за ухо, грло и нос, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Димензије фарингеалних дисајних путева се доводе у везу са морфологијом лица. Циљ рада је да испита хипотезу да је сагитална величина горњих дисајних путева код деце старости осам до 12 година са малоклузијом хипердивергентне класе II/1 мања у поређењу са општом популацијом истог узраста.

Методе На профилним телерадиограмима 31 детета старости 9,02 ± 1 година са хипердивергентном малоклузијом класе II/1 измерене су сагиталне димензије фарингеалног дисајног пута на нивоима назофаринкса, орофаринкса и хипофаринкса и упоређене са димензијама измереним код 35 деце старости 8,97 ± 0,6 година са другим облицима малоклузија.

Резултати Пронађене су статистички значајно уже сагиталне димензије горњих дисајних путева код деце са малоклузијом хипердивергентне класе II/1 у поређењу са општом популацијом истог узраста, на сва три мерена нивоа.

Закључак Потврђена је хипотеза да су код деце са малоклузијом хипердивергентне класе II/1 димензије фарингеалних дисајних путева значајно мање у поређењу са општом популацијом истог узраста. Највећи допринос разлици даје ширина орофаринкса, следи ширина назофаринкса, са најмањим доприносом хипофаринкса.

Кључне речи: величина горњих дисајних путева; фаринкс; дистална оклузија; малоклузија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effect of darbepoetin alfa on the glomerulus of new-born mice with intrauterine growth restriction

Milica Milojković, Vesna Stojanović, Nenad Barišić

University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

SUMMARY

Introduction/Objective Intrauterine growth restriction is a condition in which a fetus is not able to achieve its genetic potential for growth. It has been linked with diseases of adulthood, such as hypertension, insulin-independent diabetes mellitus and dyslipidemia.
The objective of the study was to investigate whether the application of darbepoetin alfa during pregnancy and in first week of life affects the number or size of the kidney glomerulus of mice with intrauterine growth restriction.

Methods We used animal model of intrauterine growth restriction. Darbepoetin alfa was administered to the pups on the first and the seventh day of life (doses of 1 μg/kg, 4 μg/kg, and 10 μg/kg). Two of seven groups represented the offspring of the mothers who received darbepoetin alfa during pregnancy. Four weeks after birth, kidney samples were taken, and morphological and stereological analysis of the glomeruli was performed.

Results Administration of darbepoetin alfa to newborn mice with intrauterine growth restriction led to faster weight gain in the first seven days of life. Mice born with this restriction had reduced glomerular surface and reduced cortical thickness. The application of darbepoetin alfa immediately after the birth and on the seventh day of life (4 μg/kg and 10 μg/kg, respectively) led to glomerular hypertrophy and increased thickness of the renal cortex. The application of darbepoetin alfa had no effect on the number of glomeruli.

Conclusion The administration of darbepoetin alfa to mice with intrauterine growth restriction significantly increases the surface area of the kidney glomeruli and cortical thickness.

Keywords: intrauterine growth restriction; darbepoetin alfa; kidney; glomerulus

INTRODUCTION

Intrauterine growth restriction (IUGR) is a condition characterized by failure of a fetus to achieve its genetic potential for growth [1]. IUGR is defined as a fetus, and then also as a newborn, whose birth weight is below the 10th percentile for its gestational age [1]. IUGR occurs when delivery of gases and nutrients to the fetus is not sufficient for adequate intrauterine development [1]. It is known that IUGR is a significant risk factor for type 2 diabetes, obesity, hypertension, dyslipidemia, and insulin resistance (metabolic syndrome) later in life, which ultimately leads to the premature development of cardiovascular disease [1, 2, 3]. The hypothesis "The developmental origins of adult disease" made by Barker et al. [4] states that adverse effects in early development, especially during intrauterine life, can lead to permanent physiological and metabolic changes, resulting in an increased risk of morbidity in adulthood. Brenner et al. [5] hypothesized that the fundamental kidney abnormality leading to elevated blood pressure is reduced filtration surface area. This could be due to a decrease in the number of kidney nephrons and/or a decrease in renal filtration surface per nephron, which is characteristic for kidneys of persons born with IUGR. When the renal functional reserve due to the reduced number of nephrons is greatly decreased, glomeruli will reach the limit of physiological compensatory hypertrophy and pathological mechanisms will be initiated, which can lead to hypertension. Prolonged hyperfiltration of hypertrophic glomeruli can ultimately lead to glomerular sclerosis and possibly loss of glomeruli [6].

Erythropoietin (EPO) is a 165-amino acid peptide. Studies indicate the benefit of EPO therapy in case of brain injury, retinal disease, gastrointestinal and myocardial ischemia. A positive effect of EPO on the kidneys has been demonstrated in various studies. It had been shown that EPO antagonizes endothelial cell apoptosis, increases the sensitivity of endothelial cells, and the activity of endothelial nitric oxide synthase, stimulates mitogenesis and angiogenesis of endothelial cells, increases renal blood flow, and has an anti-inflammatory effect [7, 8].

The aim of this study is to investigate whether the application of darbepoetin alfa (DA) during pregnancy and in the first week of life, affects the number or size of the kidney glomerulus of mice with IUGR.

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Correspondence to:
Milica MILOJKOVIĆ
University of Novi Sad
Faculty of Medicine
Hajduk Veljkova 3
21000 Novi Sad, Serbia
milica.milojkovic@mf.uns.ac.rs

METHODS

In the experiment, female mice and male and female pups of the Naval Medical Research Institute (NMRI) breed were used. The animals had been grown in standard laboratory conditions with food and water *ad libitum*. The experimental IUGR model was used. Female mice were mated for 24 hours with fully mature males. The day of conception was determined by serial observation of vaginal swabs by light microscopy. When the presence of spermatozoids was confirmed, it was recorded as a zero day of gestation. Gestation in NMRI mice breeds lasts 19–21 days. From the 15th to the 21st day of gestation, dexamethasone (diluted in 0.9% NaCl) was administered to pregnant females. Dexamethasone was applied subcutaneously, at a dose of 100 μg/kg per day (0.2 ml). After spontaneous delivery, the pups were weighed and left on natural nutrition. Only the newborn mice who were born from pregnancies with 6–10 fetuses (newborns) were included in the experiment. Criteria for exclusion from the study were as follows: mice born in pregnancies with less than six fetuses and mice born from pregnancies with more than 10 fetuses. According to the random selection method, the pups were classified into one of the following groups:

Group 1 (control group 1) – 10 mice with IUGR that received 0.1 ml 0.9% NaCl intraperitoneally;

Group 2 – eight mice with IUGR that received DA intraperitoneally (10 μg/kg) on the first and the seventh day of life;

Group 3 – eight mice with IUGR, that received DA intraperitoneally (4 μg/kg) on the first and the seventh day of life;

Group 4 – eight mice with IUGR, that received DA intraperitoneally (1 μg/kg) on the first and the seventh day of life;

Group 5 – eight mice with IUGR whose mothers received DA subcutaneously (10 μg/kg) on the 15th postconceptual day;

Group 6 – eight mice with IUGR whose mothers received DA subcutaneously (10 μg/kg) on 15th post conceptual day, and who received DA intraperitoneally (10 μg/kg) on the first day of life;

Group 7 (control group 2) – 10 mice who were born and raised without any prior intervention during the fetal period and after the birth.

Four weeks after birth, the experimental mice were sacrificed by decapitation. The kidneys were removed from the sacrificed animals and tissue samples were fixed in the solution of 10% buffered formalin, dehydrated, and molded into paraffin. After rehydration, the samples were cut at 5-μm-thick slices and stained with the hematoxylin-eosin. Histological examination (morphological and stereological analyses of glomeruli, intermedial and juxtamedullary zone of the renal cortex) was performed using light microscope at 400 × and 100 × magnification. Morphometric and stereological analyses included measurement of the surface of the glomerulus and the thickness of the renal cortex, as well as determining the numerical density of the glomerular profiles using commercial image analysis software ImageJ (National Institutes of Health, Bethesda, MD, USA). The area of 821–1109 glomerular profiles per group was measured. Every fifth section was a slide mounted. Only well-preserved structures that do not cut the "forbidden" lines of the test system were considered.

The numerical density (*Nv*) was determined by observing 15 microscopic fields per animal [9]. It was calculated using Weibel and Gomez formula [10]:

$$Nv = \frac{\kappa}{\beta}\left[\frac{Na^3}{Vv}\right]^{1/2}$$

$$Vv = \frac{Pp}{Pt}$$

where: Na – number of glomerular profiles in a test-area; Vv – volume density of glomerules; κ – the size distribution coefficient assuming 10% coefficient of variation (1.01); β – the shape coefficient for sphere (1.38); Pp – number of points that hit the glomerules; Pt – total number of points.

The thickness of the cortex was measured as the length of the line positioned at a right angle between the parallel tangent lines on the surface of the kidney and the boundary of the cortex and the core of the kidney on 41–83 fields.

Statistical data processing was performed using StatSoft, Inc. software packages (2007) STATISTICA (data analysis software system), version 8.0, and Glantz, Stanton A. Primer of Biostatistics, 5th Edition, McGraw-Hill, 2002.

The experiment was approved by the Ethics Committee on Animal Care and Use of the University of Novi Sad (Ethics Committee approval number I-2013-05) and were performed and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

RESULTS

It was found that birth weight of newborn mice of the Group 7 (mice that gave birth spontaneously without previous intervention on the mother) was statistically significantly higher compared to the Group 1 (IUGR) (1.675 g *vs.* 1.253 g; $p < 0.05$), Group 2 (IUGR) (1.675 g *vs.* 1.2 g; $p < 0.05$), Group 3 (IUGR) (1.675 g *vs.* 1.089 g; $p < 0.05$), Group 4 (IUGR) (1.675 g *vs.* 1.156 g; $p < 0.05$) and Group 5 (IUGR and DA on the 15th day of pregnancy) (1.675 g *vs.* 1.35 g; $p < 0.05$). Statistical significance was not established by comparing the birth weight of newborn mice between Group 6 (IUGR and DA on the 15th day of pregnancy) and Group 7 (mice that gave birth spontaneously without previous intervention on the mother) (1.75 g *vs.* 1.675 g; $p > 0.05$).

The birth weight of newborn mice in Group 6 (IUGR and DA on the 15th day of pregnancy) is statistically significantly higher compared to Group 1 (IUGR) (1.75 g *vs.* 1.253 g; $p < 0.05$), Group 2 (IUGR) (1.75 g *vs.* 1.2 g; $p < 0.05$), Group 3 (IUGR) (1.75 g *vs.* 1.35 g; $p < 0.05$), Group 4 (IUGR) (1.75 g *vs.* 1.156 g; $p < 0.05$) and Group 5 (IUGR and DA on the 15th day of life) (1.75 g *vs.* 1.35 g; $p < 0.05$).

Table 1. Comparison of body weights of pups between all experimental groups on the seventh day of life

Groups	Body weight (g)	p
7 *vs.* 1	3.825 *vs.* 2.32	0.000
2 *vs.* 1	3.625 *vs.* 2.32	0.000
7 *vs.* 4	3.825 *vs.* 2.733	0.000
5 *vs.* 1	3.45 *vs.* 2.32	0.000
6 *vs.* 1	3.438 *vs.* 2.32	0.000
3 *vs.* 1	3.18 *vs.* 2.32	0.000
2 *vs.* 4	3.625 *vs.* 2.733	0.000
7 *vs.* 3	3.825 *vs.* 3.18	0.000
5 *vs.* 4	3.45 *vs.* 2.733	0.000
6 *vs.* 4	3.438 *vs.* 2.733	0.000
4 *vs.* 1	2.733 *vs.* 2.32	0.005
3 *vs.* 4	3.18 *vs.* 2.733	0.005
2 *vs.* 3	3.625 *vs.* 3.18	0.007
7 *vs.* 6	3.825 *vs.* 3.438	0.010
7 *vs.* 5	3.825 *vs.* 3.45	0.013
5 *vs.* 3	3.45 *vs.* 3.18	0.097
6 *vs.* 3	3.438 *vs.* 3.18	0.114
7 *vs.* 2	3.825 *vs.* 3.625	0.177
2 *vs.* 6	3.625 *vs.* 3.438	0.272
2 *vs.* 5	3.625 *vs.* 3.45	0.305
5 *vs.* 6	3.45 *vs.* 3.438	0.941

Table 2. Comparison of glomerulus area sizes between the groups

Groups	Glomerulus area size (μm^2)	p
2 *vs.* 4	2471 *vs.* 1954	0.000
7 *vs.* 4	2425 *vs.* 1954	0.000
6 *vs.* 4	2289 *vs.* 1954	0.000
5 *vs.* 4	2319 *vs.* 1954	0.000
1 *vs.* 4	2247 *vs.* 1954	0.000
2 *vs.* 3	2471 *vs.* 2201	0.000
3 *vs.* 4	2201 *vs.* 1954	0.000
2 *vs.* 1	2471 *vs.* 2247	0.000
7 *vs.* 3	2425 *vs.* 2201	0.000
2 *vs.* 6	2471 *vs.* 2289	0.000
7 *vs.* 1	2425 *vs.* 2247	0.000
7 *vs.* 6	2425 *vs.* 2289	0.000
2 *vs.* 5	2471 *vs.* 2319	0.001
5 *vs.* 3	2319 *vs.* 2201	0.013
6 *vs.* 3	2289 *vs.* 2201	0.015
7 *vs.* 5	2425 *vs.* 2319	0.025
5 *vs.* 1	2319 *vs.* 2247	0.128
2 *vs.* 7	2471 *vs.* 2425	0.224
1 *vs.* 3	2247 *vs.* 2201	0.225
6 *vs.* 1	2289 *vs.* 2247	0.244
5 *vs.* 6	2319 *vs.* 2289	0.504

Table 3. Comparison of the numerical density of glomeruli between all experimental groups

Groups	Numerical density of glomeruli (mm^{-2})	p
4 *vs.* 3	2.705 *vs.* 2.381	0.061
1 *vs.* 3	2.712 *vs.* 2.381	0.064
4 *vs.* 2	2.705 *vs.* 2.449	0.166
1 *vs.* 2	2.712 *vs.* 2.449	0.167
6 *vs.* 3	2.594 *vs.* 2.381	0.237
5 *vs.* 3	2.6 *vs.* 2.381	0.267
1 *vs.* 7	2.712 *vs.* 2.534	0.306
4 *vs.* 7	2.705 *vs.* 2.534	0.308
7 *vs.* 3	2.534 *vs.* 2.381	0.388
6 *vs.* 2	2.594 *vs.* 2.449	0.448
5 *vs.* 2	2.6 *vs.* 2.449	0.467
1 *vs.* 6	2.712 *vs.* 2.594	0.504
4 *vs.* 6	2.705 *vs.* 2.594	0.515
1 *vs.* 5	2.712 *vs.* 2.6	0.565
4 *vs.* 5	2.705 *vs.* 2.6	0.576
7 *vs.* 2	2.534 *vs.* 2.449	0.652
2 *vs.* 3	2.449 *vs.* 2.381	0.725
5 *vs.* 7	2.6 *vs.* 2.534	0.732
6 *vs.* 7	2.594 *vs.* 2.534	0.732
1 *vs.* 4	2.712 *vs.* 2.705	0.967
5 *vs.* 6	2.6 *vs.* 2.594	0.975

The average birth weight of newborn mice with IUGR (Group 1) was 1.253 g, which is 25.2% less in comparison with spontaneously delivered pups without IUGR (Group 7), whose average birth weight was 1.675 g.

The average weights of mice on the seventh day of life are shown in Table 1.

The average body weight of the pups in Group 7 (mice that gave birth spontaneously without prior intervention on the mother and without intervention on them after birth) on the seventh day of life was statistically significantly higher compared to the pups in other groups ($p < 0.05$), except for the pups in Group 2.

Mice pups in Group 2 (IUGR and DA 10 μg/kg) had a statistically significantly higher body weight on the seventh day of life compared to the pups in Group 1 (IUGR) (3.625 g *vs.* 2.32 g; $p < 0.05$), Group 3 (IUGR and DA 4 μg/kg) (3.625 g *vs.* 3.18 g; $p < 0.05$) and Group 4 (IUGR and DA 1 μg/kg) (3.625 g *vs.* 2.733 g; $p < 0.05$).

The average body weight of mice pups on the seventh day of life in the Group 1 (IUGR) was statistically significantly lower compared to all other groups – $p < 0.05$.

Average values of glomerulus area size of mice are shown in Table 2.

By comparing the surface area of the kidney glomeruli, it was determined that there is no statistically significant difference between Group 2 (IUGR and DA 10 μg/kg) and Group 7 – mice that gave birth spontaneously without previous intervention on the mother (2471 μm^2 *vs.* 2425 μm^2; $p > 0.05$).

Mice pups of Group 5 (IUGR and DA on the 15th day of pregnancy) had a statistically significantly higher kidney glomerular surface compared to mice in Group 3 (IUGR and DA 4 μg/kg) (2319 μm^2 *vs.* 2201 μm^2; $p < 0.05$) and Group 4 (IUGR and DA 1 μg/kg) (2319 μm^2 *vs.* 1954 μm^2; $p < 0.05$).

The glomerular surface of the mice in Group 6 (IUGR and DA on the 15th day of pregnancy and after birth 10 μg/kg) was statistically significantly higher compared to mice in Group 3 (IUGR and DA 4 μg/kg) (2289 μm^2 *vs.* 2201 μm^2; $p < 0.05$) and Group 4 (IUGR and DA 1 μg/kg) (2289 μm^2 *vs.* 1954 μm^2; $p < 0.05$).

It was found that the glomerular surface of mice in Group 3 (IUGR and DA 4 μg/kg) is statistically significantly higher than the glomerular surface of mice in Group 4 (IUGR and DA 1 μg/kg), (2201 μm^2 *vs.* 1954 μm^2; $p < 0.05$).

It was found that there is no statistically significant difference in the numerical density of glomeruli between all experimental groups, $p > 0.05$ (Table 3).

The obtained results indicate that the thickness of the kidney cortex was statistically significantly higher in mice from the Group 2 (IUGR and DA 10 μg/kg) compared to all other groups, $p < 0.05$ (Table 4).

DISCUSSION

Unfavorable environmental conditions during prenatal or early postnatal period may increase the susceptibility to chronic diseases in later life. In 1988, Brenner et al. [5] pointed out that a small number of nephrons, acquired *in utero*, could be a common factor in the population prone to hypertension and kidney disease. A kidney with fewer nephrons, and therefore a low filtration surface area, has a reduced ability to excrete sodium, which leads to hypervolemia, which contributes to the development of hypertension. Animal experiments and epidemiological

Table 4. Comparison of the thickness of the renal cortex between all experimental groups

Group	1 862.42 µm	2 1086.3 µm	3 988.21 µm	4 931.54 µm	5 922.62 µm	6 924.49 µm	7 958.73 µm
1		0.000000	0.000417	0.748833	1.000000	0.596013	0.027405
2	0.000000		0.039828	0.000237	0.000143	0.000004	0.001626
3	0.000417	0.039828		1.000000	0.997114	0.398601	1.000000
4	0.748833	0.000237	1.000000		1.000000	1.000000	1.000000
5	1.000000	0.000143	0.997114	1.000000		1.000000	1.000000
6	0.596013	0.000004	0.398601	1.000000	1.000000		1.000000
7	0.027405	0.001626	1.000000	1.000000	1.000000	1.000000	

data support the "nephron number" hypothesis [11]. It is known that IUGR in humans can lead to a reduction in the number of nephrons. In newborns with IUGR, the kidney is of altered shape (thin, sausage-like) resulting from a smaller number of concentric layers [11, 12]. Brenner et al. [5] were the first to highlight the potential consequences of a reduced number of nephrons at birth on kidney disease in later life. They also pointed out that nephropenia, as a result of IUGR, could create a disproportion between a body size and excretory capacity leading to vasodilatation, glomerular hypertension, and progressive loss of nephrons due to glomerulosclerosis [13].

Numerous studies have shown a significant reduction in the number of nephrons as a result of IUGR [11]. There are numerous studies, both in humans and experimental animal models, showing the link between low birth weight (LBW) and long-term increase in blood pressure and the threat of developing kidney disease. The risk of kidney dysfunction later in life increases in infants with IUGR who were born prematurely [14]. A systematic review of 80 studies conducted in children, adolescents, and adults between 1996 and 2000, which examined the relationship between blood pressure and birth weight, showed a decrease in blood pressure with increased birth weight (a decrease in blood pressure of about 2 mmHg for each kilogram of birth weight) [15]. A relative increase in blood pressure of 2 mmHg is associated with a 6% higher risk of coronary artery disease and a 15% higher risk of stroke [16]. There is an inverse relationship between gestational age at birth and blood pressure levels. The study of Cooper et al. [17] have shown a decrease in systolic blood pressure by 0.53 mmHg with each additional week of gestational age at birth. White et al. [18] published a meta-analysis of 31 relevant studies and concluded that people born with LBW are at 70% higher risk of developing kidney disease.

Numerous experiments were conducted where IUGR was induced in an animal model and its effect on the kidneys was examined [19]. In our experiment, IUGR animal model was induced by glucocorticoids. Pups with IUGR had statistically significantly lower birth weight (25.2%) than those in the control group. LBW in combination with a sudden increase in body weight ("catch-up phenomenon") after the birth increases the risk of hypertension and cardiovascular disease in later life. Several studies on animal models investigated effects of "catch-up phenomenon" and demonstrated that increased oxidative stress, shortening of the telomeres and accelerated kidney, heart, and aortic aging occurring in those animals is associated with premature death. Also, there are data suggesting that accelerated aging and increased oxidative stress are features of people born with LBW [11]. In our experiment, newborn mice were measured on the seventh day of life. Newborn mice from the control groups had statistically significantly higher body weight compared to all other (IUGR) groups, except when compared to those IUGR mice who were treated with a high dose of DA (10 µg/kg). Also, mice from the latter group had larger glomeruli. Further studies, as well as long-term follow-up, are needed to prove the benefits or adverse effects of this rapid increase in body weight.

EPO is a hematopoietic growth factor whose production is regulated by hypoxia. It is a pleiotropic cytokine that exhibits various biological effects in many non-hematopoietic tissues. EPO exhibits its effects in different organs such as brain, heart, lung, kidneys and liver. A growing body of evidence indicates that EPO reduces glomerular and tubular injury and dysfunction caused by severe ischemia and reperfusion (I/R), both in experimental animals and in neonates. Mechanisms through which EPO exhibits its protective effect against renal I/R injury are an increase in renal blood pressure and an increase in diuresis due to an increase in cortical perfusion and intraglomerular pressure. EPO also protects proximal tubular epithelial cells from cellular damage and death by its anti-apoptotic, antioxidant, anti-inflammatory, and pro-angiogenic effects [7].

An experimental study conducted by Spandou et al. [20] has proven the protective effect of EPO in the sense of its inhibiting the apoptotic death of proximal and distal tubule cells. Administration of EPO at the time of renal I/R injury significantly reduces the damage of cell function and protects against cell death [21].

DA is a long-acting hyperglycolized EPO derivative, with a half-life of about three times longer than recombinant human erythropoietin (rHuEPO) and with similar effects as rHuEPO. It has been proven that DA has an anti-apoptotic effect in both toxic and hypoxic kidney damage [22].

Brenner et al. [5] have hypothesized that the fundamental kidney abnormality that leads to elevated blood pressure is reduced filtration surface. This can be caused by a decrease in the number of kidney nephrons, as well as by a decrease of renal filtration area per nephron [5]. In our experiment, morphological and stereological analysis showed that treatment with DA significantly increases glomerular area, but does not influence the number of glomeruli. Experimental animals that received DA (1 µg/kg or 4 µg/kg on the first and the seventh day of life) had statistically

significant increase of the glomerular area compared to IUGR offspring's who were not treated. However, animals that were spontaneously delivered, without any previous intervention, had a greater glomerular area compared to all three IUGR groups (Group 1 (IUGR); Group 3 (IUGR and DA 4 μg/kg); and Group 4 (IUGR and DA 1 μg/kg). Also, those experimental animals with IUGR that received DA in a high dose of 10 μg/kg on the first and the seventh day of life showed an increase in glomerular area to the extent that there was no statistically significant difference when compared with the group of healthy offsprings.

The numerical density of glomeruli in experimental animals was also investigated. Although there are differences between the observed groups, they are not statistically significant.

In the world literature, there are no clinical or experimental studies examining the effect of EPO on kidney glomeruli in IUGR. This research was conceived as a pilot study which would be the basis for further investigations on this topic.

CONCLUSION

Based on the results of our experiment, we can assume that higher doses of EPO administered immediately after birth to mice with IUGR have a positive effect on the growth of glomeruli.

Further studies are needed to determine the benefit of this effect later in the lives of IUGR-born children, as well as on comorbidity, with an emphasis on blood pressure.

Conflict of interest: None declared.

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Утицај дарбепоетина алфа на гломеруле новорођених мишева са интраутериним застојем раста

Милица Милојковић, Весна Стојановић, Ненад Баришић

Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
Институт за здравствену заштиту деце и омладине Војводине, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Интраутерини застој раста је стање у којем фетус није у стању да оствари свој генетски потенцијал за раст. Повезан је са болестима одраслог доба, као што су хипертензија, од инсулина независни дијабетес мелитус и дислипидемија.

Циљ рада је да испита да ли примена дарбепоетина алфа током трудноће и у првој недељи живота утиче на број или величину гломерула бубрега мишева са интраутериним застојем раста.

Методе Користили смо животињски модел интраутериног застоја раста. Дарбепоетин алфа је апликован младунцима мишева првог и седмог дана живота у различитим дозама (дозе 1, 4 и 10 *μg/kg*). Две од седам група су обухватале младунце женки које су примале дарбепоетин алфа и током трудноће. Четири недеље после порођаја узети су узорци бубрега и урађена је морфолошка и стереолошка анализа гломерула.

Резултати Примена дарбепоетина алфа код новорођених мишева са интраутериним застојем раста довела је до бржег повећања телесне тежине у првих седам дана живота. Мишеви рођени са овим стањем имали су смањену површину гломерула и смањену дебљину кортекса. Примена дарбепоетина алфа након рођења и седмог дана живота (4 и 10 *μg/kg*) довела је до хипертрофије гломерула и повећања дебљине кортекса бубрега. Примена дарбепоетина алфа није утицала на број гломерула.

Закључак Примена дарбепоетина алфа код новорођених мишева са интраутериним застојем раста значајно повећава површину гломерула и дебљину кортекса бубрега.

Кључне речи: интраутерини застој раста; дарбепоетин алфа; бубрег; гломерул

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Frequency and risk factors of venous thromboembolic complications in patients with active pulmonary tuberculosis and HIV/TB co-infection (tuberculosis and thrombosis)

Dmitriy Plotkin[1,2], Artur Titomer[1], Mikhail Reshetnikov[1,3], Umedzhon Gafarov[1], Sergey Sterlikov[4], Mikhail Sinitsyn[1,2,3], Elena Bogorodskaya[1,3]

[1]Moscow Research and Clinical Center for Tuberculosis Control, Tuberculosis Surgical Department, Scientific Department, Moscow, Russian Federation;
[2]Pirogov Russian National Research Medical University, Faculty of Medicine, Department of General Surgery, Phthisiology Department, Moscow, Russian Federation;
[3]Russian Medical Academy of Continuous Professional Education, Phthisiology Department, Moscow, Russian Federation;
[4]Russian Research Institute of Health, Department of Epidemiology, Moscow, Russian Federation

SUMMARY

Introduction/Objective Venous thromboembolism complications (VTEC) include: deep vein thrombosis, superficial vein thrombosis and pulmonary embolism. The aim was to assess the prevalence of VTEC in patients with active pulmonary tuberculosis and to reveal the main factors influencing the development of VTEC in this cohort of patients.

Methods A retrospective study of electronic health records of patients with active pulmonary tuberculosis was carried out. We included all patients with confirmed active pulmonary tuberculosis and VTEC during the period from January 01, 2020 to December 31, 2022.

Results An overall 214 cases of VTEC were identified. The most significant risk factors for the development of thrombotic complications in tuberculosis patients were human immunodeficiency viruses (HIV) / tuberculosis co-infection (relative risk 3.8; 95% CI: 2.7–4.5) and the duration of the disease (according to the criterion of formation of fibrosis foci and/or cavities) (relative risk 9.1; 95% CI: 4.7–17.6). The overall prevalence of VTEC in the tuberculosis hospital exceeded the literature data for non-tuberculosis clinics by 3.3 times.

Conclusion Tuberculosis is a major reversible risk factor for the venous thromboembolic events, probably due to impaired coagulation mechanisms, venous stasis and endothelial dysfunction. HIV infection in this context is the second major reversible factor in the development of VTEC.

Keywords: venous thrombosis; tuberculosis; thromboembolism; HIV; hypercoagulation

INTRODUCTION

Tuberculosis (TB) and venous thromboembolic complications (VTEC) are two global problems of modern healthcare that receive significant attention both in the scientific literature and in practical guidelines for clinical use. Against the background of a decrease in the basic incidence rate of TB in the Russian Federation to 33.5 cases per 100,000 people per year (2021), there is a growing trend in the number of severe and complicated cases of the disease [1, 2]. This situation is largely explained by the development of active TB in presence of human immunodeficiency viruses (HIV) infection, comorbid diseases (cardiovascular, autoimmune, oncological, etc.), widespread drug resistance of the pathogen, and other procoagulant conditions that increase the threat of VTEC [3, 4].

Currently, many risk factors for VTEC are known, which, under certain conditions, trigger the mechanisms of thrombosis described in the classic work of the Austrian pathologist Rudolf Virchow (1856) in the form of a pathogenetic triad: venous stasis, hypercoagulation and injury to the vascular wall [4]. Studies in recent years have shown that TB, as a chronic infection, is a procoagulant pathological condition due to the synergistic action of several factors affecting the coagulation equilibrium mechanisms [5].

Thus, the research aimed at studying the prevalence of VTEC among hospital patients with active TB and identifying the main risk factors for thrombosis is of significant practical importance and will further allow to elaborate effective methods for preventing VTEC in this cohort of patients. Moscow is the best place to conduct such a study in the Russian Federation, as a multinational region with a permanent population of more than 13 million people, which has a sufficiently developed system for recording TB patients.

The purpose was to assess the prevalence of VTEC in patients with active pulmonary TB admitted in specialized hospitals in Moscow

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Correspondence to:
Umedzhon GAFAROV
Stromynka 10
107014 Moscow
Russian Federation
umed_78@mail.ru

and to identify the main factors influencing the development of VTEC in this cohort of patients.

METHODS

To solve the set tasks, data from the Moscow Tuberculosis Epidemiological Monitoring System (TEMS) were used. The TEMS is an electronic register (based on the Barclay eo software), which contains basic information about patients with diagnosed active TB of any localization, confirmed by cultural, bacterioscopic and/or molecular genetic methods. The registers are replenished monthly on the basis of transmitted information from all TB hospitals in Moscow, regardless of the patient's residence (patients from other regions of the Russian Federation, foreign citizens, persons of no fixed abode) [6]. To assess the prevalence of VTEC, a retrospective study of medical records (electronic medical records of an inpatient) was performed by viewing them, in the course of which all cases of VTEC were detected in all TB hospitals in Moscow: Moscow Scientific and Practical Center for Tuberculosis Control, Zakhariin Tuberculosis Clinical Hospital No. 3, Rabukhin Tuberculosis Hospital for the period 2020–2022.

The study was approved by the Local Ethics Committee of Moscow Research and Clinical Center for Tuberculosis Control (Protocol No. 11/23, February 6, 2023). All enrolled patients provided written informed consent to the utilization of their anonymized clinical data.

The criteria for inclusion in the analysis were:

1. Age: 18 years and older;
2. Active pulmonary TB confirmed by X-ray, cultural, bacterioscopic and/or molecular genetic method;
3. Deep vein thrombosis (DVT) of the lower limbs, superficial vein thrombosis (SVT) of the lower limbs and pulmonary embolism (PE) confirmed by instrumental methods of examination (ultrasound angiography, computed tomography of the chest organs with intravenous contrast).

Exclusion criteria: patients with iatrogenic thrombosis after the insertion of central and peripheral venous catheters; patients receiving treatment for COVID 19 (and within 30 days after recovery); patients with inactive TB who had previously received therapy or admitted for surgical treatment; patients taking combined oral contraceptives.

The following information about patients was available for obtaining from medical records: sex, age, protocol for the diagnosis of "active TB," HIV status, protocol for ultrasound angiography of the lower limbs veins, protocol for computed tomography of the chest with intravenous contrast, the fact of taking oral contraceptives and anticoagulants during the month before the detection of active pulmonary TB.

To assess the duration of the disease, we used the fact of the presence of massive fibrosis and/or caverns in the lungs, which form no earlier than 16–24 months from the onset of the disease [7]. This is because the moment of onset of a chronic infectious disease in most cases cannot be determined due to the paucisymptomatic course at the beginning.

As part of the statistical analysis, extensive indicators and their 95% confidence intervals (95% CI) based on the Wilson's method, relative risk (RR) and its 95% CI (confidence interval) were calculated. For numerical features whose distribution differed from the normal one according to the Shapiro–Wilk's test, we determined the median (Me) and its 95% CI. To test hypotheses about the effect of age, sex, the presence of HIV infection, as well as the duration of the disease (by the criterion of formation of fibrosis and cavities in the lungs) on the risk of developing VTEC, patients were stratified according to appropriate signs, followed by an analysis of statistically significant differences in the frequency of VTEC in strata. Statistical processing of information was carried out using the program support R (R Project, Vienna, Austria), version 3.6.2 (2019-12-12) – "Dark and Stormy Night" with the connection of the DescTools library. The value of $p < 0.05$ was considered statistically significant.

RESULTS

According to the data of the Moscow Regional Register (based on Barclay SW), 4,609 patients with detected active pulmonary TB were admitted in TB hospitals in Moscow. The majority of these patients were men (2987; 64.8%), women made up about a third of all patients (1622; 35.2%). Reviewing the medical records of these patients we found 214 cases of VTEC that met the search criteria. Men prevailed among patients with VTEC (n =145; 67.8%), women accounted for 32.2% (n = 69). None of them received anticoagulant therapy. Among 214 patients, only four had anamnestic indications of cancer. In the last 30 days before the diagnosis of VTEC there was no mention of surgical operations.

Based on statistical calculations, the rate of VTEC among 4,609 TB patients was: 4.6% (95% CI: 4.1–5.3), where DVT was detected in 3.5% (95% CI: 3–4.1), SVT – in 1.5% (95% CI: 1.2–1.9), and PE in 0.6% (95% CI: 0.4–0.8) (Figure 1). A combination of DVT and SVT was registered in 16 patients (7.5%; 95% CI: 4.7–11.8), all cases of PE (n = 26) were combined with DVT (12.2%; 95% CI: 8.4–17.2), and in two cases a combination of PE and SVT was noted (0.9%; 95% CI: 0.3–3.3).

In the course of the study, it was necessary to discover the factors influencing the rate of VTEC, among which we considered age, sex, the presence of HIV infection with any immune status and the disease duration to be the most significant. Analyzing the influence of the patient's age and sex on the frequency of venous thromboembolic events, no statistically significant differences were obtained, they occurred with approximately the same frequency in both men and women (Table1). Relative risk (RR) of VTEC development in admitted men and women with TB was 1.14 (95% CI: 0.86–1.51); (p = 0.2).

According to multivariate analysis, statistically independent predictors of VTEC were: HIV infection and the duration of the disease (after development of fibrous and/or cavernous processes in the lungs). Thus, according to

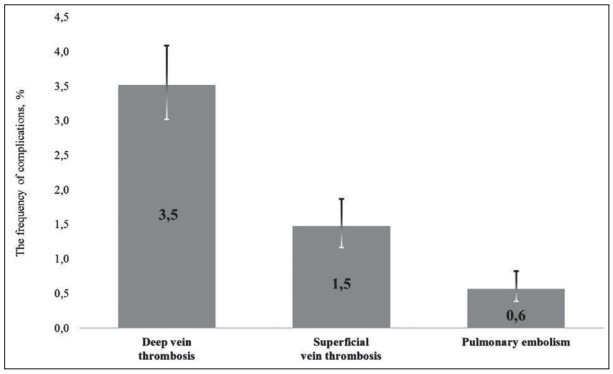

Figure 1. The frequency of certain forms of venous thromboembolism complications in patients with active pulmonary. tuberculosis, admitted in tuberculosis hospitals in Moscow (2020–2022); horizontal segments show the boundaries of 95% CI

Table 1. The frequency of venous thromboembolism complications in admitted patients with active pulmonary tuberculosis depending on sex

Parameter	n	sample	%	95% CI	p
Venous thromboembolism complications frequency	214	4609	4.6	4.1–5.3	
Men	145	2987	4.9	4.1–5.7	0.2
Women	69	1622	4.3	3.4–5.3	
Young (< 45 years old) men	89	1757	5.1	4.1–6.2	0.7
Young (< 45 years old) women	47	1004	4.7	3.5–6.2	
Over 45 years old men	56	1230	4.6	3.5–5.9	0.4
Over 45 years old women	22	618	3.6	2.4–5.3	

our data, the incidence of VTEC was 3.8 times higher in patients with HIV/TB co-infection than in patients with active TB without HIV infection. There was a statistically significant age difference in patients with HIV/TB (Me = 40; 95% CI: 38–41 years) and TB (Me = 43; 95% CI: 41–47 years) (p = 0.0003; Mann–Whitney test). For this reason, we stratified patients by age groups with a 10-year-interval and determined the frequency of VTEC in strata (Table 2).

Table 2. The frequency of venous thromboembolism complications (VTEC) in different age groups among admitted patients with human immunodeficiency viruses (HIV) co-infection/tuberculosis and HIV-negative tuberculosis patients

HIV status, age	The number of VTEC, abs.	Group size, abs.	% (95% CI)	p
HIV+, total	98	904	10.8 (9–13)	< 0.001
HIV-, total	116	3705	3.1 (2.6–3.7)	
HIV+, 18–24	0	10	0 (0–27.8)	< 0.001
HIV-, 18–24	1	455	0.2 (0–1.2)	
HIV+, 25–34	18	191	9.4 (6.2–14.4)	< 0.001
HIV-, 25–34	19	819	2.3 (1.5–3.6)	
HIV+, 35–44	58	458	12.7 (9.9–16)	< 0.001
HIV-, 35–44	40	828	4.8 (3.6–6.5)	
HIV+, 45–54	18	196	9.2 (5.9–14)	0.01
HIV-, 45–54	28	657	4.3 (3–6.1)	
HIV+, 55–64	4	45	8.9 (3.5–20.7)	0.08
HIV-, 55–64	14	493	2.8 (1.7–4.7)	
HIV+, 65 and older	0	4	0 (0–49)	0.07
HIV -, 65 and older	14	453	3.1 (1.8–5.1)	
HIV+, 45 and older	22	245	9 (6–13.2)	< 0.001
HIV-, 45 and older	56	1603	3.5 (2.7–4.5)	

Table 3. Expert assessments of the frequency of venous thromboembolism complications (VTEC) in admitted patients in non-tuberculous hospitals

№	Author	Year	Country	VTEC frequency	Note
1	Allaert F.A.	2016	USA	VTEC – 1.4% DVT – 0.9% PE – 0.7%	Non-tuberculous hospitals
2	Allaert F.A.	2016	France	VTEC – 1% DVT – 0.6% PE – 0.5%	Non-tuberculous hospitals
3	Elmi G.	2020	Italy	DVT – 1.2%	Non-tuberculous hospitals
4	Khanna R.	2014	USA	VTEC – 0.51%	Non-tuberculous hospitals

DVT – deep vein thrombosis; PE – pulmonary embolism

The results obtained allow us to reject the null hypothesis and accept an alternative one, according to which HIV infection [even when receiving antiretroviral therapy (ART)] increases the risk of developing VTEC in admitted patients with active pulmonary TB, regardless of their age.

Another factor affecting the frequency of acute venous thrombosis is the duration of the disease. Unfortunately, since we cannot have data about the moment of onset of the disease (as a rule, patients do not have these data due to the paucisymptomatic course of the disease), we used the criterion of the presence of fibrosis foci and/or cavities, which do not form earlier (and, most often, later) 16–24 months from the onset of the disease.

Compute tomography showed that the relative risk of developing VTEC in patients with fibrous and/or cavernous changes in the lungs compared with patients with pulmonary TB without these changes was 9.08 (95% CI: 4.7–17.5). Thus, the presence of fibrosis foci and cavitary necrosis, which in this case are noted in every fourth patient, significantly increases the risk of developing VTEC. The age of patients with VTEC and fibrous-cavernous changes in the lungs (Me = 49; 95% CI: 25–78 years) did not differ much from the age of patients with VTEC but without fibrous-cavernous changes in the lungs (Me = 43; 95% CI: 41–47 years) (p = 0.9). Acute venous thrombosis was almost as frequent in patients under the age of 45 with active TB and fibrous-cavernous changes in the lungs as in patients over 45 years of age; 33.3% *vs.* 23.5% (p = 0.9).

To compare the frequency of VTEC among admitted patients with active pulmonary TB and patients in non-TB hospitals, we used expert estimates in scientific publications of the European Union and the United States over the past 10 years (Table 3) [8, 9, 10].

The analysis allows us to reveal the main patterns affecting the frequency of acute venous thrombosis and embolism in patients admitted in TB hospitals for active pulmonary TB. A comparison of our data and expert estimates of the frequency of venous thromboembolic events in the hospital allowed us to assert that, in general, the frequency of VTEC in patients of TB dispensaries is 3.3 times higher than in patients in non-TB hospitals. Interestingly, the incidence of DVT is 2.9 times higher

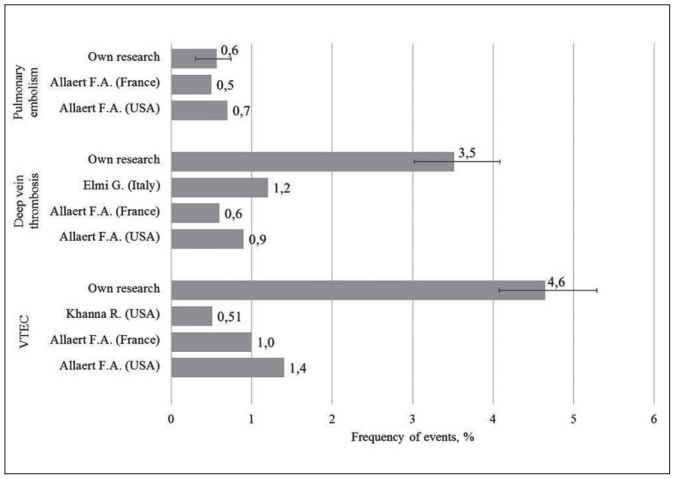

Figure 2. The incidence of venous thromboembolism complications (VTEC), deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with active pulmonary tuberculosis in comparison with expert estimates; the vertical segments show the boundaries of 95% CI

in patients with active pulmonary TB, while the rate of PE is approximately equal in both groups (Figure 2).

DISCUSSION

For a long time, the relationship between chronic infectious processes and VTEC was considered as an accidental phenomenon, so that only rare instances of DVT and PE in active TB were discussed in the literature [11]. At the same time, as early as 1948, there were reported cases of DVT and PE in TB patients without concomitant blood clotting disorders [12]. Subsequently, it was noted that according to the results of autopsies and screening ultrasound examinations, VTEC occur in patients of TB clinics in Europe, North America and the Middle East with a fairly high frequency exceeding 2.5% [12]. Based on a meta-analysis by Dentan et al. [13], hospital mortality in patients with active TB and VTEC (15%) was five times higher than mortality among TB patients without VTEC (2.7%) or patients in general hospitals with VTEC (2.5%) ($p < 0.001$). In the multifactorial analysis model, adults with active TB had a higher risk of VTEC than patients without TB, but with a risk of VTEC due to oncology [14].

It has been found that TB, as a chronic infection, has a direct impact on the processes leading to hypercoagulation. According to Turken et al. [15] this is directly manifested by an increase in the level of fibrinogen, factor VIII in blood plasma, as well as a decrease in the synthesis of antithrombin III and inhibition of protein C. Another observation showed that in the case of active TB, antiphospholipid antibodies are often found in the blood of patients, which inhibit the activation of proteins S and protein C, inhibit the functions of antithrombin III and the fibrinolysis system (decrease in the tissue plasminogen activator function), increase the expression of tissue factor (TF) on immune cells and increase platelet aggregation (due to active synthesis of thromboxanes) [16]. These processes seem to be associated with high cytokine activity in TB, which leads to endothelial dysfunction. Indeed, back in 1991, studies by Japanese scientists showed high production of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) by monocytes of patients with active TB of various localizations [17]. Additionally, it is possible to note the progressive effect of *Mycobacterium tuberculosis* itself on the expression of TF on cell membranes, which is currently considered as the main triggering factor of thrombosis [18].

It is no secret that TB patients, both pulmonary and extrapulmonary, as a rule, suffer from weight loss and hypodynamia due to several reasons including intoxication and weakness, after surgical interference, long stay in intensive care units, and skeletal muscles hypotrophy [19]. The combination of these factors creates prerequisites for the occurrence of venous stasis in the deep veins of the lower extremities. Thus, tuberculous inflammation determines all three interrelated components of the Virchow's triad: inflammatory endothelium damage, venous stasis, and hypercoagulation.

HIV infection plays another but not less important role in the processes of thrombosis formation. According to the results of the conducted studies, HIV-positive people, regardless of ART, had an increase in the frequency of VTEC due to immune system dysregulation and the development of chronic inflammation. HIV infection is recognized as a prothrombotic disease, while the incidence of VTEC among HIV-infected patients vary from 0.19% to 7.63% per year [20]. The relationship between HIV infection and VTEC was first reported by Hassell et al. [21] in 1994: according to the authors, the incidence of DVT among HIV-infected patients reached 18% in the Denver County Hospital, and researchers associated this phenomenon with the detected deficiency of protein S and antiphospholipid antibodies. A protein S concentration decrease in people living with HIV was subsequently proved in a series of works by American and Dutch scientists, a clear correlation having been observed in a concentration increase of factor VIII and fibrinogen in blood plasma [22]. It is assumed that the synthesis of protein S in endothelial cells, hepatocytes and megakaryocytes is suppressed due to the activity of TNF-alpha and/or the HIV virus itself [23]. The Funderburg et al. [24] study found a significantly higher incidence of TF – expressing monocytes in fresh blood samples in HIV-infected patients than in uninfected control groups. Presumably, various ligands of bacterial Toll – like receptors are translocated through the damaged intestinal wall in chronic HIV infection and stimulate immune activation (in addition to HIV virus replication) and TF expression by monocytes [24]. The increased TF expression in HIV infection is indirectly confirmed by high plasma levels of D-dimers and the correlation between TF expression and D-dimer levels. HIV replication and systemic translocation of microbial products from the damaged intestine and subsequent immune activation contribute to the procoagulant state in HIV-infected patients.

Changes in the hemostasis system towards procoagulant activity are associated with the severity of immunosuppression, determined by the number of CD4+ lymphocytes

[25]. Thus, it was found a statistically significant difference in the levels of D-dimer, proteins C and S, antigens to proteins C and S, and Von Willebrand factor in individuals with CD4+ levels below 200 cells/μl and above 400, which suggested a tendency to thrombosis in HIV-infected patients with deep immunosuppression [26]. The cause of the relationship between HIV infection and VTEC development has not yet been definitively clarified, but it seems to be of a multimodal nature, while all three links of the Virchow's triad are involved. For example, it has been proven that the virus primarily infects endothelial cells, which leads to increasing plasma concentration of such factors of endothelial dysfunction as thrombomodulin, Von Willebrand factor and E-selectin [27]. The concentration of the latter ones increases by more than 60% and is in inverse proportion to the number of CD4+ lymphocytes, that is, it directly depends on the availability and effectiveness of ART [28]. The concentration of the latter ones increases by more than 60% and is in inverse proportion to the number of CD4+ lymphocytes, that is, it directly depends on the availability and effectiveness of ART [28].

Currently available epidemiological data indicate that HIV infection is interlinked with an increased risk of VTEC by 2–10 times compared with the general population of the same age [29]. Some risk factors, such as low CD4+ lymphocyte count, protein S deficiency, and protein C deficiency, have shown the strongest association with VTEC. Other risk factors are still controversial, for example, protease inhibitor therapy, the presence of active opportunistic infections, and the presence of antiphospholipid antibodies, including antibodies to cardiolipin and lupus anticoagulant.

Finally, pulmonary TB patients with acute respiratory failure who are in a state of chronic hypoxia (for example, with cavernous and/or fibrous changes in the lung parenchyma) are also at the greatest risk of developing VTEC, which is probably due to a decrease in the concentration and synthesis of protein S by the liver against the background of oxygen deficiency. The mechanism of this effect hasn't been fully studied yet, but it is assumed that it is related with the expression of certain genes that respond to hypoxia and regulate a decrease in protein S levels and an associated increase in serum thrombin levels [29].

CONCLUSION

Based on the data obtained, it can reasonably be assumed that TB is a major reversible risk factor for venous thromboembolic events, probably due to impaired coagulation mechanisms, venous stasis and endothelial dysfunction. HIV infection in this context is the second major reversible factor in the development of VTEC. It is logical to assume a synergistic effect of both factors on the incidence of thrombotic events, which makes patients with pulmonary TB and patients with HIV/TB co-infection, along with cancer patients and patients in traumatology departments, the most vulnerable group with a high risk of developing VTEC. The phenomena of chronic hypoxia expand the threat and risks of acute venous thrombosis in patients with severe lung damage (fibrous and/or cavernous) and also determines the high frequency of VTEC in this part of patients. This fact dictates the need to elaborate systems for assessing the risk of VTEC in patients with pulmonary TB, specific prevention measures and effective treatment regimens.

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Учесталост и фактори ризика за венске тромбоемболијске компликације код болесника са активном плућном туберкулозом и коинфекцијом ХИВ/ТБ (туберкулоза и тромбоза)

Дмитриј Плоткин[1,2], Артур Титомер[1], Михаил Решетников[1,3], Умеџон Гафаров[1], Сергеј Стерликов[4], Михаил Синицин[1,2,3], Елена Богородскаја[1,3]

[1]Московски научно-клинички центар за борбу против туберкулозе, Туберкулозно хируршко одељење, Научно одељење, Москва, Руска Федерација;
[2]Руски национални истраживачки медицински универзитет „Н. И. Пирогов", Медицински факултет, Одељење опште хирургије, Одељење фтизиатрије, Москва, Руска Федерација;
[3]Руска медицинска академија за континуирано стручно образовање, Одељење за фтизијатрију, Москва, Руска Федерација;
[4]Руски научноистраживачки институт здравља, Катедра епидемиологије, Москва, Руска Федерација

САЖЕТАК

Увод/Циљ Венске тромбоемболијске компликације (ВТЕК) укључују дубоку венску тромбозу, тромбозу површинских вена и плућну емболију. Циљ рада је био да се процени преваленција ВТЕК-а код болесника са активном плућном туберкулозом и да се открију главни фактори који утичу на развој ВТЕК-а у овој кохорти болесника.

Методе Урађена је ретроспективна студија електронских здравствених картона болесника са активном плућном туберкулозом. Укључени су сви болесници са потврђеном активном плућном туберкулозом и ВТЕК-ом за период од 1. 1. 2020. до 31. 12. 2022. године.

Резултати Идентификовано је укупно 214 случајева ВТЕК-а. Најзначајнији фактори ризика за настанак тромботичких компликација код туберкулозе били су коинфекција ХИВ/туберкулозе (релативни ризик 3,8; 95% интервал поузданости 2,7–4,5) и трајање болести (према критеријуму формирања жаришта фиброзе и/или шупљине) (релативни ризик 9,1; 95% интервал поузданости 4,7–17,6). Укупна преваленција ВТЕК-а у болници за туберкулозу премашила је литературне податке за нетуберкулозне клинике за 3,3 пута.

Закључак Туберкулоза је главни реверзибилни фактор ризика за венске тромбоемболијске догађаје, вероватно због поремећених механизама коагулације, венске стазе и ендотелне дисфункције. ХИВ инфекција у овом контексту је други велики реверзибилни фактор у развоју ВТЕК-а.

Кључне речи: венска тромбоза; туберкулоза; тромбоемболија; ХИВ; хиперкоагулација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of the quality of life 10 years after bilateral thoracoscopic sympathicotomy in subjects with primary focal hyperhidrosis

Ivan Ergelašev[1,2], Ivan Kuhajda[1,2], Marko Galić[2], Nensi Lalić[1,3], Marko Bojović[1,4]

[1]University of Novi Sad, Faculty of Medicine Novi Sad, Novi Sad, Serbia;
[2]Institute for Pulmonary Diseases of Vojvodina, Clinic for Thoracic Surgery, Sremska Kamenica, Serbia;
[3]Institute for Pulmonary Diseases of Vojvodina, Clinic for Thoracic Oncology, Sremska Kamenica, Serbia;
[4]Oncology Institute of Vojvodina, Clinic of Radiation Oncology, Sremska Kamenica, Serbia

SUMMARY

Introduction/Objective Primary focal hyperhidrosis (PFH) is an idiopathic condition where excessive sweating affects one or more body regions, including axillae, palms, soles, and/or face. Most studies on quality-of-life (QoL) focus on the period up to one year after bilateral thoracoscopic sympathectomy (BTS). This study aims to determine the 10-year trend in QoL among patients from the Republic of Serbia with palmar-plantar-axillary PFH, treated with BTS at the R3–R4 level. A secondary goal is to ascertain the existence of compensatory sweating.

Methods All patients underwent a standardized BTS in a single act, through the cutting of ganglia with ultrasonic scissors at the R3–R4 level. For data collection, patients completed the "Hyperhidrosis Quality of Life Questionnaire," and the Hyperhidrosis Disease Severity Scale, preoperatively, postoperatively within 30 days, and 10 years after BTS.

Results The total sample consisted of 103 subjects who completed all three questionnaires. Considering the improvement in QoL from the group excellent, good, and average, the postoperative improvement was immediately postoperative in 88.4% of patients, while in the ten-year period, it was 87.4%. No statistically significant differences were found between the assessment of life satisfaction after 30 days and 10 years after BTS. Out of the total number of operated patients, two patients (1.94%) characterized their compensatory sweating as very pronounced.

Conclusion After 10 years from BTS, the QoL remains at an exceptionally high level, with an annual trend of decline of about 0.1%.

Keywords: sympathicotomy; sweat; video-assisted thoracoscopic surgery

INTRODUCTION

Hyperhidrosis represents the occurrence of pathological sweating that exceeds the physiological needs of the body for adequate thermoregulation. Primary focal hyperhidrosis (PFH) is an idiopathic condition where excessive sweating affects one or more body regions, including axillae, palms, soles, and/or face. Severe forms of PFH can have a significant impact on social life, psychological status, and daily activities. Consequently, the overall quality of life (QoL) may be diminished. Bilateral thoracoscopic sympathectomy (BTS) represents the only permanent therapeutic solution [1]. Patients usually adapt to changes in thermoregulation several months after undergoing BTS. Few studies address the long-term effect of BTS on QoL. Most studies on QoL focus on the period up to one year after BTS. A small number of studies describe the long-term effect considering a period of 5–10 years [2]. This study aims to determine the 10-year trend in QoL among patients from the Republic of Serbia with palmar-plantar-axillary PFH, treated with BTS at the R3–R4 level. A secondary goal is to ascertain the existence of compensatory sweating.

METHODS

The study was conducted as a unicentric, partly prospective, uncontrolled, and non-randomized trial, following the approval of the ethical committee of the Institute for Pulmonary Diseases of Vojvodina, Republic of Serbia (No. 25-VIII/7). Patients were operated on from January 1, 2011, to November 30, 2013. All patients underwent a standardized BTS in a single act, through the cutting of ganglia with ultrasonic scissors at the R3–R4 level. Additionally, accessory fibers of Kuntz were resected over the third and fourth rib in the length of 5–7 cm. Patients who had undergone sympathectomy at any level other than R3–R4 were excluded from the study. Only patients with palmar-plantar-axillary PFH were considered. Patients with erythrophobia, palmar-plantar, isolated axillary, plantar, or palmar hyperhidrosis were not included in the study. For data collection, patients completed the "Hyperhidrosis Quality of Life Questionnaire" (HQLQ), created by de Campos et al. [3], and the "Hyperhidrosis Disease Severity Scale" (HDSS), by the International Hyperhidrosis Society, preoperatively, postoperatively within 30 days, and 10 years after BTS

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Correspondence to:
Nensi LALIĆ
Institute for Pulmonary Diseases of Vojvodina
Clinic for Thoracic Oncology
Put Doktora Goldmana 4
21204 Sremska Kamenica
Serbia
nensi.lalic@mf.uns.ac.rs

[3, 4]. In addition to the questionnaire filled out ten years after BTS, three independent questions not included in the score were added. The questions were: "Have you developed postoperatively: diabetes mellitus, thyroid disease, malignant disease, psychiatric disease, or injuries to the head or spine?", "Do you have compensatory sweating? If yes, in which regions?". The aim of the question regarding the postoperatively acquired disease was to potentially identify the patients with secondary generalized hyperhidrosis. HDSS responses were descriptively compared, with the QoL rated as very poor – 5, poor – 4, average – 3, good – 2, and excellent – 1. As a condition for performing BTS, it was necessary for the QoL on the preoperative HDSS scale to be very poor or poor. HQLQ responses were numerically compared so that each response was scored. The maximum score was 100, representing the worst QoL, while the best QoL score was 20. The questionnaires were filled out under the supervision of the surgeon who performed the BTS. The difference in QoL after 30 days from the operation was marked as immediate postoperative, while the QoL after 10 years was marked as decadal.

For statistical data processing, the IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA) was used. Descriptive statistics methods – mean, standard deviation, minimum, and maximum values – were used to display the characteristics of variables. The prevalence of certain variables is presented numerically in the form of frequencies or percentages. For comparing the QoL in relation to time points, a repeated measures analysis of variance (Repeated Measures ANOVA) was used. Results are presented in tables and figures.

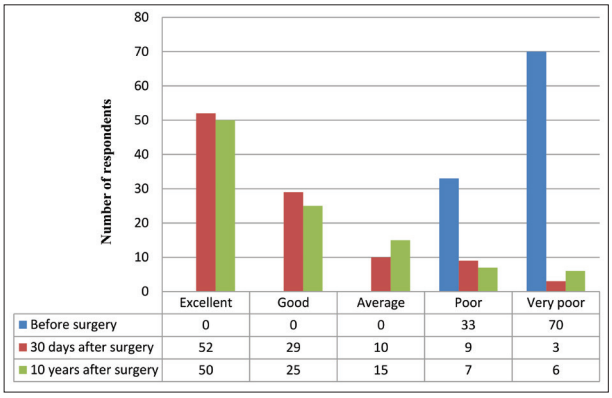

Figure 1. Number of responders to the Hyperhidrosis Disease Severity Scale questionnaire assessing the overall quality of life in three time points

RESULTS

The total sample consisted of 103 subjects who completed all three questionnaires. Initially, 483 patients were included in the study, but a vast majority was lost to follow-up after 10 years. The total sample consisted of 65 women (63.1%) and 38 men (36.9%). The age range of the subjects in the sample was from 23 to 58 years, with an average age of 39.12 years, at the point of completing questionnaire 10 years after BTS. Intraoperative complications included the need for unilateral adhesiolysis of the pleura in one patient (0.97%) and one pneumothorax (0.97%).

Pre-operatively, 68% (70/103) of respondents, after completing HDSS questionnaire, reported their QoL as "very poor" and 38% (33/103) reported it as "poor". Poor and very poor QoL was also a condition for performing BTS. Regarding the period 30 days after surgery and 10 years after surgery, the percentage of "poor" and "very poor" responses was significantly lower, 10.67% (11/103) and 11.65% (12/103), respectively. On the other hand, the percentage of respondents reporting good or excellent QoL was 78.7% (81/103) in the assessment after 30 days, and 72.8% (75/103) in the assessment after 10 years. Considering the improvement in QoL from the group excellent, good, and average, the postoperative improvement was immediately postoperative in the 88.4% (91/103) of patients, while in the ten-year period 87.4% (90/103) patients gave the same answers (Figure 1).

Mean values of 4.67/1.85/1.97 and standard deviations of 0.46/1.09/1.20 were reported respectively for the assessment of the overall QoL before surgery, 30 days after surgery, and 10 years after surgery (Table 1). In order to investigate the effect of time on patients' QoL, a repeated measures analysis of variance was conducted.

Table 1. The assessment of the overall quality of life using Hyperhidrosis Disease Severity scale

Time point	M	SD	N	Min	Max
Before surgery	4.67	0.46	103	4	5
30 days after surgery	1.85	1.09	103	1	5
10 years after surgery	1.97	1.20	103	1	5

M – mean; SD – standard deviation

The effect of the independent variable, namely time, on the assessment of satisfaction with the QoL in patients, was statistically significant, $F(2,101) = 307.062$, $p < 0.001$, partial $\eta^2 = 0.859$. Post hoc analyses (LSD) established that there are statistically significant differences in the assessment of satisfaction with QoL before surgery compared to the assessment of satisfaction with QoL 30 days after surgery ($p < 0.001$) and 10 years after surgery ($p < 0.001$). The assessment of satisfaction with QoL 30 days after surgery and 10 years after surgery was statistically significantly higher than before surgery. No statistically significant differences were found between the assessment of life satisfaction after 30 days and 10 years after surgery.

Satisfaction with the QoL during daily activities was processed through 20 items via the HQLQ questionnaire. Within each item, patients assessed their satisfaction with the QoL for a specific daily activity at the same three-time points: before surgery, 30 days after surgery, and 10 years after surgery. For those three time points we found a mean values of 74.22/37.66/36.79 and standard deviations of 17.87/15.11/15.79 (Table 2). The effect of the independent variable, namely time, on the assessment of satisfaction with the QoL during daily activities, was statistically significant, $F(2,101) = 139.285$, $p < 0.001$, partial $\eta^2 = 0.734$. As in the case of overall QoL, post hoc analyses (LSD) established that there are statistically significant differences between the

assessment of satisfaction with QoL during daily activities before surgery, 30 days after surgery ($p < 0.001$), and 10 years after surgery ($p < 0.001$). The assessment of satisfaction with QoL during daily activities 30 days after surgery and 10 years after surgery was statistically significantly higher than before surgery. Also, no statistically significant difference was found between the assessments 30 days after surgery and 10 years after surgery.

Table 2. The assessment of the overall quality of life using Hyperhidrosis Quality of Life Questionnaire

Time point	M	SD	N	Min	Max
Before surgery	74.22	17.87	103	20	100
30 days after surgery	37.66	15.11	103	20	84
10 years after surgery	36.79	15.79	103	20	78

M – mean; SD – standard deviation

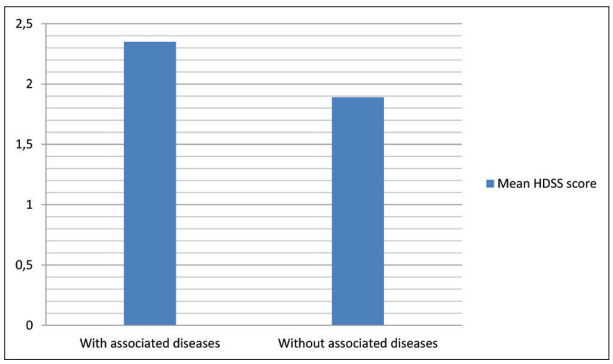

Figure 2. Ten years after surgery, mean Hyperhidrosis Disease Severity Scale (HDSS), showing difference in patient with or without postoperatively acquired associated disease

In the total sample, there were 78 (75.7%) patients who reported compensatory sweating 10 years after surgery. Compensatory sweating most commonly occurred in the abdomen area (32%), back (23%), chest (9%), and combined or other regions (36%). Of those with compensatory sweating, 30.7% stated that it affects their daily activities, while 69.3% reported that compensatory sweating does not affect their daily activities. Out of the total number of operated patients, two patients (1.94%) characterized their compensatory sweating as very pronounced.

The majority of patients in the sample did not have associated diseases (83.5%). Postoperative acquired associated thyroid gland diseases were reported by 11 patients (10.67%), psychiatric disorders by six (5.82%), sinus tachycardia by one (0.97%), diabetes mellitus by one (0.97%), head and neck injury by one (0.97%), and spontaneous pneumothorax several years after surgery by one patient (0.97%). The average HDSS scores on overall satisfaction with QoL in the group of patients who had newly acquired associated diseases was 2.35 and patients who did not have associated diseases was 1.89. As can be seen, the score is higher in the group of patients who have associated diseases, which indicates a lower QoL (Figure 2).

Due to the unevenness of the sample regarding this variable, it is not possible to conduct statistical analyses that would indicate whether these differences are statistically significant.

DISCUSSION

Since BTS fundamentally represents an operation aimed at improving the QoL of patients, it is very important to inform patients about the success rate of the surgery and the occurrence of compensatory sweating as the main side effect. Experience has shown that the more informed patients are, the higher is their satisfaction with the surgical treatment. Most studies addressing the topic of QoL after BTS focus on the immediate postoperative period or the period of up to one year [3]. Knowing the trend of QoL, especially maintaining the level of effect achieved after BTS over a multi-year or decade-long period, validates the surgery itself and provides patients with information that can influence their decision to undergo surgery or not. Long-term maintenance of the effect of surgical treatment means improvement in social life and psychological status for them. Most patients seeking surgical treatment have lived with their condition for a certain period, and many of them have tried treatment with other therapeutic options such as the application of botulinum toxin, iontophoresis, systemic anticholinergics, radio waves, or lasers [1].

In our study, patients filled out the questionnaire preoperatively to have a baseline, after 30 days to make the data comparable with most of the data available from the literature. The period after 10 years from BTS was chosen to highlight the long-term trend. Comparing data over such a long period is only possible with a small number of available studies. The examination of the QoL after BTS has never been done on the population of patients from the Republic of Serbia.

Postoperatively, after 30 days in our study, the improvement in QoL was 88.4%, which is comparable with findings reported in the studies by Patrini et al. [4] with 96%, as well as with Estrella-Gaibor et al. [5] at 95.9% (Table 3). The difference in patient satisfaction of 7.5% compared to

Table 3. Results of the quality-of-life findings from studies after bilateral thoracoscopic sympathectomy

Study	N	Follow up	Quality of life improvement (%)	Compensatory sweating (%)
Patrini et al. (2019) [4]	403	30 days	96.1	-
Estrella-Gaibor et al. (2023) [5]	49	30 days	95.9	89
Hajjar et al. (2019) [6]	100	3 months	94	92
Hemead et al. (2022) [7]	63	6 months	95.2	26.5
Zhang et al. (2021) [8]	367	14 months	90.7	94.6
Gossot et al. (2003) [9]	125	3.8 years	91.2	86.4
Wolosker et al. (2012) [10]	453	30 days 5 years	90.9 90.3	91.8
Horslen et al. (2018) [11]	58	5 years	84	84
Shabat et al. (2022) [12]	150	11 years	94	90

the Patrini et al. [4] study can be explained by the fact that preoperatively 100% of our subjects reported their QoL as very poor and poor, while in the mentioned study, this number was 87.6%. Estrella-Gaibor et al. [5] report that 98% of patients preoperatively stated their QoL as "poor" and "very poor." If we dissect this group and compare it with ours, we see that in the Estrella-Gaibor et al. [5] study, 38.8% of patients stated their QoL as "very poor," while in our study, this number was 68% [6]. This difference also explains the postoperative difference in QoL because patients who report having "poor" QoL have only one step to "good," thus immediately entering into a positive result.

The improvement in QoL in studies that examined the postoperative period from three months to 3.8 years was from 90.7% to 95.2% [6–9]. The study that provides insight into the trend is Wolosker et al. [10], who measured QoL after 30 days and after five years. After five years, they reported a decrease in QoL by 0.6% from 90.9% to 90.3%. In our study, the mentioned decline was 1% after 10 years, i.e., from 88.4% to 87.4%. Taking into account both studies, the annual decrease in QoL was about 0.1%. Horslen et al. [11] reported an 84% improvement in QoL at five-year follow-up.

Shabat et al. [12] are the only ones that allow comparison after 10 years from BTS. QoL after 11 years in the mentioned study was 94% in comparison with our 87.4%. Compensatory sweating was 90% compared to our 75.7%.

As 10 years constitutes a long period, we attempted to determine whether postoperatively acquired diseases, could influence increased sweating, leading to a decrease in patients' QoL, even though such conditions should not be related to BTS in principle. Such conditions were present in 11 patients (10.67%) in our study. In the group of patients without newly acquired diseases, the descriptive indicator (1–5) was 1.89, while in the group with newly acquired diseases, it was 2.35. Although statistical significance cannot be drawn due to the unevenness of the sample, it can direct us towards further investigation on this thesis and even potentially indicate that the QoL is higher if we exclude newly acquired associated diseases that affect the QoL. No available study we found has addressed this issue.

As the BTS is an elective surgical procedure conducted mostly on young and healthy individuals, safety of the operation is the most important factor. In our study there were no mortalities, no major bleeding, no accidental organ injuries. Only one case (0.97%) of the pneumothorax requiring chest tube was recorded. Kobayashi et al. [13] reported no intra and perioperative complications in their study which included a total of 151 patients. de Campos et al. [3] reported 7/362 cases (1.8%) with pneumothorax requiring chest tube, two cases (0.6%) with superficial phlebothrombosis and two cases (0.6%) of Horner's syndrome. Katrancıoğlu et al. [14] included 30 patients with only three patients developing small pneumothorax treated conservatively.

In our study, we reported one patient with extensive pleuropulmonary adhesions. We managed to perform adhesiolysis and BTS. Although chest tube was not removed intraoperatively, no signs of major bleeding were noted. Due to the adhesions, the sympathetic chain was obscurely seen, but symmetrical BTS was achieved, thus avoiding development of Harlequin syndrome [15].

CONCLUSION

We can say that even after 10 years from BTS, the QoL remains at an exceptionally high level, with an annual trend of decline of about 0.1%. Although the rate of compensatory sweating is highly prevalent, in only a small number of cases it is defined as disabling. Due to the high success rate and long-term sustainable QoL, BTS remains the method of choice for the permanent treatment of PFH.

Conflict of interest: None declared.

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Квалитет живота особа са примарном фокалном хиперхидрозом десет година после билатералне торакоскопске симпатикотомије

Иван Ергелашев[1,2], Иван Кухајда[1,2], Марко Галић[2], Ненси Лалић[1,3], Марко Бојовић[1,4]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за плућне болести Војводине, Клиника за грудну хирургију, Сремска Каменица, Србија;
[3]Институт за плућне болести Војводине, Клиника за плућну онкологију, Сремска Каменица, Србија;
[4]Институт за онкологију Војводине, Клиника за радијациону онкологију, Сремска Каменица, Србија

САЖЕТАК

Увод/Циљ Примарна фокална хиперхидроза је идопатско стање код којег је ексцесивним знојењем захваћен један или више региона тела, укључујући аксиле, дланове, табане и/или лице. Већина студија о квалитету живота фокусирана је на период до годину дана након билатералне торакоскопске симпатикотомије (БТС).

Циљ ове студије је да утврди десетогодишњи тренд квалитета живота код болесника из Републике Србије са палмарно-плантарно-аксиларном примарном фокалном хиперхидрозом, лечених БТС-ом на нивоу Р3–Р4. Секундарни циљ је утврђивање постојања компензаторног знојења.

Методе Свим болесницима начињена је стандардизована БТС у једном акту, путем пресецања ганглија ултразвучним маказама на нивоу Р3–Р4. У циљу сакупљања података, болесници су преоперативно, постоперативно у периоду од 30 дана и 10 година после БТС-а попуњавали Упитник о квалитету живота са хиперхидрозом (*The* Hyperhidrosis *Quality of Life Questionnaire*) и Скалу тежине симптома хиперхидрозе (*Hyperhidrosis Disease Severy Scale*).

Резултати Укупан узорак чинила су 103 испитаника, који су комплетирали сва три упитника. Узимајући у обзир побољшање квалитета живота из групе 'одличан', 'добар' и 'просечан', побољшање је непосредно постоперативно било присутно код 88,4% пацијената, док је у десетогодишњем периоду износило 87,4%. Нису добијене статистички значајне разлике између процене задовољства квалитетом живота 30 дана и 10 година од БТС-а. Од укупног броја оперисаних, два пацијента (1,94%) окарактерисала су компензаторно знојење као веома изражено.

Закључак Десет година након БТС-а, квалитет живота се задржао на изузетно високом нивоу, са годишњим трендом пада од 0,1%.

Кључне речи: симпатикотомија; зној; видеопотпомогнута торакална хирургија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of comorbidity and anesthesia technique in patients undergoing bariatric surgery at the University Clinical Center of Serbia

Ivan Palibrk[1,2,*], Marija Đukanović[1,2,*], Maja Maksimović-Mandić[2,*], Bojana Miljković[2], Dubravka Đorović[2], Jelena Veličković[1,2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Center of Serbia, Center for Anesthesiology and Reanimatology, Belgrade, Serbia;
*Authors who have contributed equally to this work and share first authorship

SUMMARY

Introduction/Objective Altered physiology and metabolism of obese patients represents a big challenge for the anesthesiologist. The objectives of the study are to investigate numbers of comorbidities, choice of anesthesia techniques, intraoperative, and postoperative complications between bariatric and non-bariatric patients.

Methods This retrospective study included 469 patients. The study group of patients included obese patients with body mass index ≥ 30. Control Group included patients in whom elective laparoscopic cholecystectomy was performed, on the same day as bariatric surgery in Control Group.

Results The study group included 235 patients who underwent bariatric surgery, while control group included 234 patients. More patients in study group had comorbidities compared with Control Group (84.4% *vs*. 63.2%, $p < 0.001$). In the study group, total intravenous anesthesia and target control anesthesia were statistically significant more delivered than in the Control Group (74% *vs*. 0.9%, $p < 0.001$; 7.2% *vs*. 1.7, $p < 0.001$, respectively). Difficult intubation was statistically significant more in Control Group (5.6% *vs*. 0.9%, $p = 0.004$). There was a statistically significant difference in the incidence of intraoperative desaturation and hypotension during induction of anesthesia between the study and Control Group (9.8% *vs*. 2.1%, $p < 0.001$; 14.5% *vs*. 2.1, $p < 0.001$, respectively). There was statistically significant difference between the study and control group in minor complication according Clavien–Dindo classification, (20.8% *vs*. 5.1%, $p < 0.001$).

Conclusion Obesity is associated with higher number of comorbidities and intraoperative complications. There was no statistically difference in major postoperative complications between bariatric and non-bariatric patients.

Keywords: obesity; bariatric surgery; comorbidities; body mass index

INTRODUCTION

According to the definition of the World Health Organization, obesity represents "abnormal or excessive fat accumulation that presents a health risk" [1]. Obesity is defined by a body mass index (BMI). BMI between 25 and 29.9 kg/m² defines overweight, while BMI over 30 kg/m² considers obesity [1, 2]. Obesity or overweight status affects about 60% of the adult population. Also, one in three children is obese. Overall, obesity has been identified as the fourth-leading cause of noncommunicable diseases [1]. In 2019, 20.8% of the population over the age of 15 was obese in Serbia [3]. Comorbidities such as cardiovascular disease, type 2 diabetes, rheumatoid arthritis, major depressive illness, polycystic ovarian syndrome, asthma, and obstructive sleep apnea (OSA) are more likely in obese patients [2, 4, 5, 6].

The metabolic, anatomical, and physiological aspects of obese patients make induction and maintenance of anesthesia challenging [7, 8]. Obese patients often have upper airway obstruction, decreased lung capacities and compliance, higher respiratory exertion, and impaired gas exchange. Respiratory pathophysiology is altered [7, 8]. Difficult ventilation and intubation are expected during anesthesia induction for bariatric surgery [8, 9]. Determining the dose of the anesthetic drugs in obese patients may be particularly challenging. Lipophilic drugs such as propofol, barbiturates, and benzodiazepines characterize high volume of distribution. To achieve adequate serum concentrations, larger loading doses are needed, therefore doses are calculated based on total body weight (TBW). For anesthesia maintenance, dosing these medications should be calculated based on the ideal body weight (IBW) or lean body weight (LBW). Loading succinylcholine dose is calculated based on TBW. Nondepolarizing muscle relaxants dose is calculated based on IBW as in non-obese patients. Fentanyl, sufentanil, alfentanil should be estimated based on LBW, whereas remifentanil on IBW [8, 10].

Obese patients are at greater risk of developing postoperative complications. Wound infection, intra-abdominal infection, bowel injury,

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Correspondence to:
Maja MAKSIMOVIĆ-MANDIĆ
Druge Srpske Armije 17/12
11000 Belgrade
Serbia
maja_maksimovic14@hotmail.com

myocardial and other major complications are more common in these patients [11]. An adequate preoperative assessment is mandatory as optimal intraoperative anesthetic management and postoperative care to prevent postoperative complications after bariatric surgery [7, 8, 12].

We hypothesized that obese patients have higher prevalence of comorbidities, and are more prone to postoperative complications.

The objectives of this study was to examine the prevalence of comorbidities in patients undergoing bariatric surgery compared to patients undergoing elective cholecystectomy. Also, we analyzed the choices of the anesthesia techniques in bariatric and elective surgery, the incidence of intraoperative and postoperative complications between bariatric and non-bariatric patients.

METHODS

This retrospective study included 469 patients, scheduled for bariatric surgery or elective cholecystectomy at the Hospital for Digestive Surgery, University Clinical Center of Serbia, during the period from June, 2011 to November, 2022. This study was approved by the ethics committee of the University Clinical Center of Serbia, protocol number (661/2).

Obese patients with a BMI ≥ 30 undergoing bariatric surgery were included in the study group (SG). The control group (CG) included patients admitted to the hospital for an elective laparoscopic cholecystectomy procedure and scheduled for surgery on the same day as SG. The preoperative interdisciplinary team of specialists decided about eligibility of the patients for bariatric surgery. This interdisciplinary health care team included an anesthesiologist, surgeon, pulmonologist (a spirometry report was mandatory), cardiologist (an ergospirometry was mandatory), psychiatrist, endocrinologist, and for women, a gynecologist. A cardiological examination with electrocardiogram (ECG) and chest X-ray not older than one month were obligatory before cholecystectomy in CG. Laboratory panel testing (complete blood count, biochemical, and coagulation analyses) within 14 days before surgery was mandatory in both groups. All patients in both groups received antibiotic prophylaxis (cephazolin) 30 minutes before the operation. Low molecular weight heparin for deep vein thrombosis prophylaxis was administered two hours before surgery. In the present study, hypertension, cardiac arrhythmias, coronary heart disease, hyperlipidemia (HLP), diabetes mellitus (DM) type 1 or 2, chronic obstructive pulmonary disease (COPD), obstructive hypoventilation syndrome or OSA, epilepsy, anemia, varicose veins of lower extremities were recorded. The other comorbidities were listed as additional comorbidities. The American Society of Anesthesiologists (ASA) status was used to rated patients conditions.

Difficult intubation was recorded according to definition from the latest the Difficult Airway Society guidelines [13]. All analyzed data were obtained from medical records of patients.

Premedication with benzodiazepines was not routinely used. Before induction of anesthesia, preoxygenation was performed in all patients. Anesthesia techniques – balanced anesthesia (BA), total intravenous anesthesia (TIVA) or target control infusion anesthesia (TCI) was chosen by attending anesthesiologist. Induction of BA was achieved with propofol 1.5–2 mg/kg according to TBW and fentanyl 2–4 mcg/kg LBW. For anesthesia maintenance sevoflurane was used, with minimal alveolar concentration 0.8–1.2 Vol% based on the patient's age. Analgesia was achieved with fentanyl 50–200 mcg/h as an intermittent intravenous bolus according to patient comfort. For TIVA, propofol was used 10–16 mg/kg/h according to TBW and remifentanil 0.25–1 mcg/kg/min according to IBW for induction. During maintenance of anesthesia, propofol was used 4–6 mg/kg/h of LBW and remifentanil 0.2–0.5 mcg/kg/min of IBW. In case of using TCI, Marsh or Schneider model was used with target concentrations of propofol 6–8 mcg/ml according to TBW or LBW, respectively for induction of anesthesia. Maintenance anesthesia doses were 2–4 mcg/ml of LBW. Remifentanil (target effect site) was used in the range 6–10 ng/ml according to IBW for analgesia. In both intravenous techniques the breathing mixture was a combination of oxygen and air. During induction, for laryngoscopy and intubation, succinylcholine was used in dose of 1–1.2 mg/kg according to TBW, or rocuronium in dose of 0.6–1.2 mg/kg according to IBW in all patients. For maintenance neuromuscular blockade rocuronium was used in all anesthesia techniques in dose of 0.3 mg/kg IBW. Reversal of the neuromuscular blockade was performed with neostigmine/atropine or sugammadex in all patients, depending on the attending anesthesiologist.

Intraoperative monitoring [heart rate (HR), ECG, noninvasive blood pressure, peripheral saturation of oxygen (SpO_2) and end-tidal CO_2 concentration] was performed in all patients from both groups. In patients in SG, two peripheral venous lines were placed, while in CG one peripheral venous line was placed. Urinary catheter was inserted and hourly urine output was monitoring in SG. Bispectral Index™ (BIS™ Medtronic, Minneapolis, MN, USA) was used for TIVA or TCI.

In all patients, trachea was extubated at the end of surgery. After the extubation, the majority of patients were transferred to the department after staying for one hour in the recovery room. Patients who required noninvasive mechanical ventilation following surgery were admitted to the intensive care unit (ICU) and stayed overnight. Postoperative multimodal analgesia was achieved with nonsteroid anti-inflammatory drugs, paracetamol and metamizole. If a patient needed additional analgesia, tramadol or morphine were administered intravenously. Intraoperative and postoperative complications were recorded in patient's medical records. Bronchospasm, pneumothorax, desaturation (defined as SpO_2 < 90%), hypotension (defined as systolic pressure < 90 mmHg), hypertension (defined as > 20% of initial arterial pressure), bradycardia (defined as HR < 50 per minute), tachycardia (defined as HR > 100 per minute), and cardiac arrhythmia

were defined as intraoperative complications and were reported in anesthesia records.

Postoperative complications were registered and categorized according to the Clavien–Dindo (CD) classification of surgical complications [14]. Minor complications were defined as CD grade I and II, major complications were defined as CD grade III and IV.

Statistical analysis was performed in IBM SPSS Statistics for Windows, Version 28.0. (IBM Corp. Armonk, NY, USA). Data were collected from medical and anesthesia records of patients. Data were described and analyzed using descriptive statistics, mean and standard deviation for continuous variables and counts and percentages for categorical variables. For clinical outcomes, for categorical variables χ^2 test or Fisher's exact test was used. For parametric variables, Student's t-test was used. For non-parametric test Mann–Whitney test was performed. Statistical significance was calculated at level of significance of $p < 0.05$.

RESULTS

Of the total number of patients (469), SG included 235 of patients, while in CG were 234 patients. There was a statistically significant difference in the BMI between SG and CG (44.9 ± 6.2 *vs*. 27.5 ± 4.6, $p < 0.001$) (Table 1). In CG, 26% of patients had BMI > 30 kg/m^2. There was a statically significant difference in the age, younger patients were in SG (40.75 ± 9.9 *vs*. 48 ± 13.6, $p < 0.001$) (Table 1). There was a statistically significant difference in the ASA status between groups ($p < 0.001$), patients in SG were rated with higher ASA status (Table 1). More comorbidities were reported in the study than in CG (84.6% *vs*. 63.2%, $p < 0.001$) (Table 2). There was statistically significant difference in prevalence of HTA, DM and COPD in SG (55.8% *vs*. 39.3%, $p < 0.001$; 58% *vs*. 12.8%, $p < 0.001$; and 19% *vs*. 7.7%, $p < 0.001$, respectively (Table 2). More cardiac arrhythmia was detected in CG (2.6 % *vs*. 6.8%, $p = 0.047$), and additional comorbidity was more verified in SG (38.1% *vs*. 25.6%, $p = 0.005$) (Table 2). Premedication was more delivered in the study compared to CG (70.6% *vs*. 33.9%, $p < 0.001$) (Table 3). There was statistically significant difference in using succinylcholine for intubation between the study and CG (87.5% *vs*. 71.7%, $p < 0.001$) (Table 3). Also, there was statistically significant difference in using TIVA and TCI between study and CG (74% *vs*. 1.1%, $p < 0.001$; 7.2% *vs*. 1.7%, $p = 0.004$) (Table 3). BA was the technique of choice in CG, and was statistically more performed (97.7% *vs*. 11.9, $p < 0.001$) (Table 3). The reversion of neuromuscular blockade was used in both groups, statistically significantly more often used in SG difference (99.1% *vs*. 96.2%, $p = 0.032$) (Table 3).

For neuromuscular reversion, sugammadex was used more in SG (82.8% *vs*. 0.4%, $p < 0.001$) (Table 3). There was no statistically significant difference in the occurrence in the total number of intraoperative complications between study and CG (42.6% *vs*. 43.2%, $p = 0.894$) (Table 4). Difficult intubation was more documented in CG in compare to SG (0.9% vs. 5.6%, $p = 0.004$) (Table 4).

Table 1. Demographic characteristics of patients

Parameters	Study group (n = 235)	Control group (n = 234)	p-value
Sex, female, n (%)	162 (68.9)	145 (62.2)	0.127**
Age, mean ± SD	40.75 ± 9.9	48 ± 13.6	< 0.001*
BMI (kg/m^2), mean ± SD	44.9 ± 6.2	27.5 ± 4.6	< 0.001*
Body weight (kg), mean ± SD	138 ± 6.7	83.04 ± 1.1	< 0.001*
ASA status			
ASA 1, n (%)	2 (0.9)	72 (30.8)	< 0.001**
ASA 2, n (%)	177 (76)	148 (63.2)	
ASA 3, n (%)	53 (22.7)	14 (6)	
ASA 4, n (%)	1 (0.4)	0 (0)	

*Student's t-test, ** Pearson's χ^2 test, $p < 0.05$ statistically significant difference
BMI – body mass index; ASA status – American Society of Anesthesiologists status

Table 2. Comorbidities

Parameters	Study group (n = 235)	Control group (n = 234)	p-value
Overall comorbidities, n (%)	198 (84.6)	148 (63.2)	< 0.001*
Hypertension, n (%)	130 (55.8)	92 (39.3)	< 0.001*
DM (type 1 or 2), n (%)	134 (58)	30 (12.8)	< 0.001*
Cardiac arrhythmia, n (%)	6 (2.6)	16 (6.8)	0.047*
HLP, n (%)	27 (12.6)	20 (8.5)	0.160*
CHD, n (%)	5 (2.2)	8 (3.4)	0.408*
Epilepsy, n (%)	3 (1.3)	3 (1.3)	0.992**
COPD, n (%)	44 (19)	18 (7.7)	< 0.001*
Anemia, no (%)	5 (2.2)	5 (2.1)	0.989*
Varicose veins of the lower extremities, n (%)	13 (5.6)	12 (5.1)	0.840*
OSA, n (%)	10 (4.3)	3 (1.3)	0.053**
Additional comorbidity, n (%)	88 (38.1)	60 (25.6)	0.005*

*Pearson's χ^2 test, **Fisher's exact test, $p < 0.05$ statistically significant difference
DM – diabetes mellitus; HLP – hyperlipidemia; CHD – chronic heart disease; COPD – chronic obstructive pulmonary disease; OSA – obstructive sleep apnea

Table 3. Anesthesia techniques

Anesthesia techniques	Study group n = 235	Control group n = 234	p-value
Premedication, n (%)	166 (70.6)	79 (33.9)	< 0.001*
Neuromuscular relaxant for intubation			
Succinylcholine, n (%)	203 (87.5)	167 (71.7)	< 0.001*
Rocuronium, n (%)	27 (11.6)	62 (26.6)	
Cisatracurium, n (%)	2 (0.9)	4 (1.7)	
TIVA, n (%)	174 (74)	2 (1.1)	< 0.001**
TCI, n (%)	17 (7.2)	4 (1.7)	0.004**
BA, n (%)	28 (11.9)	229 (97.7)	< 0.001*
Reversion neuromuscular blockade, n (%)	233 (99.1)	225 (96.2)	0.032*
Neostigmine, n (%)	40 (17.2)	221 (98.7)	< 0.001*
Sugammadex, n (%)	193 (82.8)	1 (0.4)	
Neostigmine and sugammadex, n (%)	0 (0)	2 (0.9)	

*Pearson's χ^2 test, **Fisher's exact test, $p < 0.05$ statistically significant difference
TIVA – total intravenous anesthesia; TCI – target-controlled infusion; BA – balance anesthesia

Table 4. Intraoperative complications

Parameters	Study group n = 235	Control group n = 234	p-value
Total complications, n (%)	100 (42.6)	101 (43.2)	0.894*
Difficult intubation, n (%)	2 (0.9)	13 (5.6)	0.004**
Bronchospasm, n (%)	3 (1.3)	3 (1.3)	0.999**
Pneumothorax, n (%)	2 (0.9)	0 (0)	0.49**
Desaturation, n (%)	23 (9.8)	5(2.1)	< 0.001*
Hypotension, n (%)	34 (14.5)	5 (2.1)	< 0.001*
Hypertension, n (%)	49 (20)	67 (28.6)	0.055*
Bradycardia, n (%)	20 (8.5)	19 (8.1)	0.999*
Tachycardia, n (%)	19 (8.1)	39 (16.7)	0.005*
Cardiac arrhythmia, n (%)	0 (0)	2 (0.9)	0.248 **

*Pearson's χ^2 test, **Fisher's exact test, p < 0.05 statistically significant difference

Table 5. Postoperative complications according Clavien–Dindo classification

Clavien–Dindo classification	Study group n = 235	Control group n = 234	p-value
Grade I, n (%)	43 (18.3)	11 (4.7)	< 0.001*
Grade II, n (%)	6 (2.6)	1 (0.4)	0.13**
Grade IIIa, n (%)	0 (0)	0 (0)	0.999**
Grade IIIb, n (%)	1 (0.4)	0 (0)	0.988**
Grade IV (a and b), n (%)	0 (0)	0 (0)	0.999**
Grade V, n (%)	0 (0)	0 (0)	0.999**
Minor complications, n (%) #	49 (20.8)	12 (5.1)	< 0.001*
Major complications, n (%) #	1 (0.4)	0 (0)	0.999**

*Pearson's χ^2 test, **Fisher's exact test, p < 0.05 statistically significant difference
#Minor complications – Clavien–Dindo grade I and II; #Major complications – Clavien–Dindo grade III, IV and V

Incidence of intraoperative desaturation occurred significantly more in the study than in CG (9.8% *vs.* 2.1%, p < 0.001) (Table 4). Hypotension episodes was statistically significant more documented in study compared to CG (14.5% *vs.* 2.1%, p < 0.001) (Table 4). There was statistical significance in occurrence of tachycardia between study and CG, more tachycardia was registered in CG (8.1% *vs.* 16.7%, p = 0.005) (Table 4). Postoperative complications according CD classification gradus I was significantly more documented in the study compared to CG (18.3% *vs.* 4.7%, p < 0.001). There was statistically significant difference in occurrence of minor postoperative complications (CD grade I and II) between the study and CG (Table 5).

DISCUSSION

Obesity is a chronic disease of the modern age. Obesity itself is already a severe condition and patients often have two or more comorbidities [2, 5, 6]. In the present study, more comorbidities were reported in obese patients than in patients for elective cholecystectomy. TIVA and TCI were the most common choice in bariatric patients. There were statistically significant more minor postoperative complications in SG.

In SG, average BMI was 44.9 kg/m², the mean age was 40 and 68.9% of patients were female which is in agreement with results from The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) and in the research of the North-Western Europe countries. IFSO and North-Western Europe countries reported that bariatric patients have an average BMI 40–45 kg/m², are in their forties with the majority of patients being female [11, 15].

According to the results of the National Institute for Public Health in Serbia, 20.8% of the general population is obese [3]. In CG, 26% patients were obese. It seems that a significant number of obese patients are going for the elective surgery daily.

Comorbidity frequency in bariatric patients varies significantly among countries, according to the population studies including hypertension (up to 83.2%), HLP (up to 82.1%), DMT2 (up to 47.4%), and musculoskeletal pain (43.7%) [11, 15, 16, 17]. In this study, bariatric patients suffered from hypertension (55.8%), DMT2 (58%), and HLP (12.6%). The IFSO reported a large variation of the OSA incidence from 49.5% in Canada, Ontario to the lowest rates in Russia (2.7%), and 40% in UK [15, 18]. In the current study, OSA was found in 4.3% patients. The reason for a large disparity in the OSA incidence between observed centers may be found that experts conducting polysomnography studies are needed [15]. COPD was documented in 19% of patients in SG with a statistical difference compared to CG. Verberne et al. [6] reported that one third of patients presenting with COPD have an average BMI of 33.7 kg/m². There was a statistically significant difference between the ASA status in study and CG. The majority of patients were rated with ASA score ≥ 2 in SG, while in CG the most of patients were rated with ASA status 1. According to literature, regardless whether obese patients have comorbidities, they will be rated with a higher ASA status. Patients with a BMI between 30 and 40 will be rated with ASA status 2, and for BMI over 40 with ASA status 3 [19].

The choice of anesthesia technique in obese patients depends of the excessive volume of distribution. These patients are often under- or over-dosed with anesthetic drugs [10, 20].

TIVA and TCI with current pharmacokinetic models represent safe and precise anesthetic techniques, but definitely necessary combustible dose titration in obese patients. The use of BIS monitoring is mandatory, but clinical effects are also important [20, 21]. In the present study, TIVA and TCI with mandatory BIS monitoring were used significantly more often during bariatric surgery compared to cholecystectomy, where BA was used more frequently. Research shows that opioid-free anesthesia in bariatric surgery is also a safe technique [22].

A difficult intubation is expected in bariatric patients. De Jong et al. [23] showed that succinylcholine was the most common choice for muscle relaxation for intubation in the ICU (in 70% of cases), while in the operating room succinylcholine was used in only 19% of obese patients. For intubation, atracurium and cisatracurium were the main choice in 73% of patients, whereas rocuronium was used in only 1% of patients in the operating room, and

11% of patients in the ICU [23]. The frequency of difficult intubations in obese patients was 8.2% in the operating room and 16.3% in the ICU [23]. In our study, difficult intubation was observed only in 0.9% of patients in SG, in contrast to 5.6% patients in CG. This may be explained by the fact that we expected a difficult intubation in SG, and the anesthesiologist was prepared for it. Every patient in SG was positioned according to the recommendations (rapid airway management positioner).

During the induction of anesthesia, the main complication was desaturation – 9.8% in SG compared to 2.1% in CG. De Jong et al. [23] reported severe hypoxemia in ICU obese patients (50%), while in the operating theatre no severe hypoxemia was occurred [24]. In our study, all desaturations during apnea time were lasting less than 90 seconds in both groups and did not affect patient's safety. Reduced oxygen reserve due to lung restriction is the reason for desaturation during apnea time. An adequate patient positioning and nasopharyngeal insufflation of oxygen during the apnea period is sufficient to prevent desaturation in almost 100% of morbid obese patients [25]. In the present study, only in morbid obese patients with BMI > 55 nasopharyngeal insufflation of oxygen was used during the apnea period.

The literature data favor the reversion of the complete neuromuscular blockade [7, 12, 26]. Gaszynski et al. [26] showed the benefit of using sugammadex, the train-of-four ratio was 3.5 times faster, than in the group receiving neostigmine for decurarization [26]. In our study, 82.8% of patients in SG received sugammadex in compared 0.4% of patients in CG for faster and safer reversal of neuromuscular block.

According to a multinational study of North-Western European countries, complications after bariatric intervention occurred in 6.5% of patients. The most common were bleeding, anastomotic leakage, gastrointestinal perforations and postoperative ileus [11]. In our research, the most common complications were CD grade 1 and 2 in SG. There was a statistically significant difference in minor complications between groups, but with no significant difference in major complications. More minor complications were documented in SG.

Limitations

The limitation of this study is that only elective laparoscopic gallbladders were observed in CG. The reason is that it is the most common elective laparoscopic surgery, and patients are discharged home on the first or second postoperative day.

CONCLUSION

This study showed that one third of the patients in the elective program are obese. Bariatric patients are younger with more comorbidities compared to non-bariatric patients. In order to increase the safety of anesthesia in bariatric patients a multidisciplinary approach is required. TIVA and TCI are safe anesthesia technique in bariatric surgery. This study showed that bariatric patients have the same incidence of major postoperative complications as patients after elective cholecystectomy. Further research is needed to determine the clinical significance of our findings, in particular in the safety of the anesthesia technique and incidence of perioperative complications.

Conflict of interest: None declared.

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Анализа коморбидитета и технике анестезије код пацијената на баријатријској хирургији у Универзитетском клиничком центру Србије

Иван Палибрк[1,2,*], Марија Ђукановић[1,2,*], Маја Максимовић-Мандић[2,*], Бојана Миљковић[2], Дубравка Ђоровић[2], Јелена Величковић[1,2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетски клинички центар Србије, Центар за анестезиологију и реаниматологију, Београд, Србија;
*Носиоци рада, који су дали једнак допринос раду

САЖЕТАК

Увод/Циљ Измењена физиологија и метаболизам гојазних пацијената представљају изазов за анестезиолога. Циљеви овога рада су испитивање учесталости коморбидитета, типа анестезије, учесталости интраоперативних и постоперативних компликација код пацијената који су подвргнути баријатријској хирургији и пацијената којима је учињена елективна холецистектомија.

Методе Ова ретроспективна студија је обухватила 469 пацијената. Испитивана група укључивала је гојазне пацијенте са индексом телесне масе ≥ 30. Контролну групу су чинили пацијенти за елективну лапароскопску холецистектомију оперисани истог дана када и баријатријски.

Резултати Испитивана група је укључила 235 пацијената, док је контролна група обухватила 234 пацијента. Учесталост коморбидитета била је статистички значајно већа у испитиваној у односу на контролну групу (84,6% и 63,2%, $p < 0,001$). Постојала је статистички значајна разлика у анестезиолошкој техници – тотална интравенска анестезија и анестезија циљано контролисаном инфузијом више су примењиване у испитиваној групи (74% наспрам 0,9%, $p < 0,001$; 7,2% наспрам 1,7, $p < 0,001$). Број отежаних интубација је био статистички значајно већи у контролној групи (5,6% наспрам 0,9%, $p = 0,004$). Постојала је статистички значајна разлика у инциденци десатурације и хипотензије током увода у анестезију – ове компликације су биле чешће у испитиваној у односу на контролну групу (9,8% наспрам 2,1%, $p < 0,001$; 14,5% наспрам 2,1, $p < 0,001$). Постојала је статистички значајна разлика у инциденци малих компликација између испитиване и контролне групе према класификацији Клавијен–Диндо (20,8% наспрам 5,1%, $p < 0,001$).

Закључак Гојазност је повезана са бројним коморбидитетима и вишом инциденцом интраоперативних компликација. Упркос томе, не постоји статистички значајна разлика у великим постоперативним компликацијама између ове две групе оперисаних болесника.

Кључне речи: гојазност; баријатријска хирургија; коморбидитети; индекс телесне масе

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Breech presentation – maternal and neonatal outcomes and obstetric challenges

Ivana Todić[1], Snežana Plešinac[2,3], Tomislav Stefanović[1]

[1]Zemun Clinical Hospital Centre, Hospital for Gynecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Clinical for Gynecology and Obstetrics, Belgrade, Serbia

SUMMARY

Introduction/Objective Breech presentation occurs in 3–4% singleton pregnancies at term and its management is still a controversial in obstetric practice.
The aim of this study was to determine the factors that indicate breech delivery management and to compare maternal and neonatal outcomes in vaginal breech delivery, planned Cesarean section (C-section) and emergency C-section at the Hospital for Gynecology and Obstetrics of the Zemun Clinical Hospital Centre.

Methods This was a retrospective study conducted from 2015 to 2019. Depending on the mode of delivery, patients were divided in three group. In this study, we have analyzed maternal risk factors and postpartum complications, delivery details and neonatal characteristics and outcomes.

Results The study included 176 women with singleton fetus in breech presentation. The incidence of breech deliveries was 2.12%. Most common way of delivery was vaginal with 47.72%. In all three groups, the majority of women were primiparous, at term, mostly without chronical and gestational diseases. Vaginal delivery was stimulated with oxytocin in 91.67%, and as a help for delivery various maneuvers were used. Maternal mortality and short-term complications during hospitalization period were reported in none of the groups. No significant difference in newborns birth weight between the groups was observed. The highest rate of birth injuries was in newborns from emergency C-section – 10%.

Conclusion The results of our study have shown that vaginal delivery could be a very safe option for both mother and newborn.

Keywords: breech presentation; vaginal delivery; cesarean section

INTRODUCTION

Breech presentation is defined as fetal presentation with the buttocks and/or feet entering the pelvis first, instead of the head. The incidence of breech presentation decreases with gestational age and it occurs in 3–4% singleton pregnancies at term [1]. Depending on the position of the fetal legs, there are three main types of this presentation: Frank breech, complete breech, and incomplete breech. The type of breech presentation has an impact on the course of labor and possible complications. There are several risk factors that prevent spontaneous positioning of the fetus to cephalic presentation and contribute to the occurrence of the breech presentation those included multiparity, uterine malformations, placenta previa, prematurity, excessive amniotic fluid volume, macrosomia, fetal anomaly, previous breech presentation, fetal asphyxia, maternal anticonvulsant therapy, older maternal age [2]. The diagnosis of breech presentation is based on physical examination and ultrasound scan and it should include detailed information about the type of presentation, fetal head position, estimated fetal weight, amniotic fluid index, in order to make decision about the delivery management. Due to increased incidence of perinatal, neonatal and maternal morbidity and mortality compared to delivery in cephalic presentation, breech presentation and delivery are marked as high risk [3].

Over the years the management of breech delivery, vaginal or cesarean section (C-section), has caused many controversies in obstetric practice. After the publication of the Term Breech Trial in 2000, in most countries the rate of vaginal breech delivery has significantly decreased and the cesarean birth is the preferred approach [1]. Recently, global concern about the high rate of C-section worldwide had an impact on rethinking of breech delivery management. Many international organizations and federations, including The International Federation of Gynecology and Obstetrics, the Royal College of Obstetricians and Gynecologists, and the Society of Obstetricians and Gynecologists of Canada support the vaginal breech birth [1].

The aim of this study was to determine the factors that indicate breech delivery management and to compare maternal and neonatal outcomes in vaginal breech delivery, planned C-section and emergency C-section.

METHODS

We conducted a retrospective clinical study that included women with a diagnosis of breech presentation, who were delivered at the

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Correspondence to:
Ivana TODIĆ
Zemun Clinical Hospital Centre
Hospital for Gynecology and Obstetrics
Karađorđeva 14
Belgrade 11000
Serbia
ivana9248@gmail.com

Hospital for Gynecology and Obstetrics, Zemun Clinical Hospital Centre from the January 1, 2015 to December 31, 2019. The study excluded women who had multiple gestation, intrauterine death, and those with incomplete medical data. For data collection we used birth protocols and data from computer database. All procedures in the study were following the principles of the Declaration of Helsinki. The study was approved by Ethical committee of Zemun Clinical Hospital Center on March 21, 2023, with approval number 12/1.

Depending on the route of delivery patients were divided in three groups: vaginal delivery, planned C-section, and emergency C-section. Indications for C-section were absolute and relative defined by Association of Scientific Medical Societies in Germany [4]. Absolute indications were absolute disproportion, chorioamnionitis, maternal pelvic deformity, eclampsia and HELLP syndrome, fetal asphyxia, umbilical cord prolapse, placenta previa, abnormal lie and presentation and uterine rupture. Relative indications included pathological cardiotocography, failure to progress labor and previous C-section [4].

In each of the groups the following characteristics were recorded and analyzed:

1. maternal characteristics: age, parity, mode of conception, mother's medical history and associated diseases;
2. delivery details: spontaneous or stimulated with oxytocin, use of peridural analgesia, total duration of labor, prelabor rupture of membrane (PROM), maneuvers in vaginal breech delivery, episiotomy and perineal tear;
3. neonatal characteristics and outcomes: gestational age at birth, birth weight, length, head circumference, umbilical cord wrapped around the neck, 1st and 5th minute Apgar score, fetal complications as clavicle fracture, long bones fracture, brachial plexus injury, intracranial bleeding and need for intensive care unit;
4. Maternal postpartum complications: severe hemorrhage immediately postpartum, thrombosis, embolism, complications due to pre-existing disease, infections (wound infection, urinary infection and endometriosis) and incontinence.

Obtained study data were analyzed statistically using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The categorical variables were stated as frequencies and percentages and quantitative variables as mean and standard deviation. ANOVA was used for comparation of numerical variables between followed groups. A two-sided p-value < 0.05 was defined as statistically significant. The results are presented in the tables.

RESULTS

Study included 176 women with singleton pregnancy, with fetus in breech presentation, who gave birth at the Hospital for Gynecology and Obstetrics, Zemun Clinical Centre in the observed five-year-period. The total number of deliveries over the study period was 8291, with an incidence of 2.12% of breech deliveries. Depending on the mode of delivery, patients were divided in three groups. First group included 84 women (47.72%) with breech presentation who had vaginal delivery, both spontaneously and stimulated with oxytocin. Second group included 42 women (23.86%) with breech presentation who had had elective C-section. Third group included 50 women (28.42%) breech presentation who had an emergency C-section.

Mean age of women in study was 30.79 ± 5.59 years, with age range 17–45 years. Using ANOVA, it was determined that age does not affect significantly the type of delivery (p = 1.477) (Table 1). In all three group the majority of them were primiparous women with 39 of them (46.4%) in the first group, 25 (59.5%) in the second and 36 (72%) in the third group (Table 1). The number of women with second pregnancy in the first group was 26 (31%), in the second group 12 (28.6%) and 10 (20%) in the last group, while the number of the multiparous women, with three and more pregnancies was decreasing between groups – 18 in group 1 (21.4%), five (11.9%) in group 2, and four in group 3 (8%). Common for all three groups was that the pregnancy has occurred spontaneously. In terms of maternal comorbidities, in the first group none of the women suffered from any chronic or gestational disease. In the second group, diseases were reported in five women – two women had gestational diabetes, two gestational hypertension, and one myopia and hypothyroidism in pregnancy. In the third group, gestational diseases were reported in five women – two preeclampsia, two gestational hypertension, and one gestational diabetes (Table 1).

At the time of delivery almost all women were at term 172 (97.7%). Women who gave birth vaginally were average at 38.75 ± 1.1 gestational week and there were two women in this group who were preterm, both 35 weeks. In the planned C-section group, the average gestation was 39.17 ± 1.1 weeks and there were not preterm births, but there were six post-term – 41 weeks. In the emergency The average gestation in C-section group was 38.9 ± 1.16 weeks, there were two preterm deliveries at 36 weeks, and four post term at 41 weeks (Table 1). The gestational age did not affect the way of ending childbirth (ANOVA, p = 1.93).

In the vaginal delivery group, in 80 women labor started spontaneously, two were hospitalized due to PROM, one was diagnosed with a partial placental abruption and one with an intrauterine growth restriction (IUGR) (Table 1). Vaginal delivery was mostly stimulated with oxytocin in 77 women (91.67%), and in seven women labor occurred natural without stimulation in those who were all multipara and came to the hospital with the cervical dilatation more than 6 centimeters. Only two women had a peridural analgesia. For completing delivery, manual assistance was used and in most cases by Bracht in 70 women (83.3%), 12 (14.3%) Mauriceau–Smellie–Veit and two (2.4%) Müller. Episiotomy was performed in 68 women (80.95%) and two of them had the first-degree perineum tear and one cervical rupture. Only first-degree perineum tear was reported in four women (4.75%). Due to an adherent placenta in one women manual exploration of uterine cavity was performed (Table 2). There were no cases of instrumental deliveries,

Table 1. Birth characteristics of mother and fetus by group

Parameters	Vaginal delivery	Planned C-section	Emergency C-section
Percent of delivered women	47.2%	23.86%	28.42%
Median age	30.3 ± 5.35	33.2 ± 5.45	29.6 ± 5.6
Primiparous women	46.4%	59.5%	72%
Full term	97.6%	85.7%	90%
Chronic disease or gestosis	0	14.2%	10%
Prelabor rupture of membrane	2.38%	0	62%
Fetal macrosomia	3.57%	14.3%	0
Previous uterine operation	0	21.4%	9.7%
Maternal mortality	0	0	0
Maternal short-term complications	0	0	0
Fetal weight	3077.85 g	3562 g	3115 g
Fetal length	51.65 cm	53 cm	51.6cm
Fetal head circumference	34.75 cm	36.4 cm	35 cm
APGAR score 1′/5′	9/10	9/10	9/10
Newborns birth injuries and complications	4%	0	10%

Table 2. Details of vaginal delivery

Parameters	Stimulated with oxytocin	Spontaneous delivery
Number of deliveries	77	7
Prelabor rupture of membrane	2	0
Bracht manual assistance	64	6
Mauriceau–Smellie–Veit manual assistance	11	1
Müller manual assistance	2	0
Episiotomy	67	1
First-degree perineal tear	5	1
Manual revision of uterine cavity	1	0

instrumental revision of uterine cavity, and perineal tear degree III and IV. The average time of total labor duration was three hours and 45 minutes. During hospitalization period, women who had vaginal delivery, did not had any short-term complications such as postpartum hemorrhage, infection, thromboembolic or other complications (Table 1).

In the group of women who had elective C-section indications were: nine (21.4%) had a previous operation on the uterus i.e., a previous c-section i.e., a myomectomy, six (14.3%) had fetal macrosomia, six (14.3%) post term pregnancy, five (11.9%) cephalopelvic disproportion, five (9.5%) uterine myomas, five (9.5%) oligohydramnios, five (9.5 %) advanced maternal age and in one intervertebral disc operation (Table 1). Mean duration of labor in this group was 45 minutes. In women who had undergone an elective C-section, maternal mortality and complications in postoperative hospitalization period were not reported (Table 1).

Speaking about an emergency C-section, indication we divided in two subgroups. First subgroup, 19 of them (38%), were the ones whose labor started spontaneously as a vaginal delivery stimulated with oxytocin, and afterwards due to stasis, in dilatation phase in 14 and threatened fetal asphyxia in five, thus operative management of labor was necessary. For the rest, 31 women with emergency C-section indications were:

1. in 13 women with PROM associated with other conditions such as: five threatened fetal asphyxia, three had previous uterine operation, three IUGR, uterine myomas, one preterm birth, and one had gestational diabetes;
2. in seven oligohydramnios;
3. in three post-term pregnancy;
4. severe preeclampsia (Table 1).

Average labor duration in this group was one hour and 26 minutes, because in some of the women the labor started spontaneously. In this group, maternal mortality and short-term complications during postoperative hospitalization period were not reported (Table 1).

Results related to newborns showed that the average body weight of babies from vaginal delivery were weight 3077.85 gr, length 51.65 cm and head circumference 34.75 cm, in planned C-section it was 3562 gr, length 53 cm and head circumference 36.4 cm and in newborns from the emergency C-section weight was 3115 gr, length 51.6 cm and head circumference 35 cm (Table 1). There was no statistically significant difference in newborns' birth weight between the groups ($p > 0.005$). In all three groups the mean APGAR score in first minute was 9 and in the fifth minute it was 10 (Table 1). Although in one newborn from vaginal birth APGAR score was 3/5, and in two newborns from emergency C-section was 5/7, all of them had recovered and were stable in the 10th minute of life. The umbilical cord wrapped around the neck was noticed in 12 (14%) of newborns from vaginal, in six (14.2%) from elective C-section births, and in 11 (22%) of babies from emergency C-section. Birth complications were present in three newborns vaginal delivery group and they were perinatal asphyxia and respiratory distress syndrome, intracranial hemorrhage, and a clavicle fracture (Table 1). Neonatal birth complications in emergency C-section group were present in six (10%) babies and they were: respiratory distress syndrome in three newborns, brain infection, intracranial hemorrhage, and paresis of brachial plexus (Table 1).

DISSCUSION

The incidence of breech deliveries over the five-year observed study period was about 2–3%, which is in accordance with the incidence worldwide [1]. During the last decades, overall rate of C-section has significantly increased, which is followed by an increase number of breech presentations escalating to C-section [5]. This has led to the loss of familiarity with vaginal breech delivery techniques and skills, especially in younger obstetricians, leaving the C-section often as the only available option. Today there is a global concern about high Caesarean rates worldwide and an urge to return to traditional obstetrics and vaginal delivery. Therefore, it is not surprising that lately there is more support for performing vaginal delivery in breech presentation. Nowadays, we have recommendations in this manner from the French College of Gynecologists and Obstetricians and The American College of Obstetricians and Gynecologists [6, 7].

The results of our study showed that almost a half of women had a vaginal delivery (47.72%), which was similar

to results of some authors from France and Belgium, where the breech delivery was managed following strict protocols. If we compare obtained results with other studies in Serbia, an increased rate of C-section is noticed in a five-year-period [8, 9]. The number of women undergoing vaginal breech delivery still remains high comparing to some other results both from Europe and worldwide, where C-section rates are as high as 70% and over [1, 6, 7, 10, 11]. Almost all the women who had vaginal delivery were at term, healthy, with estimated birth weight less than 4000 gr, so they had no contraindications for vaginal delivery. In terms of parity, primiparous women were the most numerous in all three groups, but with the highest rate in emergency C-section group. Nulliparity is considered as a risk factor for failed vaginal labor and other authors also reported high rates in C-section groups [12]. In this study, the majority of women were stimulated with oxytocin, which other authors do not report and we had a rare use of epidural analgesia which is considered to be effective for women in vaginal birth [1, 2, 13, 14]. Our patients did not go under labor induction, which is one of the factors that adversely affects the outcome of vaginal birth [2, 14]. Bracht's maneuver was used as a help for delivery of the fetal head, while some other reported Mauriceau–Smellie–Veit, which was present with less than 15% in our study [15]. The percentage of performed episiotomy was over 80%, which could be considered as high. due to the opinion that it is something that should not be done routinely, but the variable data are found in literature [1, 14]. Nevertheless, in our study, there were not instrumental deliveries such as outlet forceps for the delivery of fetal head [15]. In the vaginal delivery group, there were no postpartum complications such as bleeding or infections, as well as maternal death, which could be seen as a very good indicator of a safe delivery [16]. The newborns from vaginal birth had an average 9/10 APGAR score, and the majority of them was without any injuries and did not need access to intensive care units, also there was no recorded fetal or neonatal deaths [3]. Fetal birth asphyxia was less frequent in vaginal delivery than in emergency C-section [17].

The elective C-section was the least common mode of delivery and it was performed in less than third of the women (23.86%). Results of the study showed that most frequent indication for C-section was previous uterine surgery and dominantly previous C-section. This is with accordance to similar studies, which confirms that primary C-section leads to the next one, even when vaginal labor could be a safe option [18]. For primiparous women, who were the most frequent in this group, indications were cephalopelvic disproportion, fetal macrosomia, post term pregnancy and oligohydramnios. Estimated birth weight over 3500 gr and post term pregnancy are found to be common indication for elective C-section, especially in primiparous like our patients [2, 17]. In none of the women the indication was just fetal malpresentation i.e., breech presentation or maternal choice [2, 5]. There were no maternal and neonatal complications recorded in elective C-section group, which is in accordance with the current evidence on short-term benefits for the mother and baby with this way of the breech delivery [7].

In a third of patients, an emergency C-section was performed, which is more than the others have reported, mostly due to a higher rate of planned C-section as a safer option [1, 5]. The percentage of primiparous women in this group was the highest in compare to previous ones and most of them were at term pregnancies. We have noticed that in 40% of them the labor was planned as vaginal, but mostly due to statis in dilatation phase i.e., dysfunctional labor or due to threatened fetal asphyxia it was finished operatively. Previously mentioned conditions and umbilical cord prolapse, which did not occur in our population, are found as ones that leads to emergency C-section [15]. Other indications were previous uterine operation, IUGR, uterine myomas, and PROM. Although the majority of newborns had a mean APGAR score 9/10, in this group we had a 10% of birth injuries and complications and they included respiratory distress syndrome, brain infection, intracranial hemorrhage, and paresis of brachial plexus. One of the limitations of this study was that we do not have available data whether those newborns admitted to neonatal intensive care unit because after birth they were transferred to another medical institution for further diagnosis and treatment. For the same reason, eventual long-term consequences in those babies remain unknown. However, the obtained data suggest that emergency childbirth should be avoided and emphasize the importance of proper planning of breech delivery.

Concerning the fetal weight as a very important factor that affects the decision of breech delivery ending, this parameter was analyzed. The average birth weight in all three groups was over 3000 gr (3077–3159 gr) and there was no statistically significant difference in newborns birth weight between the groups, which an important predictor for a successful vaginal delivery [12]. However, the largest average birth weight was noticed in planned C-section group where the fetal macrosomia was the second most common indication for elective C-section. This result is in accordance with other researches as well with recommendations about the importance of correct estimate of the fetal size and confirms that the decision of planning C-section in cases of fetal macrosomia is completely justified [19]. In addition to fetal weight, other important factor that could affect delivery outcome are woman's characteristics presented with obstetrical conjugate. Although there was a high incidence of cephalopelvic disproportion in both planned and emergency C-section group, in the study we have not specifically analyzed this parameter, which is also one of the study limitations.

CONCLUSION

The results of our study have shown that vaginal delivery is very safe option for both mother and newborn. Obstetric skills and accurate prenatal maternal and fetal assessment are the key for making the best possible decision on delivery management.

Conflict of interest: None declared.

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Карлична презентација плода – материални, неонатални исходи порођаја и савремени акушерски изазови

Ивана Тодић[1], Снежана Плешинац[2,3], Томислав Стефановић[1]

[1]Клиничко-болнички центар „Земун", Болница за гинекологију и акушерство, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија

САЖЕТАК

Увод/Циљ Карлична презентација плода се јавља у 3–4% једноплодних терминских трудноћа и начин завршавања порођаја код ње још увек представља контроверзу у акушерској пракси.

Циљ ове студије био је да утврди факторе који су утицали на вођење и начин завршетка порођаја код карличне презентације плода и да упореди материалне и неонаталне исходе порођаја код вагиналног порођаја, планираног царског реза и хитног царског реза у Болници за гинекологију и акушерство Клиничко-болничког центра „Земун".

Методе Истраживање је спроведено као ретроспективна клиничка студија у периоду од 2015. до 2019. године. У зависности од начина завршетка порођаја породиље су биле подељене у три групе. У истраживању смо анализирали факторе ризика од стране мајке и њене постпарталне компликације, карактеристике порођаја и неонаталне исходе порођаја.

Резултати Истраживање је обухватило 176 жена са једноплодном трудноћом и фетусом у карличној презентацији. Учесталост порођаја са карличном презентацијом плода је била 2,12%. Најчешћи начин завршетка порођаја био је вагинални – 47,72%. У све три испитиване групе најзаступљеније су биле прворотке, у термину, без хроничних обољења и гестоза. Вагинални порођај је био стимулисан окситоцином у 91,67% случајева и као помоћ при порођају коришћени су различити маневри. Смртност мајке и краткорочне компликације током периода хоспитализације нису забележене ни у једној групи. Није примећена значајна разлика у тежини новорођенчета између група. Највећа стопа порођајних повреда забележена је код новорођенчади рођених хитним царским резом – 10%.

Закључак Резултати нашег истраживања указују да би вагинални порођај могао да представља врло безбедну опцију и за мајку и новорођенче.

Кључне речи: карлична презентација; вагинални порођај; царски рез

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A connection between levels of soluble Fas and Fas ligand in the aqueous humor and the parameters of structural and functional damage of glaucoma patients

Marija Trenkić[1,2], Tatjana Jevtović-Stoimenov[1], Jelena Bašić[1], Miroslav Stamenković[3], Jasmina Jocić-Đorđević[1,2], Milan Trenkić[1]

[1]University of Niš, Faculty of Medicine, Niš, Serbia;
[2]University Clinical Center of Niš, Clinic for Ophthalmology, Niš, Serbia;
[3]University of Belgrade, Zvezdara University Clinical Center, Eye Clinic, Belgrade, Serbia

SUMMARY

Introduction/Objective Fas ligand (FasL) induces apoptosis when interacting with the Fas-receptor. The aim was to determine the concentration of soluble Fas (sFas) and soluble FasL (sFasL) in the aqueous humor (AH) of open-angle glaucoma patients, and establish a connection between these markers of apoptosis and the parameters of structural and functional glaucoma damage.

Methods This study examined 88 AH samples; 35 primary open-angle glaucoma with elevated intraocular pressure (POAG-HTG) patients, 24 open angle pseudoexfoliative glaucoma patients (XFG) and 29 patients with senile cataract (CAT). The concentration of sFas and sFasL was determined by commercial ELISA tests in the AH.

Results The conducted study showed that AH sFas concentration was the highest in XFG (720.14 ± 167.39 pg/ml), and slightly lower in POAG-HTG (713.43 ± 162.69 pg/ml), than in cataract patients (632.46 ± 217.11 pg/ml), without statistical significance. There was a significant negative correlation of sFas concentration and thickness of the peripapillary nerve fibers of the retina (RNFL) inferior thickness in POAG-HTG ($p < 0.05$). The concentration of sFasL was the lowest in POAG-HTG (9.28 ± 0.551 pg/ml), higher in XFG (9.45 ± 0.61 pg/ml; $p = 0.0566$), and the highest in the cataract group (9.48 ± 0.73 pg/ml). A negative correlation of sFasL and MD in the POAG-HTG, and a negative correlation with RNFL superior in the XFG were significant.

Conclusion sFasL has an active role in the regulation of the inflammatory process in glaucoma. sFas and sFasL, as markers of apoptosis, are associated with the parameters of structural, RNFL thinning, and functional glaucoma damage, namely visual field defects.

Keywords: Fas; FasL; aqueous humor; open angle glaucoma; hypertensive glaucoma; pseudoexfoliation

INTRODUCTION

Fas is a transmembrane glycoprotein, and a type I membrane protein of the tumor necrosis family (TNF), which binds Fas ligand (FasL) to its receptor [1]. In addition to its role in the apoptosis induction, Fas causes a pro-inflammatory response of cytokines [2]. The interaction of Fas and FasL is important in controlling the T-cell immune response and affecting cell death via cytotoxic T-lymphocytes (T-Ly) [1–4].

FasL is a type II membrane protein. As a member of the TNF-cytokine family, FasL induces apoptosis when interacting with the Fas receptor. The membrane bound FasL (mFasL) can become a soluble form (sFasL), by acting of a matrix metalloproteinase as an enzyme. FasL binding to Fas leads to receptor oligomerization and causes apoptotic cell death. FasL is predominantly expressed in activated T-Ly and natural killer cells, and in tissues and immune privileged organs, such as the testicles, placenta, brain and the eye (retina, uvea and cornea) [2, 5, 6, 7].

Wax et al. [8] have indicated that the T-cell mediated degeneration of the retinal ganglion cells (RGC) takes place via the Fas/FasL signaling pathway. Some studies have shown reduced capacity of naturally produced sFasL to induce apoptosis compared to membrane-bound FasL, indicating the selectivity of sFasL. The sFasL in the aqueous humor (AH) may be present due to high FasL expression in intraocular cells [9, 10].

Primary open-angle glaucoma with elevated intraocular pressure (POAG-HTG) is closely related to elevated intraocular pressure (IOP), which may occur due to difficult outflow of humor aqueous through trabecular meshwork (TM) [11]. A finding in POAG patients suggests that the number of TM-cells is significantly reduced in relation to a healthy population of the same age. Aging-related loss of TM cells is thought to occur due to an increased rate of cell death. Also, an increased rate of apoptosis may cause loss of TM cells in POAG. Agarwal et al. [12] showed that after receptor activation by monoclonal Ig M, TM-cells express the Fas receptor and undergo transient apoptosis. Preventing the binding of membranous Fas

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Correspondence to:
Marija TRENKIĆ
University of Niš
Faculty of Medicine
Department of Ophthalmology
University Clinical Center of Niš
Clinic for Ophthalmology
Bulevar. dr Zorana Đinđića 81
18000 Niš
Serbia
marija.trenkic@medfak.ni.ac.rs

to FasL, by binding soluble Fas (sFas) to FasL, can block Fas-mediated apoptosis. Therefore, it can be hypothesized that the increase in the rate of cell death from TM results from decreased levels of sFas or increased levels of FasL in glaucoma [1, 12, 13]. Also, in glaucoma, FasL expressed in microglia promotes neuroinflammation via activation of Fas+ astrocytes, Müller cells and microglia, as well as apoptosis of Fas+ RGCs [5, 14]. Membrane-associated FasL (mFasL) and soluble FasL (sFasL) fragment show opposite effects on glaucoma development.

In the healthy eye, FasL is constitutively cleaved and sFasL maintains a non-inflammatory homeostatic environment. In experimental glaucoma models with IOP, microglia activation occurs and FasL expression increases, resulting in a shift from sFasL to mFasL that contributes to RGC apoptosis. When FasL cleavage is disabled, accelerated and much more severe glaucoma occurs. While stimulated production of sFasL by long-lived neurons provides significant neuroprotection of RGCs and axons [5, 15].

Recent studies revealed a paradoxical phenomenon related to FasL function within the eye, where ocular expression of mFasL promotes immunoreactivity. Even though it has been shown in some studies that sFasL antagonizes the functional effect of mFasL, and in others that sFasL can bind to ocular matrix proteins and thus trigger potent apoptotic activity, it remains unclear how immune-privileged sites regulate FasL activity and control the potentially dangerous consequences associated with inflammation and apoptosis [2, 16].

The aim of this study was to determine the concentration of sFas and FasL in the AH of open-angle glaucoma patients and establish a connection between these markers of apoptosis and the parameters of structural and functional glaucoma damage.

METHODS

This study examined 88 AH samples; 35 patients suffering from POAG-HTG (hypertensive glaucoma), 24 open-angle pseudoexfoliative glaucoma patients (XFG), and 29 patients with senile cataract (CAT).

The Ethical Committee of the Faculty of Medicine in Niš (decision number 01-2625-18, dated 08/04/2014) and the Ethical Committee of the University Clinical Center Niš (decision number 338/43, dated 13/01/2015) granted approval for conducting the research. Prior to engaging in the research, all participants signed informed consent according to the Declaration of Helsinki.

Clinical examination included: demographic characteristics of the patients, detailed medical history, visual acuity with refraction (Snellen chart), biomicroscopy, Goldmann applanation IOP tonometry, three mirrors Goldman gonioscopy, indirect ophthalmoscopy using a 90D lens and determination of the cup size of the optic nerve head (C/D ratio), standard automatic perimetry (Humphrey Visual Field Analyzer, Threshold Test 24-2, Carl Zeiss Meditec, Inc., Dublin, CA, USA) with determining changes in the visual field: mean deviation (MD), optical coherent tomography (OCT, Stratus, Carl Zeiss Meditec, Inc.) and measuring the average thickness of the peripapillary nerve fibers of the retina (RNFL Avg), in the superior (RNFL Sup) and the inferior (RNFL Inf) quadrants [17].

Diagnostic criteria for POAG-HTG included elevated IOP, characteristic arcuate Bjerrum scotoma, and/or paracentral scotoma, and/or Rönne's nasal step, and other corresponding visual scotomas, and/or thinning of the nerve fibers on OCT, gonioscopy open angle finding, and the absence of a secondary cause of glaucomatous optic neuropathy. Patients with a history of inflammatory eye diseases, uveitis, congenital or normotensive glaucoma and systemic factors (systemic rheumatologic and inflammatory diseases) and systemic drug usages, previous administration of corticosteroids, previous trauma, that would affect the level of the examined markers, were excluded from the study [17].

Patients with XFG had been previously diagnosed according to established criteria: elevated IOP, visual field changes, RNFL thinning, such as for POAG-HTG, with the presence of pseudoexfoliation on the anterior lens capsule and/or along the pupil margin.

Patients with POAG-HTG and XFG subjected to antiglaucomatous surgery had intraocular pressure values greater than 21 mmHg during daytime with antiglaucomatous therapy. They had had a confirmed diagnosis of glaucoma for several years and maximum drug therapy in the form of drops (prostaglandin, beta blocker, carbonic anhydrase inhibitor).

The control group consisted of patients referred for CAT surgery, without serious systemic diseases and with no personal and family history of glaucoma. Glaucoma was excluded in these patients applying the same diagnostic criteria used to diagnose POAG-HTG or XFG, i.e., after the same ophthalmological examination and procedures.

The AH sampling was performed at the very beginning of the antiglaucomatous surgery and ultrasound cataract surgery, in sterile conditions, by limbal paracentesis. Sterile insulin syringe 1 ml/cc with a needle 29G X 1/2" was used, whereas any contact with the corneal endothelium, iris and lens was avoided. Special care was taken to ensure the samples did not contain blood. The AH samples (100–150 μL) were immediately stored at -80°C.

The concentration of sFas and sFasL in the AH of the patients was determined by commercial enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions (ELH-Fas and ELH-FASL-1, RayBiotech, Peachtree Corners, GA, USA). The concentration was determined using the standard curve and expressed in pg/ml. The minimum detectable dose (MDD) for Fas was 5 pg/ml and for Fas ligand was 2 pg/ml, with no significant cross-reactivity or interference with other proteins.

Statistical processing was performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). We used descriptive statistical parameters (absolute numbers, relative numbers, arithmetic mean, standard deviation, median, and an interval of variation: minimum and maximum values). The Mann–Whitney U-test or the Student's

t-test for independent samples were used for two groups of subjects, the Kruskal–Wallis test and ANOVA were used for multiple groups, the Student's t-test and ANOVA were used for continuous variables with normal distribution. Spearman's rank correlation coefficient was used to test the strength of the association between two continuous variables. Univariate linear regression analysis was used to test the influence of independent, predictor variables on the value of the continuous dependent variable. A value of $p < 0.05$ was used as a threshold of statistical significance.

RESULTS

Demographic characteristics of 88 participants (35 POAG-HTG + 24 XFG + 29 CONTROL- CATARACT), basic clinical parameters of glaucoma (IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf), and AH levels of sFas and sFasL are shown in Table 1.

The results of this study showed no significant difference in age between the examined groups (Kruskal–Wallis test and Mann–Whitney test). POAG-HTG and XFG were found to be more prevalent in men (54.28%, i.e., 58.33%), whereas, in the control group, women were more prevalent (51.73%); however, there was no significant difference between the groups. The highest IOP value was found in XFG patients. IOP values in both glaucoma groups were significantly higher compared to the control group ($p < 0.001$). The values of the C/D ratio were almost identical in the POAG-HTG and the XFG group, without significant difference. Although the absolute value of MD was higher in XFG, it was not significantly different from the value of this parameter in POAG-HTG. All POAG-HTG and XFG patients were in the second and the third group according to the Hadopp classification, without statistically significant differences in distribution. Average RNFL thickness, RNFL thickness in the superior and inferior quadrants, were higher in XFG patients, however, not significantly compared to POAG-HTG patients.

We did not determine significant differences in sFas concentration in the AH between the groups although sFas in the AH was the highest in XFG patients (720.14 ± 167.39 pg/ml), and higher in POAG-HTG patients (713.43 ± 162.69 pg/ml), compared to the control group (632.46 ± 217.11 pg/ml). The difference between POAG-HTG and the control was nearly significant ($p = 0.0505$), whereas the difference between XFG and the control was also very close to statistical significance ($p = 0.0657$).

In addition, no differences were found in the sFasL concentration of POAG-HTG and XFG patients and

Table 1. Demographic and clinical characteristics, and aqueous humor levels of sFas and sFasL in glaucoma patients and the control group of subjects with cataract

Parameters	POAG-HTG (n = 35)	XFG (n = 24)	Control (n = 29)	Tests
Age (year) X ± SD (Me) Min–Max	70.95 ± 7.93 70 58–87	73.41 ± 6.25 76 59–84	71.77 ± 9.38 74 51–88	Kruskal–Wallis test Mann–Whitney test
Gender (M/F)	19 (54.28%) /16(45.72%)	14 (58.33%) /10 (41.67%)	14 (48.27%) /15 (51.73%)	/
IOP (mmHg) X ± SD (Me) Min–Max	21.86 ± 7.37^{c***} (20) 10–48	**23.58 ± 11.31**^{c***} (20.50) 10–56	14.76 ± 2.39 (14) 8–20	c- *vs*. control, ***-p < 0.001 Kruskal–Wallis and Mann–Whitney test
C/D X ± SD (Me) Min–Max	0.64 ± 0.20 (0.60) 0.4–1	0.63 ± 0.18 (0.55) 0.4–1	not determined	Mann–Whitney test
MD (dB) X ± SD (Me) Min–Max	-11.73 ± 9.05 (-8.46) -0.38–-31.27	-12.72 ± 11.21 (-8.62) -0.07–-29.69	not determined	Mann–Whitney test
RNFL Avg (µm) X ± SD (Me) Min–Max	78.09 ± 24.39 (80.98) 24.46–143.71	78.62 ± 21.54 (81.63) 45.77–103.69	not determined	Mann–Whitney test
RNFL Sup (µm) X ± SD (Me) Min–Max	92.38 ± 34.50 (96) 26–180	100.64 ± 37.66 (104) 44–161	not determined	Mann–Whitney test
RNFL Inf (µm) X ± SD (Me) Min–Max	94.41 ± 37.55 (101) 29–157	96.10 ± 31.11 (91) 57–144	not determined	Mann–Whitney test
sFas (pg/ml) X ± SD (Me) Min–Max	713.43 ± 162.69 (759.80) 369.95–958.22	720.14 ± 167.39 (776.63) 166.99–921.60	632.46 ± 217.11 (727.79) 83.83–862.33	Kruskal–Wallis and Mann–Whitney test
sFasL (pg/ml) X ± SD (Me) Min–Max	9.28 ± 0.551 (9.35) 8.33–10.78	9.45 ± 0.61 (9.60) 8.52–10.40	9.48 ± 0.73 (9.46) 8.44–10.82	Kruskal–Wallis, Mann–Whitney test, and Student's t-test

n – number of participants/eyes and examined samples of the aqueous humor; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; Control – control group with cataract; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillar retinal nerve fiber layer thickness; RNFL Sup – peripapillar retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillar retinal nerve fiber layer thickness in the inferior quadrant; sFas – soluble Fas; sFasL – soluble Fas ligand

Table 2. Spearman's rank correlation coefficient for sFas and the examined clinical parameters in glaucoma patients

ρ FAS (pg/ml)	VA	IOP	C/D	MD	RNFL Avg	RNFL Sup	RNFL Inf
POAG-HTG	-0.12	0.06	0.06	0.07	-0.29	-0.20	*-0.33
XFG	0.06	-0.22	-0.17	-0.38	-0.35	-0.43	-0.28
All glaucoma patients	0.01	0.14	0.03	-0.01	*-0.31	-0.27	*-0.35

*p < 0.05, - ρ – Spearman's rank correlation coefficient;
sFas – soluble Fas; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; VA – visual acuity; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillary retinal nerve fiber layer thickness; RNFL Sup – peripapillary retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillary retinal nerve fiber layer thickness in the inferior quadrant

Table 3. Spearman's rank correlation coefficient for sFasL and the examined clinical parameters of glaucoma patients

ρ FasL (pg/ml)	VA	IOP	C/D	MD	RNFL Avg	RNFL Sup	RNFL Inf
POAG-HTG	0.11	0.18	0.17	*-0.32	-0.31	-0.27	-0.30
XFG	-0.11	-0.11	-0.12	-0.29	-0.43	*0.62	-0.07
All glaucoma patients	-0.11	-0.08	0.10	*-0.31	*-0.32	*-0.35	*-0.31

*p < 0.05, - ρ – Spearman's rank correlation coefficient;
sFasL – soluble Fas ligand; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; VA – visual acuity; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillary retinal nerve fiber layer thickness; RNFL Sup – peripapillary retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillary retinal nerve fiber layer thickness in the inferior quadrant

eyes with CAT (9.48 ± 0.73 pg/ml). The concentration of sFasL in the AH was the lowest in POAG-HTG patients (9.28 ± 0.551 pg/ml); almost significantly lower in relation to XFG patients (9.45 ± 0.61 pg/ml; p = 0.0566). Spearman's rank correlation coefficient was tested for the association of sFas concentration in the AH and visual acuity, IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf of the examined patients (Table 2). POAG-HTG patients had a statistically significant negative correlation between sFas concentration in the AH and RNFL Inf (p < 0.05). All glaucoma patients (POAG-HTG and XFG) had the significant negative correlations of sFas concentration with morphological parameters obtained by OCT: RNFL Avg and RNFL Inf (p < 0.05). Spearman's rank correlation coefficient was also tested for the association of sFasL concentration in the AH and visual acuity, IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf of the examined glaucoma patients (Table 3). In the group of patients with POAG-HTG, the negative sFasL correlation with MD (p < 0.05) was statistically significant. In the group of XFG patients, a negative correlation with RNFL Sup (p < 0.05) was statistically significant. All glaucoma patients had significant negative correlations of sFasL with the functional visual field parameter MD, and morphological OCT parameters RNFL Avg, RNFL Sup, and RNFL Inf (p < 0.05).

Univariate linear regression analysis was used to assess the effect of sFas and sFasL concentration on the values of IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf parameters and confirmed FasL, as the only factor that significantly affects RNFL Sup in XFG patients (Table 4).

DISCUSSION

Various proapoptotic stimuli lead to the initiation of biochemical processes and activate a large family of proteases and caspases, which are the major executors of apoptosis. The outer and inner pathway of caspase activation is equally admixed into glaucoma, in the reduction of trabecular cellularity and RGC apoptosis, including TNF-α, FasL, IL-1α, IL-1β, and IL-6 [18, 19, 20]. However, Rolle et al. [20] state that in neurodegenerative diseases, as well as in glaucoma, necroptosis as a genetic form of cell death plays a major role. It is very similar to necrosis, and is characterized by cell swelling, granular cytoplasm, chromatin fragmentation, and cell lysis, but differs from apoptosis because the cell contents move into the extracellular matrix passively through an altered cell membrane. TNF-a, Fas, apoptosis-inducing ligand interferons can induce necroptosis [20].

Our study showed that sFas concentration in AH was the highest in XFG, and higher in POAG-HTG patients compared to the cataract group, without significant differences between the tested groups. This is not entirely in line with the results obtained by Razeghinejad et al. [1], who found the highest Fas values in XFG, followed by CAT, and POAG, respectively, nor with the results of Sugita et al. [7]. However, Okamura et al. [21] found that apoptosis plays an important role in the development of cataracts with DR, but not in CATs. Hence, there is no explanation for higher levels of sFas in cataract patients. We found a significant negative correlation between sFas concentration in AH and RNFL Inf of POAG-HTG patients (p < 0.05). Therefore, sFas may be an indicator of glaucoma damage in the inferior quadrant.

Our study showed that the AH concentration of sFasL was the lowest in POAG-HTG patients. Although the sFasL values in POAG were similar to those found by Razeghinejad et al. [1], we did not find a significant

Table 4. Estimation of the influence of sFas and sFasL factors on the values of RNFL Sup (μm); results of univariate linear regression analysis for patients with POAG-HTG and XFG

Parameters	POAG-HTG				XFG			
Factor	t	p	B	95% CI for B	t	p	B	95% CI for B
sFas (pg/ml)	-0.65	0.5209	-0.02	-0.07 - 0.04	-1.11	0.2967	-0.20	-0.62 - 0.21
sFasL (pg/ml)	-0.67	0.5100	-5.86	-23.74 - 12.02	-2.29	0.0479	*-48.47	-96.39 - -0.55

*p < 0.05;
t – statistical test value; p – statistical significance; B – regression coefficient; 95% CI for B – 95% confidence interval for B; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; sFas – soluble Fas; sFasL – soluble Fas ligand

connection, contrary to their findings. The current study confirmed a significant ($p < 0.05$) negative correlation of sFasL with MD, and a nearly significant ($p = 0.0594$) negative correlation with RNFL Avg, in the group of POAG-HTG patients. In the group of XFG patients, a negative correlation with RNFL Sup was significant ($p < 0.05$). This leads to the connection between the concentration of FasL and both structural and functional parameters of glaucoma patients.

Razeghinejad et al. [1] showed no significant difference in the sFas concentration between the XFG and the cataract group ($p = 0.72$). Although our values of sFasL are similar to those of Razeghinejad et al. [1], no significance has been confirmed either. Also, they found no correlation between sFas levels, as well as sFasL concentration, and vertical C/D ratio in POAG and XFG ($p = 0.52$, $p = 0.65$; $p = 0.58$, $p = 0.64$). The level of sFas in POAG, which was significantly lower than in the control group, was explained by the binding of FasL to Fas and a higher rate of trabecular cell apoptosis, which ultimately led to increased resistance to AH outflow [1].

Sugita et al. [7] showed significant AH levels of sFasL in patients with CAT and no ocular inflammation, thus indicating that AH in its normal condition contains significant amounts of sFasL. Contrary to these results, Borkenstein et al. [18] reported that levels of cytokines (TNF-α, IL-1α and FasL) were below the detection limit, in a multiplex bead study conducted by analyzing the AH samples of 25 patients with POAG and 29 patients with cataract, which were interpreted by choosing various methods [18–23].

This discrepancy between studies may be caused by different conditions of the puncture and sampling of the AH from the anterior chamber, as well as the use of different ELISA tests. The amount of sFasL detected in the AH can be affected by a contact of the syringes with ocular structures, blood contamination from the limbal blood vessels, or tear film with its own concentration of sFasL. In our study, special care was taken to avoid contact of needles and the iris. Samples contaminated with blood were not processed. Only 100–150 μl of AH was taken, and a certain amount always remained in the anterior chamber. On the other hand, Sugita et al. [7] extracted a critical amount of HA of 0.2 ml.

Gregory-Ksander and Marshak-Rothstein [5] in their recent studies in mice have shown that under homeostatic conditions membrane-bound FasL is preferentially cleaved into a soluble fragment, sFasL. Soluble-FasL contributes to the mechanisms responsible for immune privilege and may alter the inflammatory effects of mFasL, blocking both apoptosis and inflammation. When pathogenic mFasL isoform levels exceed normal, immune privilege is revoked and destructive inflammation begins or the onset of other ocular pathology. Therefore, it is important to study the roles of all FasL isoforms in the pathology of eye diseases [5, 20]. The neurodestructive effect of sFas in glaucoma can be blocked via sFaL or a small Fas-inhibitor peptide that blocks the activation of Fas and mFasL and prevents the neuroinflammation development and provides neuroprotection for RGCs and their axons. [5, 20, 24].

Hence, in glaucoma we can expect an increase in sFas and mFasL, while there is no increase in sFasL, the only isoform that can be measured by ELISA tests in the AH, which is partially in line with our research results.

Considering that sFasL has an active role in limiting eye inflammation, this opens up new possibilities for new therapeutic applications of sFasL in regulating the inflammatory process in glaucoma and other eye disorders [5, 20, 24, 25]. Rolle et al. [20] outlined various molecular mechanisms and new therapeutic possibilities, mentioning ONL1204. It is a small peptide antagonist of the Fas receptor, that blocks microglial activation and inhibits the induction of multiple genes involved in glaucomatous disease, and significantly reduces RGC death and axonal loss [20].

Due to all these conflicting results, the role of Fas/FasL in glaucoma is only partially elucidated. Finally, our findings do not clarify the influence of Fas/FasL, but this study shows that a larger, adequately powered, and well-designed study is needed to explore the role of sFas and sFasL in glaucoma genesis.

CONCLUSION

sFasL has an active role in the regulation of the inflammatory process in glaucoma. sFas and sFasL, as markers of apoptosis, are associated with the parameters of structural, RNFL thinning, and functional glaucoma damage, namely visual field defects.

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Веза између нивоа растворљивих Фас и Фас-лиганда у очној водици и параметара структурног и функционалног оштећења код болесника са глаукомом

Марија Тренкић[1,2], Татјана Јевтовић-Стоименов[1], Јелена Башић[1], Мирослав Стаменковић[3], Јасмина Јоцић-Ђорђевић[1,2], Милан Тренкић[1]

[1]Универзитет у Нишу, Медицински факултет, Ниш, Србија;
[2]Универзитетски клинички центар „Ниш", Клиника за офталмологију, Ниш, Србија;
[3]Универзитет у Београду, Универзитетски клинички центар „Звездара", Очна клиника, Београд, Србија

САЖЕТАК

Увод/Циљ Фас лиганд (ФасЛ) индукује апоптозу када је у интеракцији са Фас рецептором. Циљ овог истраживања је био да се утврди концентрација растворљивих Фас и ФасЛ у очној водици болесника са глаукомом отвореног угла и успостави веза између ових маркера апоптозе и параметара структурног и функционалног оштећења изазваног глаукомом.

Методе Овом студијом испитано је 88 узорака очне водице, 35 болесника оболелих од примарног глаукома отвореног угла са повишеним интраокуларним притиском (*POAG-HTG*), 24 болесника са псеудоексфолијативним глаукомом отвореног угла (*PEKSG*) и 29 испитаника са сенилном катарактом. Концентрација растворљивих Фас и ФасЛ одређена је комерцијалним ЕЛИСА тестовима у очној водици.

Резултати Спроведена студија показала је да је концентрација растворљивог Фас у очној водици највећа код болесника са *PEKSG* (720,14 ± 167,39 *pg/ml*), нешто нижа код болесника са *POAG-HTG* (713,43 ± 162,69 *pg/ml*), а најнижа код катаракте (632,46 ± 217,11 *pg/ml*), без статистичке значајности. Постојала је статистички значајна негативна корелација између концентрације растворљивог Фас и дебљине перипапиларних ретиналних нервних влакана (*RNFL*) у доњем квадранту код болесника са *POAG-HTG* ($p < 0,05$). Концентрација растворљивог ФасЛ била је најнижа код болесника са *POAG-HTG* (9,28 ± 0,551 *pg/ml*), виша код болесника са *PEKSG* (9,45 ± 0,61 *pg/ml*; $p = 0,0566$), а највећа у групи са катарактом (9,48 ± 0,73 *pg/ml*). Значајна је била негативна корелација растворљивог ФасЛ и средње девијације у групи болесника са *POAG-HTG*, као и негативна корелација са *RNFL* у групи болесника са *PEKSG*.

Закључак Растворљиви ФасЛ активно регулише инфламаторни процес код глаукома. Растворљиви Фас и ФасЛ, као маркери апоптозе, повезани су са параметрима структурног оштећења, истањења *RNFL*, и функционалног глаукомног оштећења, односно испада у видном пољу.

Кључне речи: Фас; ФасЛ; очна водица; глауком отвореног угла; хипертензивни глауком; псеудоексфолијација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Assessment of the socio-emotional state of persons with presbyacusia using hearing amplification

Ivana Maletić-Sekulić[1], Mila Bunijevac[1], Ninoslava Dragutinović[2], Vesna Simikić[1]

[1]Sveti Vračevi Public Health Institution Hospital, Bijeljina, Republic of Srpska, Bosnia and Herzegovina; [2]MediGroup General Hospital, Belgrade, Serbia

SUMMARY

Introduction/Objective Presbycusis or senile hearing loss is a physiological phenomenon that manifests as a gradual effect of hearing loss in adults. The aim of this work is to examine the socio-emotional state of elderly people with hearing loss.

Methods The research was conducted at the Department of Audiology and Vestibulology of the Zemun Clinical Hospital Center. A subjective assessment was conducted using the Hearing Handicap Inventory for the Elderly – HHIE scale. This questionnaire is designed to assess the emotional and social functioning of people with presbycusis and to monitor the effect of auditory rehabilitation. Basic data were obtained through audiological diagnostics, questionnaires and interviews with respondents.

Results 120 subjects participated in this research, 60 subjects with senile hearing loss using auditory amplification and 60 subjects with senile hearing loss without hearing amplification. In subjects with auditory amplification, there is no statistically significant difference in the results of the HHIE at the beginning of the study and after one year ($t = 1.07$, $df = 59$, $p = 0.28$), but a statistically significant difference is observed in the HHIE-S score ($t = 3.0$, $df = 59$, $p = 0.004$). In 17 subjects who did not have a hearing aid at the beginning of the research, during the research, for a period of one year, auditory amplification was carried out and a good correlation between the HHIE and the subscales on the HHIE test/retest was established.

Conclusion Hearing amplification often does not fulfill its goal in individuals – to improve listening and speech intelligibility, which may be a consequence of untimely amplification.

Keywords: old age; presbycusis; hearing impairment; hearing rehabilitation

INTRODUCTION

Presbycusis or senile hearing loss is a physiological phenomenon, which is a gradual, cumulative effect of hearing loss in adults [1]. It is a progressive and irreversible, bilateral hearing loss due to degeneration of the cochlea and related inner ear structures or auditory nerves. It is a sensorineural hearing loss characterized by the inability to translate or transmit sound signals into nerve impulses [2]. The process of hearing loss lasts several years, is gradual, and most often affects the high frequencies of hearing first, sometimes unrecognizable because the presentation and clinical course can be variable. Presbycusis is characterized by reduced hearing sensitivity and reduced intelligibility of speech in a noisy environment, slowed central processing of acoustic information, and impaired localization of sound sources [3]. In addition, hearing loss accompanied by difficulties in speech intelligibility contributes to a decrease in concentration and memory, which negatively affects the social isolation of these persons.

The cause of presbycusis is a combination of multiple factors – genetics, cumulative environmental exposures, and pathophysiological changes associated with aging [4]. Based on numerous studies, it was concluded that presbycusis most often refers to the loss of sensory structures in the inner ear, although the main causes are still unclear [5].

Living with hearing loss is, in many ways, experienced by patients as having a chronic illness. Older people often ignore their ailments and do not accept listlessness, sadness, which is due to age, shame, lack of understanding or fear of feeling rejected. Many people experience social isolation and rejection in old age as a result of single life, lack of close family ties. In people with hearing impairment, the possibility of communication is reduced, which leads to social isolation, because the sense of hearing is an important prerequisite for social interaction [6]. Difficult or impossible communication can also lead to emotional difficulties that usually accompany some chronic conditions (endocrinological, vascular, neurological, oncological) [7, 8]. Research shows that with the progression of hearing loss, anxiety occurs most often [9]. Clinically significant symptoms of anxiety are present in 15–42% of elderly people and most often occur in those who have a chronic disease or some degree of disability. The prevalence of anxiety disorders in older people ranges 12–15% in society, and up to 28% in clinical institutions [10]. Anxiety as an emotional disorder is reflected in a number of biological, social and physical factors. Anxiety symptoms, fear, poor sleep quality, loss

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Correspondence to:
Ivana MALETIĆ SEKULIĆ
Sveti Vračevi Public Health Institution Hospital
Srpske vojske 53
76300 Bijeljina
Republic of Srpska
Bosnia and Herzegovina
bosanka25@yahoo.com

of interest, reduced concentration, chronic unexplained pain are often attributed to old age, dementia or a person's poor general condition, which means that anxiety in old age can be undiagnosed for a long time and therefore inadequately treated [11]. In these patients, it is very important to diagnose poor audiology and the time when hearing amplification should be recommended in order to prevent physical, cognitive and functional conditions. The main goal of the rehabilitation of these patients is to minimize the effect of the hearing deficit and enable them to actively participate in family and social activities, helping them to cope with the hearing loss and the limitations it causes. Most often, monaural adaptations are carried out, even with bilateral hearing loss.

The reasons for this can be different: refusal to use two hearing aids, reduced ability to handle the devices, asymmetric hearing loss, reduced central processing of information, aesthetic reasons, financial problems, etc. [12]. Timely hearing rehabilitation can give significant results; however, it must be taken into account that the optimal time interval for the intervention is very short so that the hearing rehabilitation results are as effective as possible [13].

The aim of this work is to examine the socio-emotional state of elderly people with hearing loss with hearing amplification at the beginning of research and a year after that, and also of people without hearing amplification at the at the beginning of research and a year after using it.

METHODS

Study design and procedures

A total of 120 subjects participated in this research, 60 subjects with senile hearing loss using hearing amplification and 60 subjects with senile hearing loss without hearing amplification. The age of the respondents ranged 47–85 years. The selection of subjects was carried out after audiological observation and evaluation at the Department of Audiology and Vestibule at Clinical Hospital Center Zemun after establishing or confirming the diagnosis of senile hearing loss.

The research was conducted from April 2017 to September 2018 at the Department of Audiology and Vestibulology of the Zemun Clinical Hospital Center. The basic data were obtained on the basis of audiological diagnostics, through questionnaires and interviews with respondents. The first examination was conducted when the subjects came to the otorhinolaryngology or audiology clinic, and the second examination was performed one year later.

A subjective assessment of social and emotional functioning was conducted using a Likert-type scale, the Hearing Handicap Inventory for the Elderly – HHIE [14]. This questionnaire was designed to assess the emotional and social functioning of subjects with presbycusis and to monitor the effect of auditory rehabilitation. The scale is composed of two subscales – the HHIE-E subscale, which has 13 items and examines the emotional consequences of hearing impairment, and the HHIE-S subscale, which comprises 12 items and investigates social and situational aspects. Respondents responded to the offered answers: yes (4), sometimes (2), and not (0), according to the current state. HHIE scores range 0–16 (no hearing impairment), 17–42 (mild to moderate hearing disability), > 43 points (significant hearing disability).

We used a Likert scale to assess the general hearing score as bad, neither bad nor good, good, and excellent (Table 2).

In the statistical processing of the data, descriptive measures, the arithmetic mean with the associated standard deviation, as well as the minimum and maximum were used. Frequency and percentages, and t-test for dependent samples were used. The level of statistical significance was defined as $p < 0.05$ for all analyses. Statistical processing and analysis was done using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

The research has received consent by the decision of the Ethics Committee, of the Zemun Clinical Hospital Center (protocol number 224/1-2017).

RESULTS

A total of 120 respondents aged 46–85 years participated in this research. The average age of the respondents was 68.68 years, and standard deviation was 8.4.

In the group of respondents with hearing amplification, there were 31 (51.7%) male respondents and 29 (48.3%) female respondents, while in the group without hearing amplification there were 29 (48.3%) male respondents and 31 (51.7%) female respondents (Table 1).

Table 1. Structure of respondents by gender, with hearing amplification and without hearing amplification

Auditory amplification		Gender		Total
		M	F	
Yes	Number	31	29	60
	%	25.8	24.2	50
No	Number	29	31	60
	%	24.2	25.8	50
Total	Number	60	60	120
	%	50	50	100

Table 2. Hearing Handicap Inventory for the Elderly Scale – subjects with auditory amplification at the beginning of research

General hearing score	N = 60	HHIE		HHIE-S		HHIE-E	
		M	SD	M	SD	M	SD
No answer	1	/	/	/	/	/	/
Poor	4	61	9.3	36	3.65	25	7.63
Neither good nor poor	30	50.93	17.07	30.73	9.21	20.2	9.57
Good	22	45.45	21.25	26.82	11.6	18.64	11.04
Very good	3	40.7	25.32	28.67	19	12	10

HHIE – Hearing Handicap Inventory for the Elderly Scale; M – average; SD – standard deviation

The group of respondents with hearing amplification (Table 2) defines their health as neither good nor

Table 3. Hearing Handicap Inventory for the Elderly Scale – subjects without auditory amplification at the beginning of research

General hearing score	N = 60	HHIE		HHIE-S		HHIE-E	
		M	SD	M	SD	M	SD
No answer	2	/	/	/	/	/	/
Poor	2	83	4.24	47	1.41	36	2.82
Neither good nor poor	28	48.25	17.41	29.07	9.32	19.18	9.83
Good	26	37.46	15.61	24.92	8.93	12.54	7.62
Very good	2	44	2.82	29.2	13.46	14	2.82

HHIE – Hearing Handicap Inventory for the Elderly Scale; M – average; SD – standard deviation

Table 4. Hearing Handicap Inventory for the Elderly Scale – test and retest of respondents with auditory amplification

Test	M	SD	Stand. error	t	p
HHIE test HHIE retest	50.03 48.43	19.32 19.32	2.47 2.47	1.07	0.28
HHIE-S test HHIE-S retest	30.03 26.98	10.73 10.75	1.37 1.37	3	0.004*
HHIE-E test HHIE-E retest	20 21.44	10.23 10.33	1.31 1.32	-1.88	0.06

HHIE – Hearing Handicap Inventory for the Elderly Scale; M – average; SD – standard deviation; t – hearing disability; p – social interaction;
*statistically significant ($p < 0.05$)

Table 5. Hearing Handicap Inventory for the Elderly Scale – test and retest of respondents with subsequent auditory amplification

Test	M	SD	Stand. error	t	p
HHIE test HHIE retest	43.12 37.18	22.19 21.11	5.38 5.12	2.7	0.016*
HHIE-S test HHIE-S retest	26.71 21.65	12.86 9.95	3.12 2.41	2.96	0.009*
HHIE-E test HHIE-E retest	16.41 15.53	10.57 11.54	2.56 2.8	0.64	0.52

HHIE – Hearing Handicap Inventory for the Elderly Scale; M – average; SD – standard deviation; t – hearing disability; p – social interaction;
*statistically significant ($p < 0.05$)

bad (n = 30): HHIE (M = 50.93; SD = 17.07), (HHIE-S (M = 30.73; SD = 9.21), HHIE-E (M = 20.20; SD = 9.57), which is in the domain of mild to moderate hearing impairment that has a negative impact on emotional and social functioning in daily life activities. Hearing amplification enables better listening; however, its quality depends on several factors so that the impaired person people with hearing loss, despite hearing correction, often cannot clearly define their attitude and its impact on the overall state of health.

The group of respondents without hearing amplification (Table 3) defines their health as neither good nor bad (n = 28): HHIE (M = 48.2; SD = 17.41), HHIE-S (M = 29.07; SD = 9.32), HHI-E (M = 19.18; SD = 9.83), which is in the domain of mild to moderate hearing impairment that negatively affects emotional and social functioning in daily life activities.

Table 4 shows the average score (M) and standard deviation (SD) of the HHIE test and retest scores of subjects with auditory amplification: HHIE test (M = 50.03; SD = 19.32), HHIE retest (M = 48.43; SD = 19.35); HHIE-S test (M = 30.03; SD = 10.73), HHIE-S retest (M = 26.98; SD = 10.75); HHIE-E test (M = 20; SD = 10.23); HHIE-E retest (M = 21.44; SD = 10.33). A dependent samples t-test examined the difference between test and retest HHIE, HHIE-S, and HHIE-E scores, in terms of mean score, standard deviation, and degrees of freedom (SD and df) to determine whether the difference was large enough so that it could be considered statistically significant ($p < 0.05$).

In the total score of the HHIE, no statistically significant difference was observed at the beginning of the study and after one year in the subjects with hearing amplification ($t = 1.07$, $df = 59$, $p = 0.28$), but a statistically significant difference was observed in the score of the HHIE-S ($t = 3.0$, $df = 59$, $p = 0.004$), with a lower mean score of the HHIE-S on the retest (test M = 30.03, SD = 10.73 / retest M = 26.98, SD = 10.75), which confirms the audiological view of the positive effects of auditory amplification on the reduction hearing disability and improving social interaction. The analysis of the HHIE-E subscale did not reveal a statistically significant difference ($t = -1.88$, $df = 59$, $p = 0.06$) on the test and retest.

In the case of 17 subjects who did not have a hearing aid at the beginning of the research, hearing amplification was carried out during the research, over a period of one year. A good correlation of the HHIE score and subscales on the test/retest was found (Table 5). HHIE at the beginning of the research and after one year, for significance level $p < 0.05$: HHIE test/retest ($t = 2.7$, $df = 16$, $p = 0.016$); HHIE-S test/retest ($t = 2.96$, $df = 16$, $p = 0.009$); HHIE-E test/retest ($t = 0.64$, $df = 16$, $p = 0.52$). Comparing the average HHIE on the test (M = 43.12; SD = 22.19) and retest (M = 37.18; SD = 21.11), we can see that after hearing amplification the subjective assessment of hearing impairment was expressed to a lesser degree after one year. The statistical significance of the difference between the HHIE-S score on the test and the retest ($p = 0.009$) was observed, and by comparing the average score on the test (M = 26.71; SD = 12.86) and the retest (M = 21.65; SD = 9.95), a lower assessment of hearing disability was observed on the retest, which indicates a significant impact of auditory amplification on the social component of hearing disability. Auditory amplification, the ability to listen and establish communication influenced the improvement of the social life of the respondents. By comparing the value of the HHIE-E subscale score ($p = 0.52$), no statistically significant difference was observed between the non-test and the retest in subjects who underwent auditory amplification during the research.

DISCUSSION

Listening is a complex process of absorbing and interpreting sound and is essential for understanding information [15]. Hearing makes it possible to localize sound, that is – navigate in space, perform complex life functions, and exchange information. However, over the course of life, the sense of hearing decreases in each individual following the process of physiological aging [16].

In this research study, there were an equal number of male and female respondents. Among those with auditory amplification, there were 31 (51.7%) male respondents and 29 (48.3%) female respondents. In the group without auditory amplification, there were 29 (48.3%) male respondents and 31 (51.7%) female respondents. These findings are consistent with previous research [17, 18].

The age of the respondents in this study ranged 46–85 years, the average age of the respondents was 68.68 years. The results of this study are comparable with the results of a number of studies that state that hearing loss occurs in the elderly [19, 20].

Hearing loss in people with presbycusis occurs gradually; very often, the period until hearing amplification is very long (five to 10 years). Losing the ability to hear and clearly understand a particular voice message leads to alienation, isolation, loneliness, and reduced energy. In this way, a person with hearing loss becomes an observer and not an active participant in their life [21].

The results of the research in this study showed a negative impact of hearing impairment on the socio-emotional state of persons with presbycusis ($p = 0.002$, for $p < 0.05$) with greater hearing disability after one year (test / M = 44.29, SD = 15.73; retest / M = 49.29; SD = 15.73) in the group without auditory amplification, which confirms previous views about the negative impact of hearing impairment on the quality of life and deepening of complaints if hearing correction is not performed [22, 23]. Older adults with hearing loss face many of the same fears as any person with a disability. External factors also have a significant effect on the feeling of hearing impairment: environment, education, socio-economic status, satisfaction with family and professional life, as well as many other life issues and situations to which a person is exposed. Due to limited opportunities for communication, social isolation and other consequences, people with presbycusis often experience a deterioration in their general health, i.e. anxiety and depression [24]. However, in the case of 17 respondents who did not have a hearing aid at the beginning of the research, during the research, over a period of one year, hearing amplification was carried out. A good correlation of the HHIE score and subscales on the HHIE test/retest at the beginning of the study and after one year was established, for the significance level $p < 0.05$: HHIE test/retest ($t = 2.7$, $df = 16$, $p = 0.016$); HHIE-S test/retest ($t = 2.96$, $df = 16$, $p = 0.009$); HHIE-E test/retest ($t = 0.64$, $df = 16$, $p = 0.52$). Auditory amplification, the ability to listen and establish communication influenced the improvement of the socio-emotional life of these respondents. In order to enable good social and professional functioning, the rehabilitation program of the elderly should be aimed at alleviating the factors that limit their participation in society.

The goal of auditory rehabilitation is to improve listening function, maintain functionality in the social environment, increase self-esteem, improve cognitive abilities, and enable the prevention of many conditions [25, 26, 27]. Auditory rehabilitation is achieved by providing a technological device – a hearing aid in order to improve sound reception and thus the listening process. Listening support involves teaching people how to use technology and how to create an optimal environment [28, 29].

An important part of auditory rehabilitation is positive transfer with the patient, which, firstly, includes monitoring and support during auditory amplification. Considering the frequent existence of prejudices or bad experiences about the functionality of hearing aids, professional support is needed during their use. Therefore, individual screening is a very important factor that affects the success of hearing rehabilitation, as well as the improvement of the socio-emotional state of the affected persons [30].

CONCLUSION

Hearing amplification often does not fulfill its goal in individuals – to improve listening and speech intelligibility, which may be a consequence of untimely amplification. The results of our work point to the necessity of conducting hearing rehabilitation with an overview and systematic monitoring of the use of hearing aids, as well as determining the need for speech rehabilitation based on the conducted tests with the aim of improving communication and the quality of life of people with presbycusis.

Conflict of interest: None declared.

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Процена социјалног и емоционалног стања особа са пресбиакузијом које користе слушну амплификацију

Ивана Малетић-Секулић[1], Мила Буниjевац[1], Нинослава Драгутиновић[2], Весна Симикић[1]

[1]ЈЗУ Болница „Свети Врачеви", Бијељина, Република Српска, Босна и Херцеговина;
[2]Општа болница *MediGroup*, Београд, Србија

САЖЕТАК

Увод/Циљ Пресбиакузија или старачка наглувост је физиолошка појава која се манифестује постепеним губитком слуха код одраслих особа. Циљ овог рада је испитати социјално и емоционално стање код старијих особа са оштећењем слуха.

Методе Истраживање је спроведено на Одсеку за аудиологију и вестибулогију Клиничко-болничког центра „Земун". Спроведена је субјективна процена Упитником о слушном хендикепу за одрасле особе (*Hearing Handicap Inventory for the Elderly – HHIE*). Овај упитник дизајниран је за процену емоционалног и социјалног функционисања особа са пресбиакузијом, као и за праћење ефекта слушне рехабилитације. Основни подаци добијени су аудиолошком дијагностиком, путем упитника и интервјуом са испитаницима.

Резултати У овом истраживању учествовало је 120 испитаника – 60 испитаника са старачком наглувошћу који користе слушну амплификацију и 60 испитаника са старачком наглувошћу без слушне амплификације. Код испитаника са слушном амплификацијом у резултатима *HHIE* на почетку истраживања и после годину дана нема статистички значајне разлике ($t = 1,07$, df = 59, $p = 0,28$), али у скору *HHIE-S* уочава се статистички значајна разлика ($t = 3$, $df = 59$, $p = 0,004$). Код 17 испитаника који на почетку истраживања нису имали слушни апарат, током једногодишњег истраживања спроведена је слушна амплификација и утврђена је добра корелација *HHIE* и подскале на тесту/ретесту *HHIE*.

Закључак Слушна амплификација често код појединаца не испуњава свој циљ – побољшање слушања и разумљивост говора, што може бити последица неблаговремене амплификације.

Кључне речи: старост; пресбиакузија; слушна онеспособљеност; рехабилитација слуха

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Positive outcome of a twin pregnancy after the administration of tocilizumab to a pregnant woman with severe COVID-19

Isidora Dickov[1,2], Sanja Bulatović[1], Đorđe Petrović[1,2], Ksenija Antić-Trifunović[1], Anita Krsman[1,2]

[1]University Clinical Center of Vojvodina, Clinic for Gynecology and Obstetrics, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Department of Gynecology and Obstetrics, Novi Sad, Serbia

SUMMARY

Introduction Tocilizumab is an IgG1 monoclonal antibody targeting the interleukin 6 receptor. We present a case of a pregnant woman with COVID-19 pneumonia, which rapidly worsened despite the advanced treatment. Therefore, the administration of tocilizumab was deemed necessary.

Case outline Our patient was a 31-year-old pregnant woman hospitalized on the seventh day after contracting COVID-19. She was in the 21st week of a twin pregnancy, specifically monochorionic diamniotic. Her general condition was severe, accompanied by elevated inflammation markers: C-reactive protein – 94.6 (mg/L), procalcitonin – 1.44 (ng/mL), and IL-6 – 79.3 (pg/mL), along with extensive bilateral pneumonia evident in the X-ray image. She required respiratory support in the form of high flow nasal cannula, continuous positive airway pressure, and intensive monitoring. The following day, her condition deteriorated further, prompting the decision to administer tocilizumab. After receiving tocilizumab, the X-ray image deteriorated, but the inflammation markers decreased. After 33 days of hospitalization, she was discharged with normal laboratory findings and a clear X-ray. On July 16, the patient was admitted to the Clinic for Gynecology and Obstetrics of the Clinical Center of Vojvodina at 36 weeks of gestation (35 gw + 2 day) due to premature contractions. On the same day, a caesarean section was performed, and both neonates were in good general condition.

Conclusion Managing severe COVID-19 in pregnant women poses significant challenges. This case study suggests that tocilizumab may hold efficacy in treating this condition.

Keywords: tocilizumab; bilateral pneumonia; twin pregnancy; IL-6

INTRODUCTION

The cytokine storm, or cytokine release syndrome, plays a pivotal role in the progression and exacerbation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cytokine release syndrome involves an uncontrollable immune response marked by elevated cytokine levels, notably IL-6 [1]. A significant challenge during the COVID-19 pandemic is the absence of a proven antiviral drug, especially for pregnant women. Tocilizumab (TCZ) has displayed considerable efficacy in curbing the inflammatory response to SARS-CoV-2, potentially preventing cytokine storms. Hence, this medication is being explored as an off-label treatment for moderate to severe COVID-19 [2]. TCZ, known as RoActemra® in the European Union, is a humanized monoclonal IgG1 antibody targeting the IL-6 receptor. It impedes IL-6 binding to cell receptors, reducing immune-mediated damage [3]. Treating pregnant women with COVID-19 poses uncertainties [4]. The United States Food and Drug Administration (FDA) has categorized TCZ as a category C drug in pregnancy [5]. There is a general belief that due to its size and hydrophilic nature, TCZ mainly remains in the blood plasma and extracellular fluid [6]. However, the expanded circulating fluid volume in pregnant women might lead to reduced plasma concentration of many medications as is the case with TCZ [7]. Some studies have verified TCZ's ability to cross the placental barrier, detected through cord blood tests, newborn plasma, and even in breast milk [8]. Nonetheless, there is no definitive evidence indicating an elevated risk of congenital anomalies [9].

CASE REPORT

Our patient is a 31-year-old pregnant woman in her second pregnancy (G2P1) in the 21st gestation week (gw) of spontaneously conceived and regularly monitored monochorionic-diamniotic twin pregnancy without any complications. She was admitted to the Clinic for Gynecology and Obstetrics of the Clinical Center of Vojvodina (CGO CCV) on April 3, 2021, on the seventh day of the illness due to worsening general condition caused by SARS-CoV-2. Her symptoms started in the form of nasal congestion and weak unproductive cough when nasopharyngeal swab was positive for COVID-19, based on reverse transcription-polymerase chain reaction (RT-PCR). During the initial four days, the patient received oral

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Correspondence to:
Isidora DICKOV
Branimira Ćosića 37
21000 Novi Sad, Serbia
isidoradickov1@gmail.com

Table 1. Laboratory data during the course of COVID-19

Laboratory findings and reference values \ Day of the disease	7th	8th	9th	10th	11th	16th	27th	40th
Wbc * (10^9/L) (4–10)	4.75	7.97	8.67	7.16	9.33	11.27	10.62	7.21
Neutr * (10^9/L) / (%) (2–7) / (50–70)	4.26/89.7	7.36/92.4	7.77/89.6	6.12/85.5	7.77/83.3	9.41/83.5	7.95/74.8	4.52/62.7
Lymph * (10^9/L) / (%) (0.8–4) / (20–40)	0.4/8.4	0.53/6.6	0.76/8.8	0.89/12.4	1.32/14.1	1.26/11.2	1.47/13.8	1.56/21.6
CRP (mg/L) (< 5)	94.6	98.4	100.2	46.7	22.7	1.4	0.28	0.09
PCT (ng/mL) (< 0.05)	1.44	1.42	1.08	0.67	0.42	0.08	< 0.05	< 0.05
Rbc * (10^{12}/L) (3.9–5.4)	2.9	3.2	2.9	2.8	2.9	3	3.31	2.99
Hbg (g/L) (120–160)	88	94	86	82	86	89	99	89
Hct (L/L) (0.37–0.47)	0.26	0.28	0.26	0.25	0.26	0.26	0.29	0.26
PLT * (10^9/L) (140–400)	93	117	122	153	178	302	257	110
D-dimer (mg/L) FEU (< 0.5)	1.27	2.06	1.45	2.06	5.40	4.5	1.56	0.89
Blood sugar (mmol/L) (3.9–6.1)	5.2	6.6	4.3	4.4	5.4	5.3	4.5	4.8
Arterial blood analysis								
pH	7.41	7.42	7.45	7.43	7.45	7.47	7.47	
pCO_2 (mmHg)	36	37	38	42	42	38	34.4	
pO_2 (mmHg)	85	87	91	104	351	163	100.2	
Lac (mmol/L)	1.1	1	0.8	1.6	1.5	1.4	1.72	
HCO_3 (mmol/L)	22.8	25.2	26.4	27.9	29.2	27.7	25.7	
SO_2 (%)	96	96	97	98	100	100	100	

Wbc – white blood cells; Neutr – neutrophils; Lymph – lymphocytes; Rbc – red blood cells; Hbg – hemoglobin; HCT – hematocrit; PLT – platelets; pCO_2 – partial pressure of carbon dioxide; pO_2 – partial pressure of oxygen; Lac – lactate; HCO – bicarbonate; SO_2 – oxygen saturation

cephalosporin antibiotic (cefixime) as an outpatient. As her condition worsened with the increased body temperature up to 38°C, she was subsequently admitted to a secondary health facility where she underwent treatment with parenteral cephalosporin antibiotic (ceftriaxone), antipyretics, and received oxygen therapy through a nasal cannula. She had never undergone surgery, had not had any serious illnesses, did not receive regular therapy for chronic conditions and she did not have any allergies. On the admission to CGO CCV, the patient was conscious, oriented, communicative, without neurological symptoms, afebrile, normotensive, tachycardic up to 120 beats/minute, tachypneic with 26 respirations per minute, and oxygen saturation 88–92% with oxygen therapy via oxygen mask flow of 15 L/minute. We verified by ultrasound a vital monochorionic-diamniotic twin pregnancy at the 21st gw, a normal amount of amniotic fluid, placenta localized on the posterior wall, and both fetuses exhibited normal anatomical structures. During the examination, there was a further drop in oxygen saturation to 85% with 29 respirations per minute. Due to her severe general condition, respiratory insufficiency and tachydyspnea, she was transferred on the same evening to the Intensive Care Unit (ICU) and noninvasive ventilatory support was started. The continuous positive airway pressure (CPAP) started with (FiO_2 100%, PEEP 5 cmH_2O, Psupp 5 cmH_2O) with the intermittent application of high-flow nasal cannula (FiO_2 100%, flow 70 L/minute) where saturation of oxygen (SpO_2) was 100%. Gas analysis and blood count (Table 1) showed the patient's anemia with elevated values of inflammation markers CRP and procalcitonin. Next morning, the X-ray revealed bilateral diffuse opacities that radiologically correspond to massive bilateral pneumonia with preserved transparency of the lung apices (Figure 1). On the eighth day of the illness and the second day of hospitalization, dual antibiotic parenteral therapy ceftriaxone 1 gr / 24 hours and piperacillin/tazobactam 4.5 gr / 6 hours, corticosteroid dexamethasone 8 mg / 24 hours i.v., therapeutic doses of low molecular weight heparin (LMWH) dalteparin 5000 IU / 12 hours s.c., gastroprotective pantoprazole 40 mg / 24 hours *per os*, and vitamin therapy were prescribed according to the National Guide for the Treatment of SARS-CoV-2, Version 11 [9]. Dual antibiotic therapy was prescribed for only one day, after which it was continued with piperacillin/tazobactam monotherapy. During the same afternoon the patient was afebrile, normotensive, tachycardic up to 123 beats/minute, tachypneic with 27 respirations per minute with rapid desaturation on room air SpO_2 < 80%. The IL-6 value was 79.3 pg/mL, which is nearly 20 times higher compared to values in healthy pregnant women in the second and third trimesters of pregnancy. Considering the worsening of her general condition, extremely elevated IL-6 levels and values of inflammatory parameters, massive bilateral pneumonia, the need for high FiO_2 and oxygen therapy flows, in agreement with the infectious disease specialist, it was decided an administration of intravenous TCZ in a double dose of 8 mg/kg for 2 days (on the eighth and ninth days of the disease). After the second dose, there was a decrease in the values of the inflammation markers with an increased level of d-dimer (Table 1). Despite unchanged parameters of oxygen therapy, there is an improvement in arterial blood gas exchange (Table 1). On the 10th day, the patient's general condition was better. The control X-ray image, taken a day after the second dose of TCZ (Figure 2)

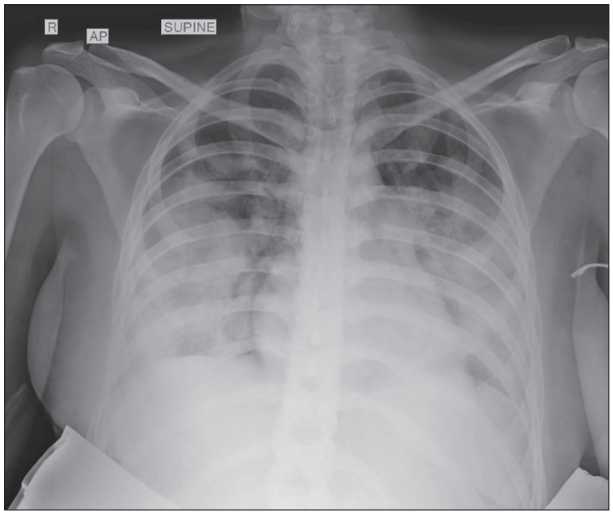

Figure 1. X-ray of the patient's heart and lungs on the eighth day of illness, before the administration of tocilizumab; chest radiograph reveals shadows in bilateral lung fields, with preserved transparency of the lung apices

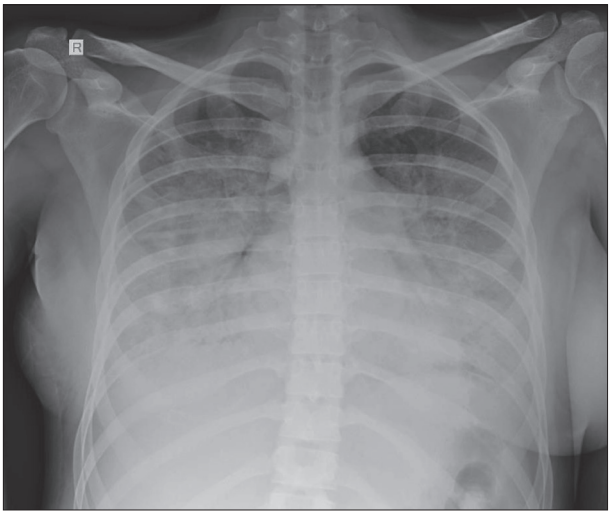

Figure 2. X-ray of the patient's heart and lungs a day after the administration of two doses of tocilizumab; lung fields on both sides with persistent diffuse shadowing, more extensive compared to the previous finding

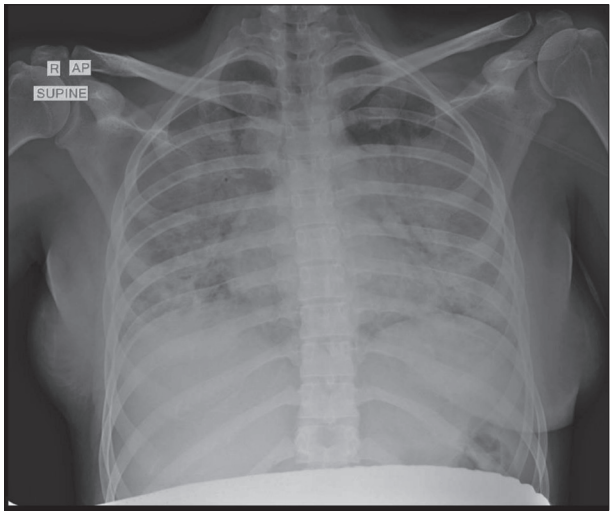

Figure 3. X-ray of the patient's heart and lungs seven days after the administration of two doses of tocilizumab; compared to the previous chest X-ray, there is slightly increased transparency in the right lung and lower part of left lung due to a mild regression in the density of merged consolidations, accompanied by a less pronounced air bronchogram and a more clearly outlined hemidiaphragm – all consistent with mild regression

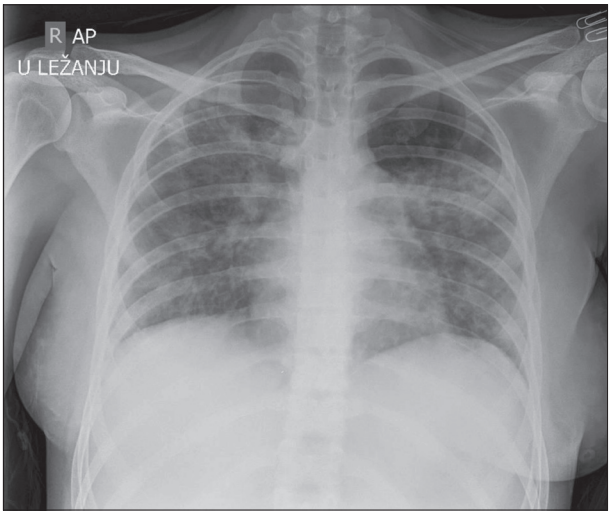

Figure 4. X-ray of the patient's heart and lungs 14 days after the administration of two doses of tocilizumab; significant regression of inflammatory changes in the lung parenchyma on both sides

indicates a progression of bilateral pneumonia with less prominent lung apex transparency. Regarding the course of the pregnancy and an ultrasound examination, everything was normal, and the pro-inflammatory markers continued to decrease. Due to the improvement in saturation, the usage of high-flow nasal cannula and continuous positive airway pressure was stopped, so the patient began using an oxygen mask with an oxygen flow of 12 L/minute. The administration of parenteral antibiotics was completed on the 16th day of the illness. The blood tests revealed normal renal and liver function tests as well as the analysis of urine and hemostatic system. Anemia was persistent in laboratory findings, with reduced iron levels of 6.5 μmol/L (reference range for the second trimester of pregnancy is 8–32 μmol/L), along with normal values of transferrin, ferritin, folic acid, and vitamin B_{12}. Mild leukocytosis was also present, a phenomenon called glucocorticoid-induced leukocytosis [10]. Due to the continuous use of corticosteroids, blood sugar levels were measured daily, which showed elevated values only once – 6.6 mmol/L. Seven days after the second dose of TCZ, an X-ray was taken again (Figure 3), where a greater transparency of both lungs and a clearer outline of both hemidiaphragms was evident, which pointed to the regression of the disease. Considering the improved general condition, the reduced need for oxygen therapy as well as the vital twin pregnancy, it was decided to transfer the patient to the CGO CCV, to a unit dedicated to pregnant women and postpartum mothers with COVID-19 named Covid-7 unit of CCV after 10 days spent in the ICU. During her stay at the CGO CCV, the vital parameters, blood, and urine laboratory analyses, as well as regular ultrasound checks, were consistently monitored.

As the gas exchange parameters improved, the patient received oxygen therapy through a 7 L/minute flow mask, but after a few days the patient switched to oxygen therapy via a nasal cannula. On the 27th day of the illness, in the laboratory findings, the inflammation marker continued to decline along with the improvement of anemia. Fourteen days after the administration of two doses of TCZ, the X-ray (Figure 4) was performed, which showed a significant regression of the inflammatory changes in the lung parenchyma on both sides. After 25 days of hospitalization, the use of corticosteroids was completely stopped, gradually decreasing the dosage daily. In the following days, the administration of oxygen therapy was discontinued. The patient was breathing spontaneously, maintaining oxygen saturation 98–99% in room air, with a respiratory rate of 16–18 breaths per minute. After 33 days spent in the hospital, the patient was discharged. She had normal vital parameters without any subjective complaints. Ultrasound findings showed a normal twin pregnancy. On July 16, 2021, the patient was hospitalized again at the CGO CCV, due to premature contractions in the 36th gw. On the same day, a caesarian section was performed, and both neonates were in good general condition. The patient was feeling well, without any respiratory complaints. The blood laboratory analysis showed persistent anemia, with negative CRP findings. Two live male neonates were born with body masses of 2850 g and 2590 g, respectively, and body lengths of 48 cm each. Both Apgar scores (AS) were 10/10. The caesarian section was uneventful under spinal anesthesia, with blood loss of about 400 mL and regular vital parameters. Neonates were eutrophic, normal muscle tone and well adapted. Due to prematurity and monochorionic twin pregnancy, both neonates were admitted to the semi-intensive care unit. Three hours after delivery, capillary blood gas analyses were performed on both twins and acid-base status, gas analysis, glycemia, and electrolytes of the capillary blood were normal. Blood cultures and CRP levels were tested and found to be negative. Still, a dual antibiotic treatment was empirically applied for a concise period of three days. The neonates went to the nursery regularly. There were no signs or effects of COVID-19. On the fifth postoperative day, the patient was discharged with both children. At the time of discharge, both twins were in a good overall condition, with normal findings in capillary blood. The postoperative period proceeded without complications or any symptoms of respiratory insufficiency. The histopathological examination of the placenta revealed a monochorionic placenta without pathological changes. On the follow-up examinations, the patient was in good general condition with an uneventful postpartum course.

In a phone conversation with the patient two years after the delivery, she mentioned having no health issues and regularly consulting a pulmonologist. Regarding her children, both boys are healthy, showing age-appropriate psychomotor development, up to date with vaccinations, and attending kindergarten alongside their peers.

The written consent to write and publish this case report was obtained from the patient. The review was approved by the Ethics Committee of the Clinical Center of Vojvodina number 00-88/22.

DISCUSSION

In light of sparse data, our objective was to evaluate the maternal and neonatal safety outcomes linked to the administration of TCZ in pregnant patients severely affected by COVID-19 at CGO CCV. The Treatment Protocol for COVID-19 in the Republic of Serbia (11th Version) [11], alongside the majority of international protocols for managing SARS-CoV-2, recommends the use of IL-6 inhibitors, corticosteroids, LMWH, and oxygen therapy, in addition to starting empirical antibiotic treatment pending the identification of specific pathogens [12]. A particularly alarming observation for our medical team was the marked elevation of IL-6 levels in our patient. It's noted that serum IL-6 concentrations are naturally higher in pregnant women compared to non-pregnant women. Furthermore, these levels are elevated in the later stages of pregnancy, the second and third trimesters (below 4.4 pg/mL), in comparison to the first trimester (below 3.52 pg/mL). Our patient's IL-6 levels were found to be almost 20-fold higher than those observed in healthy women during their second and third trimesters [13]. According to the study by Isaac et al. [14], the classification of pregnant women upon their hospital admission was based on the WHO severity scale, a tool recommended by the WHO Working Group for the Clinical Characterization and Management of COVID-19 infection to assess the progression of the disease in patients. This scale spans from 0 (uninfected) to 10 (deceased), indicating disease severity and involves signs of clinical worsening, such as increased need for oxygen, declining radiographic outcomes, and escalating levels of inflammatory markers like IL-6, CRP, and d-dimer [15]. Upon the patient's admission to the CGO CCV, the WHO score was 5, which increased to 6 in less than 12 hours. Our decision to start TCZ treatment was made as our patient exhibited clinical and radiological deterioration and her WHO score increasing. In the research conducted by Isaac et al. [14], 28 expectant mothers with a WHO severity score of six and critical COVID-19 were treated with TCZ. Their findings indicated that the majority of these patients experienced a steady recovery in both clinical and radiological terms following the initiation of therapy, with no substantial adverse reactions observed in either the mothers or their babies. Similar findings were reported by Abdullah et al. [16], in a report of two pregnant women with evidence of acute cytokine storm. Both of these patients improved clinically after the use of a single dose of intravenous TCZ in addition to supportive treatments. The most extensive trial included, RECOVERY [17], demonstrated that administering a low dose of dexamethasone reduced mortality by 20% in COVID-19 patients needing oxygen and by 33% in those requiring mechanical ventilation. Considering that pregnancy is already a thrombotic

condition, with increased production of thrombin and intravascular inflammation, we immediately started with prophylactic doses of LMWH. In our patient, the presence of multiple elevations in procalcitonin and CRP values indicated the possibility of a bacterial superinfection. This led to the commencement of empirical antibiotic treatment. Considering the heightened levels of neutrophils, as well as the requirement for non-invasive ventilatory support and a stay in the ICU, the decision was made to prescribe piperacillin/tazobactam as a category B drug for use in pregnancy by the FDA [18].

Thanks to a multidisciplinary team consisting of an infectious disease specialist, gynecologist, intensivist, pulmonologist, radiologist, anesthesiologist, and a neonatologist, the patient was successfully cured, without consequences for her or her children's health.

The additional research is certainly needed on the effectiveness of TCZ use and the potential side effects of this drug in pregnant women with severe clinical course of COVID-19.

Conflict of interest: None declared.

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Позитиван исход близаначке трудноће после примене тоцилизумаба код труднице са тешким обликом ковида 19

Исидора Дицков[1,2], Сања Булатовић[1], Ђорђе Петровић[1,2], Ксенија Антић-Трифуновић[1], Анита Крсман[1,2]

[1]Универзитетски клинички центар Војводине, Клиника за гинекологију и акушерство, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Катедра за гинекологију и акушерство, Нови Сад, Србија

САЖЕТАК

Увод Тоцилизумаб је *IgG1* моноклонско антитело против рецептора интерлеукина-6. Представљамо случај труднице са тешким обликом пнеумоније изазване ковидом 19. Упркос лечењу, стање болеснице се брзо погоршавало те је примена тоцилизумаба била неопходна.

Приказ болесника Наша болесница је била 31-годишња трудница, хоспитализована седмог дана од појаве симптома ковида 19. У питању је била близаначка монохорионска диамнионска трудноћа у 21. гестацијској недељи. Опште стање болеснице било је тешко, са повишеним маркерима инфламације: *C*-реактивни протеин – 94,6 (*mg/L*), прокалцитонин – 1,44 (*ng/mL*) и интерлеукин-6 – 79,3 (*pg/mL*), уз присутну масивну билатералну пнеумонију. Била јој је потребна респираторна подршка у виду терапије кисеоником високог протока преко назалне каниле и примене континуираног позитивног притиска преко личне маске, уз интензиван надзор. Дан после пријема опште стање јој се погоршало, па је одлучено да се примени тоцилизумаб. Непосредно после примене тоцилизумаба дошло је до прогресије пнеумоније, али су маркери инфламације били у паду. После 33 дана хоспитализације отпуштена је са уредним лабораторијским налазима и нормалним рендгенским снимком. На Клинику за гинекологију и акушерство примљена је 16. јула у 36. гестацијској недељи (35 недеља + два дана) због превремених контракција. Истог дана начињен је царски рез и оба новорођенчета су била у добром општем стању.

Закључак Лечење тешког облика ковида 19 код трудница представља изазов. Овај приказ болесника показује да тоцилизумаб може бити ефикасан у лечењу тог стања.

Кључне речи: тоцилизумаб; билатерална пнеумонија; близаначка трудноћа; *IL*-6

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

En bloc kidney transplantation of an infant to an adolescent girl – one-year follow-up

Mirjana Cvetković[1,2], Ana Petrović[1], Vladimir Radlović[1,2], Ivana Gojković[1], Brankica Spasojević[1,2]

[1]University Children's Hospital, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction *En bloc* kidney transplantation (EBKT) overcomes the problems of insufficient nephron mass of the solitary kidney of the youngest donors and the creation of a vascular anastomosis with small blood vessels. Although there are positive experiences with EBKT in adult patients, there is little data in pediatric recipients.

Case outline The kidney donor was a six-month-old male infant (7 kg), and the recipient was a 16-year-old adolescent girl (58.7 kg). The estimated glomerular filtration rate increased during the one-year follow-up after EBKT and reached 88.8 ml/min/1.73 m^2, which was accompanied by an increase in the dimensions of the medial and lateral kidneys. Normalization of proteinuria and tubular functions occurred six and 12 months after transplantation, respectively.

Conclusion EBKT in an adolescent girl was performed without vascular complications, with satisfactory kidney function and physiological values of proteinuria after a one-year follow-up. EBKT of infants could increase the number of cadaveric donors but also enable better function and survival of the graft, given that the growth and functional maturation of the infant's kidneys continue postnatally in the body of the graft recipient.

Keywords: *en bloc* kidney transplantation; small infant donor; pediatric recipient; postnatal kidney maturity

INTRODUCTION

Kidney transplantation is the gold standard for renal replacement therapy in children [1]. Although pediatric recipients have priority in the allocation of cadaveric grafts [2], the number of pediatric cadaveric transplants is low primarily due to the small number of quality cadaveric grafts. By changing the demographic characteristics of adult cadaveric donors after brain death (older age, higher body mass index, comorbidities such as hypertension and diabetes), the quality of the cadaveric graft worsened [3]. Having in mind that every pediatric patient with end-stage renal disease needs at least two to three kidney transplants for an average life span, the importance of long-term survival of the transplanted kidney is clear, from which it follows that borderline donors are not the best solution for them. *En bloc* kidney transplantation (EBKT) implies transplanting both kidneys in a pair together with part of the aorta and inferior vena cava, which overcomes the problems of insufficient nephron mass of the solitary kidney of the youngest donors and the creation of a vascular anastomosis with small blood vessels [4]. Application of this transplantation method is one way to increase the donor pool of quality grafts for pediatric patients [5–8]. There are numerous positive experiences with EBKT in adult patients [3, 9–13]. However, there are few studies related to the outcome of EBKT in pediatric recipients, especially if the graft donor was an infant [5, 7, 8, 14, 15]. The aim of our work is to present the one-year clinical course of EBKT of a six-month-old infant to an adolescent girl.

CASE REPORT

The kidney donor was a six-month-old infant (7 kg), whose cause of death was a ventricular arrhythmia caused by a fetal rhabdomyoma of the heart. The recipient of the kidney was a 16-year-old girl (58.7 kg), with a congenital anomaly of the urinary tract. At the age of 12.5 years the girl was referred to a nephrologist for the first time, due to unrecognized advanced chronic kidney disease. She was on chronic hemodialysis from the age of 13.5 years, until transplantation. EBKT was performed by creating a venous T-L anastomosis between the external iliac vein of the recipient and inferior vena cava of the donor, and the arterial anastomosis was created between the external iliac artery of the recipient and the aorta of the donor (Figure 1). Cold ischemia lasted 6 hours and 35 minutes, and warm ischemia 52 minutes. Immunosuppressive therapy with basiliximab, corticosteroids, tacrolimus and mycophenolatemofetil was administered. Due to delayed graft function, the patient required three hemodialysis sessions. The urinary catheter, clogged

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Correspondence to:
Mirjana CVETKOVIĆ
Tiršova 10
11000 Belgrade, Serbia
mirjanacvetkovic6@yahoo.com

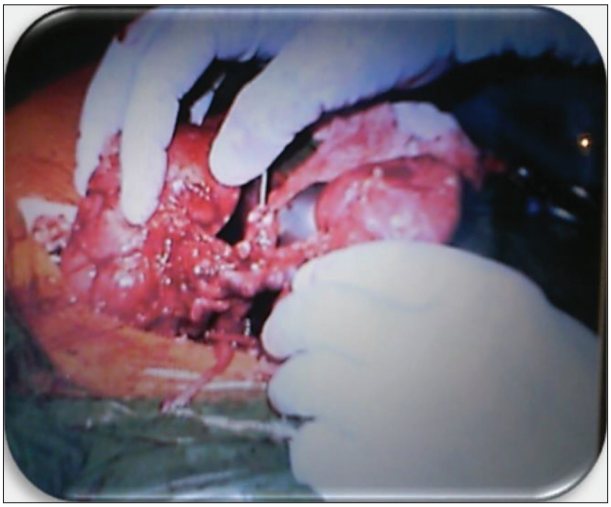

Figure 1. Kidneys transplanted using the *en bloc* surgical technique, after the creation of vascular anastomoses and established reperfusion

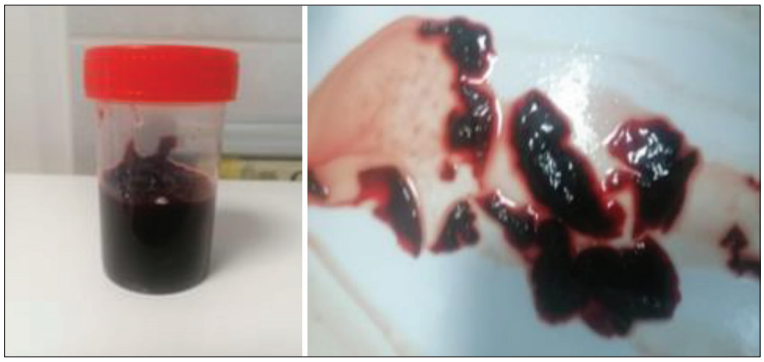

Figure 2. Spontaneously voided coagulums from the urinary bladder after removal of the urinary catheter on the eighth post-transplantation day

by a large coagulum, was removed on the eighth post-transplantation day, after which the patient spontaneously passed out several more coagulums (Figure 2). On the 10th post-transplantation day, a perirenal collection was verified by ultrasound, positioned in front of both transplanted kidneys and ureters, which progressively increased, and on the 17th post-transplantation day its dimensions were 97 × 61 × 25 mm. Due to compression on the venous flow in the lateral kidney, two months after transplantation, drainage of this perirenal collection was performed. Cytological and biochemical findings indicated a lymphocele. Recurrent lymphocele was treated by laparoscopic fenestration at the end of the third post-transplantation month. During the second post-transplantation month, the clinical course was complicated by cytomegalovirus disease, treated with valganciclovir, human cytomegalovirus immunoglobulin, and immunosuppressive therapy reduction. In the fourth post-transplantation month, the patient was diagnosed with SARS-CoV2-infection, which was successfully treated with immunosuppression therapy reduction and supportive therapy. None of the listed complications affected the functional maturation of the grafts (Table 1). The estimated glomerular filtration rate (eGFR) during the one-year follow-up increased, which was accompanied by an increase in the dimensions of the medial and lateral kidney, measured by ultrasound. Normalization of proteinuria occurred six months after transplantation. Tubular functions reached physiological values one year after transplantation.

The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved. No personal data of the patient were presented in the manuscript. Written consent was obtained from the patient and her parent.

DISCUSSION

Survival, growth, cognitive development and quality of life of transplanted children are incomparably better and morbidity rate is lower, compared to children on dialysis [1]. Pediatric patients on dialysis have a 78% higher risk of cardiovascular death compared to age-matched transplanted patients [16]. Furthermore, early transplantation in children limits the accumulation of cardiovascular risk such as intima-media thickness, marker of atherosclerosis, which increases in children on dialysis over time, and remains stable for years after kidney transplantation [17]. Worldwide there is a growing discrepancy between the number of available cadaveric grafts and the number of potential recipients, which is the cause of longer waiting time for a cadaveric kidney [7]. Also, with changing the demographic characteristics of adult cadaveric donors, the number of borderline donors increased [3]; however, they are not a good option for pediatric patents due to the extreme importance of long-term graft survival in this population. Therefore, the importance of increasing the donor pool of organs for child transplantation is clear, and EBKT is one of the possible solutions to this problem [8, 18]. Furthermore, children who receive a kidney from a pediatric donor have a better long-term graft outcome compared to children who receive a kidney from an adult donor [19]. EBKT remains a challenge for surgeons, given that it is accompanied by a higher frequency of vascular and urological complications [18]. A good selection of donors and recipients, improvement of surgical technique, shorter cold ischemia time, better immunosuppressive therapy, as well as postoperative anticoagulation and antiplatelet therapy, contributed to a significant reduction in the rate of these complications [4, 7, 8, 12, 13]. Regarding early post-operative complications, our patient had large coagulums in the urinary bladder (Figure 2) and perirenal lymphocele, which was successfully treated by laparoscopic fenestration.

Utilization of very small pediatric donor kidneys can provoke hyperfiltration injury, but careful recipient selection and EBKT technique (doubling the nephron mass) with adequate follow-up of transplanted patients, successfully overcomes this problem, and provides similar graft survival in comparison with adult deceased donor or even

Table 1. Functional maturation and growth of infant kidneys transplanted in pair

Parameters	Months after EBKT				
	1	3	6	9	12
eGFR (ml/min/1.73 m^2)	26.1	46.2	68.6	77.2	88.8
Medial kidney size (mm)	68 × 35	86 × 38	95 × 34	95 × 42	102 × 44
Lateral kidney size (mm)	64 × 41	76 × 44	91 × 44	100 × 44	105 × 49
Tubular functions (%)	FeNa 5.5 FeK 46.7 TRP 53		FeNa 2.47 FeK 18.9 TRP 74.2		FeNa 1.96 FeK 12.01 TRP 84.3
Urine protein creatinine ratio (UPCR) (mg/mg)	1.27		0.21		0.14

EBKT – en bloc kidney transplantation; eGFR – estimated glomerular filtration rate; FeNa – fractional excretion of sodium; FeK – fractional excretion of potassium; TRP – tubular reabsorption of phosphate; UPCR – urine protein creatinine ratio

living donor kidneys [4, 7, 11]. One year after transplantation, our patient had eGFR 88.8 ml/min/1.73 m^2 with normal proteinuria values, which points against hyperfiltration damage of EBKT.

The newborn kidney differs from the mature kidney anatomically, histologically and functionally. The GFR of a term newborn is low and after birth it continuously increases. Functional maturation of the nephron is completed by the end of the second year of life [20]. In case the kidney donor is an infant, the functional maturation and growth of the infant kidneys continue in the body of the graft recipient [4, 8, 21]. Table 1 clearly shows the functional maturation of nephrons and the growth of infant kidneys transplanted in a pair to the adolescent girl.

Numerous studies have shown the excellent outcome of EBKT of small pediatric kidneys in adult graft recipients in terms of graft function and survival [4, 11, 12, 22]. Recently published follow-up results (mean follow-up of 65 months, range 7–220 months) of adult patients after EBKT indicated excellent results: 100% patient survival and creatinine clearance which increased during the first three years before reaching stabilization (at 10 years, the mean creatinine clearance was 112 ml/minute, 95% confidence interval 107–117) [4]. During the last year, two EBKT to adults from preterm neonate donors after circulatory death (< 30 weeks gestation and weight < 1.2 kg) with acceptable results five and nine months post-surgery have been described in the literature [23]. On the other hand, a low percentage of EBKT was performed in pediatric recipients [7]. This is why there is a small number of studies assessing the long-term survival of grafts transplanted with this surgical technique in pediatric graft recipients. However, the experience of individual centers indicates promising results [5, 7, 8, 14, 15]. Yaffe HC et al. [14] and Winnicki et al. [7] compared pediatric recipients with grafts from small pediatric donors and pediatric recipients with grafts from standard donors, and showed that the one-year survival of grafts was slightly poorer in the group of recipients of small pediatric grafts, but five years after transplantation the outcome was practically the same. Chesnaye et al. [15] analyzed the five-year graft survival of small pediatric donors under five years of age who were transplanted into pediatric recipients. They divided the recipients according to age into four groups (0–3 years, 4–5 years, 6–11 years, and 12–19 years) and showed that the five-year graft survival was 70%, 75%, 81%, and 83%, respectively. This year, Azzam et al. [8] published the results of a follow-up (mean duration 6.86 ± 1.35 years) of pediatric patients after EBKT from donors with body weight < 15 kg and showed excellent renal function outcome on the last follow-up (eGFR 79.8 ± 30.8 ml/min/1.73 m^2). The outcome of EBKT of infant kidneys in our adolescent girl one year after the transplant was excellent, despite numerous complications in the first four months after the surgical intervention. EBKT from infants could increase the number of cadaveric donors, as well as the quality grafts for pediatric recipients, and also could enable better function and survival of the graft given that the growth and functional maturation of the infant kidneys continue postnatally. We should not hesitate to use this potential pool of donors because the data in the literature is truly positive and encouraging. Certainly, in the future, multicenter studies are necessary, considering the small number of pediatric patients transplanted with this technique per center, which will show us the long-term outcome (> 10 years) of grafts transplanted with the *en bloc* surgical technique in the youngest patients.

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En bloc трансплантација бубрега одојчета адолесценткињи – једногодишње праћење

Мирјана Цветковић[1,2], Ана Петровић[1], Владимир Радловић[1,2], Ивана Гојковић[1], Бранкица Спасојевић[1,2]

[1]Универзитетска дечја клиника, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Трансплантацијом бубрега у блоку (*en bloc*) (ЕБТБ) превазилазе се проблеми недовољне нефронске масе солитарног бубрега најмлађих донора и креирања васкуларне анастомозе са малим крвним судовима. Иако постоје позитивна искуства са ЕБТБ код одраслих болесника, мало је података код педијатријских прималаца.

Приказ болесника Донор бубрега било је шестомесечно мушко одојче (7 *kg*), а прималац адолесценткиња узраста 16 година (58,7 *kg*). Процењена јачина гломерулске филтрације током једногодишњег праћења после ЕБТБ је расла и достигла 88,8 *ml*/*min*/1,73 m^2, што је праћено порастом димензија медијалног и латералног бубрега. Нормализација протеинурије постигнута је шест месеци после трансплантације, а тубулских функција после 12 месеци.

Закључак ЕБТБ код адолесценткиње је протекла без васкуларних компликација, са задовољавајућом функцијом бубрега и физиолошким вредностима протеинурије после једногодишњег праћења. ЕБТБ одојчади могла би да повећа број кадаверичних донора, али и да омогући бољу функцију и преживљавање графта с обзиром на то да се раст и функционално сазревање одојачких бубрега настављају постнатално и у телу примаоца графта.

Кључне речи: *en bloc* трансплантација бубрега; одојче донор бубрега; педијатријски прималац; постнатално сазревање бубрега

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Metastatic melanoma of the gallbladder

Aleksandar Ninić[1,2], Dunja Stankić[1,2], Nikola Grubor[2], Milica Mitrović-Jovanović[2,3], Nikica Grubor[1,2]

[1]University Clinical Centre of Serbia, Clinic for Digestive Surgery, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Center for Radiology and Magnetic Resonance Imaging, Belgrade, Serbia

SUMMARY

Introduction Malignant melanoma is a tumor of the melanocytes and is one of the most aggressive tumors. In most cases, the first symptoms appear in the metastatic phase of the disease. In clinical practice, malignant melanoma very rarely metastasizes to the gallbladder. Modern diagnostic methods include 18F-fluorodeoxyglucose positron emission tomography, new computed tomography protocols, new nuclear magnetic resonance for melanoma protocols, and contrast-enhanced ultrasound. The article aims to emphasize the necessity of radical surgical treatment of metastatic melanoma of the gallbladder.

Case outline We present a rare case of metastatic malignant melanoma of the gallbladder, which was treated with cholecystectomy and radical surgical excision of all metastatic lesions.

Conclusion All patients with a positive anamnesis for malignant melanoma require to be checked for the spread of the disease to the gallbladder and subsequent surgical treatment.

Keywords: malignant melanoma; gallbladder; metastasis; surgical treatment

INTRODUCTION

Malignant melanoma (MM) is caused by the malignant proliferation of melanocytic cells. Most commonly, primary MM occurs in the skin, and less commonly in the eyes, gastrointestinal tract, genitourinary system, lymphatic system, and soft tissues [1, 2, 3]. Metastases most often occur in the lymph nodes, lungs, liver, and brain [4, 5]. According to the literature, primary and secondary MM of the gallbladder has been diagnosed only in 58 patients so far [6]. Wieting and Hamdi [7] reported the first case of MM metastasizing to the gallbladder in 1907. About 50% of gallbladder metastases are attributed to MM. Apart from the embryological origin, one of the explanations may be that MM often spreads hematogenously [8, 9]. For most patients, the primary tumor is asymptomatic until metastatic disease is diagnosed [10, 11, 12]. Namely, diffuse metastatic disease involves other intra-abdominal organs in 60% of cases [13]. Preoperative diagnosis of MM of the gallbladder is challenging [14]. In addition to clinical presentation, other diagnostic procedures such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) of the abdomen, and 18F-fluorodeoxyglucose positron emission tomography (FDG PET-CT) could be performed, enabling the differentiation of a malignant from a benign gallbladder tumor [15]. However, pathohistological and immunohistochemical examination is the gold standard. Surgical treatment is the preferred method of treatment.

In this article, we present a rare case of metastatic MM of the gallbladder.

CASE REPORT

A 35-year-old man was admitted to our department due to pain in the right hypochondrium and nausea. A year earlier, the patient underwent left pneumonectomy due to large cell lung cancer. He had no other comorbidities. The tumor markers were within the normal ranges. US, CT, and MRI examinations of the abdomen and pelvis revealed a tumor in the lumen of the gallbladder, 64 × 39 mm in diameter. Also, several soft tissue nodular lesions were detected in other locations: one lesion in the greater omentum, 8 × 8 mm; two lesions in the front abdominal wall at the level of the right rib arch, 40 × 30 mm in size, and suprapubically, 8 × 6 mm in size; one lesion in the right inguinal region, 25 × 20 mm in size; and one lesion in the subcutaneous region of right shoulder measuring 18 × 15 mm (Figure 1).

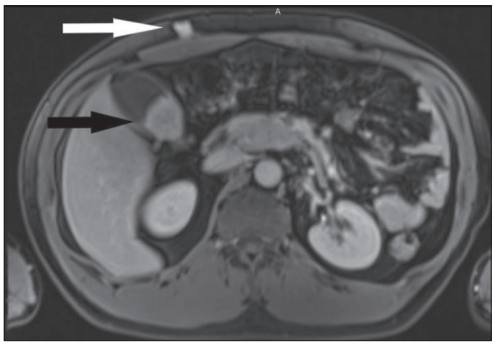

Figure 1. Magnetic resonance imaging scan: axial post-contrast T1-weighted image in the portal venous phase clearly depicts an intraluminal viable tumorous lesion of the gall bladder (black arrow), and also an opacified nodular lesion, subcutaneously in the right anterior abdominal wall (white arrow)

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Correspondence to:
Aleksandar NINIĆ
University Clinical Centre of Serbia
Clinic for Digestive Surgery
Koste Todorovića 6
11000 Belgrade
Serbia
ninic.aleksandar89@gmail.com

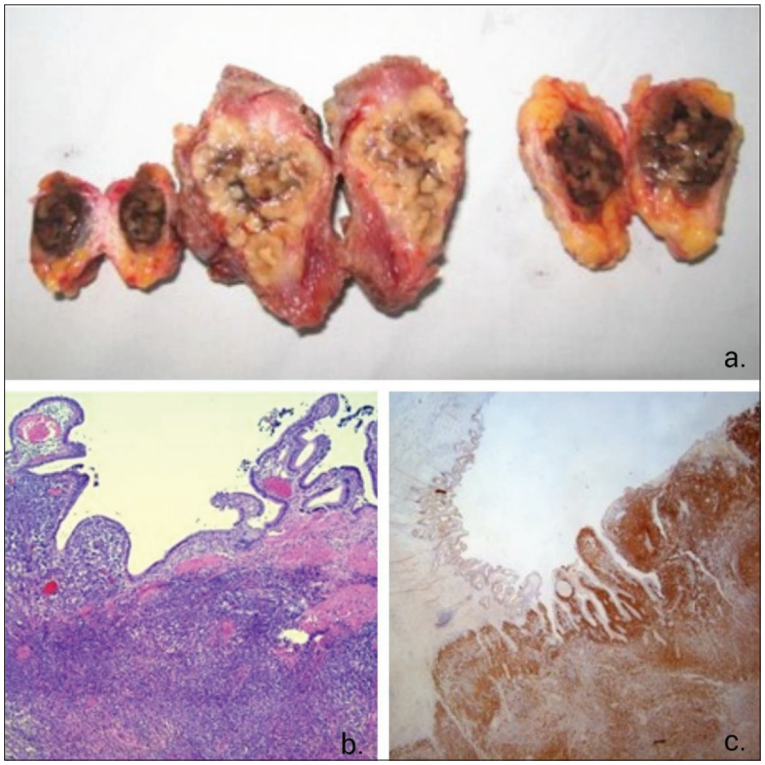

Figure 2. a – macroscopic image: solid and black-pigmented tumorous lesions were verified by cutting out the lesions from the subcutaneous fatty tissue; b – insular and solid/trabecular histological organization of melanoma cells with areas of hyperpigmentation; c – tumor cell showed strong cytoplasmic immunoexpression of HMB-45

During the same surgical procedure, cholecystectomy, excision of the tumorous lesion from the greater omentum, and lymphadenectomy were performed. Two nodular lesions were excised from the anterior abdominal wall, one was removed from the right groin area, and one was excised from the right shoulder region (Figure 2a). Complete surgical exploration found no other tumorous lesions in the abdomen and pelvis.

Definitive histopathological and immunohistochemical findings confirmed metastatic melanoma of the gallbladder, the greater omentum, and subcutaneous tissue of the subcostal, shoulder, and right inguinal regions (Figure 2b). All of the examined tissue samples showed nodular metastatic tumor deposits, of whom most showed clear borders and had free margins, indicating R0 resection. All tumor cells showed clear diffuse cytoplasmic immunoreactivity, positive for Vimentin, HMB-45, S-100, while a part of the tumor cells was positive for Melan A and Synaptophysin, and focally for epithelial membrane antigen (Figure 2c). The Ki-67 proliferative index was 80%.

The article was approved by the ethics committee of the University of Belgrade Medical Faculty (No. 1038/7).

DISCUSSION

MM is a very aggressive tumor with a high metastatic potential and a high mortality rate. Men and women are affected almost equally. The pathogenesis of metastases has not yet been fully elucidated. The migration of melanin-producing cells from the neural crest to derivatives of the endoderm during embryonic development might explain the presence of melanocytes within their mucosa. This could explain the possibility of the development of primordial melanoma in these organs [16]. MM of the gallbladder makes up 50–67% of all gallbladder tumors [17]. According to autopsy findings, gallbladder and biliary tract metastases occur in approximately 15% of patients with MM metastases in the gastrointestinal tract. However, there are significant statistical discrepancies in the scientific literature regarding this issue [18]. In some cases, patients are asymptomatic or have symptoms such as are pain under the right rib cage, nausea and vomiting, food intolerance, weight loss, and diarrhea [11]. Jaundice can develop due to the infiltration of the bile ducts by the tumor or as the result of their compression. Rarely, a biliary fistula may develop and hemobilia may occur [15]. We must always bear in mind the differential diagnosis, such as primary malignant tumors of the gallbladder, benign polyps, and adenomyomatosis. Preoperative diagnosis is established based on US, CT, MRI, or PET/CT examinations. A definitive diagnosis is often established by combining multiple imaging modalities. However, it is very difficult to distinguish preoperatively between gallbladder metastases and primary gallbladder tumors. US can be the initial examination for evaluating metastasis of melanoma in the gallbladder. Contrast-enhanced US is useful in differentiating between solid wall lesions and tumefactive biliary sludge, but it is not possible to make a differential diagnosis between adenocarcinoma and gallbladder metastases. Compared with contrast-enhanced US, CT is the method of first choice and the most commonly used method for staging and monitoring therapeutic response in melanoma patients. CT examination of the gallbladder is based on the detection of tumor localization (fundus, body, neck, cystic duct, diffuse), tumor morphology (infiltrative, polypoid, mass-forming), degree and pattern of enhancement, depth of invasion and signs of concurrent cholecystitis. The MRI protocol for gallbladder examination should include thin slices (< 5 mm) axial T1/weighted images, coronal and axial T2/weighted, 3D-cholangiopancreatic images, axial dynamic contrast-enhanced images, after intravenous injection of gadolinium contrast agent [19]. CT and MRI can reveal single or multiple exophytic masses or polyps arising from the gallbladder wall or infiltrative lesions invading the mucosal, muscular, or serous layers of the gallbladder. MM metastases are generally larger than 1 cm and attached to the gallbladder wall. If the mass involves the biliary tree, ductal dilatation and intraluminal masses may be visualized. The presence of melanin results in hyperdensity in unenhanced CT images and hyperintensity in T1-weighted MRI, facilitating the differential diagnosis of MM from other primary or secondary gallbladder lesions [7].

Endoscopic retrograde cholangiopancreatography and magnetic retrograde cholangiopancreatography are also helpful, as they can identify biliary obstruction. PET/CT is very useful in detecting MM metastases throughout the body, as well as for evaluating response to treatment. The sensitivity and specificity of FDG PET/CT in the detection of distant metastases are reported to be 92% and 90%, respectively. FDG PET/CT is being developed as a standard diagnostic imaging method in melanoma patients [20]. If radical surgical treatment of MM of the gallbladder is performed, one-year survival is possible in 100% of patients, while it is 0% in non-operated patients [11]. Surgical treatment reduces symptoms and prevents the further spread of the tumor. The effect of adjuvant and immunotherapy has not yet been determined. According to some studies, the application of Interleukin-2 leads to tumor remission in 15% of patients, with a significant effect in the early stages of the disease. However, its use is very limited due to its toxicity [21]. The most important prognostic factor is tumor biology, as demonstrated by numerous retrospective survival studies of patients with metastatic disease [10].

MM entails poor prognosis, as few patients survive two years past diagnosis. All patients with a positive anamnesis for MM should be evaluated for gallbladder disease spread if the clinical presentation points to biliary involvement.

Conflicts of interest: None declared.

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Метастатски меланом жучне кесе

Александар Нинић[1,2], Дуња Станкић[1,2], Никола Грубор[2], Милица Митровић-Јовановић[2,3], Никица Грубор[1,2]

[1]Универзитетски клинички центар Србије, Клиника за дигестивну хирургију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија

САЖЕТАК

Увод Малигни меланом је тумор меланоцита и спада у један од најагресивнијих тумора. У већини случајева први симптоми се јављају у метастатској фази болести. У клиничкој пракси веома ретко се виђа метастазирање малигног меланома у жучну кесу. Савремене дијагностичке методе су позитронска емисиона томографија са 18Ф-флуородеоксиглукозом, нови протоколи компјутеризоване томографије и нуклеарне магнетне резонанце за меланом и ултразвук са контрастом. Циљ рада је истаћи неопходност радикалног хируршког лечења метастатског меланома жучне кесе.

Приказ болесника Представићемо случај ретке метастатске болести малигног меланома у жучној кеси, који је лечен холецистектомијом и радикалном хируршком ексцизијом свих метастатских промена.

Закључак Сви болесници са позитивном анамнезом малигног меланома захтевају и проверу раширености болести у жучну кесу, а потом и хируршко лечење.

Кључне речи: малигни меланом; жучна кеса; метастаза; хируршко лечење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Congenital tongue base cyst as uncommon cause of laryngeal stridor in an infant

Dejana Bajić[1], Zoran Komazec[2,3]

[1]University of Novi Sad, Faculty of Medicine, Department of Biochemistry, Novi Sad, Serbia;
[2]Clinical Center of Vojvodina, Clinic for Otorhinolaryngology and Head and Neck Surgery, Novi Sad, Serbia;
[3]University of Novi Sad, Faculty of Medicine, Department of Otorhinolaryngology, Novi Sad, Serbia

SUMMARY

Introduction Congenital tongue base cysts are uncommon in everyday clinical practice and they could be asymptomatic or cause stridor, respiratory distress, and asphyxia. We are presenting a case of a two-month-old infant with the symptoms of stridor and the acute respiratory insufficiency caused by congenital tongue base cyst.

Case outline A two-month-old apyretic male infant was admitted to the hospital with the symptoms of severe dyspnea, nonproductive cough, and stridor. Due to severe respiratory insufficiency the infant was on mechanical ventilation. Computed tomography scans of the thorax and neck was performed along with the application of the intravenous contrast where a cystic formation was shown. The depicted formation narrowed the lumen of oropharynx which is the same as the size of valleculas (3 mm). The formations pressed both valleculas, more significantly the left one. The same day the marsupialization of the cyst was done and the material was sent to the pathohistological analysis (the report of the pathologist indicates the cyst of the thyroid channel).

Conclusion Clinical manifestations of the cyst depend on the level of obstruction and can be presented as inspiratory stridor, apnea, cyanosis, chronic coughing, and feeding difficulty. The flexible nasopharyngeal laryngoscopy or bronchoscopy, computed tomography and magnetic resonance imaging help consider the differential diagnosis. The symptoms of stridor were removed completely after applied marsupialization of the cyst.

Keywords: airway obstruction; thyroglossal cyst; stridor; respiratory insufficiency

INTRODUCTION

Laryngomalacia is considered to be the most common cause of stridor (noisy breathing) in the neonatal period and infancy [1]. The obstructions of respiratory airways are common, while congenital tongue base cysts are not frequent in everyday clinical practice [2]. A tongue base cyst may cause stridor, respiratory distress, or be totally asymptomatic [3]. Owning to their specific position, tongue base cysts may cause perilous complications through mass effects on the hypopharynx as well as by displacing the epiglottis. In the most serious cases, a cyst can lead to the fatal outcome due to asphyxia [4]. The mortality rate among the patients with the diagnosed congenital tongue cyst in the infant period vary, and in some studies goes to 40% [5]. Surgical treatment has been verified as the most efficient method with a significant improvement of the symptoms generated by the compressive effects of the cyst [6]. We are presenting a case of a two-month-old infant with the symptoms of laryngeal stridor and the acute respiratory insufficiency caused by congenital tongue base cyst.

CASE REPORT

A two-month-old apyretic male infant was admitted to the hospital with the symptoms of severe dyspnea, nonproductive cough, and noisy breathing (stridor). He had been examined four days before admission by a pediatrician and the initial treatment included inhalation of short acting agonist beta 2 bronchodilators (fenoterol ipratropium bromide) and parenteral corticosteroids (methylprednisolone). The difficulties were persistent, and on admission day, the child was inconsolably crying for hours, breathing heavily, and had cyanotic attacks. The child had been previously hospitalized for seven days due to bronchial obstruction and dyspnea caused by whooping cough *(Diagnosis Pertussis per Bordetella Pertussis*, confirmed by polymerase chain reaction technique) when he was only one month old. DTP (diphtheria, tetanus and pertussis) vaccine should be given at the age of two months, and because the infant was only a month old, he was given solely *Euvax-B*® (prevent hepatitis B) and BCG (Bacillus Calmette–Guérin) vaccine (prevents tuberculosis) after labor.

On admission, he was conscious and alert, pale, tachypneic with the respiratory rate of 50 breaths per minute, oxygen saturation of 97% on room air, heart rate of 150 beats per minute, and the normal body weight of 4800 gr.

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Correspondence to:
Dejana BAJIĆ
University of Novi Sad
Faculty of Medicine
Department of Biochemistry
Hajduk Veljkova 3
21137 Novi Sad
Serbia
dejana.bajic@mf.uns.ac.rs

In physical examination lung auscultation revealed wheezing, bilateral early-inspiratory crackles on the lungs and inspiratory stridor. All other physical findings were normal. The initial analyses were within normal ranges [C-reactive protein (CRP) 3.8 mg/L, white blood cells (WBC) 10.9 10^9/L, red blood cells (RBC) 3.77 10^{12}/L, hemoglobin (HGB) 101 g/L, hematocrit (HCT) 29.0%, platelets 361 × 10^9/L]. Testing of his arterial blood gases showed combined metabolic and respiratory acidosis (pH 7.291, pCO_2 4.42 kPa, pO_2 7.8 kPa, standard bicarbonate HCO_3-std 16.6 mmol/L, base excess BE -9.7 mmol/L). Due to repeating noisy breathing and wheezing, alpha-1 antitrypsin (1.51 g/L) and total immunoglobulin E (IgE < 30 µg/L) were estimated and results were within referent values. Chest X-ray showed bilateral decreased transparency of lungs.

After admission, the inhalations with bronchodilator (ipratropium bromide/fenoterol hydrobromide) every four hours and corticosteroid (budesonide) every 12 hours were included. Respiratory physiotherapy (postural drainage aspiration) was applied. On the second day of the treatment around 13:00 p.m., the deterioration of the respiratory status and symmetrically weakened breathing sound were noted. The noisy high tonal wheezing with the saturation drops up to 70, and a heartbeat of over 200/min with occasional apneas lasting over 10 seconds occurred. The infant was tachydispneic (respiratory rate / 60 min), with ash gray skin, with visible intercostal and xiphoid retraction, nares dilatation (flaring) using additional intercostal musculature, with seesaw respiration. The deteriorating inspiratory stridor was present. The oxygen therapy through nasal cannula initially two liters per min up to six liters per minute was applied, and systemic corticosteroid methylprednisolone was given. Because of the general status deterioration empiric antibiotic ceftazidime was included parenterally. The gas analyses were urgently done (pH 6.946, pCO_2 7.21 kPa, pO_2 7.6 kPa, BE(B)-20.9 mmol/ L, HCO_3 std 9.3 mmol/ L) indicating the non-compensative critical metabolic and respiratory acidosis. The inflammatory markers in the laboratory analyses were still normal, not showing the acute infection (CRP 2.2 mg/L, WBC 15.9 × 10^9/L, RBC 3.44 × 10^{12}/L, HGB 90 g/L, HCT 26.8%). The progressive deterioration of the respiratory status was caused by the obstruction of the upper airways. Applied measures did not give signs of improvement. Due to the development of the respiratory insufficiency, the infant was intubated and on synchronized intermittent-mandatory ventilation. During the evening hours of the same day, the increase of the inflammatory parameters occurred (CRP 38.3 mg/L) so the therapy switched another antibiotic vancomycin. The parameters of the mechanical ventilation were gradually decreasing, so the infant was extubated the next day and initially transferred to high flow nasal cannula and then to oxygen therapy through nasal cannulas. Because the gas exchange was stable, oxygen saturation satisfactory, the needs for additional oxygen ceased on the fourth day of hospitalization. Further on, the infant was in good general condition, while the parameters of acute inflammation were dropping.

The dual antibiotic therapy of ceftazidime and vancomycin continued during 14 days in total. At the same

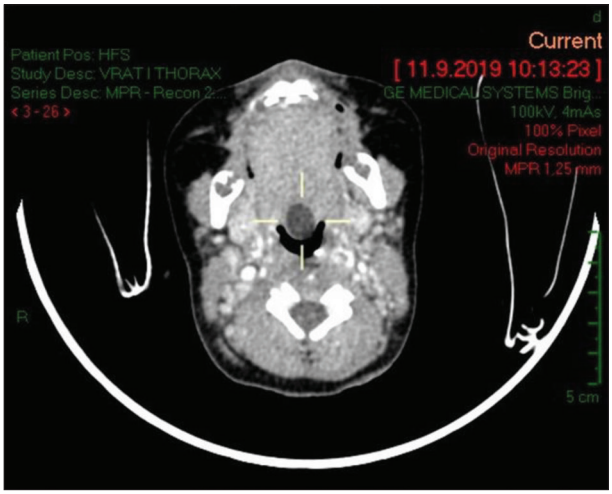

Figure 1. Cystic formation on the base of the tongue

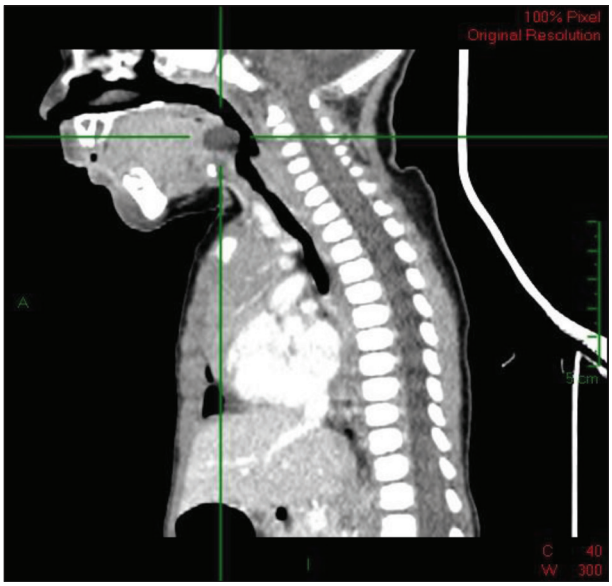

Figure 2. Sagittal computed tomography scan of neck with detected cystic formation at the base of tongue which narrow respiratory airway

time, bronchodilator inhalations went on every six hours, while the interval between the inhalations was gradually prolonged. The infant was put in the high headboard bed with his head tilted back because of the laryngeal stridor in order to relieve airways. A cardiologist and a pulmonologist were consulted, all potential causes of stridor and difficult breathing in infancy were considered, so the directoscopy of larynx and rigid bronchoscopy were recommended. The otolaryngologist was consulted and unusual formation was detected. A computed tomography (CT) of the thorax and thoracic neck was performed along with the application of the intravenous contrast where a cystic formation on the base of the tongue was shown (Figure 1). On the posterior tongue base in the middle section right above the epiglottis and between valleculas and piriform recess uses, the clearly visible cystic formation with the dimensions of 12 × 9 × 9.4 mm was positioned, liquid density without central, post contrast imbibition (Figure 2). The depicted formation narrows the lumen of oropharynx which is the same as the

anterior posterior (AP) diameter of valleculas (3 mm). The formation compressed both valleculas, more significantly the left one. An otorhinolaryngologist indicated the operative removal of the cyst. The directoscopy of the larynx and rigid bronchoscopy were performed and on the left side of the tongue base an oval whitish formation leaning on the left entrance of the larynx was spotted causing the difficult intubation. The trachea had normal ring-shaped form, with the membrane wall and preserved lumen. Other results of the bronchoscopy were normal. The same day, the marsupialization of the cyst was done and the tissue specimen was sent to the pathohistological analysis. After the operation parenteral antibiotic therapy with cefepime (cephalosporin of IV generation) was applied along with bronchodilator and corticosteroid. A few days later child was in a good general condition, with regular gas exchange and peroral nutrition (adapted milk formula), with gradually increased intake. At the control otorhinolaryngologist examination, the result after marsupialization of the cyst was normal, without stridor. The pathohistological analysis of the tissue showed that it was formed of smooth laminar layer of epithelium with mucosal glands. In the deeper layer, there was transverse muscle tissue and edematous connective tissue. The report of the pathologist described the cyst of the thyroid channel.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from the parents.

DISCUSSION

Causes of heavy breathing in infants are numerous and can be the result of innate states, congenital anomalies or inherited diseases. Clinical manifestations depend on the level of obstruction (choanal atresia for instance, larynx) and the degree of the obstruction (different size of the cyst or some other formation that obstruct the airway [7]. The common cause of bronchial obstruction and wheezing in infancy is the atopic constitution of a child and the tendencies of later development of allergic diseases (asthma, allergic rhinitis, conjunctivitis and eczemas) [8]. Acute airway obstruction can be life threatening condition which requests prompt reaction and treatment. Seldom, the deterioration of respiratory status can be that serious to require around the clock monitoring at the intensive care wards with the applied intubation and ventilation.

In medical literature, a variety of terms have been used for tongue base cysts, such as epiglottic cyst, lingual cyst, vallecular cyst, or laryngeal cyst [9]. Two major hypotheses to explain the pathogenesis of these cysts are the ductal obstruction of mucus glands or an embryological malformation [10]. The most affected infants have symptoms during the first week of life [11]. Clinical manifestations consist of various degrees of upper airway obstruction such as inspiratory stridor, chest retraction, apnea, cyanosis, and feeding difficulty. Stridor is the most common symptom [12]. In neonatal stridor, evaluation of the airway anatomy and differential diagnosis from other causes of stridor are important to prevent any mortality and morbidity from these sources [10, 11]. Clinical presentation is usually related to upper respiratory tract. Obstruction and stridor are the most frequently encountered symptoms of vallecular cyst cases. Other symptoms include dyspnea, feeding difficulties, voice changes, chronic coughing and cyanotic attacks.

Definitive diagnosis can be obtained from bronchoscopy or laryngoscopy [13]. Primary diagnostic approach to laryngeal or vallecular cyst should be a flexible nasopharyngeal laryngoscopy or bronchoscopy. CT and magnetic resonance imaging help narrow the differential diagnosis, and note differences between lingual, thyroid, proximal cystic dilatation of the thyroid duct, lymphangia or hemangioma, dermoid cyst, lipoma, fibroma, or carcinoma [14].

Timely differential diagnosis of laryngeal stridor and its consequences is crucial in critically ill patients with severe respiratory failure. Laryngomalacia is the most common cause of noisy breathing in infancy [15]. While having deteriorations of the respiratory status, our patient had the episodes of apnea (breathing breaks longer than 10 seconds followed by desaturation and bradycardia). It is significant to differ periodical breathing from apnea, the type of apnea (central, obstructive, or mixed), as well as to determine if its cause is a certain metabolic disorder which is manifested by apnea [16]. Subsequent management consists of determining the underlying etiology and instituting specific targeted therapy to the identified cause.

Congenital base cysts are rare and can be confused with laryngomalacia due to their nonspecific symptoms. They present a bulging mass at the base of tongue, obstructing the upper airway and are responsible for severe respiratory distress that sometimes can be fatal. Direct laryngoscopy, neck CT scan, and pathological analysis are key for proper diagnosis. Cyst marsupialization was the treatment of choice. The symptoms of heavy breathing were removed completely after marsupialization. The incidence of relapse within the monitoring period is low.

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Урођена циста базе језика као неуобичајен узрок ларингеалног стридора одојчета

Дејана Бајић[1], Зоран Комазец[3,4]

[1]Универзитет у Новом Саду, Медицински факултет, Катедра за биохемију, Нови Сад, Србија;
[2]Клинички центар Војводине, Клиника за оториноларингологију и хирургију главе и врата, Нови Сад, Србија;
[3]Универзитет у Новом Саду, Медицински факултет, Катедра за оториноларингологију, Нови Сад, Србија

САЖЕТАК

Увод Урођене цисте базе језика не срећу се свакодневно у клиничкој пракси, а могу бити асимптоматске или изазивати стридор, отежано дисање или асфиксију. Приказујемо случај двомесечног одојчета са стридором и развијеном акутном респираторном инсуфицијенцијом услед притиска цисте на бази језика.

Приказ болесника Мушко афебрилно одојче, узраста два месеца, примљено је у болницу због отежаног дисања, непродуктивног кашља и стридора. Услед тешког погоршања респираторне функције дете је прикључено на механичку вентилацију. Скенер главе и врата са применом контраста детектовао је цисту у пределу врата, тачније у корену језика. Описана формација је сузила лумен орофаринкса на 3 *mm*, колико је и лумен валекула. Циста је притискала обе валекуле, више леву, услед чега је настала опсежна опструкција дисајног пута. После радиолошког налаза, урађена је марсупијализација цисте, која је послата на патохистолошку анализу. Извештај патолога указује на цисту тиреоглосног канала.

Закључак Клиничке манифестације цисте зависе од нивоа и обима опструкције, а могу да се испоље као инспиратирни стридор, апнеа, цијаноза, хроничан кашаљ и потешкоће са храњењем. Флексибилна назофарингеална ларингоскопија, бронхоскопија, компјутеризована томографија и магнетно снимање могу да помогну у диференцијалној дијагностици. Симптоми стридора и отежаног дисања су потпуно нестали после марсупијализације цисте.

Кључне речи: опструкција дисајних путева; тиреоглосална циста; стридор; респираторна инсуфицијенција

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REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Intolerance of gluten-containing cereals

Zoran Leković[1,2], Vladimir Radlović[1,2], Marija Mladenović[3], Siniša Dučić[1,2], Petar Rosić[2], Goran Đuričić[1,2], Jelica Predojević-Samardžić[4,5], Nedeljko Radlović[6]

[1]University Children's Hospital, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Singidunum University, Faculty of Health, Legal and Business Studies, Valjevo, Serbia;
[4]University Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[5]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[6]Serbian Medical Society, Academy of Medical Sciences of the Serbian Medical Society, Belgrade, Serbia

SUMMARY
Intolerance of gluten containing cereals (wheat, rye, and barley) is an etiopathogenetically heterogeneous and relatively common problem of modern man. It occurs as an adverse immune-mediated condition in genetically predisposed individuals. According to the pathogenetic mechanism of intolerance to the components of these cereals, it is classified into celiac disease as an autoimmune disease, wheat allergy as an allergic disease, and non-celiac gluten sensitivity as a non-autoimmune and non-allergic disease. Each of these disorders is characterized by specific intestinal and/or extraintestinal manifestations, which resolve on a gluten-free diet. This review article presents the basic characteristics of these disorders in accordance with modern knowledge.
Keywords: gluten-containing cereals; clinical forms of intolerance; celiac disease; diagnostics; nutrition; pediatrics

INTRODUCTION

Gluten-containing cereals (wheat, rye, and barley) represent an everyday part of the diet of a large part of the human population [1, 2]. They are an important source of polysaccharides, proteins, B vitamins, minerals, and a small amount of fat [1, 2]. Wheat flour is extensively included in the menu of man from 10,000 years ago [1, 3]. It is introduced into the infant's diet 4–12 months after birth [4].

Gluten, a complex storage protein consisting of prolamins and glutenins, makes up about 75–80% of the total flour proteins of wheat, rye, and barley [5]. They are characterized by high contents of proline-rich polypeptide residues resistant to effective gastric and pancreatic proteolysis and accordingly high antigenic potential followed by an inadequate immune reaction in genetically predisposed individuals [5–8]. Although both protein components of gluten can cause an inadequate immune reaction, the main causes of intolerance to these grains are prolamins, i.e. wheat gliadin, rye secalin, and barley hordein [6]. In addition to gluten, wheat, rye, and barley flour contains α-amylase/trypsin inhibitors (ATIs), lectins, non-specific lipid transfer proteins (LTPs) and other proteins, which can also cause adverse immune reactions in predisposed individuals [5, 8].

The spectrum of gluten-related disorders consists of celiac disease, wheat allergy (WA), and non-celiac gluten sensitivity (NCGS) [2]. Each of these disorders is characterized by specific intestinal and/or extraintestinal manifestations, which resolve on a gluten-free diet [2]. This review article presents the basic characteristics of these disorders in accordance with modern knowledge.

CELIAC DISEASE

Celiac disease (CD) is a systemic autoimmune disease that occurs in polygenically predisposed individuals on a gluten-containing diet [7, 9, 10]. In members of the white population, it presents with a prevalence of about 1%, while in other population groups it is much rarer or extremely rare [10–13]. It is particularly common in first- and second-degree relatives (5–15%), and somewhat rarer (3–10%) in patients with other autoimmune diseases, selective IgA deficiency, and Down, Turner, and Williams syndromes [9, 10, 13, 14]. As other autoimmune diseases, it is more common in persons of the female versus male sex (1.5–2:1) [15, 16].

Although the pathogenesis of CD is based on a polygenic predisposition and exposure to gluten, additional factors, such as gastrointestinal infections, alteration of the intestinal microbiota, some medications and others, are also involved in its occurrence, which explains its incomplete prevalence in monozygotic twins (83–86%) [3, 8, 17, 18]. The basic factors in the hereditary predisposition to CD are the HLA genes DQ2 and DQ8 (6p21.32), which are registered in 98–99% of patients [8, 13, 19]. HLA

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Correspondence to:
Zoran LEKOVIĆ
University Children's Hospital
10 Tiršova
Belgrade 11000
Serbia
zoran.lekovic@med.bg.ac.rs
zlekovic2000@yahoo.com

DQ2 molecules are found in 85–95% of patients, and HLA DQ8 in 5–15% [20, 21, 22]. However, apart from HLA DQ2 or DQ8 genes, non-HLA genes also have an indispensable presence in the occurrence of the disease [8, 10]. The importance of DQ2 and DQ8 glycoproteins present on antigen-presenting cells (dendritic cells and macrophages) in the pathogenesis of CD lies in their ability to, after binding with deaminated gluten polypeptide hydrolysates, activate intestinal CD4+ T-cells [7, 10]. The deamidation of gluten hydrolysates, which increases their affinity for binding to HLA DQ2 and DQ8 molecules, is catalyzed by tissue transglutaminase (tTG). Activated CD4+ T-cells by releasing proinflammatory cytokines activate intraepithelial cytotoxic CD8+ T-cells, which lead to enterocyte apoptosis and inflammation of the small intestine mucosa, and at the same time, by differentiation of B lymphocytes into plasma cells, to the production of antibodies against gluten peptides and autoantibodies to tTG, endomysium, and other body structures [8].

Gluten-sensitive enteropathy, i.e. non-specific inflammation of the small intestinal mucosa that resolves on a gluten-free diet, is the main feature of the CD and the basis of its diagnosis [9, 10, 13, 17, 23]. According to the modified Marsh criteria, inflammation of the small intestine mucosa is classified into infiltrative (I), infiltrative-hyperplastic (II), and destructive (III), whereby the destructive type is additionally differentiated into partial (IIIa), subtotal (IIIb), and total (IIIc) [24]. A fourth type of mucosal damage is also possible, which is characterized by complete atrophy of the villi, but without crypt hyperplasia and typical signs of mucosal inflammation.

Observed from the clinical aspects, CD is differentiated into symptomatic and asymptomatic, while symptomatic, according to the type of manifestation, into classical and non-classical [7, 9, 17]. The classical form of the disease is characterized by chronic diarrhea, anorexia, occasional vomiting and general malnutrition, while in the clinical picture of the non-classical disease, extraintestinal manifestations dominate, the only manifestations in a significant number of cases [7, 9, 17, 25]. The classical form of the disease is most often seen in infants and young children, and the non-classical in later childhood and in adults [17, 25, 26]. The most frequent symptoms of CD in later childhood and adolescence are sideropenic anemia, poor appetite, malnutrition, short stature, delayed maturation, recurrent abdominal pain, constipation, enamel hypoplasia, recurrent aphthous stomatitis, chronic malaise and change in the personality [10, 13, 17, 25, 27]. The main manifestations of CD in adults are anemia, chronic fatigue, weight loss, recurrent abdominal pain, bloating, flatulence, constipation, mouth ulcer, headaches, depression, and osteopenia or osteoporosis [26, 28]. In addition, women have an increased risk for infertility, miscarriage, and early menopause [28]. In about 1–1.5% of total cases of CD, celiac crisis (CC) and refractory CD (RCD) occur [10, 16]. CC is an urgent and potentially fatal complication of untimely recognized CD most often seen in early childhood [16]. It is clinically manifested by deterioration and rapid progression of serious digestive dysfunction followed by profuse watery diarrhea, severe dehydration, metabolic acidosis, meteorism and very pronounced global malnutrition [16]. RCD, which primarily affects adults, is characterized by malabsorption, weight loss, as well as persistent villous atrophy after one year of a strict gluten-free diet [7, 13]. There are two subtypes of RCD – type 1, in which the phenotype of the intraepithelial lymphocyte population is normal (CD3+CD8+), and type 2, in which it is abnormal [10]. RCD, particularly type 2, is highly associated with serious complications, such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma [10, 19]. Although the classical type of the CD is described most often and best studied, today it is known that it represents only the "tip of the celiac iceberg" and that the largest number of patients, both children and adults, are those with a non-classical and asymptomatic form of the disease [17].

The diagnosis of CD is based on pathohistological examination of the small intestinal mucosa obtained via endoscopic biopsy [9, 10, 13, 17, 23]. Since the histologic changes may be patchy in distribution and confined to the duodenal bulb, one or two samples should originate from the bulb and four or more from the distal duodenum [9, 10, 17]. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), as part of the recommendations published in 2012 considers that enterobiopsy is not necessary in patients with symptoms and/or signs consistent with CD, and in addition, they have an IgA titer antibodies to tissue transglutaminase (AtTG-IgA) ≥ 10 times above the upper reference value, positive antiendomysial antibodies of the same class (EMA-IgA) and "celiac HLA" (DQ2 and/or DQ8) [9]. ESPGHAN, as part of the additional modification of the criteria for the diagnosis of CD, published in January 2020, consider that enterobiopsy is not necessary even in asymptomatic patients with a serum level of AtTG-IgA class ≥ 10 times above the upper reference level values and positive EMA-IgA in a second serum sample [19]. This year's guide related to the diagnosis of CD in children and adults of the American College of Gastroenterology (ACG) do not differ from the latest ESPGHAN recommendations [13]. The American Gastroenterological Association also agrees with the ESPGHAN and ACG guidelines in the diagnosis of CD in children, with the fact that in adults, for purposes of differential diagnosis, upper gastrointestinal endoscopy with duodenal biopsy can also be performed [23]. However, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for the Study of Celiac Disease in their guidelines for the diagnosis of CD include endoscopic enterobiopsy as a mandatory [10, 17]. This attitude is based on the fact that without an endoscopic diagnostic approach, comorbid conditions with CD, such as peptic and eosinophilic esophagitis or *Helicobacter pylori* gastritis, can be overlooked.

The basis of CD therapy is a gluten-free diet [9, 10, 13, 17, 23]. Most patients with a symptomatic type of the disease, especially with the classical one, during the initial phase of treatment require the correction of micronutrient deficiencies, primarily iron and folate, and sometimes temporary restriction of lactose [13]. Patients

with CC, in addition to the correction of hydroelectrolyte and acid-base imbalance and removal of edema, require semi-elemental and/or parenteral nutrition, and sometimes short-term glucocorticoid therapy [10, 16]. RCD therapy also includes parenteral nutrition and immunosuppression with steroids or azathioprine, 6-mercaptopurine, and methotrexate, whereas in the treatment of RCD2 additional medications are applied, such as cyclosporine, cladribine, and fludarabine associated with anti-CD52 monoclonal antibodies (alemtuzumab) [10, 29]. RCD1 usually responds to a gluten-free diet, nutritional support, and immunosuppressive medications, while the therapeutic response in RCD2 is incomplete and, accordingly, prognosis is often poor [13].

The prognosis of timely recognized and consistently treated CD is excellent, while its late detection or non-compliance with the gluten-free diet, however, can lead to numerous consequences, and sometimes to life-threatening complications [10, 16, 27, 25, 30].

NON-CELIAC GLUTEN SENSITIVITY

Non-celiac gluten sensitivity is a non-allergic and non-autoimmune type of intolerance to wheat, rye and barley flour [31, 32]. It is characterized by a wide range of gastrointestinal and/or extraintestinal manifestations that resolve on a gluten-free diet [10, 31, 32]. Due to the lack of objective diagnostic indicators, the exact frequency of NCIG is not known and according to data from the literature, it occurs in 0.6–6% of members of the general population, whereby six times more often in adult women compared to men [8, 31, 33].

The pathogenesis of NCIG is not clear [2, 8, 10, 31]. It is assumed that the basis of the disorder is an inadequate innate immune reaction to gluten [8, 31, 34, 35]. Activated adaptive immunity is probably involved in the problem [8, 35]. Also, apart from gluten, other components present in wheat, rye, and barley flour participate in the pathogenesis of NCGS, such as wheat germ agglutinins, amylase/trypsin inhibitors, and fermentable oligo/di/monosaccharides and polyols [8, 10, 31, 35, 36].

The clinical picture of NCIG is highly variable, both in terms of severity and type of disturbance. It consists of different and most often combined gastrointestinal and/or extraintestinal manifestations [31, 32, 35]. The major gastrointestinal symptoms are episodes of abdominal pain, nausea, heartburn, flatulence, pronounced flatulence, diarrhea, and constipation, and extraintestinal symptoms are chronic fatigue, lethargy, anxiety, intermittent headache, depression, skin rash, arthralgia, fibromyalgia, and others [8, 31, 33, 35]. Symptoms disappear on a gluten-free diet and appear again after a gluten challenge within a few hours or a couple of days [10, 35].

For now, there are no clearly defined criteria for the diagnosis of NCIG. Studies have shown that half of patients with NCIG have HLA DQ2 and/or DQ8 and positive antigliadin antibodies of the IgG class, but these findings, although almost twice as common as in gluten-tolerant individuals, have no diagnostic value [2, 8, 31, 33]. Also, the microscopic appearance of the mucosa of the small intestine is normal, except for minimal lymphocytic infiltration of the *lamina epithelialis* in a small number of cases [8, 10, 33]. Hence, the basis of the NCIG diagnosis, after excluding CD and wheat flour allergy, is the disappearance or alleviation of symptoms on a gluten-free diet and their reactivation after switching to a standard diet [10, 31, 32, 33]. In cases where the gluten-free diet does not result in the desired effect, when considering the cause of the problems, one should take into account gastrointestinal intolerance of carbohydrates, primarily lactose, idiopathic irritable colon and other conditions with a similar clinical presentation [10, 31, 32].

The basis of the NCIG therapy is the gluten free diet [10, 31, 32, 36]. Unlike CD and WA, fewer patients with NCGS tolerate smaller amounts of gluten containing cereals [10, 35, 37, 38].

WHEAT ALLERGY

Wheat allergy is the rarest clinical entity within gluten-related disorders. It occurs in 0.2–0.5% of children and in about 0.8% of adults as an immunoglobulin E (IgE) or non-IgE-mediated reaction [33, 38, 39]. An important feature of the disorder is the relatively frequent association with other food allergies, such as cow's milk, egg, peanuts, tree nuts, fish, and seafood [33, 40].

IgE-mediated WA is characterized by gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), dermal (redness, urticaria, angioedema), respiratory (rhinitis, cough, bronchial obstruction), cerebral (headache, dizziness, migraine) and systemic (anaphylaxis) manifestations [31, 33, 38]. Depending on the severity of the reaction, it can be mild to life-threatening, such as anaphylaxis. Adverse reactions are of a rapid type, i.e. occur within two hours after exposure to gluten-containing cereals, usually after a few minutes [38]. The reaction is a consequence of T helper type 2 activation and IgE production by B and T cells [38]. The diagnosis is based on the connection between the mentioned clinical manifestations and wheat ingestion, as well as positive *in vivo* (skin prick tests) and/or *in vitro* (specific serum IgE) tests [39]. Therapy involves a strict diet without gluten-containing cereals. In severe allergic reactions, it is necessary to use antihistamines, and in anaphylaxis epinephrine, inhalation beta2-adrenergic agonists, glucocorticoids, and other measures [41].

Non-IgE-mediated WA (delayed-onset WA) represents the pathogenetic basis of eosinophilic esophagitis (EoE) and gastritis (EoG), as well as food protein-induced enteropathy (FPE), food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enterocolitis syndrome (FPIES), which occur in infants and young children [33, 38, 42, 43]. As a consequence of eosinophilic inflammation, symptoms related to EoE are dysphagia, chest pain, regurgitation and food impaction, and for EoG loss of appetite, nausea, vomiting, abdominal pain and sometimes diarrhea [33, 39, 40, 44]. Unlike IgE-mediated WA, the

etiopathogenesis of these disorders is based on the stimulation of innate immunity through alteration of the mucosal barrier inducing the activation of IL-C2 cells that produce IL-13 and IL-5 responsible for eosinophil recruitment [39, 44]. The diagnosis is confirmed by pathohistological verification of eosinophilic inflammation in biopsies of affected organs [33, 39, 40]. Treatment for EoE and EoG includes proton pump inhibitors (PPI) therapy, corticosteroids, and elimination diets [40, 45]. Esophageal dilation is indicated for treatment of esophageal strictures and fibrostenotic changes [40, 45]. FPE is manifested by chronic malabsorptive diarrhea, intermittent vomiting and failure to thrive, FPIAP with visible specks or streaks of blood mixed with mucous in the stool or mild mucous-bloody prolonged diarrhea, and FPIES with repeated vomiting, profuse diarrhea and severe dehydration [38, 42, 43]. The pathogenesis of these clinical entities is not sufficiently clear, but it is considered that cellular immunity is responsible for driving the allergic inflammatory response [43, 46]. The diagnosis of FPIAP and FPIES, with the exclusion of other diseases with a similar clinical picture, remains, for the most part, a clinical one, with the exception of FPE, in which histological confirmation is usually required [43]. In addition to a strict elimination diet, FPE requires the correction of a nutritional deficit, and FPIES the normalization of hydroelectrolyte and acid-base status.

IgE-mediated WA that occurs during early childhood usually disappears with age, while disorders that continue from childhood into adulthood or are adult-onset usually remain permanent [42]. EoE and EoG are usually lifelong disorders, while FPE and FPIAP disappear by the age of 1–2 years, and FPIES by 3–5 years [42, 43].

CONCLUSION

Intolerance of gluten-containing cereals consists of three different immune-mediated disorders: CD as an autoimmune, WA as an allergic, and NCGS as a non-autoimmune or allergic. After lactose intolerance, it is the most common food-related disorder. This fact should not be surprising, because gluten-containing cereals, as well as animal milk, viewed from the aspect of evolution, have relatively recently become a daily ingredient in the diet of the majority of the human population. They are characterized by highly variable and largely non-specific gastrointestinal and extraintestinal symptomatology, and accordingly the necessity of a subtle diagnostic approach. CD is a permanent disorder, while WA is in a high percentage, especially if it occurs in early childhood, of a transient nature. Also, NCGS can be a transient disorder. The basis of the treatment of all three disorders is a gluten-free diet, with the fact that in NCGS, unlike CD and WA, it does not have to be strict.

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Интолеранција на житарице са глутеном

Зоран Лековић[1,2], Владимир Радловић[1,2], Марија Младеновић[3], Синиша Дучић[1,2], Петар Росић[2], Горан Ђуричић[1,2], Јелица Предојевић-Самарџић[4,5], Недељко Радловић[6]

[1]Универзитетска дечја клиника, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитет „Сингидунум", Факултет здравствених, правних и пословних студија, Ваљево, Србија;
[4]Универзитетски клинички центар Републике Српске, Бања Лука, Република Српска, Босна и Херцеговина;
[5]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[6]Српско лекарско друштво, Академија медицинских наука Српског лекарског друштва, Београд, Србија

САЖЕТАК

Интолеранција на житарице које садрже глутен (пшеница, раж и јечам) етиопатогенетски је хетероген и релативно чест проблем савременог човека. Јавља се као нежељено имунолошки посредовано стање код генетски предиспонираних особа. Према патогенетском механизму интолеранције на компоненте ових житарица, класификује се на целијачну болест као аутоимунску болест, алергију на пшенично брашно као алергијску болест и нецелијачну осетљивост на глутен као неаутоимунску и неалергијску болест. Сваки од ових поремећаја карактеришу специфичне интестиналне и/или екстраинтестиналне манифестације, које се повлаче на дијети без глутена. У овом прегледном чланку приказане су основне карактеристике ових поремећаја у складу са савременим сазнањима.

Кључне речи: житарице са глутеном; клинички облици интолеранције; целијачна болест; дијагностика; исхрана; педијатрија

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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Perspective of robotic-assisted treadmill training effect in children with cerebral palsy on motor functions and gait

Dragana Đurić, Sunitha Bhagavathi Mysore
Fatima College of Health Sciences, Abu Dhabi, UAE

SUMMARY
Robotic-assisted treadmill training has been applied in the last two decades for children with cerebral palsy. The high technology of robotic devices enables an individualized approach, physiological gait pattern, intensive training through a large number of repetitions, while enhancing motivation with active attention that influence motor learning and neuro plasticity. The results of clinical studies are controversial regarding the effectiveness of robotic-assisted gait training on speed and endurance in walking, gross motor functions, postural control, and balance in children with cerebral palsy who are at different levels of motor functioning. Scientific evidence does not highlight the superiority of robotic gait rehabilitation over conventional therapies. The intensity, frequency, duration of therapy, and sustainability of effects are current research questions. Future studies should involve a larger number of participants, higher methodological quality, standardization of reporting robotic parameters, and the impact on the activity, participation, and quality of life of children with cerebral palsy.
Keywords: cerebral palsy; robotic-assisted gait training; motor functions; gait; children

INTRODUCTION

Cerebral palsy (CP) is a non-progressive neurodevelopmental disorder affecting a child's motor and sensory system due to brain lesion, and consequently movement, posture, and walking [1].

Gross motor function classification system (GMFCS) is an evidence-based tool that measures the severity of motor functioning in CP. The functional mobility of CP children is classified into different levels as independent walking (Level I–II), walking with handheld aids (Level III), and wheelchair mobility (Level IV–V) [2].

Children with CP have impaired gait function due to motor impairments such as spasticity, muscle weakness, lack of selective motor control, reduced range of motion and joint contractures. Common gait deviations seen in CP children as equines or crouch gait include reduced speed and endurance, decreased step and stride length, decreased toe clearance, decreased balance, fatigue and pain [3, 4, 5]. As the children mature, they tend to have decreased balance and gait stability due to growing related musculoskeletal impairments which have negative implications on the activity, participation, and quality of life especially for children at level III and IV on GMFCS, who are the most at risk for losing locomotor abilities [6]. Hence, there is high emphasis on gait training in children with CP for maintaining their gait pattern for a long period of time [7].

ROBOTIC-ASSISTED GAIT TREADMILL TRAINING (RAGTT)

There are different ways of providing gait training on the ground with and without body weight support (BWS) and one of the advantages of robotic gait training is that it allows children on level III and IV to walk while maintaining the same quality for longer periods. RAGTT is a high-technology intervention with increasing popularity in rehabilitation centers [8]. Lokomat® (Hocoma AG, Volketswil, Switzerland) is one of the most popular RAGTT that supports the patient on a treadmill with adjustable robotic orthoses (exoskeletons) for each leg, suspension system controlling body weight, treadmill, and feedback screen [9]. The system offers varying levels of BWS, to enable stepping practice for both ambulatory and non-ambulatory patients. Robotic orthosis movements synchronize with the treadmill speed through a computer algorithm for hip and knee joint motion, providing a near physiological gait phases [10]. The multimodal Lokomat control has adjustable settings for muscle assist ranging from passive to active resistance, allowing muscle activity and incrementally reducing dependence on robotic support by progressively decreasing BWS and guidance while increasing the treadmill speed [6]. The computer algorithm for treadmill walking is connected to a video game that sets target, provides feedback on the screen and constantly engaging active cognitive and motor participation of the children during the training.

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Correspondence to:
Dragana ĐURIĆ
Fatima College of Health Sciences
Al Mafraq
Abu Dhabi
UAE
dragana.djuric11@gmail.com

RAGTT has shown positive possibilities for increasing gait speed, stride length, lower limb strength, muscle endurance, balance spatiotemporal gait parameters in children and adolescents with CP due to its high repetition, intensive practice [6, 11]. In addition, it is known to enhance cardiovascular endurance, improve muscle strength, balance, motor planning and other physiological functions [10, 12, 13]. The hip and knee extension can be adjusted to allow standing even in severely affected CP children, which could have an impact on muscles flexibility, range of motion, spasticity, balance, gait, and postural control [14].

RAGTT is a stationary type of robot and has a few limitations – it is a costly device, takes up much space, therapists require training, and the equipment requires ongoing maintenance. It allows only forward-walking without any opportunities to change direction, practice walking backwards, or walking on uneven terrain.

MOTOR LEARNING AND NEUROPLASTICITY ASSOCIATED WITH RAGTT

RAGTT provides intensive, repetitive, task-oriented motor activities by increasing motivation, attention, and active participation which influences motor learning and neuroplasticity [12]. RAGTT produces bilateral changes in cortical areas, which are involved in motor coordination and complex movements, in proprioceptive control, in spatial memory and in attention, in self-control, and in working memory [12].

A neuroimaging study using functional near-infrared spectroscopy in children with CP after 12 RAGTT sessions as an adjunct to conventional therapy showed significant differences in the activation of sensorimotor cortex. The increase in prefrontal activity was found to be positively related to concentration, attention, and engagement with therapy [15].

EFFECTIVES OF RAGTT ON GROSS MOTOR FUNCTIONS, GAIT SPEED, GAIT ENDURANCE ACCORDING TO THE LEVEL ON GMFCS AND AGE

Level of motor functioning, comorbidities, and age are important factors influencing effectiveness of any CP interventions [16].

Most of the randomized control trials in their RAGTT studies for children with bilateral spastic CP use functional tests such as Gross motor function measure (GMFM) dimensions D (standing) and E (walking, running, jumping), six-minute walk test for gait endurance, 10-meter walk test for gait speed. The studies on the effectiveness of RAGTT have mixed results with most studies showing improvements in gait speed and endurance. A systematic review with meta-analyses done by Cortés-Pérez et al. [12] that included 15 articles with 413 CP children, a mean age of 10.33 ± 4.1 years concluded that RAGTT is more effective than conventional therapy on gait speed, walking distance, and dynamic balance associated with locomotion (improvement in dimension E on GMFM). Similarly, a systematic review by Volpini et al. [17] synthesizing seven studies with a total of 77 participants showed improvements in gait endurance.

A study done by Cherni et al. [4] showed improvements in gait speed, endurance, and step length, regardless of the severity level on GMFCS. A study done by Jin et al. [16] showed more improvement in the GMFM (D and E score) in ambulatory compared to non-ambulatory children indicating that children with mild and moderate impairments benefit more from RAGTT.

In contrast, systematic reviews done by Olmos-Gómez et al. [18] and Conner et al. [19], on eight papers each, found a weaker and inconsistent evidence on the use of RAGTT for gait and motor function on children, adolescents, and young adults with CP. Vezér et al. [5] in a meta-analysis that included seven papers on CP did not show a difference between RAGTT and conventional physiotherapy [5]. This raises an important question about the high cost involved with RAGTT and it may not always be justifiable [19].

A study done by Ammann-Reiffer et al. [9] reported no significant changes in motor function and walking with 15 sessions of RAGTT for children 6–18 years of age with level II–IV on GMFCS. This is because the participants included in this study had reached their maximal motor capabilities with early intervention programs, intensive rehabilitation, and prior RAGTT [9].

Most of the studies included only children and adolescents, with a few older than 21 years [19, 20]. Klobucká et al. [20], for adolescents and adults with bilateral spastic CP, levels II–IV on GMFCS, found statistical improvement on GMFM in the RAGTT group in comparison to conventional therapy.

INTENSITY, FREQUENCY, DURATION AND FOLLOW UP OF RAGTT

The optimal training intensity, duration, and frequency of RAGTT sessions is an ongoing discussion among researchers and clinicians [10]. As the cost of RAGTT is very high, it is important to have evidence of the optimal number of sessions required for RAGTT.

The number of sessions utilized in the current literature on RAGTT range 12–40, for 3–12 weeks, with a frequency of 1–5 times per week, with session duration lasting 20–45 minutes. The studies that have shown positive changes on gait and motor function have an average of 20 Lokomat sessions with short intervention duration of four weeks and high frequencies, five sessions per week [4, 20]. The effectiveness of therapy if repeated more than once is still not very well understood.

A recent study by Choi et al. [21] examined different intensities of speed and BWS on RAGTT for children with level II–III on GMFCS. With 18 sessions, better results were seen on GMFM with high-intensity (fastest walking

speed and lowest BWS) and comfortable intensity (intermediate speed and intermediate BWS) when compared to the low-intensity group.

Several studies have 3–6 months of follow-up assessments after the RAGTT. In adolescents and adults, scores on all dimensions of GMFM were maintained 3–4 months after RAGTT [20]. Six months of sustained effects were seen in a study done by Cherni et al [4] after 24 sessions of RAGTT.

FURTHER STUDIES

It is well known that RAGTT is considered an adjunct therapy rather than the substitute for conventional physiotherapy [3, 21, 22]. To get precise information about the effectiveness of RAGTT, high-quality randomized studies are needed, involving larger number of participants, homogenized patient groups, research standardization, and monitoring sustainability of the effects [3, 5, 6, 18].

As there is no standardized protocol for RAGTT, determining the parameters of robotic training is an individual decision of the physiotherapist. To optimize RAGTT, guidelines for selection of parameters are essential [6], and emphasis must be placed on walking speed, BWS, and guidance force, which contribute to a better understanding of the effects of RAGTT and correlate the results to clinical practice [23].

Furthermore, assessments on the influence of RAGTT on functional activities, participation, and quality of life need to include patient- or parent-reported outcomes [5]. To what extent children improve fitness level, reduce tiredness in physical activities, and decrease assistance in daily life after RAGTT is yet to be explored.

CONCLUSION

RAGTT is an enjoyable and safe intervention for CP children, with simultaneous motor and cognitive engagement with positive effect on motor learning and neuroplasticity**.**

The main goal of this paper was to synthesize and reflect on the research findings about efficiency of RAGTT on motor functions, gait speed, endurance and intensity of the sessions and sustainability of RAGTT effects.

Studies have shown that children with mild and moderate impairments improve dynamic skills such as locomotor skills, walking distance and speed. However, for those with severe impairment, improvements are seen only in rolling and sitting, which might be due to better postural control.

Most of the studies used intensive training of 20 sessions as an adjunct to conventional therapy with pre-, post-, and follow up at three and six months, demonstrating the sustained functional effects of RAGTT.

The future studies need to consider larger sample size, longer follow-up, and influence on participation restriction and quality of life.

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Разматрање утицаја роботски потпомогнутог тренинга хода на покретној траци на моторичке функције и ход деце са церебралном парализом

Драгана Ђурић, Сунита Багавати Мајсор

Колеџ здравствених наука „Фатима“, Абу Даби, Уједињени Арапски Емирати

САЖЕТАК

Роботски потпомогнут тренинг хода на покретној траци примењује се у последње две деценије код деце са церебралном парализом. Висока технологија роботског уређаја омогућава индивидуални приступ, физиолошки образац хода, интензиван тренинг кроз велики број понављања уз поспешивање мотивације и активне пажње, које утичу на моторичко учење и пластицитет мозга. Резултати клиничких студија су контроверзни у погледу ефикасности роботски потпомогнутог тренинга хода на брзину и издржљивост у ходу, грубе моторичке функције, постуралну контролу и баланс код деце са церебралном парализом која су на различитом нивоу моторичког функционисања. Научни докази не истичу супериорност роботске рехабилитације хода у односу на конвенционалну терапију. Интензитет, учесталост, трајање терапије и одрживост ефеката су актуелна истраживачка питања. Будуће студије треба да обухвате већи број испитаника, виши методолошки квалитет, стандардизацију извештавања роботских параметара и утицај роботски потпомогнутог тренинга хода на активност, партиципацију и квалитет живота деце са церебралном парализом.

Кључне речи: церебрална парализа; роботски потпомогнут тренинг хода; моторичке функције; ход; деца

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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Gastroesophageal junction cancer – current topic and treatment dilemmas

Nikola Milošević[1], Suzana Stojanović-Rundić[1,2], Srđan Milanović[1], Ebrahim Keramatollah[2,3], Predrag Sabljak[2,3], Ognjan Skrobić[2,3], Miloš Bjelović[4]

[1]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Clinic for Digestive Surgery – First Surgical Clinic, Belgrade, Serbia;
[4]Euromedik Hospital, Belgrade, Serbia

SUMMARY
Treatment of gastroesophageal junction carcinomas have been debated for many years. This type of carcinomas has been classified as either gastric or esophageal carcinomas until Siewert's classification was established and they were defined as a distinct entity. Risk factors for the development of these cancers are gastroesophageal reflux and Barrett's esophagus, obesity, *Helycobacter pylori* infection, smoking, and alcohol. Symptoms of this disease include retrosternal pain, dysphagia to aphagia, and weight loss. Esophagogastroduodenoscopy with biopsy and pathohistological verification as well as CT of the chest and abdomen are crucial in establishing the diagnosis. Adenocarcinoma is predominant histological type of these tumors. The stage of the disease is defined by the TNM classification. Treatment of gastroesophageal junction cancer is complex, multidisciplinary, and multimodal, and involves the use of surgery, chemotherapy, and radiotherapy, alone or in different combinations. Surgery is the major treatment modality for these tumors, especially in local stages. Radiotherapy is used in the treatment of these tumors in all stages of the disease, and especially in the multimodal treatment of locally advanced gastroesophageal junction cancer, both preoperatively and postoperatively, usually in combination with chemotherapy. Chemotherapy is used in the treatment of these cancers as preoperative, postoperative and systemic. Immunotherapy and target therapy, as new promising therapy, is usually applied in a systemic and postoperative approach. Future directions in the treatment of these cancers are directed towards new surgical procedures, new types of immunotherapy, as well as new radiotherapy techniques.
Keywords: gastroesophageal junction cancer; surgery; radiotherapy

INTRODUCTION

Gastroesophageal junction (GEJ) carcinomas are relatively rare and aggressive tumors with an increase in the incidence rate in recent decades [1].

Siewert's classification defines them as tumors located within 5 cm of the anatomical cardia (distal or proximal):

1) type I – adenocarcinoma of the distal esophagus with tumor epicenter 1–5 cm above the GEJ,

2) type II – adenocarcinoma of the cardia with the epicenter of the tumor 1–2 cm below the GEJ, and

3) type III – subcardial gastric carcinoma with the epicenter of the tumor 2–5 cm below the GEJ.

Risk factors for GEJ cancers are gastroesophageal reflux and Barrett's esophagus, obesity, *Helicobacter pylori* infection and smoking [2]. The most common symptoms include retrosternal pain, dysphagia to aphagia, regurgitation of the stomach contents and weight loss. The key methods for diagnosing GEJ cancers are esophagogastroduodenoscopy with biopsy and thoracic and abdominal computed tomography. Histopathology with immunohistochemical staining is used for definitive diagnosis and the majority of GEJ cancers are adenocarcinomas, less often they are squamous type. The genome of gastroesophageal carcinoma is complex and includes mutation of the most common genes (especially TP53), high microsatellite instability, and mutation of oncogenic kinases (EGFR, HER2, and MET). According to the TNM staging, GEJ carcinomas can be divided as follows:

1) local (early) stage (Tis-T1 N0 M0),

2) locally advanced stage (T2-4 N1-3 M0), and

3) metastatic stage (T1-4 N1-3 M1).

TREATMENT

The multimodality and multidisciplinarity are necessary in the treatment of GEJ cancer. Surgery, radiotherapy (RT), and chemotherapy (CT) are treatment modalities. The basic principles of treatment are that early GEJ cancers are treated only with surgery, locally advanced cancers with a combination of surgery, CT, and RT, and metastatic cancers with CT or RT. Most widely used recommendations for the treatment algorithm are the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO).

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Correspondence to:
Nikola MILOŠEVIĆ
Institute for Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade, Serbia
milosevicnikola43@gmail.com

Early stage

Local (early) GEJ carcinomas includes Tis and T1a-b N0 stage of disease.

The primary approach in early stage of the disease is radical surgery and includes endoscopic techniques such as endoscopic mucosal resection and endoscopic submucosa dissection (ESD), as well as classical surgical techniques such as esophagectomy with gastrectomy and lymphadenectomy.

Endoscopic mucosal resection is an option for T1a lesions smaller than 10–15 mm and ESD may be considered in T1a lesions larger than 15 mm [3]. If after endoscopic resection histopathology parameters show poor differentiation, lymphovascular invasion, or positive margins, further steps may include adjuvant radiochemotherapy (RCT).

For T1b GEJ cancers esophagectomy is indicated, but for T1b cancers with favorable histopathological pattern (well-differentiated, smaller than 2 cm and without LVI) ESD may be a good alternative to esophagectomy. Two types of esophagectomy are used, transthoracic (Ivor-Lewis procedure) and transhiatal. The radicality of surgery is imperative due to the significant deep and *per continuitatem* spread of these tumors (significantly more in type I and II than in type III) [4]. The consensus in surgical treatment of GEJ type I cancer is esophagectomy with transthoracic approach [5]. GEJ type II carcinomas are true junctional tumors, so the choice of surgical approach is very controversial. Two types of surgery are used, total gastrectomy with transhiatal distal esophagectomy and transmediastinal esophagectomy with proximal gastrectomy [6]. Total gastrectomy with distal esophagectomy is needed for GEJ type III carcinomas [6]. Lymphadenectomy implies a dissection of mediastinal and abdominal lymph nodes ("two-field"). Recommendations for lymphadenectomy in GEJ type I cancer are upper, middle, and lower mediastinal and abdominal dissection, in type II are upper, middle, and lower mediastinal and abdominal dissection, and in type III these are lower mediastinal and abdominal dissection [7].

In recent years, newer surgical procedures in the treatment of GEJ carcinoma such as robot-assisted, hybrid, and minimally invasive esophagectomies may have the potential to achieve better results compared to conventionally accepted surgical techniques [8].

Locally advanced stage

Locally advanced GEJ carcinomas include T2-T4 N0-3 stage of the disease.

For patients who are medically fit and present with good performance status (ECOG PS 0–1) with potentially resectable locally advanced disease stage T2-T4a, indication is preoperative RCT with/without surgery, perioperative CT with surgery or neoadjuvant/perioperative immune checkpoint inhibitors therapy with/without surgery. T4b tumors with involvement of the surrounding organs are unresectable, so that patients, if they are medically fit with ECOG PS 0–2 are candidates for definitive CRT or CT.

Today, a standard in the treatment of a locally advanced GEJ carcinoma is a multimodal approach (a combination of RT, CT, and surgery). Even though RCT provides higher rates of complete pathologic response and better locoregional control then perioperative CT, survival in both types of therapy is similar [9]. The ESOPEC-trial [10], which compares these two modalities in neoadjuvant setting in patients with esophageal adenocarcinoma, is in progress, and results are expected. For GEJ adenocarcinomas preoperative RCT is generally used in the USA, while perioperative CT is favored in most European countries, but for GEJ squamous cell carcinomas, preoperative RCT is the standard of care in general. The most important study that established the benefit of preoperative RCT is the Dutch CROSS trial [11], with over 300 patients that compared the five-year survival of two groups of patients, treated with surgery alone or with a combination of preoperative RCT (CT with paclitaxel/carboplatin and 3D conformal RT with TD 41,4 Gy) and surgery. The percentage of R0 resection was 92% *vs*. 69%, five-year survival was 43.2 *vs*. 27.1 months (RCT and surgery group *vs*. surgery group), pCR was 23%, and grade III toxicity was up to 10%. The most relevant study on the role of perioperative CT in gastric and GEJ cancer is MAGIC trial [12], with 500 patients, which compares two groups of patients treated with surgery alone and patients treated with perioperative CT (epirubicin/CDDP/5-FU) with surgery. The results showed acceptable toxicity (0.3–23.8% of hematological grade III and 2.6-6.4% of non-hematological grade III), and five-year survival rate of 36% *vs*. 23% in favor of the CT group.

The combination of radiotherapy and CT enhances the effect of the therapy. The most modern radiotherapy techniques include intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) [13]. Radiotherapy doses in preoperative RCT are ~ 41.4–50.4 Gy in ~ 23–28 fractions.

After preoperative RCT, if there is local disease (partial tumor regression or stable disease), patients are referred for surgery. However, in the case of a complete clinical response, patients can undergo esophagectomy or continue to follow-up [14].

Perioperative CT with FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) has become the gold standard treatment for medically fit patients with operable gastroesophageal adenocarcinoma [15]. In patients who are intolerant to multiple agents, HT with 5FU/CDDP can be used [16]. Perioperative CT is incorporated in guidelines such as ESMO and NCCN, but preoperative RCT is emerging as the standard in the treatment of locally advanced GEJ carcinomas [17, 18]. Preferred regimens combination of cytostatic drugs in preoperative RCT are 5-FU/CDDP and paclitaxel/carboplatin.

Definitive radiotherapy is performed less often on GEJ cancer patients who are considered medically unfit for surgery, in unresectable disease (cT4b stage) cases, and on patients with resectable disease who decline surgery. RT technics and a combination of cytostatic drugs are the same as in preoperative RCT, and RT doses are 45–54 Gy in 25–30 fractions.

In postoperative approach after esophagectomy, further therapy depends on previous therapy (preoperative CT/RCT), margin resection status, nodal status, number of extracted lymph nodes, tumor stage, tumor differentiation, and tumor invasion [17, 18].

In general, there is no consensus in adjuvant treatment of GEJ cancers. Although most patients with locally advanced disease receive preoperative therapy, postoperative RCT remains a standard of care for GEJ/gastric cancers in the USA. Postoperative CT is a standard of care in the East [19].

Research that can serve as a landmark regarding the application of postoperative RCT in GEJ cancers is INT 0116/SWOG 9008 trial [20]. In this trial, surgery or surgery plus postoperative RCT have been used in over 500 patients with gastric or GEJ cancer (RT with 45 Gy in 25 fractions and CT with 5-fluorouracil/leucovorin). Three-year survival was 50% *vs*. 41% in favor of the RCT group, and local and regional relapse was reduced in the RCT group (19% *vs*. 29% and 65% *vs*. 72%). The radiation techniques used in postoperative RT are also IMRT and VMAT, and the doses are also in the range of 45–50.4 Gy in 25–28 fractions.

The use of adjuvant CT after surgery is established after the CLASSIC trial [21], which included 1000 patients with gastric and GEJ cancer and showed enhanced five-year survival in patients who had postoperative CT over the patients who had only surgery. Preferred combination of cytostatic drugs in postoperative CT are also 5-FU/CDDP and paclitaxel/carboplatin.

Advancements in radiotherapy techniques are improving tumor delineation (RT planning based on MRI and PET), reducing interfraction motion (using IGRT and 4DCT) and intrafraction motion (respiratory-gated RT), increasing the dose to the tumor [simultaneous integrated boost (SIB) technique of RT] [22]. Recently, proton therapy has shown promising results especially in sparing of organs at risk.

In the treatment of GEJ cancers, immunotherapy with monoclonal antibodies is used, such as trastuzumab and "checkpoint" inhibitors such as pembrolizumab and nivolumab.

Adjuvant nivolumab after surgery in patients with esophageal and GEJ cancers, who had received neoadjuvant RCT and have evidence of residual pathological disease in the resection specimen (>ypT1 and/or >ypN1) leads to significant improvement in disease-free survival [23].

Metastatic stage

Metastatic GEJ carcinomas include T1-T4 N1-N3 M1 stage of the disease.

CT with/without immunotherapy is the standard of treatment in metastatic disease, followed by palliative radiotherapy. Patients with good ECOG PS (0–2) are considered for systemic CT.

Combination treatments with two drugs (fluoropyrimidines + platinum) are the treatment standard, combinations with three drugs (5-FU + platinum + docetaxel) are controversial but could be applied in patients with excellent ECOG PS, while monotherapy (fluoropyrimidine, irinotecan, weekly taxane) could be the choice in patients with poor ECOG PS [24]. Adding transtuzumab to standard CT in the first-line setting led to improved outcomes in patients with HER2-positive, advanced GEJ cancers [25]. Nivolumab in combination with standard first-line CT demonstrate superior results [26]. Both paclitaxel and irinotecan are reasonable second-line treatment options because there is no statistically significant difference between them in the overall survival [25].

The first clinical trials on the application of immunotherapy based on human dendritic cells showed good tolerance and prolonged survival time in patients with gastrointestinal tract cancers, but the application is still a great challenge [27].

More than 40% of patients with metastatic cancer receive palliative radiotherapy [28]. Indications are local recurrence, bleeding, obstruction, pain, and bone and brain metastases, and radiation doses are 8 Gy in one fraction, 16 Gy in four fractions, 20 Gy in five fractions, or 30 Gy in 10 fractions.

CONCLUSION

Treatment of GEJ cancers is complex and involves the use of RT, CT, surgery, and immunotherapy alone or in different combinations. Surgery is the first choice of GEJ cancer treatment, especially in the localized stage of the disease. RT has a significant role in the treatment of these tumors in all stages of the disease, especially in locally advanced cancers in the neoadjuvant approach, usually in combination with CT, but also in the adjuvant approach. The modern RT techniques have enabled the application of higher doses of radiation with significant protection of the surrounding healthy tissues in this region, leading to a significant reduction in the toxicity of RT alone or in combination with CT. Various CT regimens are unavoidable in the treatment of GEJ cancer in a neoadjuvant, adjuvant, or systemic approach. Immunotherapy as a new promising therapy is being imposed in the treatment of these cancers. The future of treatment of these cancers is directed toward new surgical procedures, wider application of immunotherapy, as well as new RT techniques.

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Карцином гастроезофагеалног споја – актуелна тема и дилеме у лечењу

Никола Милошевић[1], Сузана Стојановић-Рундић[1,2], Срђан Миланović[1], Ебрахим Кераматолах[2,3], Предраг Сабљак[2,3], Огњан Скробић[2,3], Милош Бјеловић[4]

[1]Институт за онкологију и радиологију Србије, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за дигестивну хирургију – Прва хируршка клиника, Београд, Србија;
[4]Болница „Еуромедик", Београд, Србија

САЖЕТАК

Карциноми гастроезофагеалног споја дуго су изазивали дилеме и класификовани су као карциноми желуца или једњака све до Сивертове класификације када су дефинисани као посебан ентитет. Фактори ризика за развој карцинома гастроезофагеалног споја су гастроезофагеални рефлукс и Баретов једњак, гојазност, инфекција бактеријом *Helycobacter pylori*, пушење и алкохол. Симптоми ове болести укључују ретростернални бол, дисфагију до афагије, регургитацију желудачног садржаја и губитак тежине. Езофагогастродуоденоскопија са биопсијом и патохистолошком верификацијом, као и компјутеризована томографија грудног коша и абдомена кључне су у постављању дијагнозе. Аденокарцином је доминантни хистолошки тип ових тумора. Стадијум болести се дефинише *TNM* класификацијом. Лечење карцинома гастроезофагеалног споја је комплексно, мултидисциплинарно и мултимодално и подразумева примену хирургије, хемиотерапије и радиотерапије, самостално или у различитим комбинацијама. У мултимодалном лечењу локално узнапредовалог карцинома гастроезофагеалног споја постоје дилеме као што су оптималан хируршки приступ и терапијски редослед. Хирургија је главни начин лечења ових тумора, посебно у локалним стадијумима. Радиотерапија се користи у лечењу ових тумора у свим стадијумима болести, а посебно у мултимодалном лечењу локално узнапредовалог карцинома гастроезофагеалног споја, преоперативно и постоперативно, најчешће у комбинацији са хемиотерапијом. Хемиотерапија се користи у свим облицима у лечењу ових карцинома као преоперативна, постоперативна и системска. Имунотерапија и циљна терапија, као најновији облици лечења, обично се примењују системски и постоперативно. Будући правци у лечењу ових карцинома су усмерени ка новим хируршким процедурама, новим типовима имунотерапије, као и новим техникама радиотерапије.

Кључне речи: карцином гастроезофагеалног прелаза; хирургија; радиотерапија

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ARTICLE FOR PRACTITIONERS / РАД ЗА ПРАКСУ

National clinical practise guidelines – prevention and treatment of uncomplicated urinary tract infections

Nada Dimković, Višnja Ležaić

Serbian Medical Society, Academy of Medical Sciences of the Serbian Medical Society, Belgrade, Serbia; University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY
Uncomplicated urinary tract infections occur in persons with morphologically and functionally normal lower and upper urinary tract, normal kidney function, and a competent immune system. They are one of the leading reasons of antibiotics misuse. There is much controversy regarding the screening, diagnosis, and treatment of urinary tract infection. This article summarizes the most common urinary tract infections and those that cause the most doubts in daily clinical practice. The goal is to stimulate physicians in using the latest recommendations of the national guidelines that may help them in daily clinical practice.
Keywords: uncomplicated urinary tract infection; recommendations; national guidelines

INTRODUCTION

Urinary tract infections (UTIs) are one of the leading cause of antibiotics use worldwide. On the annual level, UTIs are found in more than 150 million people globally, which ranks them among the most common infectious diseases [1]. The true incidence of UTIs in Serbia is not easily determined because they are not subject to mandatory reporting.

Uncomplicated UTIs are defined as UTIs occurring in persons with morphologically and functionally normal lower and upper urinary tract, normal kidney function, and a competent immune system. There is much controversy regarding the screening, diagnosis, and treatment of these infections. The new national guidelines have given recommendations for uncomplicated UTIs [2]. This overview summarizes the most common topics that cause the most doubts for treatment in clinical practice. The goal is to stimulate physicians in using the guidelines in appropriate medical situations so that the practice of all doctors in our country could be uniform.

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria (AB) is a significant concern in current guidelines due to its link to unnecessary antibiotic use. AB is defined as the presence of one or more bacterial species in urine taken properly ($\geq 10^5$ colony-forming units per ml) regardless of the presence of pyuria and without symptoms of urinary infection [3]. In some cases, especially among the elderly, AB can be mistaken for a UTI when patients show general deterioration (e.g., mental state changes, lethargy, loss of appetite). However, these symptoms might be caused by factors other than a UTI. Therefore, it is crucial to explore other potential causes before attributing such conditions to UTI and initiating antibiotic treatment [3].

Screening for AB is not recommended except for pregnant women (when it is treated and controlled) and before urological interventions that are accompanied by bleeding (such as transurethral resection of the prostate). A single dose of antibiotics is given before the intervention, and the drug is possibly used for a short time or while a temporary urinary catheter is in place. Screening and treatment of AB before spinal surgery is recommended for patients with a urinary catheter, neurogenic bladder or urinary incontinence in order to reduce the risk of Gram-negative infection at the surgical site.

ACUTE UNCOMPLICATED CYSTITIS

Acute uncomplicated cystitis refers to sudden inflammation of the bladder without underlying health issues or urinary tract abnormalities. Around half of women experience it at least once in their lives, and a third have it by the age of 24. Diagnosis is often based on symptoms like pain during urination and urgency without vaginal discharge or pain [4]. In typical cases, urine analysis might not be necessary [4]. However, in older women, symptoms might not always signify cystitis, requiring laboratory confirmation [5]. The presence of leukocytes in urine is not specific for UTI, but detecting nitrites is highly indicative of bacterial presence. However, some bacteria types (*Staphylococcus*, *Enterococcus*, *Pseudomonas*)

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Correspondence to:
Nada DIMKOVIĆ
Hadži Ruvimova 19
11000 Belgrade
Serbia
dim@eunet.rs

do not convert nitrates to nitrites, and the absence of nitrites does not rule out infection (e.g., due to diluted urine or certain bacteria types).

Urine culture is indicated when the diagnosis of acute uncomplicated cystitis is not clear, in case of persistence of symptoms, early return of infection, suspected resistant infection or when therapeutic options are limited due to multiple allergies.

The first-choice drugs for uncomplicated cystitis treatment are fosfomycin trometamol in a single dose of 3 g, nitrofurantoin 100 mg twice a day for five to seven days, and pivmecillinam 400 mg three times a day for three to five days [6]. Trimethoprim + sulfamethoxazole, the most commonly used drug for this indication, can only be used empirically if the local *E. coli* resistance rate is less than 20% [7]. Fluoroquinolones are extremely effective in three-day regimens, but they should be considered as alternative antibacterial drugs because of side effects.

RECURRENT URINARY TRACT INFECTIONS

Recurrent UTIs (rUTI) are common in women across various demographics. Around 60% of women experience an acute bladder infection in their lifetime, 20–40% of them might have recurrent episodes, and almost half experiencing multiple recurrences [8]. A diagnosis of rUTI typically requires two infections in the past six months or three within the previous year [8].

To identify the underlying causes of rUTI, medical examinations are crucial including pelvic, gynecological, and urological evaluations. These examinations may detect anatomical or functional issues like stones, diverticula, or nerve-related bladder problems. Bowel issues, prior antibiotic use, *Clostridium difficile* infection, antibiotic resistance, allergies, menopausal status, contraceptive use, sexual activity, and genital tract symptoms should be taken into consideration. Additionally, conditions like bladder or vaginal prolapse, rectal issues, cysts, and infections in genital areas need consideration. Examining pelvic floor muscles, especially in elderly and women who have given birth multiple times, is essential [9]. Neurological conditions (brain and spinal cord damage, diabetes and vegetative polyneuropathy) and ongoing therapies affecting urine flow should also be taken into account. Treating the primary issue often resolves the recurring infections.

Positive urine culture is necessary for diagnosing rUTI. Routine cystoscopy and upper urinary tract imaging are not routinely advised but might be considered in case of poor response to therapy or if infections return rapidly with the same microorganism. It is recommended to wait for urine culture results before starting treatment [10]. Antibiotic selection relies on prior culture results, favoring first line therapy like nitrofurantoin, trimethoprim-sulfamethoxazole, or fosfomycin for shorter courses, typically lasting up to seven days. Prophylactic antibiotics might be considered after discussing the risks and benefits either on the daily basis or during the risk conditions (sexual intercourse, travel, all-day work, diarrhea, or constipation). The duration of prophylaxis varies from three to 12 months with periodic patient monitoring. Immunoprophylaxis with polyvalent vaccines [Uro-Vaxom® (OM-89, OM Pharma, Meyrin, Switzerland)] or autovaccines can be advised. Peri- and postmenopausal women, without contraindications, may consider using vaginal estrogen [11, 12]. Post-treatment, urine analysis is needed only for those with persistent symptoms.

ACUTE UNCOMPLICATED PYELONEPHRITIS

Acute uncomplicated pyelonephritis is an inflammation of the renal pelvis, calyces, and tubules, typically caused by bacteria and presenting with fever and signs of systemic infection [13]. Urine analysis is crucial for diagnosis, which reveals blood, leukocytes, and nitrites via a test strip. Microscopic urine analysis shows high leukocyte counts, leukocyte cylinders, and bacteria. In *E. Coli* infections, erythrocytes might be present. Initial Gram staining may help in selecting the most suitable therapy. Urine culture confirms the infection and identifies the causative agent and its sensitivity [14]. Blood tests often show increased leukocytes, neutrophils, sometimes anemia, rarely low platelets. Inflammation is indicated by increased values of C-reactive protein, D-dimer and accelerated sedimentation. Electrolyte imbalances, kidney failure, and elevated procalcitonin levels are indicators of systemic infection or even sepsis [15].

Acute uncomplicated pyelonephritis treatment can be on outpatient or in hospital basis depending on the severity of the disease. Outpatient treatment begins after urine sampling with empirical antibiotics like fluoroquinolones or third-generation cephalosporin. Mild form of the disease may start with a single dose of intravenous antibiotics initially [16].

Moderate form of the disease can be treated on an outpatient basis if the patient can consume liquids, food, and medications orally or if home-based intravenous therapy is feasible. Otherwise, hospitalization is recommended. Severe, septic form of pyelonephritis requires hospital treatment with carbenicillin or ureidopenicillin with/without aminoglycosides (adjusted to kidney function) along with supportive measures [16].

URINARY TRACT INFECTIONS DURING PREGNANCY

UTIs often occur during pregnancy and present a risk factor for maternal and fetal morbidity [17]. Pregnancy increases the risk of UTI due to changes in the function of the endocrine and immune systems, but also due to the mechanical compression of the ureters and bladder by the enlarged uterus.

Screening for AB by urine culture is recommended for all pregnant women during the first trimester of pregnancy with the aim of reducing the risk of pyelonephritis, premature birth, and low birth weight [18]. In pregnant women with AB, empirical use of antibiotics and one-day

use of antibiotics is not recommended (exception is fosfomycin-trometamol in single dose of 3 g). Women with proven group B streptococcal bacteriuria should be treated with appropriate intravenous antibiotics, aiming to prevent diseases in newborns, and the drugs of choice are penicillin, Cephalexin (Hemofarm AD, Vršac, Serbia) and Clindamycin (CHEPHASAAR chem. - pharm. Fabrik GmbH, St. Ingbert, Germany) [19]. Urine culture control is advised until delivery.

Cystitis in pregnant women requires empiric therapy (after urine is taken for analysis) with cefpodoxime, amoxicillin-clavulanate, and fosfomycin for three to seven days, unless fosfomycin is used. Urine culture is advised one week after the end of therapy [20]. Antimicrobial prophylaxis is advised if pregnant women have three or more episodes of cystitis during pregnancy.

Most episodes of acute pyelonephritis (AP) occur during the second and third trimester of pregnancy, and are accompanied by numerous complications. For pregnant women who have fever and/or pain in the loins or back, some other obstetric complications should be considered such as: intra-amniotic infection, placental abruption, nephrolithiasis and acute abdomen [20]. Radiological diagnostics of the kidneys and urinary tract may be justified when AP recurs or responds slowly to treatment [20]. Treatment of AP is carried out in hospital setting for the first 48 hours, where empiric antibiotic therapy with parenteral beta-lactam antibiotics is started. Fluoroquinolones and aminoglycosides should be avoided. If bacterial resistance to the empirical antibiotic is found, a change of antibiotic is necessary regardless of whether the symptoms of the infection improve or not. The duration of AP treatment is 10–14 days, and antibiotic prophylaxis is recommended for women who have had at least two episodes of AP during pregnancy.

URINARY TRACT INFECTIONS IN ELDERLY PEOPLE

UTIs are responsible for about 15.5% of hospitalizations due to infectious diseases in persons ≥ 65 years of age and are the cause of death in about 6% [21]. Elderly individuals face increased infection risks due to hormonal changes, prostate hypertrophy, reduced mobility, incontinence, and urinary catheter use. Obtaining urine samples from the elderly is challenging, often requiring single-time catheterization for women and clean condom catheters for men. Diagnosing UTIs in the elderly is challenging due to atypical symptoms. Urine characteristics (color, odor, turbidity) may not always indicate infection but could relate to dehydration or incontinence. Laboratory tests are crucial for diagnosis and treatment, especially considering high microorganism resistance [22].

Screening and treatment of AB is not recommended. Diagnosis of UTI in this group relies on the recognition of atypical symptoms, especially in nursing homes. Initiation of therapy is based on acute symptoms like dysuria, high fever, confusion, or worsening of genitourinary symptoms. Parenteral therapy is necessary for unstable patients, impaired oral absorption, or resistant infections. If aminoglycosides are indicated for more than a week, monitoring of drug levels and kidney function is necessary.

Long-term antimicrobial prophylaxis lasting 6–12 months can prevent repeated infections. The first line is nitrofurantoin 50 or 100 mg per day or trimethoprim-sulfamethoxazole half a tablet per day or every other day. Proper hydration is essential.

In elderly with a urinary catheter, AB is common and does not require screening or treatment. Symptoms of infection might differ, typically showing high fever, malaise, confusion, back pain, and sometimes catheter blockage or blood in urine. When infection is suspected, a urine sample should be taken after catheter replacement if it lasts for over two weeks. Treatment starts after catheter replacement and usually lasts seven days, occasionally 10–14 days if the response to therapy is delayed. Systemic antibiotic prophylaxis is advised only if catheter insertion, replacement or removal is accompanied by hematuria [23].

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Националне смернице клиничке праксе – превенција и лечење некомпликованих инфекција мокраћних путева

Нада Димковић, Вишња Лежаић

Српско лекарско друштво, Академија медицинских наука Српског лекарског друштва, Београд, Србија;
Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Некомпликоване инфекције мокраћних путева се односе на особе са морфолошки и функционално нормалним уринарним трактом и очуваним имунским системом. Оне су и најчешћи разлог злоупотребе антибиотика. Постоји више контроверзи о скринингу, дијагностиковању и лечењу некомпликованих инфекција мокраћних путева. У овом чланку сажете су препоруке о дијагностиковању и лечењу најчешћих инфекција мокраћних путева које су и најчешћи узрок дилема у клиничкој пракси. Циљ је да се лекари подстакну да користе препоруке најновијег водича у свакодневном клиничком раду.

Кључне речи: некомпликоване инфекције мокраћних путева; препоруке; национални водич

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био разматран за објављивање у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

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AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

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Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
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