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СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

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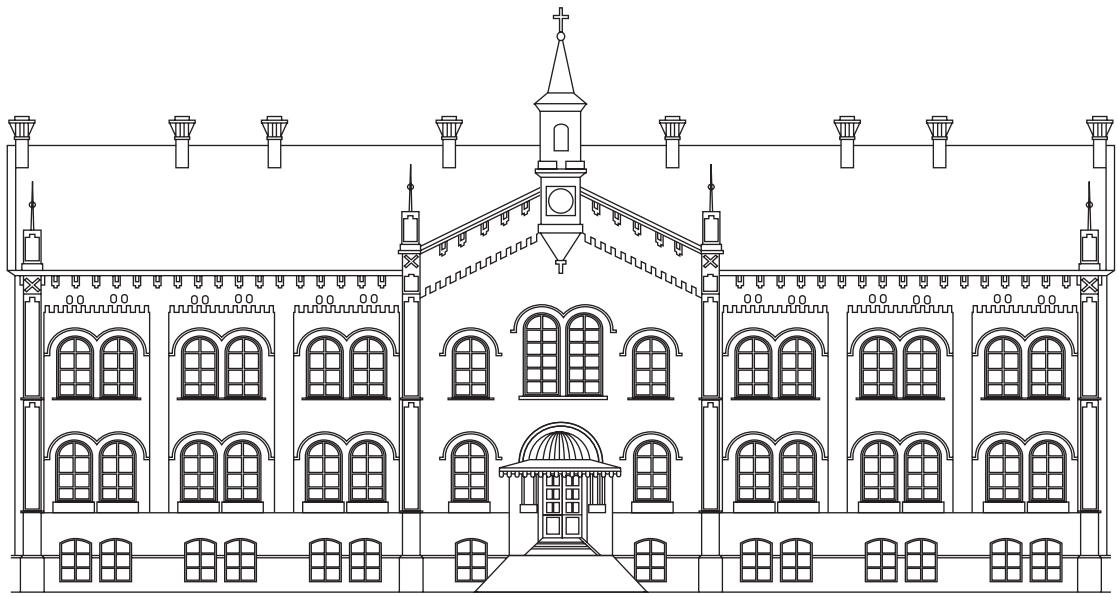

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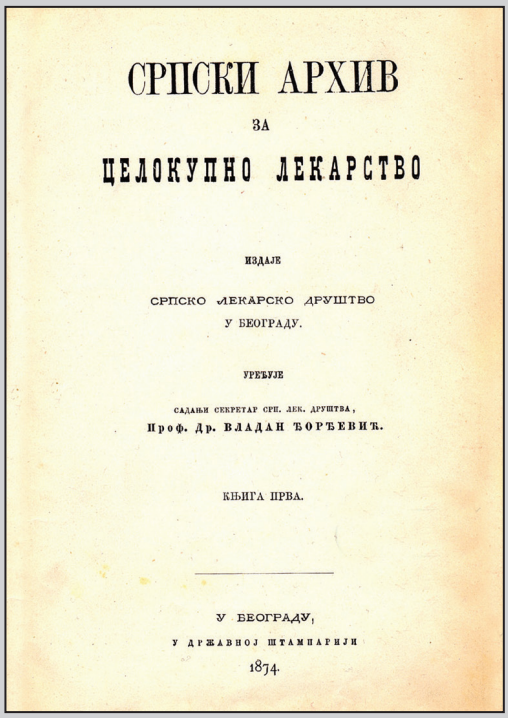

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

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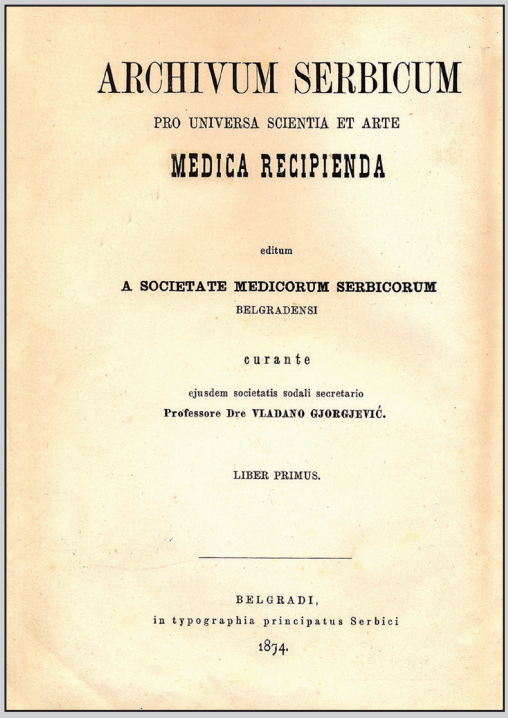
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основаног 1872. године, први пут штампан 1874. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Објављују се: 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 и 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.

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EDITORIAL / УВОДНИК

Dear and Honorable Colleagues,

For us at the Serbian Archives of Medicine, the beginning of 2021 is a time to first and foremost thank our reviewers whose help was invaluable at an unprecedented time for mankind. The majority of us have never had such an experienced in our lives. Although fighting for their patients' lives, exhausted for months and even hospitalized due to COVID–19, they would still reply to emails and process reviews for the Serbian Archives of Medicine, showing an admirable collegiality despite all professional and personal misfortunes. We are convinced their dedication was part of their noble mission to help the 148 year-long tradition of the Serbian Medical Society and its official journal stand the cruel test of time that spared no one.

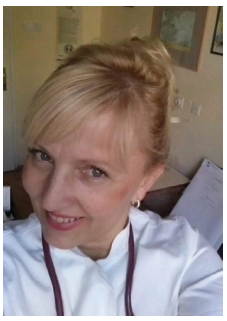
We are deeply indebted to our international reviewers as well, for their respective corners of the world may have suffered differently depending on the time of the year, but devastatingly facing the same consequences eventually. Yet, time and again, medicine and science showed that they know no borders in the most inspiring of ways.

Back in January 2020 (Srp Arh Celok Lek 2020 Jan–Feb;148(1–2):6–9), I tried to raise our readership's awareness of burnout, a work-related syndrome, which has nowadays reached an epidemic level, and therefore has been recognized by the World Health Organization. My awareness of the problem among our doctors was a result of 40 years in pedagogy – as a Professor of Gross Anatomy at Belgrade University's Faculty of Medicine and visiting professor at the Faculty of Pharmacy (Belgrade, Serbia) and Georgetown University's School of Medicine (Washington DC, USA) – and I still deem further burnout-related research in Serbia sorely needed.

Unfortunately, the March 2020 outbreak of COVID-19 pandemic made us all fight for nothing but mere survival. So many lives were lost both here and worldwide, and so many more irreversibly changed. Serbia is grieving its fallen frontline healthcare workers and is sadly yet to face all the burdens of later complications, as the rest of the planet did. But, we expect all involved in healthcare to keep researching and endeavoring to diminish both acute and chronic losses, for all our casualties are far from fully counted and accounted for. We, at the Serbian Archives of Medicine, aiming to help our readers with timely scientific content, processed and offered expedited publication of all COVID–19 related papers of both national and international authors with the highest priority. I would like to take this opportunity to apologize to all other authors whose manuscripts got delayed in the process, due to that reason.


Professor
Nevena Kalezić


Professor
Slobodan Savić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Professor
Ivan Palibrk


Professor
Ljubomir Todorović

Finally, we owe special gratitude to reviewers who contributed the most in 2020. Ranked as the first, second and the third review winner due to slight differences in the number of reviews they did in 2020 are the following: the first being professor Nevena Kalezić [University of Belgrade, Faculty of Medicine, (UBFM), University Clinical Center of Serbia, Belgrade, Serbia], the 2nd, Professor Slobodan Savić (UBFM, Institute of Forensic Medicine "Milovan Milovanović", Belgrade, Serbia), and the third one is shared between professors Nensi Lalić (University of Novi Sad, Faculty of Medicine, Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia), Ivan Palibrk (UBFM, University Clinical Centre of Serbia, Belgrade Serbia) and Ljubomir Todorović (University of Belgrade, School of Dental Medicine, Belgrade Serbia).

We hope the 2020 experience of adversity, availability of new vaccines worldwide, and more social solidarity will help us soon embrace the "new normal" in a serene and happier way.

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215. Pasternak Janko
216. Pašić Srđan
217. Pavlović Aleksandra
218. Pavlović Milorad
219. Pavlović Popović Zora
220. Pavlović Sonja
221. Pejčić Tanja
222. Pejović Milovančević Milica
223. Perović Milan
224. Petrlin Borut
225. Petronić Ivana
226. Petrović Ljubomir
227. Petrović Milan
228. Petrović Milorad
229. Petrović Milorad
230. Petrović Tomislav
231. Petrović Vanja
232. Petrović Violeta
233. Plećaš Darko
234. Plešinac Snežana
235. Popović Dragan
236. Popović Dušan
237. Popović Jelena
238. Popović Milka
239. Popović Miroslav
240. Popović Petrović Svetlana
241. Poskurica Mileta
242. Povazan Đorđe
243. Prijić Sergej
244. Puškar Tatjana
245. Putnik Svetozar
246. Radenković Miroslav
247. Radlović Nedeljko
248. Radosavljević Aleksandra
249. Radovanović Drakče
250. Radovanović Saša
251. Radovanović Zoran
252. Radović Ivana
253. Radović Milan
254. Radulović Danilo
255. Radunović Nebojša
256. Rajić Karlo
257. Raković Dejan
258. Ranin Lazar

259. Rebić Predrag
260. Reginster Jean-Yves
261. Risimić Dijana
262. Ristanović Momčilo
263. Ristić Arsen
264. Ristić Branko
265. Ristić Gorica
266. Rizzoli Rene
267. Roby-Brami Agnès
268. Roksandić Marina
269. Romić Predrag
270. Rybarova Silvia
271. Sajkovski Aleksandar
272. Savić Slobodan
273. Schönfeldt-Lecuona Carlos
274. Sečen Nevena
275. Sedláčková Miroslava
276. Sekulić Aleksandar
277. Sević Siniša
278. Shane Tubbs R
279. Shtarker Haim
280. Siller-Matula Jolanta
281. Simić Dušica
282. Simić Radoje
283. Simić Tatjana
284. Slavković Nemanja
285. Spremović Rađenović Svetlana
286. Srećković Sunčica
287. Srkalović Gordan
288. Stamenković Dragoslav
289. Stamenković Miroslav
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292. Stanić Vojkan
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295. Stanojević Goran
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312. Stokić Edita
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314. Svetel Marina
315. Svorcan Petar
316. Šaponjski Jovica
317. Škodrić Trifunović Vesna
318. Šumarac Dumanović Mirjana
319. Tasić Lidija
320. Tasić Nebojša
321. Teofilovski Parapid Gordana
322. Till Viktor
323. Timotijević Ivana
324. Tiosavljević Danijela
325. Todić Jelena
326. Todorović Ljubomir
327. Todorović Zoran
328. Tomić Slavko
329. Topić Aleksandra
330. Trbojević Stanković Jasna
331. Trifković Branka
332. Trivić Aleksandar
333. Trivunić Dajko Sandra
334. Trofenciuc Nelu-Mihai
335. Trpković Slađana
336. Tulić Cane
337. Tulić Goran
338. Tuzuner Tamer
339. Vacić Zoran
340. Vasiljević Dragan
341. Vasiljević Mladenko
342. Velicki Lazar
343. Velimirović Dušan
344. Veljković Snežana
345. Vojinov Saša
346. Vojinović Jelena
347. Vojvodić Nikola
348. Vučetić Čedomir
349. Vučević Danijela
350. Vučinić Predrag
351. Vujisić Tešić Bosiljka
352. Vujkov Sanja
353. Vujotić Ljiljana
354. Vukomanović Đurđević Biserka
355. Vuksanović Aleksandar
356. Vuletić Biljana
357. Zidverc Trajković Jasna
358. Žarković Miloš
359. Živaljević Vladan
360. Živković Slavoljub
361. Živković Vesna
362. Živković Vladimir
363. Živković Zorica
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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Low-level laser therapy effectiveness in patients with temporomandibular disorders

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SUMMARY

Introduction/Objective Low-level laser therapy has been suggested as an alternative pain relief therapy in temporomandibular disorder patients. The aim of this study was to examine the effects of low-level laser therapy on reducing pain intensity in temporomandibular disorder patients, compared to nonsteroidal anti-inflammatory drugs.

Methods A total of 63 patients diagnosed with Research Diagnostic Criteria for Temporomandibular Disorders were divided into two groups. In the first group of 35 patients, low-level laser therapy was applied three times a week, 15 treatment sessions during five weeks (wavelength: 780 nm; power density: 70 mW/cm^2; radiant energy: 4.2 J; energy density: 4.2 J/cm^2; total treatment dose: 16.8 J/cm^2). The second group included 28 participants subjected to nonsteroidal anti-inflammatory drugs therapy (ibuprofen) during two weeks (first three days 3 × 400 mg, remaining time 2 × 400 mg per day). Pain was evaluated using 100 mm visual analog scale, at the baseline, during therapy, two weeks and three months after treatments.

Results Statistically significant reduction of pain intensity was achieved in both low-level laser therapy and in nonsteroidal anti-inflammatory drugs therapy groups and remained steady in the follow-up period of three months ($p < 0.01$). Differences in visual analog scale scores between the observed groups were not statistically significant in each of the evaluation periods, ($p = 0.375$, $p = 0.665$, $p = 0.52$, respectively).

Conclusion The low-level laser therapy protocol applied in this research was efficient in reducing pain in patients with temporomandibular disorders.

Keywords: myofacial pain; pain management; anti-inflammatory agents; visual analog scale

INTRODUCTION

Temporomandibular disorders (TMDs) represent a group of musculoskeletal disorders affecting temporomandibular joints (TMJs) and masticatory muscles, including other associated structures [1]. The most commonly occurring symptom of TMDs is pain localized in the masticatory muscles and TMJs, accompanied by restricted or irregular movements and stiffness of the lower jaw, headaches, ear pain, clicking and/or crepitus sounds produced during mandibular function.

The modern treatment concept of TMDs involves different modalities that are most often applied simultaneously or successively. Therapeutic modalities include pharmacotherapy, physical therapy, occlusal, surgical, behavioral therapy, and psychotherapy [2, 3].

Low-level laser therapy (LLLT) has been recently suggested as an alternative pain relief therapy in different musculoskeletal disorders, such as myofascial pain, acute and chronic neck and low back pain, osteoarthritis, etc. [4, 5]. The main effects of LLLT are anti-inflammatory, analgesic, and biostimulative [6]. The benefits of LLLT are its non-invasiveness, minimum contraindications, affordability, and cost-effectiveness.

The results of recent studies on the application of LLLT in the treatment of TMDs are still contradictory. Many studies have confirmed the effectiveness of LLLT in decreasing pain and improving the function of orofacial system in patients with TMDs [7–12]. On the other hand, the results of some placebo-controlled studies negate the positive effects of LLLT in reducing pain and improving function of orofacial system compared to placebo [13, 14]. Since the results of previous research are inconsistent, increasing attention in the research is attributed to finding adequate radiation characteristics and LLLT protocols in TMD management.

The aim of this study was to investigate the effects of LLLT on reducing pain in TMD patients.

METHODS

Patients

A total of 70 patients with a diagnosis of TMD examined at the Clinic for Prosthodontics, School of Dental Medicine, University of Belgrade, Serbia, participated in the study. The subjects were evaluated from December 2014 to May 2015 using the Research Diagnostic Criteria for TMD (RDC/TMD) [15]. Inclusion criteria were as follows: pain or tenderness on palpation of the masticatory muscles; pain in the preauricular area; pain or tenderness on palpation of the lateral condyle; restricted and

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Table 1. Initial characteristics of patients in LLLT and NSAID groups

Characteristics		Th		p
		LLLT	NSAID	
Limited mouth opening n (%)	Yes	25 (71.4%)	19 (67.9%)	
	No	10 (28.6%)	9 (32.1%)	a0.759
Pain duration n (%)	< 6 months	14 (40%)	15 (53.6%)	
	> 6 months	21 (60%)	13 (46.4%)	a0.283
Diagnosis n (%)	TMD of muscular origin	25 (71.4%)	17 (60.7%)	
	TMD of articular origin	5 (14.3%)	4 (14.3%)	b0.556
	TMD of muscular and articular origin	5 (14.3%)	7 (25%)	

LLLT – low-level laser therapy;
NSAID – non-steroid anti-inflammatory drugs;
*statistically significant difference;
[a] χ^2 test;
[b] Fisher's exact test

painful movements of the lower jaw; stiffness of the lower jaw accompanied by pain. Exclusion criteria were the following: ongoing treatment of TMD or treatment of TMD performed in the last three months; head and neck trauma; odontogenic, otogenic, neurogenic, or vascular pain; pregnancy; patients younger than 20 years, and patients who did not agree to participate in the study.

The patients were randomly divided into two groups: LLLT (40 patients) and nonsteroidal anti-inflammatory drugs therapy (NSAID) group (30 patients). Seven subjects were excluded from the study. Five patients dropped out from the LLLT group because of the irregular attendance of LLLT sessions, and two patients from the NSAID group because of the irregular drug use. The final sample included 63 patients. The average age of the LLLT group was 45.77 ± 18.72 years and that of the NSAID group 38.75 ± 14.4 years. No significant differences were found between the groups regarding sex and age ($p = 0.929$ and $p = 0.10$, respectively). Initial characteristics of patients in LLLT and NSAID groups are shown in Table 1.

All procedures performed in the study were in accordance with the ethical standards of the Ethics Committee, Faculty of Dental Medicine, University of Belgrade, Serbia, No. 36/33, as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Pain assessment

All patients were asked to report any pain evoked by the masseter muscle or condyle's lateral pole palpations, and their answers were evaluated on the 100 mm visual analog scale (VAS), where left end indicates "no pain" and right end indicates "the worst possible pain." The pain evaluation was conducted by the independent investigator who was blinded to treatment groups. In the LLLT group, pain evaluation was performed before treatment (T0), after the fifth session (T1), after the 10th session (T2), after treatment (T3), two weeks after the last session (T4), and three months after the last session (T5). In the NSAID group, outcome measures were taken at baseline, at the end of treatment, two weeks after treatment, and at three months follow-up. The success rate of the therapeutic outcome was ranged from "minimally important changes" (< 30% reduction in pain intensity), through "moderate improvement" (30–50% decrease) to "substantial improvement" (≥ 50% reduction in pain intensity), in accordance with the recommendations (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) [16]. Successful therapeutic outcome considered any improvement ≥ 30%. All respondents in whom a successful therapeutic outcome was registered were monitored for a period of three months after the completion of therapy.

LOW-LEVEL LASER THERAPY

LLLT was conducted at the Department of Physical Medicine and Rehabilitation, Clinical Center of Serbia, using gallium-aluminium-arsenide (GaAlAs) semiconductor diode laser (Eco Medico Laser, Electronic Design, Belgrade, Serbia). A total of 15 sessions were applied three times a week for five consecutive weeks. The first three sessions were performed in three consecutive days. The application was done placing laser probe orthogonally to the skin on the four most painful tender points in the region of the masseter muscle or TMJ. In accordance with the optimal doses for the temporomandibular joint region recommended by the World Association for Laser Therapy (WALT), the applied energy was 4.2 J per point [17]. The characteristics of the laser beam and LLLT protocol are presented in Table 2. All subjects wore safety goggles with protection against infrared radiation during the treatment. Testing of optical output of laser device was performed at baseline (Table 2).

Table 2. Characteristics of laser beam and low-level laser therapy protocol

Characteristics	Values
Wavelength	780 nm
Output power – maximum	120 mW
Output power – operating	70 mW
Probe aperture	1 cm^2
Power density	70 mW/cm^2
Energy density	4.2 J/cm^2
Radiant energy	4.2 J per point
Time	60 seconds per point
Laser frequency	1600 Hz
Number of treatment sessions	15
Number of treated points	4
Application mode	Stationary in skin contact 16.8 J
Daily energy delivered	252 J
Total energy delivered	16.8 J/cm^2
Total treatment dose	252 J/cm^2
Cumulative dose	120 mW

Pharmacotherapy

Pharmacological treatment involved the use of NSAID, ibuprofen (Brufen®, 400 mg, Abbott Logistics, Zwolle, the Netherlands) during two weeks. A dose of 400 mg, three times per day after meal during the first three days and

Table 3. Distribution of patients according to treatment success rate

Th	Minimally important changes	Moderate improvement	Substantial improvement	p
LLLT	3 (8.6%)	6 (17.1%)	26 (74.3%)	$\chi^2 = 1.52$; p = 0.467
NSAID	5 (17.9%)	3 (10.7%)	20 (71.4%)	

LLLT – low-level laser therapy; NSAID – non-steroid anti-inflammatory drugs

Table 4. Descriptive parameters of visual analogue scale pain intensity scores in the low-level laser therapy and non-steroid anti-inflammatory drugs groups measured at different evaluation time points

VAS pain intensity scores	n	Med.	Min.	Max.	Range	p
VAS after treatment						
LLLT	32	16	0	50	50	0.375*
NSAID	23	20	0	50	50	
VAS two weeks after treatment						
LLLT	32	9	0	60	60	0.665
NSAID	23	10	0	40	40	
VAS three months after treatment						
LLLT	32	5	0	50	50	0.520*
NSAID	23	0	0	35	35	

LLLT – low-level laser therapy; NSAID – Non steroid anti-inflammatory drugs; VAS – visual analogue scale;
*Mann–Whitney U-test

a dose of 400 mg, two times per day during the rest of the treatment period were administered. Proton pump inhibitor, pantoprazole (Controloc Control ®, 20 mg, Takeda Pharmaceutical Company Limited, Tokyo, Japan), one tablet a day in the morning before meal was administered, in order to protect the gastrointestinal tract.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). Normality of the data was tested using the Kolmogorov–Smirnov test. The level of significance was set to 5% ($\alpha = 0.05$). For an intra-group comparison of the median values of VAS scores – repeated measures, Friedman test was used. A Wilcoxon signed-ranks test was used for post-hoc analyses. For between-group comparison of VAS pain intensity scores, Wilcoxon signed-rank test was used. In the case of multiple tests of the same set of data, the Bonferroni correction α-values test was used. To test the difference between the groups' parameters, Fisher's exact test and the χ^2 test were used.

RESULTS

Clinically significant improvement was achieved in 32 out of 35 patients in the LLLT group, and in 23 out of 28 subjects in the NSAID group. The distribution of subjects within LLLT and NSAID groups according to success rate of the therapeutic outcome is shown in Table 3. Although there were more subjects who reported clinically significant pain reduction in the LLLT than in the NSAID, the between-group difference in the treatment outcome was not significant ($\chi^2 = 1.52$, p = 0.467) (Table 3).

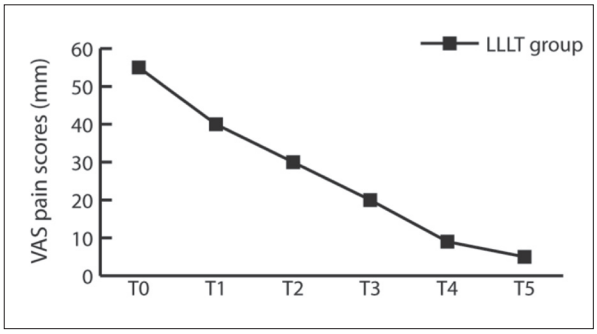

Figure 1. Line chart indicating visual analogue scale (VAS) score values in low-level laser therapy (LLLT) group at different evaluation time points

Comparing the LLLT and NSAID groups, no significant difference was found in the variance of VAS scores at any of the treatment evaluation time points (Table 4). The repeated measures analysis of VAS pain scores in the LLLT group are shown in Figure 1. Post-hoc testing (Wilcoxon test) has shown that there was a statistically significant difference in the pain intensity measured on the VAS scale in the LLLT group before the start of the treatment and after each subsequent measurement, i.e. the fifth/tenth visit, immediately after treatment, two weeks after treatment, and three months after treatment: Z = -4.71, p < 0.01; Z = -5.01, p < 0.01; Z = -5.09, p < 0.01; Z = -4.94, p < 0.01; Z = -4.94, p < 0.01, respectively (Table 4).

DISCUSSION

The treatment of TMD is aimed at reducing or eliminating the symptoms and improving function of the orofacial system, which significantly affects the quality of a patient's life. Priority is given to non-invasive methods, avoiding irreversible therapeutic procedures such as surgical therapy and occlusal adjustment. Reversible therapy of TMDs usually involves the combined use of occlusal splints, pharmacotherapy, self-management program, behavioral therapy, and physical therapy, including LED-LLLT, transcutaneous electrical nerve stimulation, ultra-sound, and physical exercise [1, 18]. LLLT has become the subject of many researches in recent years. In fact, many studies have investigated the application of LLLT in different types of TMDs, but the results are contradictory.

In 2011, Petrucci et al. [19] suggested in their review that further studies are needed, since there is no evidence to support the effectiveness of LLLT in the treatment of chronic TMD pain. Melis et al. [20] concluded in their systematic review that LLLT is probably more effective for the treatment of TMD of articular origin, and less effective for the treatment of TMD of muscular origin. The recent meta-analysis by Chen et al. [21] indicated that LLLT has limited efficacy in reducing pain but can increase the function of orofacial system in patients with TMD. It seems that overall conclusion of the most meta-analysis and reviews is that comparison of the results is not easy to be performed, because of the dissimilarity of wavelength, frequency, and

output of the laser beam and, therefore, different energy dosage applied on the target site. Conclusions about the effects of LLLT on TMD signs and symptoms can be made only on the effects of the application of certain LLLT protocols, in order to establish the adequately aligned characteristics of laser radiation, dose, number, and dynamics of the sessions.

This study investigated the effect of 780-nm GaAlAs LLL on reducing pain in patients with TMDs, compared to pharmacological treatment with NSAID. As far as we know, this is the first study on the effects of LLLT on TMDs conducted on Serbian population.

We used an output power of 70 mW with 4.2 J/cm² of power density, 4.2 J per point, and total energy of 16.8 J per session. The infrared spectrum laser had been selected since the laser rays of the infrared spectrum penetrate deeper into the tissues than the red spectrum laser [22]. Maia et al. [23] stated that LLLT effectiveness is more pronounced when using the infrared laser associated with the application protocols involving higher irradiation levels (energy density and/or power density), the greater number of sessions, and the frequency of application. In accordance with the optimal prescribed doses recommended by WALT for the region of the temporomandibular joint, energy applied in our study was 4.2 J per point [17].

The results of the present research indicate a positive effect of the applied LLLT protocol in the reduction of painful symptoms of TMD. Clinically significant pain intensity reduction was achieved after the applied therapeutic modalities in both groups. Also, there was no statistically significant difference between the groups in the therapeutic success rate, indicating that the applied LLLT protocol was effective in reducing pain and could be proposed as adequate therapeutic procedure for treating painful TMD. Namely, 91.4% of subjects in the LLLT group and 82.1% of subjects in the NSAID group reported a decrease in intensity of pain greater than 30% after treatment. In both examined groups, more than 70% of subjects reported a decrease in intensity of pain greater than 50%, which was considered a significant improvement from a clinical aspect. In addition, there was no statistically significant difference between the groups of subjects in the average intensity pain scores measured before and after therapy.

The study that compared the effects of LLLT and naproxen pharmacotherapy in subjects with myofascial pain indicated that LLLT was effective in reducing pain intensities and increasing the range of painless mouth opening, while improvement was not observed in the group of naproxen-treated patients [24].

Wavelength is one of the important parameters of the laser beam, considered to be the most crucial characteristic that might influence the laser penetration and absorption in biological tissue [25]. In previous studies on the effects of LLLT on TMD, laser's wavelength ranged 632.8–1064 nm, and the number of sessions ranged 1–20 sessions [21]. The results of this study are consistent with the results of several studies that used an infrared 780 nm laser [7, 26]. Although the output power (70 mW) and the dose per point (4,2 J) in this study were the same as in the study by da Silva et al. [26], the energy density differed between studies, amounting to 4.2 J/cm² and 105 J/cm², respectively.

In addition to the wavelengths and energy density dosages, an important parameter is also the total number of sessions and dynamics LLLT sessions. In the present study, 15 sessions were applied, three times a week for five weeks, with the first three sessions applied three days in a row. Most of the other studies included two to three sessions per week [7, 14, 26]. In addition to all the advantages of LLLT, one important disadvantage is that a larger number of sessions can contribute to the patient's withdrawal. In our study, 40 patients started with LLLT and 35 (80%) of them attended all 15 sessions. On the other side, the necessity of attending LLLT session allows the therapist to monitor the patient during treatment and to modify the application site, since the localisation of the most painful tender point may change over time. Also, in this way a better contact between the therapist and the patient can be achieved.

Comparing groups, no statistically significant difference was registered between the LLLT and the NSAID group in each evaluation moment, indicating that LLLT could be an optimal treatment in patients with contraindications for NSAID pharmacotherapy.

The pain intensity of many musculoskeletal disorders varies greatly over time, from little or no pain to very painful days. This variation may occur for months. We chose the two weeks and three months follow-up period, starting at the end of the treatment, in order to decrease the possibility that pain variation masks the pain intensity and stability of achieved results of the LLLT. In the current study, all subjects with significant therapeutic success were followed for a period of three months after treatment, in order to evaluate the stability of the effects of the applied therapeutic modalities. The results of an analysis of repeated measurements in both groups indicate a tendency of pain intensity to decrease during the follow-up period. These results can in part be due to the usual fluctuation of TMD symptoms, which is particularly characteristic of muscle pain. A longitudinal study by Rammelsberg et al. [27] indicated that in a total of 165 subjects, the symptoms and signs of myofascial pain persisted for five years in 31% of the subjects, they disappeared in 33% of the respondents, while the recurrent course of the disease was registered for the remaining 36% of the subjects.

Similar to present study, other authors also examined the stability of LLLT effects. Ahrari et al. [28] evaluated the effect of 810 nm LLL in patients with myofascial pain one month after treatment and concluded that the effects of reducing the intensity of the pain and the increase in the mouth opening range were maintained. Some placebo-controlled studies indicated that LLLT was not effective compared to placebo [13, 14, 29]. In contrast, a recent study by Magri et al. [29] showed that there was no difference in the effects of active LLL or placebo on the decrease in pain intensity measured by VAS scale and sensory and affective pain components. In both groups of patients, a decrease in the pain intensity measured on the VAS scale

was noticed, while no significant difference in pain sensitivity measured using a digital compression algometry was noticed. The results were sustained in both groups of subjects for a period of 30 days, based on which the authors conclude that LLLT is not effective in treating TMD.

In further research on the effectiveness of the LLLT protocol used in the current study, it would be useful to extend the follow-up period, in order to minimize the impact of the usual natural fluctuation of TMD symptoms on results. A recent survival study indicated a low maintenance rate for LLLT effects within 180 days after completion of therapy [30].

Although the results of our study indicate the positive effects of the applied LLLT protocol, there should be caution in interpreting results. One of the limitations of the present study is that pain was assessed subjectively, using VAS scale, so the results almost depend on the patients' personal responses. In addition, pain threshold was variable as well. We did not use a method for objectifying pain intensities, such as measuring sensitivity using a digital algometer. Another limitation is that the evaluation moments of the groups were different. LLLT lasted five weeks and NSAID pharmacotherapy lasted two weeks, so the evaluation moments appeared three weeks earlier for the NSAID group. The use of NSAIDs in lower doses is part of the routine therapy of painful acute and chronic TMD disorders. In this regard, LLLT therapy has shown to be a more effective alternative to analgesics, both due to the shorter duration of therapy and due to the avoidance of side systemic effects of drug therapy. The depth of penetration and focus of the laser beams enables the targeting of damaged and inflamed tissue, improving the local blood supply and reparative effect. The biggest perceived disadvantage of LLLT therapy is the frequent absence of patients at the scheduled time.

CONCLUSION

According to the results of this study, it can be concluded that applied protocol of LLLT (in duration of 15 sessions, three times per week) was effective in reducing pain in patients with TMD. LLLT was as effective as NSAID pharmacotherapy, so it could be an alternative to it, both in case of contraindications or adverse events occurring during pharmacological treatment.

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Ефикасност терапије ласером мале снаге код болесника са темпоромандибуларним дисфункцијама

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САЖЕТАК

Увод/Циљ Терапија ласером мале снаге предложена је као терапијски модалитет у лечењу бола код болесника са темпоромандибуларним дисфункцијама.

Циљ истраживања био је да се испитају ефекти терапије ласером мале снаге на смањење интензитета бола код болесника са темпоромандибуларним дисфункцијама, у поређењу са нестероидним антиинфламаторним лековима.

Методе Укупно 63 болесника код којих је извршена дијагностика темпоромандибуларних дисфункција помоћу протокола за дијагностику предложеног од стране Дворкина и Лереша, подељено је у две групе. У првој групи, коју је чинило 35 испитаника, примењена је терапија ласером мале снаге три пута недељно током пет недеља (таласна дужина ласера: 780 *nm*; густина снаге (интензитет): 70 *mW/cm*^{2}; предата енергија по тачки: 4,2 *J*; укупна предата енергија по третману: 16,8 *J*; густина енергије (доза): 4,2 *J/cm*^{2}; доза по третману: 16,8 *J/cm*^{2}; кумулативна доза: 252 *J/cm*^{2}). Другу групу чинило је 28 испитаника код којих је спроведена терапија нестероидним антиинфламаторним лековима (ибупрофен) током две недеље (прва три дана 3 × 400 *mg*, преосталих дана 2 × 400 *mg*). Евалуација интензитета бола вршена је помоћу визуелно-аналогне скале пре почетка терапије, током терапије ласером мале снаге, непосредно по завршетку терапије, две недеље по завршетку терапије и три месеца по завршетку терапије.

Резултати Статистички значајно смањење интензитета бола постигнуто је у обе групе испитаника и остало је стабилно током праћења од три месеца ($p < 0,01$). Разлике у интензитету бола између посматраних група нису биле статистички значајне ни у једном од периода евалуације ($p = 0,375$, $p = 0,665$, $p = 0,52$).

Закључак Протокол терапије ласером мале снаге примењен у овом истраживању био је ефикасан у смањењу интензитета бола код болесника са темпоромандибуларним дисфункцијама.

Кључне речи: миофацијални бол; управљање болом; антиинфламаторни лекови; визуелно-аналогна скала

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Association between non-communicable diseases and satisfaction with healthcare and self-rated health – experiences from post-conflict communities

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SUMMARY

Introduction/Objective Estimating the prevalence of non-communicable diseases (NCD), multimorbidities, and their association with self-rated health as well as satisfaction with healthcare.

Methods This cross-sectional study was conducted among ethnic Serb communities at Kosovo and Metohija during 2015–2016. Data of socio-demographic and lifestyle characteristics, self-rated health status and satisfaction with healthcare was obtained through a survey which included 1067 adults, 535 of whom reported presence of NCD. Multinomial regression was performed to analysis factors associated with self-rated health and self-rated satisfaction with the healthcare.

Results Presence of one NCD was reported by 50.1% respondents, whereas 23.1% of the respondents reported multimorbidity. While self-reported NCD presence was negatively associated with self-rated health (p = 0.001–0.016), no association between NCDs and satisfaction with healthcare was observed (p = 0.178–0.974). Being single (p = 0.011–0.017), lower educational level (p = 0.031–0.047), regular breakfast (p = 0.032), frequent vegetable intake (p = 0.009–0.029), no alcohol use (p = 0.010), shorter waiting time (p = 0.001–0.004) and sufficient finance for dental care (p = 0.021) were factors statistically significantly correlated with greater satisfaction with the healthcare.

Conclusion Presence of NCD was negatively associated with self-rated health status, while shorter waiting time and adequate finances were associated with higher level of satisfaction with the healthcare. The results of our study could be of the importance for policy makers in creating the more effective healthcare service in unstable political and security situations.

Keywords: chronic diseases; health status; adult population

INTRODUCTION

In the last two decades, global burden of disease expressed as disability-adjusted life year has increased mainly due to non-communicable diseases (NCD) [1, 2]. Population ageing and unhealthy lifestyles are considered to be the main factors contributing to the NCD development [3]. In the primary healthcare setting, especially in high-income countries, presence of two or more chronic diseases (multimorbidity) is increasingly accepted as the norm rather than exception [4]. Presentation of NCD and multimorbidity is related with shorter life expectancy, compromised mental health, frequent hospitalization and overall deterioration in life quality, which places a significant burden on the healthcare system [5].

Reliable data on the NCD and multimorbidity frequency are necessary for optimal healthcare provision and resource management [6]. Owing to their nature, NCDs are often considered a significant predictor of self-rated health and satisfaction with health care [7, 8]. On the other hand, self-rated health status and satisfaction with health care are important indicators of the healthcare system quality and can guide healthcare policy [9].

Studies have shown that residing in post-conflict areas increases the NCD risk, leads to worsening of existing NCDs and consequently to an increase in disability and death [10, 11, 12]. Post-conflict countries usually go through a protracted transition process, which typically includes rapid urbanization, due to which social systems tend to deteriorate [10, 13]. In such a situation, long-term stress exposure leads to mental health problems, unhealthy habits impair physical health and all of that represent ideal conditions for increase in NCD prevalence in the future [10, 13]. Thus, the aims of our study were to assess the prevalence of NCDs and multimorbidities among the population residing on the Autonomous Province of Kosovo and Metohija (KM) and to determine their association with self-rated health and satisfaction with healthcare.

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METHODS

Study setting

This cross-sectional study focused on ethnic Serbian communities residing in KM. Data collection was conducted from October 2015 to January 2016. Approval for this study was obtained from the Ethics Committee of the Faculty of Medicine of the University of Priština temporarily settled in Kosovska Mitrovica (approval no. 67–11, issued on May 27, 2014).

Following the ethnic conflict in 1999, the Serbian KM province was segregated into a smaller predominantly Serbian territory north of the river Ibar (composed of four municipalities) and a much larger Albanian territory to the south. Ethnic Serbian population also resides in six isolated municipalities in the predominantly Albanian southern part of KM, which are (with certain restrictions) still subject to the Republic of Serbia (RS) governance [14]. Owing to these political conditions, many social systems and infrastructure services are compromised, including healthcare provision [15]. Given the limited presence of RS institutions on the KM, local population has not been included in population surveys conducted in the RS in the last 20 years [16, 17].

Study participants

Respondents of interest for this study were adults (aged 18 and over) residents of four KM municipalities, two of which (Kosovska Mitrovica and Zubin Potok) are located north of the river Ibar, while the remaining two (Gračanica and Štrpce) are in the southern part of KM.

Households were randomly selected for inclusion in the survey through stratification and two-phase sampling. Four of the ten municipalities with predominantly ethnic Serb population were designated as primary strata, whereby local communities served as sampling units in the first phase of the two-phase sampling process. From each stratum, 50% of the local communities were selected, by choosing all odd-numbered local communities from the randomly generated list. In the second phase, households served as sampling units, whereby the units of analysis were identified as study participants from the households.

Out of a total of 400 households, 365 agreed to participate in the study with response household rate of 91.25%. In the end, 1067 adults were interviewed.

Data collection instrument

Data required to meet the study objectives were collected via a purposefully-developed questionnaire designed in accordance with the European Health Interview Survey, Methodological Manual [18].

Socio-demographic variables included sex, age, residential status (North/South KM), educational level (≤ 8 years; 8–12; > 12 years), employment status (unemployed/employed) and marital status (married/single). Lifestyle variables included daily habits, such as regular breakfast consumption (daily/occasionally), fruit and vegetable intake (rarely or never/weekly/daily), substance abuse (yes/no), smoking (yes/no), alcohol consumption (yes/no), excessive drinking, i.e., consumption of more than six alcoholic beverages on a single occasion (never or rarely/monthly/weekly/daily). Physical activity (active/inactive) was defined as continuous moderate physical activity of at least 10-minute per day that results in increased respiration or elevated heart rate [18, 19].

Presence of 17 predefined NCDs in the preceding 12 months was self-reported by the participants. Based on the number of reported NCDs, the sample was segregated into three groups: no NCDs/one NCD/multimorbidity.

The Likert scale was used to estimate the self-rated health (good/very good/moderate/poor/very poor) and self-rated satisfaction (very satisfied/satisfied/neutral/unsatisfied/very unsatisfied). Further, respondents' self-rated health status was stratified into three categories for the purpose of the study analyses: good or very good/moderate/poor or very poor. Similarly, self-rated satisfaction with the healthcare was grouped under: very satisfied or satisfied/neutral/unsatisfied or very unsatisfied.

Unmet health care needs are defined as the difference between the health services that are considered necessary to deal appropriately with health problems and services that are actually received [20]. Unmet healthcare needs were classified in accordance with the factors that contribute to not receiving adequate health services (long waiting time, distance to the healthcare facility or transport issues, and inadequate finances for healthcare, dental care, mental care and medical prescription). Unmet health needs were assessed through closed-ended questions in which respondents have chosen between the offered alternatives (I did not need it/No/Yes).

Statistical analyses

Statistical analyses were conducted using SPSS statistical package for MS Windows ver. 17 (SPSS Inc., Chicago, IL, USA) [21], where $p < 0.05$ was considered as statistically significant. Descriptive sample statistics included measures of central tendency (mean), variance (standard deviation) and relative values (percentages). Differences between studied parameters were assessed via the Kruskal–Wallis test (KW χ^2).

Multinomial regression analysis was performed when analyzing factors associated with self-rated health and self-rated satisfaction with the healthcare, which were treated as dependent variables. When examining self-rated health status and healthcare system quality, "poor or very poor" and "unsatisfied or very unsatisfied," respectively, served as referent categories.

RESULTS

The study sample comprised of 1067 respondents aged 42.6 ± 16 years and 51.3% of them were female. In Table 1 are summarized participants' socio-demographic characteristics.

Hypertension (24.6%) was the most prevalent NCD in the study sample. The prevalence of other NCDs were: hyperlipidemia (10.3%), allergies (9.9%), lower spine deformities (8.1%), renal problems (5.9%), upper spine deformities (5.6%), diabetes (5.2%), depression (5%), angina pectoris (4.1%), arthrosis (3.7%), urinary incontinence (3.1%), chronic bronchitis (2.4%), asthma (1.9%), myocardial infarction (1.4%), cancer (1.3%), stroke (1%) and cirrhosis (0.5%). Moreover, relative to men, a statistically significantly higher percentage of women reported suffering from chronic bronchitis (p = 0.024), arthrosis (p = 0.001), skeletal deformities (p = 0.001) and depression (p = 0.002) (Data not shown).

One-half of our participants (50.1%) reported that they have one NCD, whereas multimorbidity was declared by 23.1% of the participants (Table 1). Greater multimorbidity frequency was observed among older individuals, women, residents of south municipalities, less educated and unemployed respondents, and those in a relationship. Individuals with multimorbidity more often declared that they did not practice regular physical activity, and were more frequently to be smokers, but did not consume drugs or alcohol (Table 1).

Table 2 described self-rated health status and satisfaction with healthcare. The majority (71.2%) of the respondents rated their health as good or very good. As expected, those with multimorbidity were more frequent to perceive their health as moderate, poor, or very poor. On the other hand, those that did not report any NCDs were least satisfied with the healthcare (p = 0.029).

Unmet healthcare needs due to long waiting time, distance to health facility or inadequate finances for healthcare, dental care, mental care and medical prescription were more frequently reported by participants with multimorbidities (p = 0.001) (Table 2).

Table 1. Socio-demographics and lifestyle characteristics

Variables	Number of non-communicable diseases				p-value
	None (532)	One (288)	Multimorbidity (247)	Total (1067)	
	n (%)	n (%)	n (%)	n (%)	
Gender					
Male	266 (51.2)	153 (29.4)	101 (19.4)	520 (48.7)	**0.013**
Female	266 (48.6)	135 (24.7)	146 (26.7)	547 (51.3)	
Age	34.8 (12.3)	46.8 (15.8)	52.7 (15.4)	42.6 (16)	**0.001**
Place of residence					
Northern Kosovo	235 (48.5)	149 (30.7)	101 (20.8)	485 (45.5)	**0.031**
Southern Kosovo	296 (51)	139 (23.9)	146 (25.1)	581 (54.5)	
Relationship status					
Single	209 (19.6)	70 (6.6)	59 (5.5)	338 (31.7)	**0.001**
In a relationship	323 (30.3)	218 (20.4)	188 (17.6)	729 (68.3)	
Education					
≤ 8 years	7 (9.1)	20 (26.0)	50 (64.9)	77 (7.2)	
8–12 years	310 (51)	178 (29.3)	120 (19.7)	608 (57)	**0.001**
> 12 years	215 (56.3)	90 (23.6)	77 (20.1)	382 (35.8)	
Employment					
Unemployed	226 (44.8)	138 (27.4)	140 (27.8)	504 (47.2)	**0.001**
Employed	306 (54.4)	150 (26.6)	107 (19)	563 (52.8)	
Having breakfast					
Irregular	93 (48.9)	50 (26.3)	47 (24.8)	190 (17.8)	0.848
Regular	439 (50.1)	238 (27.1)	200 (22.8)	877 (82.2)	
Fruit intake					
Rare or never	86 (45.5)	53 (28)	50 (26.5)	189 (17.7)	
Weekly	274 (51)	151 (28.1)	112 (20.9)	537 (50.3)	0.562
Daily	172 (50.4)	84 (24.6)	85 (25)	341 (32)	
Vegetable intake					
Rare or never	62 (44.6)	36 (25.9)	41 (29.5)	139 (13)	
Weekly	293 (50.9)	161 (28)	122 (21.1)	576 (54)	0.757
Daily	177 (50.3)	91 (25.9)	84 (23.9)	352 (33)	
Physical activity					
No	247 (41.3)	166 (27.8)	185 (30.9)	598 (56)	**0.001**
Yes	285 (60.8)	122 (26)	62 (13.2)	469 (44)	
Drug use					
No	527 (49.9)	286 (27.1)	243 (23)	1056 (99)	0.549
Yes	5 (45.5)	2 (18.2)	4 (36.3)	11 (1)	
Smoking					
No	301 (53.7)	143 (25.5)	117 (20.8)	561 (52.6)	**0.029**
Yes	231 (45.6)	145 (28.7)	130 (25.7)	506 (47.4)	
Alcohol use					
No	243 (42.6)	158 (27.7)	170 (29.7)	571 (53.5)	**0.001**
Yes	289 (58.3)	130 (26.2)	77 (15.5)	496 (46.5)	
Alcohol use (binge drinking)					
Never or rare	318 (45.6)	188 (27)	191 (27.4)	697 (65.3)	**0.001**
Monthly	162 (57.6)	80 (28.5)	39 (13.9)	281 (26.3)	
Weekly	49 (62)	17 (21.5)	13 (16.5)	79 (7.4)	
Daily	3 (30)	3 (30)	4 (40)	10 (1)	

Statistics: KW χ^2, mean and SD

Table 3 shows factors associated with self-reported health status. Based on the multinomial regression analysis findings (χ^2 = 536.093; p = 0.001), absence or smaller number of NCDs, younger age, being employed, and alcohol consumption emerged as the factors most closely associated with positive self-rating health.

Multinomial regression analysis was also performed to assess the association between presence of NCDs and satisfaction with healthcare. Both models developed for this purpose were statistically significant in explaining this relationship ("General socio-demographic" χ^2 = 108.080, p = 0.001; "Healthcare unavailability" χ^2 = 92.383; p = 0.001). Multinomial regression results failed to reveal any connection between NCD presence and satisfaction with the healthcare.

Being single, lower educational level, healthier lifestyle (regular breakfast, frequent vegetable intake and no alcohol use), shorter waiting time, and sufficient financial means for meeting the dental care needs were factors associated with higher level of satisfaction with the healthcare. Table 4 describes factors associated with healthcare satisfaction among respondents.

DISCUSSION

This study found that more than half of the survey respondents in post-conflict area suffered from at least one NCD. While presence of NCDs was negatively associated with

Table 2. Self-rated health status and satisfaction with healthcare compared to the number of non-communicable diseases

Variables	Number of non-communicable diseases				p-value
	None (532)	One (288)	Multimorbidity (247)	Total (1067)	
	n (%)	n (%)	n (%)	n (%)	
Self-rated health status					
Poor, very poor	3 (5.5)	10 (18.2)	42 (76.3)	55 (5.2)	
Moderate	36 (14.3)	93 (36.9)	123 (48.8)	252 (23.6)	0.001
Good, very good	493 (64.9)	185 (24.3)	82 (10.8)	760 (71.2)	
Satisfaction with healthcare					
Unsatisfied, very unsatisfied	55 (46.6)	31(26.3)	32 (27.1)	118 (11.1)	
Neutral	152 (45.8)	90 (27.1)	90 (27.1)	332 (31.1)	**0.029**
Satisfied, very satisfied	325 (52.7)	167 (27.1)	125 (20.2)	617 (57.8)	
Long waiting time					
I did not need it	336 (58.7)	144 (25.2)	92 (16.1)	572 (53.6)	
No	172 (42)	116 (28.4)	121 (29.6)	409 (38.3)	**0.001**
Yes	24 (27.9)	28 (32.5)	34 (39.6)	86 (8.1)	
Availability due to transportation					
I did not need it	343 (57.3)	156 (26.1)	99 (16.6)	598 (56)	
No	178 (42)	123 (29.1)	135 (31.9)	436 (40.9)	**0.001**
Yes	11 (33.3)	9 (27.3)	13 (39.4)	33 (3.1)	
Lack of finance for healthcare					
I did not need it	338 (58.6)	139 (24.1)	100 (17.3)	577 (54.1)	
No	179 (42.3)	129 (30.5)	115 (27.2)	423 (39.6)	**0.001**
Yes	15 (22.4)	20 (29.9)	32 (47.7)	67 (6.3)	
Lack of finance for dental care					
I did not need it	324 (57.3)	139 (24.6)	102 (18.1)	565 (53)	
No	188 (42.3)	134 (30.2)	122 (27.5)	444 (41.6)	**0.001**
Yes	20 (34.5)	15 (25.9)	23 (39.6)	58 (5.4)	
Lack of finance for medication prescription					
I did not need it	334 (58.1)	141 (24.5)	100 (17.4)	575 (53.9)	
No	190 (41.9)	134 (29.6)	129 (28.5)	453 (42.5)	**0.001**
Yes	8 (20.5)	13 (33.3)	18 (46.2)	39 (3.6)	
Lack of finance for mental care					
I did not need it	50 (56.4)	150 (24.2)	121 (19.4)	621 (58.2)	
No	182 (41.7)	136 (31.1)	119 (27.2)	437 (41)	**0.001**
Yes	0 (0)	2 (22.2)	7 (77.8)	9 (0.8)	

Statistics: KW χ^2, mean and SD

Table 3. Multinomial regression model describing factors associated with self-reported health status

Variables	Self-rated health status (Moderate *vs*. Poor, very poor)		Self-rated health status (Good, very good *vs*. Poor, very poor)	
	p-value	OR (95% CI of OR)	p-value	OR (95% CI of OR)
Number of chronic diseases				
None	0.195	2.35 (0.64–8.56)	**0.001**	23.33 (6.53–83.35)
One	**0.016**	2.68 (1.20–5.98)	**0.001**	7.38 (3.19–17.06)
Multimorbidity	1		1	
Gender				
Male	0.184	0.60 (0.29–1.26)	0.991	0.99 (0.46–2.13)
Female	1		1	
Age	0.272	0.99 (0.96–1.01)	**0.001**	0.93 (0.90–0.95)
Place of residence				
Northern Kosovo	0.851	1.07 (0.54–2.11)	0.242	0.65 (0.32–1.33)
Southern Kosovo	1		1	
Relationship status				
Single	0.293	0.67 (0.32–1.41)	0.325	0.67 (0.30–1.49)
In a relationship	1		1	
Education				
≤ 8 years	0.339	0.59 (0.20–1.73)	0.082	0.34 (0.10–1.15)
8–12 years	0.892	1.06 (0.44–2.58)	0.462	0.72 (0.29–1.75)
> 12 years	1		1	
Employment				
Unemployed	0.128	0.53 (0.24–1.20)	**0.032**	0.40 (0.18–0.93)
Employed	1		1	
Having breakfast				
Irregular	0.101	2.43 (0.84–7.02)	0.341	1.71 (0.57–5.13)
Regular	1		1	

Table 3. Continued				
Fruit intake				
Rare or never	0.631	1.31 (0.44–3.89)	0.324	0.56 (0.18–1.78)
Weekly	0.733	1.16 (0.50–2.69)	0.908	0.39 (0.39–2.28)
Daily	1		1	
Vegetable intake				
Rare or never	0.607	0.73 (0.23–2.39)	0.729	0.80 (0.23–2.79)
Weekly	0.945	1.03 (0.44–2.40)	0.901	0.95 (0.39–2.27)
Daily	1		1	
Physical activity				
No	0.495	1.31 (0.60–2.86)	0.909	0.96 (0.43–2.11)
Yes	1		1	
Drug use				
No	0.474	2.55 (0.19–32.93)	0.301	4.27 (0.27–66.83)
Yes	1		1	
Smoking				
No	0.903	1.04 (0.52–2.09)	0.362	1.40 (0.68–2.89)
Yes	1		1	
Alcohol use				
No	**0.004**	0.23 (0.09–0.62)	**0.002**	0.20 (0.06–0.55)
Yes	1		1	

Bold values are statistically significant; 1 – reference category

Table 4. Multinomial regression model describing factors associated with healthcare satisfaction among respondents

Variables	Satisfaction with healthcare (Neutral *vs.* Unsatisfied, very unsatisfied)		Satisfaction with healthcare (Satisfied, very satisfied *vs.* Unsatisfied, very unsatisfied)	
	p-value	OR (95% CI of OR)	p-value	OR (95% CI of OR)
Model 1. Socio-demographic and and lifestyle characteristics				
Number of chronic diseases				
None	0.974	0.99 (0.55–1.79)	0.178	1.48 (0.84–2.60)
One	0.778	1.09 (0.59–2)	0.209	1.45 (0.81–2.58)
Multimorbidity	1		1	
Gender				
Male	0.315	0.78 (0.48–1.27)	0.592	1.13 (0.72–1.79)
Female	1		1	
Age	0.806	0.99 (0.98–1.02)	0.580	1.01 (0.99–1.02)
Place of residence				
North of Kosovo	0.498	1.17 (0.75–1.83)	0.206	0.76 (0.49–1.16)
South part of Kosovo	1		1	
Relationship status				
Single	**0.017**	2.02 (1.14–3.59)	**0.011**	2.06 (1.18–3.57)
In relationship	1		1	
Education				
≤ 8 years	0.164	1.97 (0.76–5.11)	0.496	0.72 (0.28–1.85)
8–12 years	**0.031**	1.69 (1.05–2.73)	**0.047**	1.58 (1.01–2.47)
> 12 years	1		1	
Employment				
Unemployed	0.563	0.87 (0.55–1.39)	0.406	0.83 (0.53–1.29)
Employed	1		1	
Having breakfast				
Irregular	0.384	0.79 (0.47–1.34)	**0.032**	0.57 (0.34–0.95)
Regular	1		1	
Fruits intake				
Rare or never	0.423	1.35 (0.65–2.84)	0.212	0.64 (0.32–1.29)
Weekly	0.225	1.426 (0.80–2.53)	0.225	0.72 (0.42–1.23)
Daily	1		1	
Vegetable intake				
Rare or never	**0.009**	0.32 (0.14–0.75)	0.633	0.82 (0.37–1.83)
Weekly	**0.013**	0.48 (0.27–0.85)	**0.029**	0.54 (0.31–0.94)
Daily	1		1	
Physical activity				
No	0.549	1.16 (0.72–1.86)	0.543	0.87 (0.56–1.36)
Yes	1		1	
Drug use				
No	0.374	2.53 (0.33–19.50)	0.931	1.08 (0.19–5.87)
Yes	1		1	

Table 4. Continued				
Smoking				
No	0.472	0.85 (0.54–1.34)	0.520	1.15 (0.75–1.77)
Yes	1		1	
Alcohol use				
No	0.352	1.26 (0.77–2.07)	**0.010**	1.85 (1.16–2.95)
Yes	1		1	
Model 2. Unavailability of healthcare				
Number of chronic diseases				
None	0.368	0.76 (0.45–1.35)	0.720	1.10 (0.65–1.88)
One	0.909	0.97 (0.53–1.78)	0.542	1.20 (0.67–2.16)
Multimorbidity	1		1	
Long waiting time				
I did not need it	**0.001**	7.27 (2.15–24.59)	**0.004**	4.95 (1.65–14.88)
No	**0.001**	5.39 (2.59–11.19	**0.001**	7.37 (3.68–14.74)
Yes	1		1	
Availability due to transportation				
I did not need it	0.368	0.52 (0.13–2.16)	0.185	2.69 (0.62–11.64)
No	0.660	0.79 (0.27–2.29)	0.320	1.82 (0.56–5.94)
Yes	1		1	
Lack of finance for healthcare				
I did not need it	0.555	0.68 (0.19–2.45)	0.712	0.79 (0.22–2.79)
No	0.775	0.88 (0.35–2.17)	0.940	1.04 (0.42–2.56)
Yes	1		1	
Lack of finance for dental care				
I did not need it	0.960	1.03 (0.31–3.47)	**0.021**	4.37 (1.25–15.27)
No	0.607	0.79 (0.31–1.97)	0.168	1.99 (0.75–5.27)
Yes	1		1	
Lack of finance for medication prescription				
I did not need it	0.184	0.35 (0.08–1.64)	0.150	0.33 (0.07–1.50)
No	0.131	0.34 (0.09–1.38)	0.297	0.47 (0.12–1.94)
Yes	1		1	
Lack of finance for mental care				
I did not need it	0.315	3.14 (0.34–29.36)	0.784	1.37 (0.15–12.87)
No	0.548	1.94 (0.22–16.88)	0.912	1.13 (0.13–9.99)
Yes	1		1	

Bold values are statistically significant; 1 – reference category

health self-ratings among our participants, it was unrelated with participants' satisfaction with healthcare.

NCD prevalence in the study sample was congruent with that reported for other Serbian territories [17]. The survey respondents were most frequent to report hypertension, which coincided with the findings of previous studies conducted in other countries [22, 23]. Comprehensive literature review revealed that armed conflicts tend to result in greater cardiovascular diseases incidence, as well as more frequent adoption of risky behaviors [10]. For example, Spiegel and Salama [24] reported that cardiovascular diseases are more frequent cause of mortality in areas affected by interethnic conflict, compared to contagious diseases and conflict-related violence.

In a five-year-long study focusing on the 12 most common NCDs, it was found that multimorbidity prevalence varies by the countries, with estimated range 45–70% [25]. The lower multimorbidity prevalence found in this study relative to the results reported by other authors could be attributed to the nature of self-reported data, whereas in most previous studies prevalence was calculated based on data from official medical records [25]. Likewise, disparities in the multimorbidity prevalence for different countries are ascribed to incongruence in the utilized data sources, differences in target population characteristics and NCD types included in the analysis [22]. In the present study, respondents with multimorbidity more frequently reported unemployment, lower educational level and sedentary lifestyle. On the other hand, they more frequently adopted other healthy habits. It is possible that severely compromised health of persons living with multimorbidities precludes them from preforming everyday physical activities, but following medical advice regarding healthy lifestyle and diet.

A higher percentage of participants in our study rated their health as very good and good compared to that of the previous study conducted throughout Serbia [17]. Our results coincide with those reported by the European Union, where almost 70% of the surveyed population rated their health status as good [26]. In our sample, absence or a smaller number of NCDs, younger age, being employed and alcohol consumption are correlated with more positive self-rated health, which is in line with the findings reported in literature [27]. It is interesting to note that the survey respondents who consumed alcohol tend to rate their health more favorably. Given the anxiolytic effects of smoking and alcohol consumption, these habits are more prevalent among individuals living in post-conflict zones, as they serve as a coping mechanism [10, 28]. The studies have found that individuals who consume alcohol regularly in moderate quantities perceive their health status more favorably compared to those that abstain from alcohol or consume it occasionally [29].

In contrast to the self-rated health, presence of self-reported NCDs was not associated with satisfaction with healthcare. Available evidence indicates that satisfaction with healthcare is determined by the educational level, income, age, and residence type [30]. Most of the studies examining patients' satisfaction with healthcare in the United States and European countries indicate that shorter waiting time, better-qualified medical personnel and lower healthcare cost are associated with more favorable healthcare system ratings [31, 32]. Our findings coincide with these observations. Available evidence further indicates that positive interactions with healthcare professionals correlate with greater satisfaction with the healthcare irrespective of the number and complexity of present diseases [33, 34]. In general, most Serbs residing within KM struggle to access required medical treatments and attribute these issues to inadequate healthcare system organization [16]. To sum up, patient satisfaction is derived from a combination of prior experiences with medical services and perceived efficacy, safety and utility of available medical transportation [35].

The significance of the present study stems from the large sample size, thus ensuring its representativeness of the ethnic Serb population residing in KM. Consequently, the results reported in our study provide valuable insight into the NCD prevalence and perceived health status among individuals living in post-conflict zones, and their satisfaction with the healthcare, which is inevitably compromised due to previous conflict. Namely, previous studies from other countries affected by the conflict have found a higher burden of NCDs and mental illness among the population and exacerbations of existing NCDs due to serious psychological distress, less access to health care, interruptions in medication supply, lack of financial stability [11, 12, 23]. However, there are some limitations. Cross-sectional design adopted in the present study precluded us from reaching any conclusions regarding the causality of the observed relationships. Moreover, given that analyses were based on self-reported data that to a degree relied on accurate recall, informer bias could have affected the obtained results. Finally, our lifestyle measures were broad. For example, the measure of alcohol intake and smoking has not been accurately quantified.

CONCLUSION

Based on our findings, it could be concluded that the presence of NCDs is negatively associated with the self-rated health, but not with satisfaction with healthcare. Interestingly, being single, lower educational level, regular breakfast, frequent vegetable intake, no alcohol use, financial stability, dental care and shorter waiting time that mostly depends of organization of health service have positive influence on patients' satisfaction with healthcare. As patients' satisfaction with healthcare is one of the determinants of healthcare system quality, the findings reported in this work could be utilized when formulating healthcare policy, in particular when allocating inevitably limited resources, to ensure that they are most optimally utilized to provide as effective and efficient healthcare as possible.

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Повезаност хроничних незаразних болести са задовољством здравственом заштитом и самопроценом здравственог стања – искуства из постконфликтне средине

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САЖЕТАК

Увод/Циљ Испитивали смо учесталост хроничних незаразних болести (ХНБ) и мултиморбидитета, као и њихову повезаност са самопроценом здравственог стања и задовољством здравственом заштитом.

Методе Студија пресека спроведена је у српским срединама на територији Косова и Метохије током 2015/2016. године. Укупно је анкетирано 1067 одраслих становника коришћењем упитника о социодемографским карактеристикама, животним навикама, самопроцени здравственог стања и задовољства здравственом заштитом, од којих је 535 пријавило присуство неке од ХНБ. Мултиномијална регресија спроведена је за анализу фактора повезаних са задовољством здравственом заштитом и самопроценом здравственог стања.

Резултати Присуство ХНБ је пријављено од стране 50,1% испитаника, док је присуство мултиморбидитета пријавило 23,1% испитаника. Присуство ХНБ је показало негативну повезаност са самопроценом здравственог стања (p = 0,001–0,016), док повезаност ХНБ са задовољством здравственом заштитом није уочена (p = 0,178–0,974). Бити без емотивног партнера (p = 0,011–0,017), ниже образовање (p = 0,031–0,047), редован доручак (p = 0,032), редовно конзумирање поврћа (p = 0,009–0,029), некоришћење алкохола (p = 0,010), краће време чекања (p = 0,001–0,004) и поседовање довољно финансија за остваривање стоматолошке здравствене заштите (p = 0,021) показали су повезаност са већим задовољством здравственом заштитом.

Закључак Присуство ХНБ је показало негативну повезаност са самопроценом здравственог стања, док су краће време чекања и финансије били повезани са већим задовољством здравственом заштитом. Резултати нашег истраживања могу бити од значаја креаторима здравствене политике приликом доношења одлука у правцу стварања што ефикасније здравствене службе.

Кључне речи: хроничне болести; здравствено стање; одрасло становништво

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Thyroid replacement therapy effects on cardiac function in patients with hypothyroidism

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SUMMARY

Introduction/Objective Hypothyroidism is a hypometabolic syndrome with insufficient production or inadequate action of thyroid hormones. It is characterized by hypercholesterolemia, elevated LDL-C. The most common echocardiographic changes are in left ventricular (LV) diastolic function.
The aim of this study was to investigate the effects of achieving adequate thyroid hormone replacement therapy in hypothyroid patients on improving systolic and diastolic cardiac function and correcting serum lipid profile.

Methods Prospective study was conducted on 42 patients with newly diagnosed hypothyroidism, both sexes, aged 18–60 years, without comorbidity. The determined blood tests before, six, 12, and 24 weeks after starting the therapy with L-thyroxine were: FT4, TSH, total cholesterol, HDL-C, LDL-C and triglycerides. The effects of thyroid hormone replacement therapy on systolic and diastolic cardiac function were assessed by echocardiography.

Results It was concluded that 25 (59.5%) patients had subclinical and 17 (40.5%) overt hypothyroidism. The LV end-systolic diameter decreased statistically highly significant ($p < 0.01$) after 12 weeks and end-diastolic diameter of the right ventricle after six months of therapy. There was no significant decrease in LV end-diastolic diameter after six months of thyroid hormone replacement therapy. Mitral annular plane systolic excursion (MAPSE), left ventricular ejection fraction (LVEF), and tricuspid annular plane systolic excursion (TAPSE) values increased significantly ($p < 0.01$) after six weeks of therapy. Total cholesterol and LDL-C significantly decreased, HDL-C increased ($p < 0.01$) and there was no change in triglyceride concentrations after 24 weeks of therapy.

Conclusions Thyroid replacement therapy in hypothyroid subjects statistically significantly improves echocardiographic parameters of diastolic and systolic left and right ventricular function, reduces total serum cholesterol and LDL-C, and increases HDL-C.

Keywords: hypothyroidism; L-thyroxine; diastolic cardiac function; systolic cardiac function; lipid profile

INTRODUCTION

Thyroid hormone deficiency leads to changes in cardiovascular hemodynamics, phenotype and contractility, and accelerated atherosclerosis. Overt hypothyroidism exerts effects on systolic and diastolic cardiac function and cardiac anatomy [1, 2].

Hypothyroidism increases the risk of developing atherosclerotic cardiovascular disease by increasing circulating LDL cholesterol (LDL-C) levels, inducing the development of diastolic hypertension, increasing blood coagulability, as well as having direct effects on vascular smooth muscle. Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL-C and apolipoprotein B [3].

In subclinical hypothyroidism, diastolic cardiac function is most commonly impaired, which is already manifested in patients with mild thyroid dysfunction with TSH between 5 and 10 mU/L [4]. Subclinical hypothyroidism is associated with a small increase in LDL cholesterol (LDL-C), a decrease in HDL cholesterol (HDL-C), increasing the risk of developing atherosclerosis and coronary artery disease [5].

The most common echocardiographic changes in hypothyroidism are characterized by changes in left ventricular (LV) diastolic function parameters resulting from impaired myocardial relaxation presented by prolonged isovolumic relaxation time (IVRT) and a significantly reduced early and late diastolic flow rate (E/A) of transmitral flow. Echocardiographic diastolic dysfunction is defined by the existence of at least one of the following parameters: E/A < 1.0, IVRT > 100 m/s, or decelerating time > 220 m/s [6].

The interaction between the right and left ventricles is one of the most important causes of impaired right ventricular function that results from an increase in LV filling pressure and the consequent increase in pulmonary flow and pressure in the right ventricle. It has been shown that impaired right ventricular mechanics are completely repaired after adequate thyroid hormone replacement therapy [7].

The aim of this study was to examine the effects of achieving adequate thyroid hormone replacement therapy in hypothyroid patients on:

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1) improving systolic and diastolic cardiac function;
2) correction of serum lipid profile;
3) the effect of time needed to reach the euthyroid state on the repair of the examined parameters of cardiac function and lipid status.

METHODS

A prospective study was conducted on 42 patients over a 24-week follow-up period. The study was performed from September 2017 until March 2019 at the Zlatibor Special Hospital for Thyroid gland and Metabolic Diseases. The study was approved by the Ethics Committee and all study participants were informed of the study methodology and gave their consent to participate in the study.

The study included patients with newly diagnosed hypothyroidism whose TSH was greater than 10 mU/L, both sexes, aged 18–60 years, without comorbidity. Echocardiographic examinations were determined by transthoracic echocardiography on a Vivid 3 apparatus (GE Healthcare, Solingen, Germany). The systolic function was determined by the following echocardiographic parameters: LV ejection fraction (LVEF), mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE). Diastolic function was determined by the following echocardiographic parameters: E wave (m/s), A wave (m/s), E/A ratio, IVRT of the left ventricle (ms). The left and right ventricular systolic function parameters were measured using the M-mode in the parasternal long-axis view and the apical 4-chamber view. The LVEF, expressed in %, was determined by a Teicholtz formula calculation. Transmitral flow rates were measured using a pulsed Doppler in the apical four chamber view. Using a continuous Doppler in the apical five-chamber view, IVRT was determined. Echocardiographic parameters were assessed before and after received L-thyroxine therapy at weeks six, 12, and 24.

The following laboratory parameters were determined from the blood: total cholesterol (TC), cholesterol fractions HDL and LDL, and triglycerides. Thyroid function was assessed by measuring free-thyroxine (FT4) and thyrotropin (TSH) levels. After determining basal FT4 and TSH levels, patients with TSH greater than 10 mU/L included in the study were administered L-thyroxine with a gradual increase in dose until euthyroid condition was achieved. Lipid status and thyroid function were assessed before and after received L-thyroxine therapy at weeks six, 12, and 24.

Descriptive and analytical statistical methods were used in this study. Descriptive methods used absolute and relative numbers, measures of central tendency (arithmetic means, median) and dispersion measures (standard deviation). Analytical statistical methods used difference tests, parametric and non-parametric tests. The selected level of significance, that is, the probability of an error of the first type is 0.05. All data were processed in IBM SPSS Statistics, Version 20.0. (IBM Corp., Armonk, NY, USA) software package.

RESULTS

Of the 42 respondents included in the study, 9 (21.4%) were male and 33 (78.6%) were female. The mean age of studied patients was 40.1 ± 9.1 years. The youngest patient was 19 years old and the oldest was 59 years old. The mean BMI values were 24.67 ± 2.81 kg/m^2.

Of the 42 subjects enrolled, 25 (59.5%) had a subclinical form of hypothyroidism and 17 (40.5%) had an overt form of hypothyroidism.

FT4 before starting the therapy was 10.82 ± 3.19 pmol/L, in the repeated measurements after six, 12 and 12 weeks were in the reference range (10.2–24.5 pmol/L) for all subjects (Table 1) and after 24 weeks were 16.23 ± 3.77 pmol/L indicating a statistically highly significant difference ($p < 0.01$). Out of the 42 enrolled subjects, 34 achieved TSH in reference range (0.3–4.2 mU/L) after 24 weeks of therapy while 8 did not. Out of the eight subjects with inadequate TSH values (greater than 4.2 mU/L), five patients had slightly elevated TSH values above the reference range (up to 6 mU/L) and only one subject had a TSH value greater than 10 mU/L. There was a statistically significant difference in the TSH value after six and 12 weeks ($p < 0.05$) and a highly statistically significant difference in the TSH value after 24 weeks of thyroid replacement therapy ($p < 0.01$) compared to the initial TSH values.

Results of the systolic cardiac function parameters

The results of LV systolic function are presented in Table 2. There was no statistically significant decrease in LV end-diastolic diameter (LVEDD) after 24 weeks of therapy ($p > 0.05$), whereas end-systolic LV diameter (LVESD) decreased statistically highly significant ($p < 0.01$) from the 12th week of L-thyroxine therapy.

MAPSE and LVEF were statistically significant ($p < 0.01$) improved after six, 12 and 24 weeks of therapy, significant improvement in LV function after beginning of thyroid hormone therapy (Table 2).

Results of the diastolic cardiac function parameters

Hypothyroid subjects had a statistically highly significant ($p < 0.01$) increase in E wave velocity and increase

Table 1. Thyroid hormone values in the function of time (n = 42)

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
FT4 (pmol/L)	10.82 ± 3.19	15.34 ± 2.74	15.85 ± 3.81	16.23 ± 3.77
TSH (mU/L)	min–max	min–max	min–max	min–max
	10.2–100	0.62–39.4	0.05–53.7	0.29–18.5

FT4 – free-thyroxine; TSH – thyrotropin

Table 2. Left ventricular size and systolic function parameters

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
LVEDD (mm)	49.07 ± 3.70	49.02 ± 3.83	48.64 ± 3.45	48.48 ± 3.58
LVESD (mm)	31.02 ± 2.99	30.45 ± 3.39	29.21 ± 3.35	27.67 ± 2.82
MAPSE (mm)	14.52 ± 1.42	15.21 ± 1.37	16.24 ± 1.62	16.81 ± 1.67
LVEF (%)	65.19 ± 3.57	66.52 ± 3.74	69.09 ± 3.77	72.45 ± 3.55

LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; MAPSE – mitral annular plane systolic excursion; LVEF – left ventricular ejection fraction

Table 3. Left ventricular diastolic function parameters

Parameter	Before therapy	Six weeks later	12 weeks later	24 weeks later
E (m/s)	0.71 ± 0.14	0.74 ± 0.12	0.77 ± 0.11	0.80 ± 0.11
A (m/s)	0.76 ± 0.12	0.72 ± 0.12	0.66 ± 0.1	0.61 ± 0.11
E/A	0.94 ± 0.13	1.04 ± 0.14	1.19 ± 0.17	1.32 ± 0.19
IVRT (ms)	102.59 ± 8.43	94.54 ± 8.76	87.59 ± 8.14	80 ± 7.29

E wave – early diastolic velocity of transmitral flow; A wave – late diastolic velocity of transmitral flow; E/A – a ratio of early and late diastolic velocity of transmitral flow; IVRT – isovolumic relaxation time of the left ventricle

Table 4. Parameters of right ventricular size and systolic function

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
RV (mm)	24.79 ± 1.93	24.69 ± 2.02	24.36 ± 2.18	24.24 ± 2.13
TAPSE (mm)	19.88 ± 1.63	20.88 ± 1.74	21.78 ± 1.6	22.52 ± 1.61

RV – right ventricular end-diastolic diameter;
TAPSE – tricuspid annular plane systolic excursion

Table 5. Blood lipid values as a function of measurement time

Parameter	Before therapy (I)	Six weeks later (II)	12 weeks later (III)	24 weeks later (IV)
TC (mmol/L)	6.00 ± 1.27	5.32 ± 0.84	5.49 ± 1.05	5.23 ± 0.87
HDL-C (mmol/L)	1.26 ± 0.20	1.36 ± 0.29	1.37 ± 0.29	1.40 ± 0.26
LDL-C (mmol/L)	3.94 ± 0.97	3.31 ± 0.74	3.45 ± 0.88	3.25 ± 0.78
TG (mmol/L)	min–max	min–max	min–max	min–max
	0.50–5.94	0.54–4.69	0.40–5.25	0.39–3.00

TC – plasma total cholesterol; HDL-C – high-density lipoprotein-associated cholesterol; LDL-C – low-density lipoprotein-associated cholesterol; TG – triglycerides

in transmitral flow ratio (E/A), whereas the decrease in A wave velocity was a statistically highly significant ($p < 0.01$) after six, 12 and 24 weeks of therapy (Table 3). There was a trend of increasing the rate of E/A in successive measurements during L-thyroxine therapy.

The isovolumic LV relaxation time (IVRT) was highly statistically significant ($p < 0.01$) decreased after six and 24 weeks of therapy, whereas the difference was not statistically significant ($p > 0.05$) in successive measurements of IVRT between six and 12 weeks, as well as between 12 and 24 weeks of therapy (Table 3). There was a constant decrease in IVRT during successive measurements after the beginning of L- thyroxine therapy.

Results of the right cardiac function parameters

There was a highly statistically significant increase ($p < 0.01$) in TAPSE values six, 12 and 24 weeks after initiation of L-thyroxine therapy. No statistically significant difference was found in successive measurements of right ventricular (RV) end-diastolic diameter after six and 12 weeks of therapy, as well as successive measurements between the 12th and the 24th week ($p > 0.05$), and the difference was highly statistically significant ($p < 0.01$) at the end of the 24th week of therapy relative to baseline right ventricular diameter values - prior to initiation of therapy (Table 4).

Serum lipid profile test results

Triglyceride values were in the range of 0.50–5.94 mmol/L before therapy and in the range of 0.39–3.00 mmol/L after 24 weeks of therapy (Table 5). There was no statistically significant difference ($p > 0.05$) in serum triglyceride values after six, 12, and 24 weeks L-thyroxine therapy.

Total cholesterol values were in the range of 4.73–7.27 mmol/L, HDL-C in the range of 1.06–1.46 mmol/L and LDL-C in the range of 2.97–4.91 mmol/L before therapy and in the range of 4.36–6.10 mmol/L for total cholesterol, 1.14–1.66 mmol/L for HDL-C and 2,47–4.03 mmol/L for LDL-C after 24 weeks of therapy. Serum concentrations of total cholesterol (TC) and LDL-C were statistically highly significant decreased ($p < 0.01$), whereas serum values of HDL-C were highly statistically significant ($p < 0.01$) increased after six and 24 weeks of therapy. There was no statistically significant difference ($p > 0.05$) in the measured serum concentrations of total cholesterol, HDL-C and LDL-C between sixth and 12th week and 12th and 24th week of therapy (Table 5).

The trend line of mean values of serum lipid concentrations (total cholesterol, HDL-C and LDL-C) in successive measurements (Figure 1) showed an increase in HDL-C which was observed after the beginning of thyroid replacement therapy. The trend lines for total cholesterol and LDL-C showed a decrease in serum concentrations after six weeks of therapy, with an unexpected increase in serum concentrations of total cholesterol and LDL-C after 12 weeks. After 24 weeks the serum levels of total cholesterol and LDL-C were lower in relation to values before the starting L-thyroxine therapy.

DISCUSSION

The prevalence of subclinical hypothyroidism (elevated serum TSH and normal FT4) is 8% in women (10% in women over 55 years) and 3% in men (UK Whickham cohort study) [8]. In our study, the distribution with a higher prevalence of a subclinical hypothyroidism (in 25 subjects – 59.5%) also corresponds to its higher prevalence

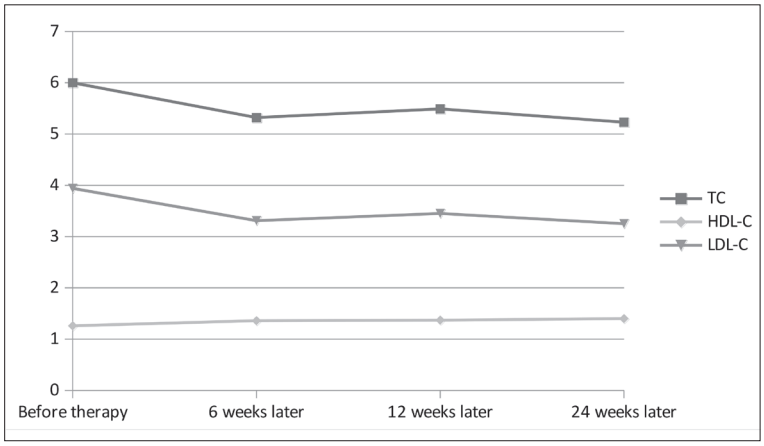

Figure 1. The trend line of mean lipid values in successive measurements: TC, HDL-C, LDL-C; TC – plasma total cholesterol; HDL-C – high-density lipoprotein-associated cholesterol; LDL-C – low-density lipoprotein-associated cholesterol; TG – triglycerides

in the general population compared to the overt form of hypothyroidism.

The panel of experts supports the use of L-thyroxine in patients with subclinical hypothyroidism when TSH is greater than 10 mIU/L. L-thyroxine administration might be considered in women planning a pregnancy or in pregnant women, as well as in symptomatic patients with subclinical hypothyroidism with TSH below 10 mU/L [9].

The reported high values of TSH in our study after 24 weeks of therapy in eight subjects can be explained by the various causes of intermittent or persistently elevated TSH levels in patients on thyroid replacement therapy, such as:

1) poor drug compliance and adherence;
2) interaction with other drugs;
3) using L-thyroxine with food;
4) drug malabsorption;
5) coexistent celiac disease or autoimmune gastritis;
6) interference with a laboratory test mediated by heterophilic antibodies;
7) the presence of resistance to thyroid hormones [10, 11].

Multiple meta-analyses involving patients with subclinical hypothyroidism under the age of 60 have shown that the prevalence of LV diastolic dysfunction is significantly more common in subclinical hypothyroidism than in healthy subjects. In 10 randomized studies with selected patients with mild thyroid dysfunction, improvement in diastolic function was demonstrated as early as three months after L-thyroxine therapy [12, 13, 14].

There is a milder degree of LV hypertrophy in the overt hypothyroidism with an increase in posterior wall thickness more than the interventricular septum, suggesting that concentric remodeling of the left ventricle is developed during thyroid dysfunction, which is reversible by L-thyroxine administration [15, 16]. The LVEF is usually normal or slightly reduced in thyroid dysfunction, with a slight increase during therapy, mainly during exercise and less at rest [17].

Subclinical hypothyroidism is associated with systolic and diastolic dysfunction of the right ventricle, and L-thyroxine therapy leads to an improvement of right ventricular function. Some studies have shown an association between clinical hypothyroidism and right ventricular diastolic dysfunction, as well as an increase in right ventricular wall thickness. A number of studies have shown that damaged right ventricular mechanics are completely repaired after adequate thyroid hormone dose [18, 19].

The thyroid replacement therapy in hypothyroid subjects significantly improves the echocardiographic parameters of LV diastolic function, especially after three months of L-thyroxine therapy with an average transmitral flow rate E/A>1.0 (1.1 ± 0.17) and IVRT < 100 m/s (87.59 ± 8.14 m/s). The use of L-thyroxine significantly improves the echocardiographic parameters of LV systolic function (LVEF, MAPSE). After six months of therapy there was no significant change in the diastolic diameter of the left ventricle. L-thyroxine therapy also improves the right ventricular systolic function. In our study, improvements of the parameters of left and right ventricular systolic and diastolic function after the administration of L-thyroxine were expected and consistent with the reported study results.

The increased prevalence of the atherosclerotic cardiovascular disease in subclinical hypothyroidism was demonstrated in a Rotterdam study, which showed that middle-aged women with subclinical hypothyroidism (with TSH greater than 4 mU/L) had a higher prevalence of coronary artery disease than the control sample with TSH less than 4 mU/L [20].

Increased serum concentrations of LDL cholesterol, triglycerides, apolipoprotein B and increased LDL oxidation might explain the association between subclinical hypothyroidism and cardiovascular disease. This pattern of serum atherogenic profile is more pronounced in patients with serum TSH levels greater than 10 mU/L and in smokers. A meta-analysis of 55,287 patients from 11 prospective cohort studies showed that subclinical hypothyroidism in patients with higher TSH levels were associated with higher mortality and prevalence of coronary diseases [21].

Studies have shown that increase in serum TSH levels by 1 mU/L increased total serum cholesterol by 0.09 mmol/L in women and by 0.16 mmol/L in men [22]. A meta-analysis of studies that monitored the effects of levothyroxine therapy on lipid profile in subclinical hypothyroidism showed that serum total cholesterol decreased by about 0.2 mmol/L or serum LDL cholesterol by about 0.3 mmol/L after L-thyroxine therapy, while triglycerides and HDL-C remained unchanged [23]. McGowan et al. [24] have shown a significant increase in HDL cholesterol by normalizing serum TSH concentrations by levothyroxine therapy.

In our study thyroid replacement therapy had been shown to reduce serum total cholesterol and LDL-C concentrations, increase HDL-C, and no significant effects

on serum triglyceride concentrations. The effects of L-thyroxine therapy on the parameters of the lipid profile in the subjects described in our study indicate consistent and expected results, as shown in the studies cited by other authors. The paradoxical and unexpected increase in total cholesterol and LDL-C after 12 weeks of therapy could be explained by the uncontrolled conditions of the trial, i.e., inability to control the dietary regime of the subjects in addition to the advice given at the controls, as well as fluctuations of thyroid hormones (FT4 and TSH), which is a characteristic at the beginning (in the first three months) of the use of levothyroxine therapy.

CONCLUSIONS

Thyroid replacement therapy in hypothyroid subjects significantly improves the echocardiographic parameters of LV diastolic function, especially after the third month of initiation of therapy. Administration of L-thyroxine leads to a significant improvement in left and right ventricular systolic parameters. Levothyroxine therapy significantly reduced the risk factors for the development of atherosclerosis and coronary artery disease: reduction of total serum cholesterol and LDL-C, and increase of HDL-C.

Conflict of interest: None declared.

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Ефекат тиреосупституционе терапије на функцију срца код болесника са хипотиреоидизмом

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САЖЕТАК

Увод/Циљ Хипотиреоидизам је синдром хипометаболизма са недовољном производњом или неадекватним дејством тиреоидних хормона. Карактерише се хиперхолестеролемијом, повишеним ЛДЛ-холестеролом, а најчешћа ехокардиографска промена је поремећај параметара дијастолне функције леве срчане коморе.

Циљ истраживања је испитивање утицаја постизања адекватне супституције тироидним хормонима код хипотиреоидних болесника на побољшање систолне и дијастолне функције срца и кориговање липидног профила у серуму.

Методе Спроведена је проспективна студија на 42 болесника са новооткривеном хипотиреозом, оба пола, узраста 18–60 година, без коморбидитета. Одређиване су вредности ФТ4, ТСХ, укупног холестерола, ХДЛ-Х, ЛДЛ-Х и триглицерида пре започињања, шест, 12 и 24 недеље после терапије Л-тироксином. Утицај супституције тироидним хормонима на систолну и дијастолну функцију срца процењиван је ехокардиографским прегледом.

Резултати Двадесет пет (59,5%) испитаника је имало субклиничку, а 17 (40,5%) манифестну форму хипотиреоидизма. Ендсистолни дијаметар леве коморе се значајно смањио ($p < 0,01$) после 12 недеља терапије, а енддијастолни дијаметар десне коморе после шест месеци терапије. Није било промена енддијастолног дијаметра леве коморе после шест месеци терапије тироидним хормонима. Вредности амплитуде систолне екскурзије равни митралног анулуса, ејекционе фракције леве коморе и вредности амплитуде систолне екскурзије равни трикуспидног анулуса су статистички значајно повећане ($p < 0,01$) после шест недеља терапије. Двадесет четири недеље после увођења тироидних хормона долази до статистички значајног смањења ($p < 0,01$) концентрација укупног холестерола и ЛДЛ-Х, пораста ХДЛ-Х, а без утицаја на серумске концентрације триглицерида ($p > 0,05$).

Закључак Супституционом терапијом тироидним хормонима код хипотиреоидних испитаника значајно су побољшани ехокардиографски параметри дијастолне и систолне функције леве и десне коморе, смањен је укупни холестерол и ЛДЛ-Х, а повећан ХДЛ-Х.

Кључне речи: хипотиреоза; Л-тироксин; дијастолна функција срца; систолна функција срца; липидни профил

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prognostic significance of clinical parameters in patients with cerebral low-grade glioma

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SUMMARY
Introduction/Objective Low-grade gliomas affect younger adults and carry a favorable prognosis. We aim to describe clinical patterns of low-grade gliomas as well as prognosis in different groups of patients. Our intention was to determine clinical parameters that may affect prognosis, and whether a greater extent of resection would increase the long-term progression-free or overall survival of patients with low-grade gliomas.
Methods We analyzed data obtained from the files of the patients with a diagnosis of the World Health Organization classification grade II gliomas. The relationships among categorical variables were analyzed using standard statistical tools and a 95% confidence interval.
Results We analyzed 118 patients with median age of 34 years. Over 57% were male and the primary site location was the cerebrum. All these patients were operated on and some of them received radiation and/or chemotherapy. Median overall survival was 9.6 years and better prognosis is associated with younger age, frontal and noneloquent zone location, seizures as the first symptom of the disease, and gross total resection of the tumor. Indications for early surgery are increased intracranial pressure, preoperative neurologic deficit, tumor size larger than 6 cm with contrast enhancement, and older age.
Conclusion Tumor location, 1p/19q co-deletion, and age were the main determinants of treatment received and overall survival, likely reflecting tumor biology differences. Any form of treatment was preferred over watchful waiting. This study found that a greater extent of resection could significantly increase the overall survival of patients with low-grade gliomas.
Keywords: low-grade glioma; surgery; prognosis; survival

INTRODUCTION

Low-grade gliomas (LGG) are in general relatively slow-growing primary brain tumors, but they have a very heterogenous clinical behavior. They are an extremely important problem for a number of reasons: estimation of the timing of surgery, intraoperative procedure (extent of surgical removal), value of intraoperative mapping, application of radiotherapy and chemotherapy, as well as treatment with recurrent tumor.

The best treatment policy for these tumors is still unclear. Some physicians advocate early and extensive surgery or early radiation therapy, whereas others tend to postpone treatment until functional deficits are present [1, 2]. Several studies have attempted to identify prognostic factors in LGG. However, except for age, the importance of other prognostic factors for survival in LGG remains a matter of debate. A number of patient and tumor characteristics, such as age at diagnosis, performance status, histology subtype, primary tumor classification, tumor site, presence of seizures at diagnosis, and extent of resection, have been proposed as prognostic factors for progression-free or overall survival. In this review, the current approaches to different LGGs presenting with different symptoms in different regions of the brain will be reviewed and the rationale for making decisions discussed.

Gliomas are classified as grades I to IV based on histology and clinical criteria [3]. Under the recent World Health Organization (WHO) classification of primary intracranial tumors, LGGs would encompass grade I and grade II neuro-epithelial tumors. The difference between these two groups is important since the grade I tumors are generally benign and can be cured by surgical excision [4]. Grade II tumors are generally incurable but have median survival times of more than five years [5]. Tumors with oligodendroglial components generally do better than astrocytomas, with prognosis being partially related to gene deletions on chromosome 1p and 19q [6]. Essentially, all grade II lesions eventually progress to high-grade glioma (grade III/IV or HGG). Grade IV tumors (glioblastoma multiforme or GBM) that arise from LGG are termed "secondary GBM" to differentiate them from "primary" or "de-novo" GBM [7]. Even with the best magnetic resonance imaging (MRI, Figure 5), differentiation between grade I and II tumors is very difficult, therefore establishing tissue diagnosis can be important [8].

Most patients initially receive surgical resection/biopsy at time of diagnosis and then radiation therapy (XRT) and/or the single chemotherapeutic agent temozolamide (TMZ) at some point. A surgical gross total resection appears associated with better survival for

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patients able to undergo such a procedure [9, 10]. Some clinical studies suggest XRT prolongs time to recurrence but not overall survival and may be associated with reduction in the quality of life and cognition [10], while the impact of the primary single TMZ now used to treat LGG has shown benefit primarily in HGG but is not fully assessed in LGG [10, 11]. The goal of this review is to examine population-based survival rates for LGG within Serbia by standard patient demographics.

METHODS

Patients

We performed a retrospective review of 118 patients with LGG, 68 males and 50 females (mean age 34.20 ± 2.23 years). All of these patients had been operated on one or more times over a 10-year period at the Clinic of Neurosurgery, Clinical Center of Serbia, Belgrade. The youngest patient was six years old and the oldest one was 64 years old. Written consents from each subject were obtained before screening according to the Declaration of Helsinki and the local ethics committee of the participating institution approved the study.

Both adult and pediatric patients were eligible for this study. The patients were divided into the following three age categories: (I) the patients younger than 35 years (52.5%), (II) those aged 35–45 years (25.4%), and finally (III) the patients over 45 years (22.1%). The total follow-up period for these subjects was 18 years. In order to describe the characteristics of these patients, we used descriptive statistics methods such as absolute numbers and proportions, but also distribution analysis of a single variable including its central tendency (mean, median, and mode) and dispersion (range, standard deviation).

Clinical evaluation

Clinical evaluation of the performed surgical treatment was done according to data obtained from patients' files and clinical examinations. We have also performed neurological examination both preoperatively and postoperatively in each patient. All patients undergoing biopsy, subtotal resection (STR), and gross total resection (GTR) were compared for the outcome measures of overall survival (OS), postoperative Karnofsky performance status (KPS), progression-free survival, mortality, and morbidity.

Follow-up computed tomography (CT) or magnetic resonance (MR) scans of the brain were done for each patient at regular intervals, paying particular attention to the localization and size of the tumor lesion, its characteristics after contrast administration, the extent of surgery, the appearance of relapse, etc.

Neurologic deficit was defined as absent [Medical Research Council (MRC) neurologic scale 1 or 2, Table 1] or present (MRC grade > 2).

Table 1. Medical Research Council Neurologic Scale

1	No neurologic deficit
2	Some neurologic deficit but function adequate for useful work
3	Neurologic deficit causing moderate functional impairment, e.g., able to move limbs only with difficulty, moderate dysphasia, moderate paresis, some visual disturbances (e.g., field defect)
4	Neurologic deficit causing major functional impairment, e.g., inability to use limbs, gross speech, or visual disturbances
5	No useful function – inability to make conscious responses

Treatment

Tumor characteristics were recorded based on the local interpretation of preoperative CT scans. Predominant site and side were coded as binary factors (fronto-temporal, temporo-parietal, left side, right side, central). Extent of surgical resection, which had been determined intraoperatively and judged by the neurosurgeon, was scored as gross total resection (GTR, 90% to 100% tumor excised), versus less extensive excision (subtotal resection, STR in which 50–89% of tumor volume was removed) or biopsy, partial or minimal tumor removal (less than 50% resection). Histology subtype was grouped as group I and group II according to the official WHO classification.

Prognosis

Survival or death and relapse were taken as outcome variables and monitored dynamically as a function of time.

Survival was calculated as the time from diagnosis until death but provided that the death was due to causes related to the treatment of LGG and not to other associated diseases. Kaplan–Meier estimate is one of the best options to be used to measure the fraction of subjects living for a certain amount of time after treatment. By means of Cox regression, we identified and validated important factors for survival that could be of value for staging patients into low- and high-risk groups. The log-rank test was used to assess whether the difference of survival times between two groups is statistically different or not, and to identify the factors that have an impact on the overall survival or tumor regrowth.

RESULTS

The study was conducted over a period of 10 years. The summarized patient characteristics, sex, age, and associated diseases are shown in Table 2. We report on one-year OS in 112 patients (94.91%), five-year OS in 80 patients (67.80%), 10-year OS in 58 patients (49.15%), and 15-year OS in 29 patients (24.57%). At the end of the 18-year follow-up period, 20 patients (16.94%) survived. Median OS of all patients was 9.6 years ($CI_{95\%}$ = 8–12 years).

At the end of the first year of follow-up, 94.4% patients were without tumor recurrence, after five years the percentage was 71.09%, and after 10 years it was 39.79%. The

Table 2. Sex, age, and associated diseases in our series

Parameters		Absolute frequency (n)	Relative frequency (%)
Sex	Male	68	57.6
	Female	50	42.4
Age	< 35 years	62	52.5
	35–45 years	30	25.4
	> 45 years	26	22.1
Associated diseases	Yes	25	21.2
	No	93	78.8

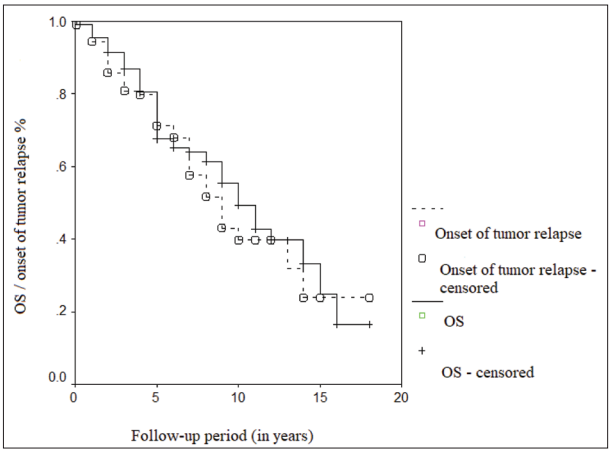

Figure 1. Kaplan–Meier estimate of overall survival (OS) and the onset of tumor relapse for a certain amount of time after initial treatment (follow-up period)

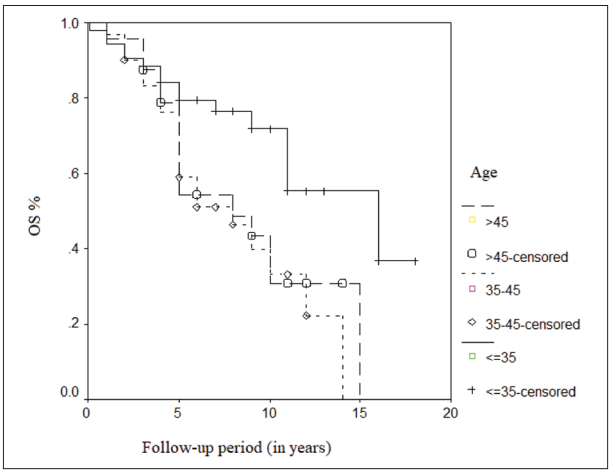

Figure 2. Kaplan–Meier estimate of overall survival (OS) for three different age groups

probability of non-recurrence at the end of the 15-year period was 23.87%. The median onset of relapse was nine years ($CI_{95\%}$ = 7–11 years), Figure 1.

The age of the subjects had a statistically significant effect on OS. Log-rank cross-group analysis showed that patients in the first group (those younger than 35 years) had statistically significantly longer survival than the other subjects in groups II or III. The results obtained indicate a significant predictive value of the patient's age factor and further prognosis of the disease, so that the group of the youngest patients stands out as the group with the best prognosis. The median OS in the first group of patients was 16 years ($CI_{95\%}$ = 7–25 years), Figure 2.

Clinical course, symptoms, and signs are summarized in Table 3. Using log-rank test, we noticed something statistically significant among patients in whom seizures were the principal symptom of the disease – they had longer OS compared to those patients in whom disease started gradually, without epi-manifestations. Patients with seizures also had a better prognosis regarding the occurrence probability of tumor regrowth – median probability of tumor relapse was 14 years ($CI_{95\%}$ = 5-23 years), compared to the group of patients without seizures and gradual onset of symptoms, in which median probability of tumor recurrence was seven years ($CI_{95\%}$ = 6–8 years).

Table 3. Clinical course, symptoms, and signs of disease

Parameters		Absolute frequency (n)	Relative frequency (%)
Onset of disease	Acute (seizures)	64	54.2
	Gradual	54	45.8
Clinical course of disease	Intermittent	79	68.1
	Progressive	37	31.9
Visual test findings	Normal	93	78.8
	Papilledema	17	14.4
	Other abnormalities	8	6.8
Symptoms	Due to increased ICP	20	16.9
	Seizures	47	39.8
	Motor deficits	11	9.3
	Cognitive deficits	11	9.3
	Other abnormalities	29	24.6
Signs	No signs	64	54.2
	Motor signs	30	25.4
	Other signs	14	11.9
	Combination of more signs	10	8.5
Karnofsky performance status	70–80	17	14.4
	90	32	27.1
	100	69	58.5
Neurologic deficit on admission	No	81	68.6
	Yes	37	31.4

ICP – intracranial pressure

We also identified several factors that have negative influence on OS: increased intracranial pressure (ICP), preoperative neurologic deficit, and KPS lower than 70. Median OS in patients with symptoms of increased ICP was not reached, indicating that increased ICP had a big impact on postoperative neurologic findings, final outcome, and overall OS, Figure 3. Median OS in patients with different KPS were as follows: five years for those with KPS 70–80, also five years for those with KPS 90, but 12 years for those with KPS 100, which is statistically significantly longer OS.

Neuroradiological interpretation of CT and MR findings is shown in Table 4. Patients with some foci of hyperdensity on preoperative CT had significantly shorter OS; their median OS was just two years ($CI_{95\%}$ = 0–4 years), Figures 4 and 5A–B. Tumor size also has a statistically significant effect on OS in LGG patients. Based on CT images, the tumors were divided into four groups: up to 2 cm in

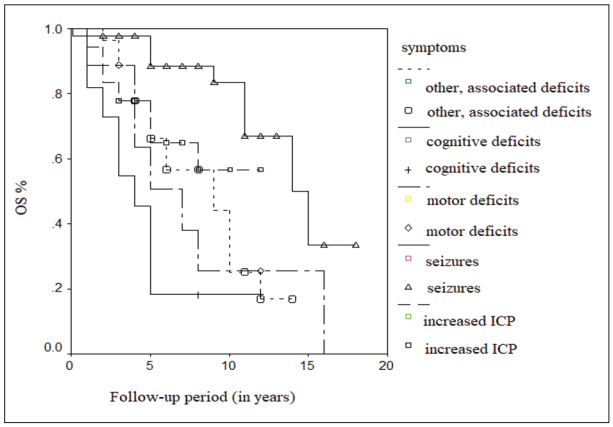

Figure 3. Kaplan–Meier estimate of overall survival (OS) for different symptoms

Table 4. Computed tomography (CT) and magnetic resonance (MR) findings on admission

Parameters		Absolute frequency (n)	Relative frequency (%)
Density on CT	Hypodensity	59	50
	Isodensity	47	39.8
	Hyperdensity	12	10.2
Clear tumor borders on CT	Yes	56	47.5
	No	62	52.5
Size of LGG on CT	Up to 2 cm	11	9.3
	2–4 cm	47	39.8
	4–6 cm	41	34.7
	> 6 cm	19	16.1
Contrast enhancement	No enhancement	78	66.1
	Homogenous	11	9.3
	Marginal enhancement	29	24.6
Intensity on MR	Hypointensity	8	19.5
	Isointensity	27	65.9
	Hyperintensity	6	14.6
Side	Left	47	39.8
	Right	66	55.9
	Bilateral	5	4.2
Cortical presentation	Yes	45	38.1
	No	73	61.9

LGG – low-grade gliomas

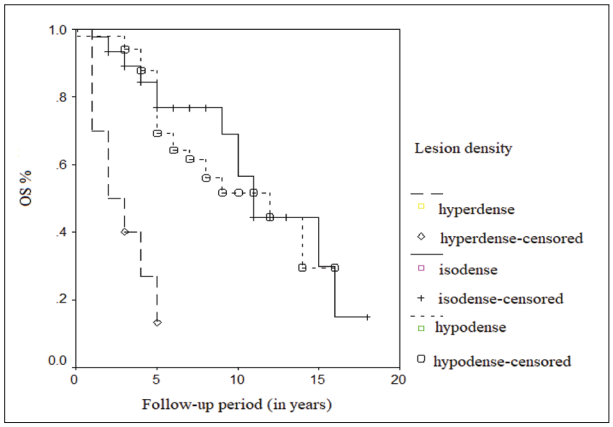

Figure 4. Kaplan–Meier estimate of overall survival (OS) for different density of lesion on preoperative computed tomography

Table 5. Surgical treatment and its complications

Parameters		Absolute frequency (n)	Relative frequency (%)
Principal reason for surgery	Progress of neurologic deficit	28	23.7
	Increased ICP	32	27.1
	Deterioration – seizures	28	23.7
	Others	30	24.4
Extent of tumor resection	Biopsy	5	4.2
	STR	68	57.7
	GTR	45	38.1
Tumor consistency	Firm	38	32.2
	Tough	45	38.1
	Soft	35	29.7
Margins towards brain	Infiltrative	73	61.9
	Clear margins	45	38.1
General complications	None	101	85.6
	Present	17	14.4
Surgical complications	None	73	61.9
	Requiring surgery	8	6.8
	Not requiring surgery	37	31.4

STR – subtotal resection; GTR – gross total resection

diameter, 2–4 cm in diameter, 4–6 cm in diameter, and over 6 cm in diameter. Using the log-rank test, we showed that subjects in the first and second group in whom the tumor was smaller than 4 cm had significantly longer OS than patients in the remaining two groups. However, no statistically significant difference in the likelihood of recurrence was observed among subjects with different tumor sizes. Therefore, we can conclude here that the size of the tumor has nothing to do with the likelihood of recurrence.

All analyzed patients were operated on while some were operated on more than once. In this regard, we considered indications for surgical treatment, extent of surgical resection of the tumor, characteristics of the tumor during surgery, and postoperative complications. These data are summarized in Table 5. Of all these variables, only the extent of tumor resection would be emphasized here. Those patients who underwent GTR had a statistically significantly longer OS than all other groups. The median survival in the GTR group was not even reached, the median survival in the STR group was eight years, while the patients in the biopsy group lived five years on average.

Looking at the literature data, it is possible to conclude that over time, sooner or later, almost all subtotal resected LGGs, and even those tumors in which GTR is achieved, relapse. The most common cause of death in LGG is disease progression, as nearly 50% of these tumors undergo malignant transformation. These data are summarized in Table 6.

DISCUSSION

After analyzing this data, we came to the conclusions that there are good reasons why these tumors are called just that – benign or slow-growing tumors. Although these are primary brain tumors, our results give a lot of optimism as the five-year OS in our series was 67.55% and the 10-year

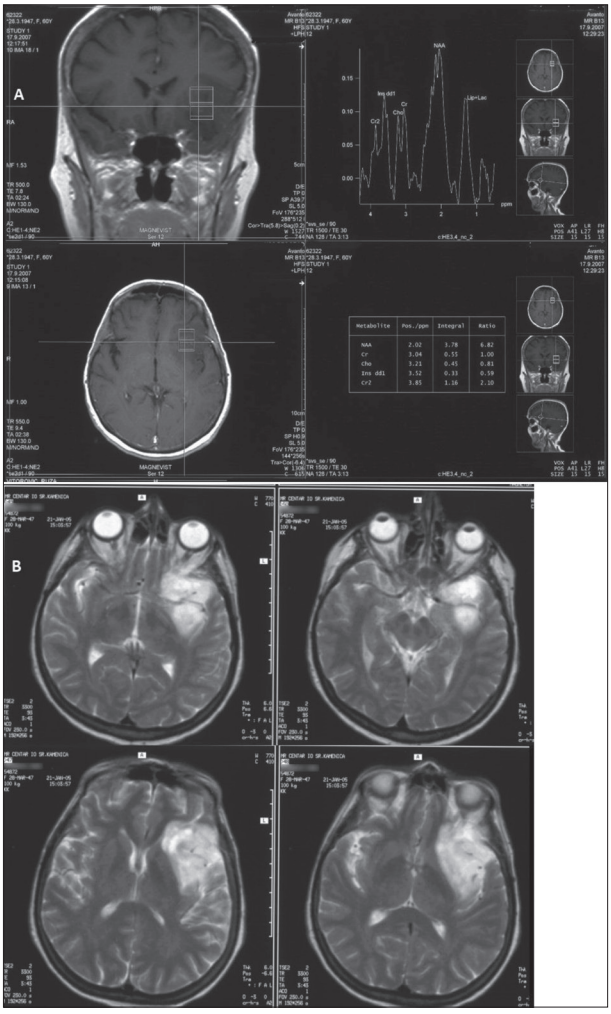

Figure 5. (A) Magnetic resonance (MR) of the brain (T1W sequence) with MR spectroscopy, of a patient from our series, showing intra-axial lesion in the left frontotemporal area; (B) MR of the brain (T2W sequence) of a patient from our series, showing intra-axial lesion in the left frontotemporal area

Table 6. Redo surgery and histopathological finding after redo-surgery

Parameters		Absolute frequency (n)	Relative frequency (%)
One single operation	Yes	73	61.9
	No	45	38.1
Second surgery	Yes	45	38.1
	No	73	61.9
Third surgery	Yes	9	7.6
	No	109	92.4
HP after redo-surgery	Same finding (LGG)	26	48.1
	Progression to astrocytoma gr. III	19	35.2
	Progression to GBM	9	16.7

HP – histopathological finding; LGG – low-grade gliomas; GBM – glioblastoma

OS was 49.22%, which is very similar to the data from other authors.

This study highlights the predictive factors for good prognosis in patients with LGG and emphasizes different variables that may have some influence on OS. Results of the present study also show the importance of regular follow-up after initial surgery, because we know that nearly half of these patients with LGG have a chance of developing a malignant alteration to anaplastic astrocytoma gr. III or GBM.

It should be acknowledged that some LGGs are not eligible for a meaningful extent of resection with an acceptable risk. We have demonstrated that early resection is associated with a clinically relevant survival benefit when compared with watchful waiting in LGGs. However, an overall treatment strategy in favor of watchful waiting cannot be recommended in patients eligible for resection. Finally, malignant transformation usually occurs with time but extensive surgical resection may delay this process [12].

High-risk features for mortality in patients with a diagnosis of LGGs include age older than 45 years, tumor diameter greater than 6 cm, midline crossing, presence of neurological deficit, and astrocytic histology [13]. Duffau and Taillandier [13] determined that patients defined as low-risk after gross total resection have a 50% risk of tumor progression at five years [14, 15]. However, due to the overlapping molecular prognostic factors, heterogeneity of these tumors, and challenges of completing clinical trials in a rarer and long-surviving cancer, treatment recommendations remain unestablished.

With the updated WHO classification of the nervous system in 2016, molecular profiling is required for proper LGG classification. Risk assessment is based on three groups: IDH mutant tumors with 1p/19q co-deletion (predominantly oligodendroglial), IDH mutant without 1p/19q co-deletion (predominantly astrocytic), and IDH wild-type tumors.

In surgical treatment, the technique of classical craniotomy was applied, after which, depending on the localization of the tumor, the most commonly used microsurgical extirpation of tumors of different extent was applied. In our conditions, stereotaxic biopsy was not performed due to technical impossibilities, but only open biopsy in small tumors that were localized in the motor cortex. One of the major dilemmas in the treatment of slow-growing astrocytomas is the degree of surgical resection. Many patient series show quite opposite results: in some we find that the degree of resection is proportional to the length of survival, while in other series they do not find this correlation at all. The strongest argument against GTR is the evidence that there are tumor cells at sites that are substantially distant from the tumor itself. Other arguments that support the inability of GTR are invasive and infiltrative tumor growth, multifocal lesion, and the possibility of an additional neurological deficit. The proponents of GTR, on the other hand, point out their arguments: cytoreduction that allows for reduction of ICP, improvement of neurological deficit, reduction or even elimination of epi-attacks; maximal tumor reduction enables the immune response to better effect to smaller number of cells; the potential error in HP tumor verification is reduced; by reducing the total number of tumor cells, the possibility of malignant transformation of tumors is also reduced. In our study, GTR was achieved in about 40% of cases, but more importantly, we observed that

there was a statistically significant interdependence between the degree of tumor resection and the length of survival.

The same conclusion was reached by Thon et al. [16] in their series of 86 patients as well as by Xia et al. [17], who published the results of 77 patients with LGG. By a retrospective analysis of 132 patients, Sanai et al. [18] found that the five-year survival in those who achieved GTR was about 80% and in those operated on in terms of STR, the overall five-year survival was 52%. However, in some other series, no correlation was found between the survival rate and the extent of surgical tumor resection. This again opens the dilemma of significance, usefulness, and harm of radical surgical resection.

Our results reflect the benefits of surgery with maximal safe resection. We have done surgery as the first treatment step in over 70% of our patients and this strategy has clearly shown usefulness, as surgical resection and its extent both have a significant survival benefit [18, 19].

CONCLUSION

A typical patient with LGG is a person in the second half of the fourth decade of life, with near-normal neurological findings and epilepsy as the first symptom of the disease. For definitive diagnosis, mandatory MR examination with paramagnetic contrast application is also required. Longer OS was statistically significant in patients in the first group (younger than 35 years), whose symptoms lasted longer in the preoperative period and in which the GTR procedure was performed. Factors that have a statistically significant negative effect on OS are increased ICP, pronounced preoperative neurological deficit, and KPS below 70. Sex, associated diseases, and, interestingly, postoperative XRT have no impact on OS.

Time interval between the first surgery and the second one because of the occurrence of tumor regrowth is statistically shorter in patients with progressive course of the disease and preoperative neurologic deficit, in those with signs and symptoms of increased ICP, if there is a contrast enhancement of tumor on preoperative CT, and if there is a larger volume of residual tumor following initial surgery. Malignant transformation of LGG into anaplastic astrocytoma or GBM occurred in 51% of patients who relapsed. This transformation is particularly rapid in elderly patients. Immediate perioperative mortality was 4.2%.

Conflict of interest: None declared.

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Прогностички значај клиничких параметара код болесника са нискоградусним глиомом мозга

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САЖЕТАК

Увод/Циљ Нискоградусни глиоми су тумори мозга који углавном погађају младе одрасле особе.

Циљ овог рада је одређивање клиничких параметара као могућих прогностичких фактора у лечењу нискоградусних супратенторијалних глиома. Наша намера је и уочавање корелације између обима хируршке интервенције и дужине преживљавања.

Методе Користили смо податке из историја болести болесника са нискоградусним глиомом по класификацији Светске здравствене организације, градуса 2. Однос између варијабли анализиран је уз помоћ стандардних статистичких тестова уз интервал поверења од 95%.

Резултати Анализирали смо 118 болесника, просечне старости 34 године. Око 57% њих су мушког пола уз предоминантну супратенторијалну локализацију тумора. Сви ови болесници су оперисани, али је код неких спроведен и постоперативни зрачни третман са хемотерапијом или без ње. Средње време преживљавања је било 9,6 година. Фактори боље прогнозе су нађени код млађих болесника, код локализације тумора фронтално и у неелоквентним зонама, у случају да су епи-напади први симптом болести и код оних болесника код којих је постигнута потпуна екстирпација тумора. Индикације за рану операцију биле су постојање повишеног интракранијалног притиска, преоперативног неуролошког дефицита и тумор већи од 6 *cm*.

Закључак Локализација тумора, 1*p*/19*q* коделеција и узраст болесника су биле главне детерминанте у лечењу и укупном преживљавању. Било која врста третмана боља је од праћења болесника у дужем периоду. Овај рад потврђује примарни значај хируршког лечења болесника са нискоградусним глиомима мозга – што је обимнија ресекција туморске масе, то је преживљавање дуже.

Кључне речи: нискоградусни глиоми; операција; прогноза; преживљавање

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Incomplete Circle of Willis and cerebrovascular reactivity in asymptomatic patients before and after carotid endarterectomy

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SUMMARY

Introduction/Objective Circle of Willis (CoW) provides the most significant collateral flow in the presence of significant stenosis or occlusion of internal carotid artery. In terms of collateral flow "incomplete" type and "complete" type of CoW can be recognized. Patients with carotid artery disease with incomplete CoW have lower cerebrovascular reactivity and higher risk for stroke. Cerebrovascular reactivity refers to the residual capacity of dilatation of cerebral blood vessels in the condition of insufficient blood flow. In this study we analyzed changes in cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients with respect to complete and incomplete CoW morphology.

Methods In this study in 97 patients with asymptomatic carotid artery disease we measured cerebrovascular reactivity before and after carotid endarterectomy by using method of "apnea test" and "breath-holding index" (BHI). Patients were divided into two following groups: patients with "complete" CoW and "incomplete" CoW based on non-contrast magnetic resonance angio performed previously to the operation. Descriptive statistics, univariate analysis, and ANOVA for comparison of BHI values between groups were used.

Results The results showed significant increase in cerebrovascular reactivity at the side of stenosis in both groups of patients with complete CoW (BHI value increased from 0.897 to 1.090; $F(1.65) = 30.788$, $p < 0.0005$, parc. $\eta^2 = 0.321$) and incomplete CoW (BHI value increased from 0.690 to 1.010; $F(1.27) = 62.318$, $p < 0.0005$, parc. $\eta^2 = 0.698$) and the more significant increase in the group of incomplete CoW compared to the group with complete CoW ($F(1.92) = 4.557$, $p = 0.035$, parc. $\eta^2 = 0.047$)

Conclusion In most asymptomatic patients, cerebrovascular reactivity restores to normal following carotid endarterectomy. Parameters of cerebrovascular reactivity are lower in patients with incomplete CoW and the increase after carotid endarterectomy is more significant in such patients.

Keywords: breath-holding index; extracranial carotid disease; internal cerebral artery; asymptomatic carotid patients risk stratification

INTRODUCTION

Circle of Willis (CoW) provides the most significant collateral flow in the presence of significant stenosis or occlusion of internal carotid artery (ICA). Anterior collateral segment of CoW (ACA1, AcomA) is a connection between opposite carotid arteries and posterior collateral segment (ACP1, AcomP) provides collateral from posterior cerebral circulation [1].

Morphology of CoW can be evaluated by non-contrast enhanced magnetic resonance angiography and it depicts the functional status of collateral flow [2]. Although there is a number of CoW morphology types, in terms of collateral flow "incomplete" and "complete" types of CoW can be recognized. Contrary to the "complete" CoW that depicts normal CoW morphology, "incomplete" CoW refers to the hypoplasia or occlusion of anterior and posterior collateral segment and consequent absents of collateral flow provided by CoW.

In the presence of significant ICA stenosis, incomplete CoW can be associated with impaired cerebral blood flow, reduction of cerebral autoregulation decreased circulatory reserve and low cerebrovascular reactivity leading to increased stroke risk [3]. Cerebrovascular reactivity describes the capacity of adaptation of cerebral blood flow as a reaction to different stimuli. If insufficient cerebral blood flow is present, blood vessels are maximally dilated, and the residual capacity to increase blood flow is limited.

In this study, we analyzed changes in cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients with respect to complete and incomplete CoW morphology.

METHODS

The research included 97 out of 171 patients, who were operated from asymptomatic extracranial carotid stenosis from January 2017 to June 2019. Prior to the operation, all patients underwent Duplex Ultrasound Examination (DUS) od carotid arteries and at least one of the following imaging: Magnetic Resonance Imaging (MRI) and Magnetic Resonance

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Angiography (MRA) (Siemens 1.5T, Siemens Healthineers, Erlanger, Germany) or Computed Tomography Imaging (CT) and Computed Tomography Angiography (CTA) (64 or 128 lines) of head and neck. MRI and MRA with three-dimensional time of flight (3D TOF) sequence for examination of extracranial portion of carotid and vertebral arteries and CoW and intracranial arteries was mandatory for patients who were included into the study.

Based on aforementioned diagnostic procedures, inclusion and exclusion criteria for this study were defined: patients with unilateral carotid disease (contralateral carotid stenosis was less than 50%) were included, with no significant lesions on intracranial portion of carotid arteries, vertebral and basilar arteries and cerebral arteries and no evidence of "silent brain infarctions" larger than one centimeter. Patients who were presented with insufficient data, poor insonation window for measurement of cerebrovascular reactivity or low compliance with the procedure, patients who refused to give their written consent were also excluded from the study.

We collected preoperative data on patients' general characteristics, risk factors and comorbidity: age, gender, presence of hypertension, diabetes, smoking, hyperlipoproteinemia, history of ischemic heart disease or heart failure, left ventricle hypertrophy, significant heart valve diseases, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease and peripheral artery disease (PAD). Assessment of clinical cardiologist has been provided.

Morphology of CoW was determined based on 3D TOF sequence of MRA. By morphology, patients were classified into two groups:

1. Group of patients with "complete CoW" in which all arteries of CoW were shown on 3D TOF sequence MRA (67 patients – 69%)
2. Group of patients with incomplete CoW: underdeveloped or occluded anterior (ACA1, AcomA) and posterior (ACP1, AcomP) collateral segment of CoW (30 patients – 31%)

Degree of ICA stenosis was estimated by DUS based on European Carotid Surgery Trial criteria and two groups of patients were recognized: group of patients with 75–84% ICA stenosis and group of patients with 85–99% ICA stenosis.

All patients underwent operation under general anesthesia; one of the following techniques was used: Carotid Endarterectomy (CEA) with patch plasty and intraluminal shunt protection or Eversion endarterectomy (EEA). Standardized perioperative protocol included administration of clopidogrel 75 mg at least five days prior to the operation with no discontinuation for the operation day, administration of statins starting at least 30 days before the operation. In the postoperative period, strict blood pressure control was indicated, with the aim to maintain systolic blood pressure below 160 mmHg.

For estimation of cerebrovascular reactivity, we used "Apnea test" method, previously described by Silvestrini et al. [4]. In Apnea test, the patients were asked to hold their breath for 30 seconds, and consequent increase in blood CO_2 is used as a stimulus for dilatation of cerebral blood vessels. The increase in blood flow during apnea test is registered with Transcranial Doppler ultrasound (TCD) (Multidop X4, DWL Elektronische Systeme Compumedics GmbH, Singer, Germany) with 2 MHz probe and Sonara Viasys version 04 (Vyaire Medical Inc., Mettawa, IL, USA) with 2MHz probe on proximal portion of the middle cerebral artery. As a result of the test the breath-holding index (BHI) is calculated as ratio between stimulated (CBF30 sec) and basal cerebral blood flow (CBFbasal):

$$BHI = ((CBF30\,sec - CBFbasal)/CBFbasal)/(sec/100).$$

The "cut-off" point for normal finding was set on 0.69. In this research apnea test was done to all patients a day before and a month after surgery.

We compared BHI values before and after surgery in groups of patients with complete and incomplete CoW for both sides: ipsilateral and contralateral to stenosis.

Statistical analysis included descriptive statistics: mean value, frequency (count) and relative frequency (percentage) for categorical data; comparative statistics included univariate analysis of variables with odd's ratio calculation; differences between BHI values before and after surgery in groups of patients with complete and incomplete CoW for both sides: ipsilateral and contralateral to stenosis has been analyzed by ANOVA. SPSS Statistics ver. 25.0 (IBM Inc. Armonk, NY, USA) was used.

Subjects' written consents have been obtained. All studies have been approved by the ethics committee of the Clinical Centre of Vojvodina and the Faculty of Medicine of the University of Novi Sad, and conforms to the legal standards. In most of the patients, MR examinations were done as a part of the project "Registration of New Ischemic Lesions with Magnetic Resonance Imaging Before and After Carotid Endarterectomy and Carotid Stenting", financed by the Provincial Secretariat for Higher Education and Scientific Research of Vojvodina. Subjects' written consent have been approved by the ethics Committee of the Clinical Centre of Vojvodina and Faculty of Medicine of the University of Novi Sad and conforms to the legal standards.

RESULTS

A total of 97 asymptomatic patients with ICA stenosis, 75 males, and 24 females, aged 54–79 years, median value 66.33, underwent carotid endarterectomy due to extracranial carotid disease. Both techniques of carotid endarterectomy with patch angioplasty and intraluminal protection (44%) and eversion endarterectomy (54%) were used depending on preferences of surgeon performing the operation, all under general anesthesia. We did not register any major perioperative adverse event (stroke or death) and we registered one postoperative case of acute coronary syndrome that was successfully treated by percutaneous coronary angioplasty. Patients' general characteristics and comorbidities with respect to complete and incomplete CoW morphology are shown in Table 1.

In both groups of patients with complete CoW and incomplete CoW degree of ICA stenosis (patients were classified into groups 75–84% and 85–99% stenosis) was equally distributed, as shown in Table 2.

Table 1. Distribution of patients' general characteristics, risk factors, and comorbidity in the groups with complete and incomplete Circle of Willis (CoW)

Variables	Complete CoW	Incomplete CoW	Total	OR	p value
Circle of Willis	70	27	97	-	-
Age (median value)	67.9	65,9	66.33	-	0.465
Males	78%	76%	76%	1.105	0.8734
Hypertension	83%	87%	86%	0.792	0.811
Diabetes mellitus	38%	36%	36.5%	1.131	0.819
Smoking	50%	53%	51%	1.077	0.870
Hyperlipoproteinemi	58%	73%	62%	0.882	0.759
Ishaemic heart disease or heart failure	27%	26%	27%	0.939	0.903
Left ventricle hypertrophy	22%	23%	22%	1.047	0.932
Significant heart valve disease	0%	1%	1%	7.981	0.207
Atrial fibrillation or other arythmia	11%	15%	12%	1.291	0.697
Chronic kiddney disease	4.2%	3.7%	4.1%	0.827	0.871
Chronic obstructive pulmonary disease	8.5%	11%	9%	1.333	0.700
Peripheral artery disease	13%	7%	11%	0.629	0.562

Table 2. Degree of Internal Carotid Artery stenosis by European Carotid Surgery Trial criteria estimated by duplex ultrasound in the groups of patients with complete and incomplete Circle of Willis (CoW)

CoW morphology	Degree of stenosis		Total	p value
	75–84%	85–99%		
Incomplete CoW	21	9	30	0.78
Complete CoW	45	22	68	
Total	66	31	97	

Preoperative values of BHI at the side of stenosis were 0.897 for the group of patients with complete CoW and 0.617 in the group of patients with incomplete CoW. In 34% of patients with complete CoW and 70% of patients with incomplete CoW preoperative BHI value were lower than previously defined "cut-off" value of 0.69. After the operation BHI values were 1.09 for group of patients with complete CoW and 1.01 in group of patients with incomplete CoW. Only 5.8% of patients with complete CoW and 6.7 % with incomplete CoW had postoperative BHI value less than 0.69.

Observing BHI values lower than 0.69 as pathological, we registered significant reduction of number of pathological findings of BHI level after the operation in the group of patients with incomplete CoW (63.3%) compared to the group of patients with complete CoW (28.2%) and the difference was statistically significant ($p = 0.0016$, OR = 4.36 CI 1.75–10.78) as shown in Figures 1a and 1b.

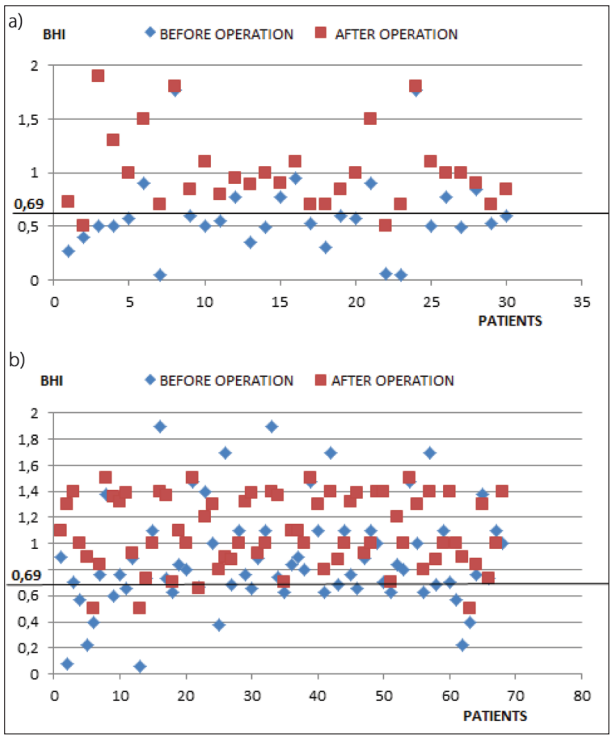

Figure 1. Breath-holding index values before and after operation in asymptomatic patients with a) incomplete Circle of Willis; b) complete CoW

By using ANOVA, we tested primary effects of two following variables: morphology of CoW ("complete" and "incomplete" CoW) and operation status (before and after surgery) on BHI values. It was determined that there was a significant difference in BHI values before the surgery between groups of patients with complete and incomplete CoW, $F(1.94) = 16.208$, $p < 0.001$, parc. $\eta^2 = 0.150$ and significant difference in BHI values between same groups after the surgery, $F(1.94) = 4.134$, $p < 0.05$, parc. $\eta^2 = 0.043$. We found significant influence of carotid endarterectomy on the BHI values in the group of patients with incomplete CoW, $F(1.27) = 62.318$, $p < 0.0005$, parc. $\eta^2 = 0.698$ and in the group of patients with complete CoW, $F(1.65) = 30.788$, $p < 0.0005$, parc. $\eta^2 = 0.321$, as shown in Figure 2a.

By using ANOVA, we tested interaction effect of following variables: morphology of CoW ("complete" and "incomplete" CoW) and operation status (before and after surgery) on BHI values. There was a significant interaction between the completeness of the CoW and operation status and their impact on the level of BHI, $F(1.92) = 4.557$, $p = 0\ 035$, parc. $\eta^2 = 0.047$. More significant increase in BHI value was registered in group of patients with incomplete CoW after the operation compared to patients with complete CoW. The difference proved to be statistically significant for $p = 0.035$. Therefore, carotid endarterectomy affected the patients with incomplete CoW more, in terms of improvement of cerebrovascular reactivity, as shown in Figure 2a.

For the side opposite to stenosis, ANOVA showed significant difference in BHI value before and after operation in both groups ($F = 7.357$, $p = 0.008$, parc. $\eta^2 = 0.072$), but no difference between the groups ($F = 0.831$, $p = 0.34$, parc. $\eta^2 = 0.009$), as shown in Figure 2b.

DISCUSION

In asymptomatic significant ICA stenosis, revascularization is indicated only in low risk patients, who feature increased risk of stroke [5]. In this respect, investigation of

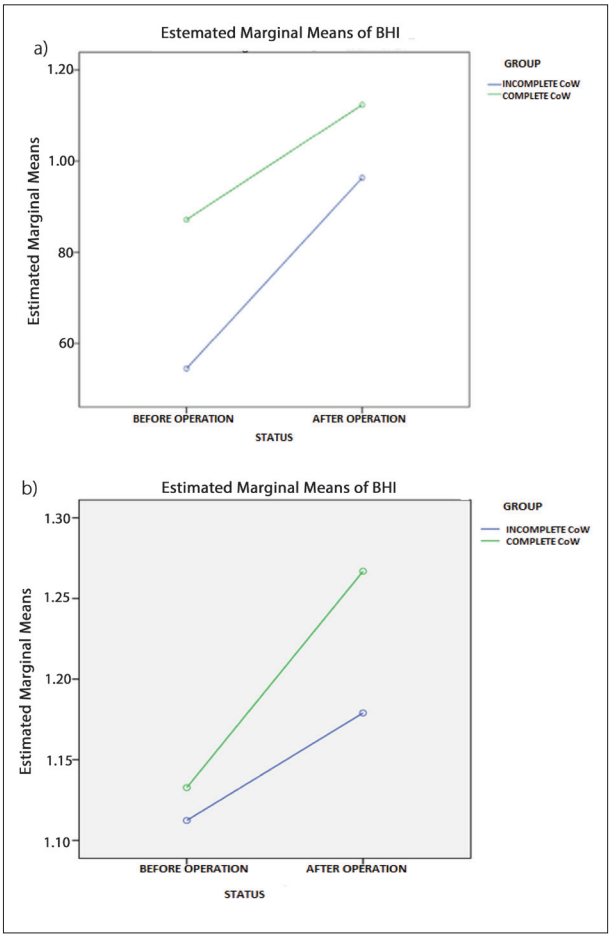

Figure 2. Estimated marginal means of breath-holding index before and after operation in asymptomatic patients with complete and incomplete Circle of Willis (CoW) at the a) operated side; b) contralateral side

cerebrovascular reactivity in asymptomatic patients has been recognized in up-to-date guidelines in preoperative assessment and risk stratification of patients with carotid artery stenosis [6]. Low cerebrovascular reactivity means that the cerebral arteries are already dilated to the maximum due to low cerebral perfusion and there is a limited reserve of adaptation of cerebral flow. In asymptomatic patients with significant carotid artery stenosis reduced cerebrovascular reactivity increases risk of stroke 13–25% per year [7–11]. Decreased circulatory reserve and lack of collateralization may increase the risk of stroke by the mechanism of impaired hemodynamics and due to the fact that arterio-arterial embolization from diseased carotid artery occurs more often in the zone of reduced circulatory reserve [12, 13].

Association of incomplete CoW finding on non-contrast enhanced magnetic resonance angiography and low cerebrovascular reserve has been documented as well [14]. Non-contrast enhanced magnetic resonance angiography that was used in our research, represents functional morphology of CoW as it displays only blood flow within the vessels [2]. Although numerous types of CoW morphology have been described, simplification to "complete" and "incomplete" CoW has been accepted for easier use in clinical practice [15]. It is evidenced that 25–30% of asymptomatic patients and 45–60% of symptomatic patients with carotid artery disease have incomplete CoW [16]. In symptomatic patients with significant ICA stenosis, if the incomplete CoW is present, there is an increased annual risk of stroke up to 13–17% [17, 18]. For asymptomatic patients with ICA stenosis, there is a lack of data from controlled prospective studies [19]. Retrospective post-hoc analyzes of a SMART group showed increased but not statistically significant risk of stroke in patients with "incomplete" CoW [14].

Our study showed that in patients with incomplete CoW, circulatory reserve at the side of ICA stenosis was significantly lower (median BHI = 0.62) compared to the patients whose MRA findings showed the complete CoW (BHI median = 0.88). Ass well BHI at the side of ICA stenosis was lower compared to the side opposite to the stenosis (BHI median = 1, 09). BHI in the group of patients with incomplete CoW tended to be lower than the proposed cut-off value for normal findings which is 0.69 [4].

Operative treatment resulted in the significant increase in BHI at the side of the stenosis both in groups of patients with complete and incomplete CoW. We registered both significant improvement circulatory reserve and normalization of the findings in the majority of patients in which BHI was below the threshold of 0.69. Such effect indicates that the revascularization of stenosed ICA removes the cause of impaired circulatory reserve and reduced vasomotor reactivity. More beneficial effect of surgical treatment we found to be in asymptomatic patients with incomplete CoW with more significant increase of BHI. For the opposed side, we found a trend of greater postoperative increase in BHI value in the group with complete CoW, which can be explained by the phenomenon of "stealing" from the healthy side over active collaterals that was present before the operation.

The literature emphasizes the importance of the effect of carotid endarterectomy on patients with extremely low parameters of cerebral vasoreactivity [20, 21]. Soinne et al. [22] founded beneficial effect of surgery only in symptomatic but not in asymptomatic patients. In aforementioned research, the asymptomatic patients were not stratified according to CoW morphology. A significant improvement of cerebrovascular reactivity after carotid endarterectomy in asymptomatic patients can be registered in both sides of brain [23, 24]. Surgical treatment of asymptomatic and symptomatic patients is followed by normalization of cerebrovascular reactivity and collateral flow in the CoW [25]. Improvement of cognitive function after carotid endarterectomy along with the improvement of cerebrovascular reactivity is emphasized [26]. Previously mentioned SMART study group was one of the rare studies that followed operated and non-operated asymptomatic patients with complete and incomplete CoW, still it was the retrospective study [14].

Apnea test and its modifications are easily available, and can be done in most vascular labs, it is also proved to be comparable to other methods of measurement of cerebrovascular reactivity [27]. Still there is a problem of its reliability especially in patients who are poorly compliant

with the procedure, which is recognized as a limitation of this study. Association of incomplete CoW and low cerebrovascular reserve is evident, as well as the effect of ICA revascularizations on cerebrovascular reactivity, but whether the presence of incomplete CoW can be observed as a risk feature in asymptomatic ICA stenosis is still to be debated.

CONCLUSIONS

In most asymptomatic patients, cerebrovascular reactivity restores to normal following carotid endarterectomy. Parameters of cerebrovascular reactivity are lower in patients with incomplete CoW and the increase after carotid endarterectomy is more significant in such patients. This suggests that carotid endarterectomy is more beneficial in asymptomatic patients with incomplete CoW in terms of cerebrovascular reactivity, but does it indicate clinical benefit in such patients (i.e. reduction of the risk of stroke) is yet to be approved by future prospective studies.

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Некомплетност Вилисовог прстена и цереброваскуларна реактивност код асимптоматских болесника пре и после каротидне ендартеректомије

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САЖЕТАК

Увод/Циљ Вилисов прстен представља најзначајнији колатерални пут којим се обезбеђује проток у хемисферама мозга код екстракранијалне каротидне стенозе или оклузије. У погледу присуства колатералног протока разликујемо комплетни и некомплетни Вилисов прстен. Болесници са екстракранијалном каротидном болешћу који имају некомплетан Вилисов прстен имају слабију цереброваскуларну реактивност и повишен ризик можданог удара. Цереброваскуларна реактивност описује резидуални капацитет за дилатацију церебралних крвних судова у условима можданe хипоперфузије.

Циљ ове студије био је да се утврде промене у цереброваскуларној реактивности после каротидне ендартеректомије код асимптоматских болесника са комплетним и некомплетним Вилисовим прстеном.

Методе Студија је укључила 97 болесника са асимптоматском каротидном екстракранијалном болешћу код којих смо одређивали цереброваскуларну реактивност методом апнеа теста пре и после каротидне ендартеректомије. Болесници су на основу налаза безконтрастне магнетне резонантне ангиографије били подељени у две групе: болесници са комплетним Вилисовим прстеном и болесници са некомплетним Вилисовим прстеном. Статистичка анализа подразумевала је дескриптивну статистику, униваријантну анализу и *ANOVA* за поређење параметара цереброваскуларне реактивности пре и после каротидне ендартеректомије.

Резултати Резултати су показали значајно повећање параметара цереброваскуларне реактивности на страни стенозе у обе групе болесника са комплетним Вилисовим прстеном (пораст *BHI* са 0,897 на 1,090; F (1,65) = 30,788, $p < 0,0005$, *parc.* $\eta^2 = 0,321$) и некомплетним Вилисовим прстеном (пораст *BHI* са 0,690 на 1,010; F (1,27) = 62,318, $p < 0,0005$, *parc.* $\eta^2 = 0,698$), при чему је пораст у групи са некомплетним Вилисовим прстеном био значајнији за $p = 0,035$ (F (1,92) = 4,557, *parc.* $\eta^2 = 0,047$).

Закључак Код већине асимптоматских болесника са каротидном болешћу каротидна ендартеректомија доводи до нормализације параметара цереброваскуларне реактивности. Цереброваскуларна реактивност је нижа код болесника који имају некомплетан Вилисов прстен, а пораст цереброваскуларне реактивности после операције израженији је код ових болесника.

Кључне речи: индекс задржавања даха; унутрашња каротидна артерија; екстракранијална каротидна болест; стратификација ризика код асимптоматских каротидних болесника

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effect of graduated elastic compression stockings on clinical findings, complications, and inflammatory and thrombotic markers in patients with superficial vein thrombophlebitis

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SUMARRY

Introduction/Objective The objective of the paper is an assessment of the effect of graduated elastic compression stockings on clinical findings, complications, and inflammatory and thrombotic markers in patients with superficial vein thrombophlebitis.

Methods This prospective study was conducted between January and July of 2017, at the Clinic for Vascular and Endovascular Surgery of the Clinical Centre of Serbia. All the patients were clinically examined, and color duplex ultrasonography of the superficial and deep venous systems was performed. In all cases, we follow clinical finding, inflammatory and thrombotic markers, and superficial vein thrombosis (SVT) complication.

Results SVT was detected in 60 patients (36 women, aged 23–75 years and 24 men, aged 18–76 years. Most patients were with unilateral, subacute, above-knee located SVT. Regarding the typical clinical symptoms of SVT, patients were divided into four groups. The majority of our patients (group D) had all the symptoms associated. Regarding the severity of SVT and risk factors, the patients were divided into a greater risk group (Group I) and a lesser risk group (Group II), and treated with low-molecular-weight heparin, aspirin and two classes of graduated elastic compression stockings regarding the level of SVT. Laboratory testing of inflammatory and thrombotic markers in patients with SVT was performed at the beginning and at the end of therapy.

Conclusions In treatment of SVT, higher class of graduated compression therapy has stronger influence in decrement of inflammatory and thrombotic factors and prompt and adequately chosen therapy of SVT allows stoppage and regression of the thrombotic process.

Keywords: graduated elastic compression stockings; inflammatory and thrombotic markers; superficial vein thrombophlebitis

INTRODUCTION

Acute superficial thrombophlebitis of the lower extremities is one of the most common vascular diseases affecting the population. Although it is generally considered a benign disease, it can be extended to the deep venous system and cause pulmonary embolism.

Superficial vein thrombophlebitis (SVT) frequently occurs in varicose veins. It can be caused by trauma, such as catheter insertion or direct intimal injury. It is believed that hidden infection in varicose veins is a potential factor for the development of thrombophlebitis, which might be exacerbated after operations, injection treatments, trauma, or exposure to radiation therapy. While considering factors leading to SVT, the clinician must remember all the components constituting Virchow's triad – namely intimal injury, stasis, and changes in blood coagulation [1, 2]. SVT manifests as a local pain, itching, tenderness, reddening of the skin, and hardening of the surrounding tissue [3].

The color duplex ultrasonography of superficial and deep veins is a highly reliable diagnostic method and has an important role in deciding between conservative and surgical treatment or follow-up of the patients who were operated on [4].

Conservative treatment of SVT depends on its etiology and extent, as well as the severity of symptoms. It usually implies platelet antiaggregation and anticoagulation therapy, combined with graduated elastic compression stockings (GECS) [5, 6].

This study was performed in order to estimate the effect of the GECS on the clinical finding, complication, and inflammatory and thrombotic markers in patients with SVT.

METHODS

This study was designed as a prospective study. It was conducted between January and July of 2011, at the Clinic for Vascular and Endovascular

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Surgery of the Clinical Centre of Serbia. This study was approved by the institutional ethics committee, and written consent was obtained from all the patients for the publication of the paper and any accompanying images.

The criterion for inclusion in this study was the presence of acute or subacute SVT, located below the knee or distally above the knee, but without propagation into deep or perforating veins. All the patients were clinically examined, after which color duplex ultrasonography of the superficial and deep venous systems was performed. All the cases were treated as outpatients.

Coagulation profile was examined in 10 patients. This included protein C activity level, protein S activity level, activated protein C resistance, antithrombin III level and activity, and lupus anticoagulant antibodies.

Classification of patients into groups was made based on estimation of the potential risk for spreading of thrombosis and affecting deep or perforating veins. The main criterions were level of SVT, proximity of perforating veins, as well as obesity, immobility and physical inactivity. According to this, the patients were classified into a group with greater risk (Group I) or lesser risk (Group II).

Patients in Group I were treated with low-molecular-weight heparin (LMWH) and those in Group II with aspirin (ASA). Patients in both groups have also been treated with GECS, class I (18–21 mmHg) or class II (23–32 mmHg) depending on the Clinical-Etiological-Anatomical-Pathophysiological classification. Patients with C0 and C1 stage were treated with class I, while patients with C2–C6 were treated with class II GECS.

The effect on the biochemical parameters, inflammatory and thrombotic markers (leukocyte number, D-dimmer, fibrinogen, C-reactive protein, alkaline phosphatase, creatine kinase, lactate dehydrogenase, gamma glutamyl transferase, alanine transaminase, and aspartate transaminase) was estimated 14 days after the initial examination.

All cases in which rapid propagation or propagation toward sapheno-femoral venous junction was detected were excluded from the study. Those patents were usually treated surgically (by performing ligation or crossectomy).

Data analysis was assessed using statistical evaluation in addition to various descriptive and analytic statistical methods (measures of central tendency, t-test, f-test, and others).

RESULTS

SVT was detected in 60 patients: 36 women (aged 23–75 years) and 24 men (aged 18–76 years). Group I consisted of 28 and Group II of 32 patients. No patient had a history of malignancy or was peripartum. No patient reported a history of trauma to the lower extremities. Patients' demographic characteristics are presented in Table 1.

Most patients were with unilateral, subacute, above-knee located SVT. Table 2 presents clinical characteristics of SVT.

Regarding the typical clinical symptoms of SVT, the patients were divided into four groups (Table 3). Patients in groups A, B, and C had isolated erythema, pain, or swelling. Majority of our patients (group D) had all symptoms associated.

Table 1. Demographic characteristics

Characteristic		Group I	Group II
Sex	Men	11	13
	Women	17	19
Mean Age		48.29	51.69

Table 2. Superficial vein thrombophlebitis (SVT) characteristics

Characteristics		Group I	Group II
Topographic map	Above knee	9	23
	Below knee	19	9
Type	Acute SVT	10	18
	Subacute SVT	18	14

Table 3. Clinical presentation of superficial vein thrombophlebitis

Group	Symptoms	n (%)
A	Erythema or inflammation	7 (11.7)
B	Pain, induration and tenderness	9 (15)
C	Swelling and tissue warmth	18 (30)
D	Symptoms associated	26 (43.3)
Total		60 (100)

Table 4. Patients' groups regarding therapy and class of graduated elastic compression

Group	Therapy, compression	n (%)
Group I	LMWH + class I	14 (23.3)
	LMWH + class II	14 (23.3)
Group II	ASA + class I	16 (26.7)
	ASA + class II	16 (26.7)
Total		60 (100)

ASA – acetylsalicylic acid; LMWH – low-molecular-weight heparin

Regarding the severity of SVT and risk factors, the patients were divided into a greater risk group (Group I) and a lesser risk group (Group II). Patients in Group I were treated with LMWH, while patients in Group II were treated with ASA. Patients were treated with two classes of GECS regarding the level of SVT. Patients with below-knee SVT were treated with class I compression, whereas the patients with above-knee SVT were treated with class II compression (Table 4).

Laboratory testing of inflammatory and thrombotic markers in patients with SVT was performed at the beginning and at the end of therapy (mean values are presented in Figure 1). All our patients with SVT had D-dimer value elevated over the baseline. Also, in all patients, increase in the values of inflammatory parameters, CRP and fibrinogen was observed.

After a two-week therapy, we have noticed that there was a subjective improvement in most patients (57 of them, 95.5%), with stoppage of thrombosis progression.

In two patients treated with ASA and class I GECS there was thrombus propagation into Cockett perforating veins. Afterwards, they were treated with LMWH, and eventually with oral anticoagulants.

One patient treated with LMWH and class II GECS suffered proximal propagation of SVT through sapheno-femoral junction into the common femoral vein. Two

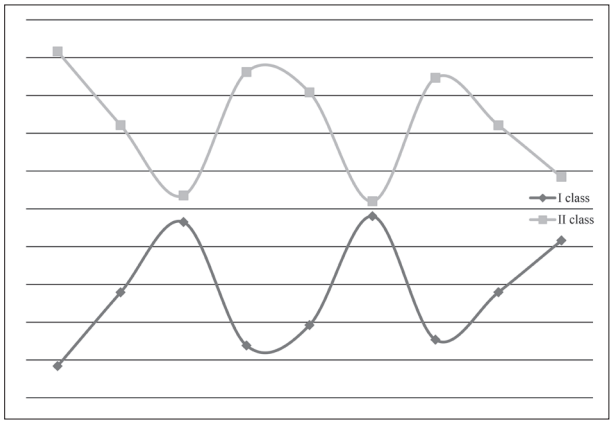

Figure 1. The graduated elastic compression stockings compression effects on inflammatory and thrombotic markers

months later, that patient had a malignant process in the lungs established.

None of our patients suffered a pulmonary embolism.

DISCUSSION

Pharmacological and mechanical methods are used in the prevention and therapy of superficial and deep vein thrombosis. Pharmacological methods alter the blood coagulation, while mechanical methods include pneumatic compression and, especially, GECS. The exact mechanism how GECS function remains partially unknown. It is assumed that graded circumferential pressure, combined with activity of muscles, causes propulsion of blood from superficial to deep venous system through perforating veins [5–8].

SVT is characterized by the formation of thrombi inside superficial veins, with involvement or occlusion of the lumen and inflammatory reaction along the venous path [9]. Inflammation and thrombosis are closely connected. Several clinical studies have examined the relation between levels of inflammatory markers and venous thrombosis. The common conclusion for all of them is that the risk of developing venous thrombosis is associated with elevations in plasma levels of CRP, interleukin 6 (IL-6) and IL-8, monocyte chemotactic protein 1, tumor necrosis factor alpha (TNF-α), and others. In the acute phase of SVT, a majority of inflammatory markers were increased, particularly hsCRP, IL-6 and TNF-α. This finding was expected, since inflammation represents one of the basic pathogenetic mechanisms of SVT and is not limited only to the vessel wall, but usually affects the surrounding tissue as well [10].

One of the recent studies has shown that CRP is elevated in patients with acute deep vein thrombosis (DVT) compared to controls, and that levels decline during the first few days of DVT treatment. Similar conclusions were made for IL-8 levels, leading to the conclusion that the thrombotic process produces a systemic inflammation. It is also believed that the decrement in levels of inflammatory factors is partly caused by heparin treatment (because of its anti-inflammatory effects) [11].

The fragments of the disintegrating fibrin in the clot are fibrin degradation products, one of which is D-dimer, which consists of variously sized pieces of cross-linked fibrin. Almost all patients with acute superficial or deep venous thrombosis have an elevated D-dimer level. An elevated D-dimer level is associated with many illnesses, and therefore is not specific to venous thromboembolism. D-dimer tests can have high sensitivity, which is useful because a normal test excludes the diagnosis of venous thromboembolism. D-dimer testing is most appropriate in the assessment of outpatients since the prevalence of disease and the likelihood of comorbidity are lower than in the inpatient population, making a test of exclusion particularly valuable. Therefore, it is often used in conjunction with clinical probability scoring or color duplex ultrasonography to reduce the need for further imaging [11, 12].

In the literature, few papers study the biochemical parameters of inflammation with the treatment of SVT. One of the earliest and most cited papers is a study in which De-Takats [13] speculated that dormant infection in varicose veins was a factor in the development of thrombophlebitis. The paper mentions the experience with the treatment of 1500 patients with resting infection using parenteral therapy.

All examined biochemical markers of inflammation (leukocyte number, CRP, and fibrinogen) were significantly reduced in Group I with ASA therapy, probably due to larger decrease in markers of inflammation with aspirin therapy, possibly because of anti-inflammatory effects of ASA.

The paper by Harenberg et al. [14] has shown a decrease of D-dimer during unfractionated heparin (UFH) and LMWH treatment of deep vein thrombosis. Also, in patients with acute venous thromboembolism (VTE), D-dimer was elevated and it decreased after three days of treatment with UFH or with LMWH, but remained above the normal levels for the first week of treatment. The role of the pretest clinical probability score and/or the D-dimer concentration in the diagnostic management of thrombophlebitis and/or DVT has been the objective of many studies. D-dimer testing is most appropriate in the assessment of outpatients because the prevalence of disease and the likelihood of comorbidity are lower than in inpatient populations, making a test of exclusion particularly valuable [15]. We found that no significant decrease of D-dimer was noted in both groups, but all values remained above the cut-off value.

Uncu [16] has evaluated the efficacy of LMWH compared to combined therapy of LMWH with non-steroidal anti-inflammatory drugs (NSAIDs) in treatment of SVT. He has found that significant improvements were achieved for both groups after the treatment in terms of all SVT symptoms. The results of their study suggest that the combined therapy of LMWH with an anti-inflammatory agent is more effective than LMWH, and that it might be an important option in the standard treatment of SVT.

Yasim et al. [17] evaluated serum concentrations of procoagulant, endothelial, and oxidative stress markers in early primary varicose veins compared to healthy volunteers. They investigated vascular endothelial marker levels and the effect of endothelial damage on coagulation parameters

and vasodilator substances to determine metabolic markers of oxidative stress in patients with varicose veins and vascular endothelial damage caused by oxidative stress.

They did not find a statistically significant difference between the study group and the control group. Their conclusion was that systemic increased oxidative stress seems not to be related to the early stages of chronic venous insufficiency.

Poredos and Jezovnik [18] noted that inflammation has been accepted as a possible mechanism through which different factors cause formation of thrombus. They suggested that inflammation of the vein wall initiates thrombus formation, and that inflammation and coagulation systems are coupled by a common activation pathway. Therefore, the key event in the initiation of venous thrombus formation is most probably vein wall inflammation, but expected relationship between inflammatory markers as indicators of inflammatory process and clinical VTE has not been recognized yet. In their opinion, C-reactive protein does not appear to be useful in predicting future venous thrombosis or to be useful in the diagnosis of VTE [17]. In patients with SVT, levels of inflammatory markers are increased in the acute phase of the disease and most of the markers significantly decrease after 12 weeks. Also, levels of circulating inflammatory markers are negatively related to the recanalization rate of thrombosed superficial veins, which indicates that inflammation inhibits the resolution of thrombus and the recanalization of occluded veins [18].

According to the results of the present trial, which are supported by coherent data from the literature, it is not justified to recommend compression stockings in addition to LMWH and NSAIDs for prolonged time periods, but they might have beneficial effects early in the disease process [19].

GECS provide the graded compression to the leg, highest at the level of ankle. They assist the calf muscle pump and reduce elevated venous tension and valvular reflux. The final effect is reduction of edema, improvement of tissue microcirculation, and prevention of development of skin lesions. The same effect is documented with using knee-length and thigh-length compression stockings; however, knee-length stockings are easier to apply and wear. Existing studies investigating the effect of GECS in patients with chronic venous disease have been graded as having low quality, while a Cochrane review concluded that there is insufficient high quality evidence to determine whether compression stockings are effective as the sole and initial treatment of varicose veins [20].

Some studies also confirm that compression stocking therapy in the varicose vein wall may change the levels of biomarkers associated with vein insufficiency [21]. A higher level of class II GECS in our study led to a significant reduction of symptoms, equivalent to a greater effect on venous hypertension.

CONCLUSION

1. D-dimer is a successful diagnostic test in the initial phase and recovery phase.
2. In treatment of superficial venous thrombosis, higher class of graduated compression therapy has stronger influence in decrement of inflammatory and thrombotic factors.
3. The prompt and adequately chosen therapy of superficial venous thrombosis allows stoppage and regression of thrombotic process.
4. Elastic bandage combined with an anticoagulant therapy with anti-inflammatory drugs is the method of choice.

Conflict of interest: None declared.

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Утицај градуисане еластичне компресивне бандаже на клинички налаз, компликације, као и на маркере инфламације и тромбозе код болесника са површним венским тромбофлебитисом

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САЖЕТАК

Увод/Циљ Циљ рада је процена утицаја градуисаних еластичних компресивних чарапа на клинички налаз, компликације, као и на маркере инфламације и тромбозе код болесника са површним тромбофлебитисом.

Методе Ова проспективна студија је спровођена од јануара до јула 2017. године на Клиници за васкуларну и ендоваскуларну хирургију Клиничког центра Србије. Сви болесници су подвргнути клиничком прегледу, а после тога је учињена и колор-дуплекс ултрасонографија површног и дубоког венског система. Код свих болесника праћени су клинички налаз, маркери инфламације и тромбозе, као и компликације површног венског тромбофлебитиса (ПВТ).

Резултати ПВТ је дијагностикован код 60 болесника (36 жена старости од 23 до 75 година и 24 мушкарца старости од 18 до 76 година). Већина болесника је имала унилатерални, субакутни ПВТ локализован изнад колена. Имајући у виду клиничке симптоме, болесници су били подељени у четири групе. Већина болесника у нашој студији (група Д) имала је све удружене симптоме ПВТ. Узимајући у обзир степен ПВТ и факторе ризика, болесници су били подељени у групу са повишеним ризиком (група II) и у групу са мањим ризиком (група I) и третирани су применом хепарина мале молекулске масе, аспирином и са две класе градуисане компресивне терапије узимајући у обзир ниво ПВТ. Лабораторијско испитивање инфламаторних и тромботских маркера код болесника са ПВТ обављено је пре започињања и по завршетку терапије.

Закључак У третману ПВТ виши степен градуисане компресивне терапије има значајнији утицај на смањење вредности маркера инфламације и тромбозе, а брза и адекватно одабрана терапија ПВТ омогућава заустављање и регресију тромботског процеса.

Кључне речи: градуисане еластичне компресивне чарапе; маркери инфламације и тромбозе; површни венски тромбофлебитис

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical features of non-classical celiac disease in children and adolescents

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SUMMARY

Introduction/Objective Nonclassical celiac disease (CD) is characterized by a very heterogeneous and non-specific clinical presentation.
The aim of this study was to determine the basic symptoms and clinical signs of this CD subtype in children and adolescents

Methods The study was based on a sample of 58 children and adolescent, 38 female and 20 male, ages 1.75 to 17.75 (10.01 ± 4.62) years with a nonclassical CD diagnosed according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition criteria from 1990 and 2012.

Results Except four patients who were between the ages of 1.75 to 2.50 years, all others were older than three years. The main clinical symptoms and signs suggestive of non-classical CD were anemia caused by iron deficiency (48.28%), short stature (34.48%), and intermittent abdominal pain (18.97%), anorexia with stagnation or weight loss (13.79%), and chronic constipation (6.9%). Thirty patients had one symptom or sign of the disease, 15 had two and 13 had three. In addition, 12 patients had dental enamel hypoplasia, 18 sideropenia without anemia and five mild isolated hypertransaminasemia. A gluten-free diet, apart from the dental enamel hypoplasia, has resulted in the withdrawal of all indicators of the disease.

Conclusion The main symptoms and clinical signs of nonclassical CD in children and adolescents were iron deficiency anemia, short stature and intermittent abdominal pain, and less frequently anorexia with stagnation or weight loss and chronic constipation. Excluding dental enamel hypoplasia, a gluten-free diet leads to a complete recovery of the patient.

Keywords: nonclassical celiac disease; children and adolescents; symptoms and signs

INTRODUCTION

Celiac disease (CD) is one of the most frequent autoimmune diseases of the modern man [1, 2, 3]. It primarily occurs in white population (~1%) as a result of polygenic predisposition and exposure to gluten and related prolamins of wheat, rye, and barley [1, 4, 5, 6]. The basis of the disease and the key finding in its diagnostics is gluten-sensitive enteropathy, i.e., a non-specific inflammation of the small intestinal mucosa that resolves by gluten-free diet [6–9]. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by different extraintestinal manifestations [8–11]. From the clinical aspect, CD is divided into two basic types: symptomatic and asymptomatic [10]. Symptomatic disease is further differentiated to classical (typical) and non-classical (atypical) [8, 9, 10]. Classical CD is characterized by poor appetite, chronic diarrhea, failure to thrive, muscle wasting, abdominal distension and irritability, while non-classical forms of the disease are dominated by atypical digestive and/or various extraintestinal manifestations, such as constipation, abdominal pain episodes, isolated hypertransaminasemia, apthous stomatitis, iron deficiency anemia, short stature, delayed puberty, decreased bone density (osteopenia or osteoporosis), alopecia, chronic fatigue, anxiety, depression, and others [10–16]. The classic CD form is most often seen at the age of 9–36 months and non-classical in later childhood, adolescence and in adulthood [8, 17].

The aim of our study was to analyze the symptoms and clinical signs of non-classical CD in children and adolescents. In addition, the degree of damage to the small intestinal mucosa obtained by enterobiopsy in this CD subtypes was also considered.

METHODS

The objectives of the study were considered on a sample of 58 children (38 female; with age

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range 1.75–17.75 years, mean 10.01 ± 4.62 years) nonclassical CD confirmed in two of the five reference centers in Serbia during the period from January 1994 to December 2019. The study protocol was approved by the local Committees on Ethics. The diagnosis of CD was based on the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) from 1989 and on the new ESPGHAN guidelines published in 2012 [9, 18]. The Oslo definitions for CD were used for differentiation of non-classical and classical type of the disease [10].

In each patient's anamnesis, the exact data related to the onset, duration and type of symptoms on the clinical signs of the underlying disease are required, while in the context of the complete clinical examination each of them accurately measured body length/height and weight and the obtained values compared to the standard for the appropriate age and gender [19]. The values of body length/height are expressed in percentages, and deviations in body weight in relation to the ideal in percent. Additionally, in all patients with short stature, in order to evaluate the maturity of the bone, the x-ray of the left hand "en face" was performed. The used reference standard for determining bone age was the Greulich and Pyle Atlas [20].

Blood count, serum iron and ferritin concentrations and other laboratory nutritional indicators (total proteins, albumin, urea, total cholesterol, 3-glyceride, calcium, phosphorus and alkaline phosphatase), as well as the liver function test (bilirubinemia, total and conjugated, ALT, AST and gamma-glutamyl transferase) were determined by standard laboratory methods from a blood portion taken in the morning and before breakfast. The obtained findings are compared with standard reference values [21]. The diagnostic criterion for anemia was level of the hemoglobin (Hb) for children up to the age of five below 110 g/l for those 5–11 years below 115 g/l and for those over 11 years of 120 g/l [22]. The Hb value of 100–109 g/l was classified as a mild anemia, 70–99 g/l moderate, and below 70 g/l severe [22]. The reference value for the iron serum concentration was 10.7–31.3 μmol/l [21]. In patients with hypertransaminasemia, the serum creatine phosphokinase activity was determined, so any of them, in addition to the absence of cholestas and hemolysis, had no elements for rhabdomyolysis. In addition, none received any of the medications followed by an increase in the serum level of transaminases, nor did it have an intercurrent infection that would produce this effect.

In addition to enterobiopsy with pathohistological analysis of small intestine mucosa as a basis for diagnosis of the disease, which was done in all 58 patients, in 45 of them, the level of anti-tissue transglutaminase (anti-TTG) antibodies was determined, and in 11 the presence of HLA DQ2 and HLA DQ8 genotype. Classification of pathohistological changes of the small intestinal mucosa was performed according to modified Marsh criteria on infiltrative (I), infiltrative-hyperplastic (II) destructive (III) and hypoplastic (IV) type [23]. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb) and total (IIIc).

RESULTS

Except for four patients who were between the ages 1.75–2.50, out of 58 patients, all the others were over three years of age (Figure 1). The main clinical symptoms and signs suggestive of non-classical CD were anemia caused by iron deficiency (48.28%), short stature (34.48%), and intermittent abdominal pain (18.97%), anorexia with stagnation or weight loss (13.79%), and chronic constipation (6.9%) (Table 1). None of the patients had diarrhea. Most patients, 30 (51.72%), had one symptom or a sign of the disease, 15 had two and 13 had three. In addition, in 18 (30.03%) patients sideropenia without anemia was found, in 12 (20.69%) dental enamel hypoplasia, and in five mild isolated hypertransaminasemia (up to 1.5 times above the reference value).

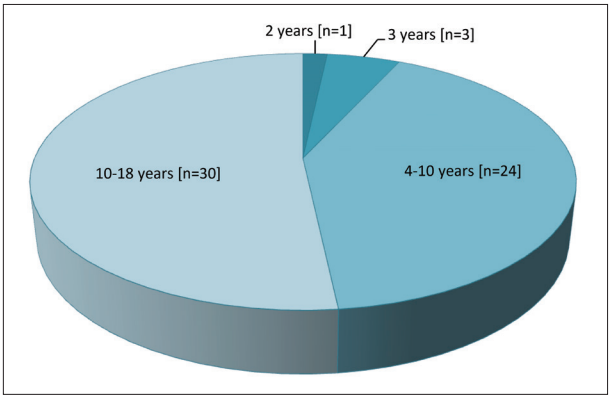

Figure 1. Distribution of our patients by age (n = 58)

Table 1. Symptoms and clinical signs that indicated nonclassical CD in our patients (n = 58)

Iron deficiency anemia	28
Short stature	20
Intermittent abdominal pain (> 2 months)	11
Anorexia and stagnation or weight loss	8
Chronic constipation (> 2 months)	4
Alopecia areata	2
Recurrent aphthous stomatitis	1
Dermatitis herpetiformis	1

The Hb values in the patient group with anemia ranged from 56–114 (93.11 ± 15.02) g/l. In 12 out of 28 patients, anemia was mild, moderate in 13, and severe in three patients. Serum iron levels in this group of patients were 1.2–10.5 (5.24 ± 2.33) μmol/l.

The degree of longitudinal growth retardation compared to the average for the appropriate age and sex in our 20 patients ranged from -10.5 to -19.22% (-13.65 ± 2.07%). In 15 patients with short stature, the bone marrow was slowed 0.5–2.5 (1.57 ± 0.65) years. Other clinical and standard laboratory findings were within normal limits.

In all 45 patients who were tested for anti-TTG antibodies, level values were elevated. In 43 of them, the anti-TTG IgA class ranged from 28.6 to over 800 U/ml, while in two with a selective IgA deficiency, a high level of anti-TTG antibody IgG class (75.8 U/ml and over 1000 U/ml) was

recorded. In all 11 patients tested for "celiac HLA", the presence of HLA DQ2 antigen was determined. Histological analysis of small intestinal mucus samples in 54 (93.10%) patients revealed a destructive enteropathy, in 15 partial (IIIa), in 23 subtotals (IIIb) and in 16 total (IIIc), while in only four it was infiltrative-hyperplastic (II). In addition to enteropathy, in three of our patients, lymphocytic gastritis has been identified.

With a gluten-free diet and oral iron administration in all patients with anemia, normal Hb and serum iron levels were registered within 2–4.5 months. Also, during 0.5–2 years of a gluten-free child, none of the patients with short stature had a height below the third percentile. A gluten-free diet, apart from the dental enamel hypoplasia, has resulted in the elimination of other symptoms and signs of the disease.

DISCUSSION

CD is etiopathogenetically multifactorial and clinically very heterogeneous autoimmune disease [1, 8]. With the development and application of modern highly sensitive and specific serological tests, in addition to clinically classic forms of the disease, today it is sovereign and more frequently diagnosed and its non-classical (atypical) and asymptomatic forms [1, 11]. Contribution to the improvement of diagnostics CD has also tested for the presence of HLA DQ2 and HLA DQ8 antigens as the main immunogenic markers of the disease [1, 11]. Although elevated levels of autoantibodies to tissue transglutaminase and endomycin and antibodies to deamidated gliadin, as well as the absence of HLA DQ2 and HLA DQ8 antigens do not have an absolute diagnostic value, their use is important in the selection of patients for enterobiopsy that remains the gold standard in the CD diagnostics [1, 9]. Bearing in mind the symptomatology that is also encountered in other pathological conditions, for the sake of reliable diagnostics, all of our patients were subjected to enterobiopsy with a pathohistological analysis of the small intestine mucosa. Excluding four patients, with verified infiltrative-hyperplastic enteropathy, in all other damage of the small intestinal mucosa was destructive type.

Unlike adults, CD in children is, in general, a reversible disease [11, 16, 24]. The only exception is dental enamel hypoplasia and in large part the gluten-induced cerebellar ataxia, which remains permanently, as well as short stature and reduced bone density if the disease is detected at the final stage of adolescence [11, 24, 25]. In addition, diagnostics and adequate CD treatment in childhood also prevent its complications that occur during adulthood, such as infertility in the generative period and fragility of the skeleton, peripheral neuropathy, dementia, and some malignancies in later years [1, 11]. That is why its detection and adequate treatment in the developmental period are of particular importance. A gluten-free diet as a key therapeutic measure, apart from the dental enamel hypoplasia, has resulted in the elimination of all indicators of the disease in our patients.

Nonclassical type of CD is usually discovered in children over the age of three [8, 17]. Except for four out of 58 patients, one in the second year and three in the third year, all others were older than three years.

Iron deficiency anemia and short stature is the most common extraintestinal manifestations of the pediatric CD, including its nonclassical subtype [11, 25, 26, 27]. In some cases, iron deficiency anemia or short stature may be the only signs of a CD [27, 28]. Other symptoms and signs of nonclassical CD, such as chronic constipation, recurrent abdominal pain, isolated hypertransaminasemia, osteopenia or osteoporosis, apthous stomatitis, alopecia and others, are significantly less common or rare [11, 25, 26]. Although these symptoms and clinical signs do not have a specific character, in the context of their consideration, the nonclassical CD should be considered as a possible cause.

The basis of the iron deficiency in CD is the absorption disorder caused by the morphological and functional damage of the proximal part of the small intestine mucosa, i.e., in the segment where iron is absorbed [29]. As with other inflammatory diseases, additional involvement in iron malabsorption has a suppressive effect of hepcidin [29]. Negative iron balance in the CD is also significantly contributed by its insufficient intake caused by anorexia. In our group of patients, iron deficiency anemia was registered in 28 (48.28%) cases, of which in 12 (20.69%) as the only sign of CD. In addition, 18 (33.33%) patients were found to have sideropenia without anemia.

The pathogenesis of short stature in CD is a consequence of a negative nutritional balance, and possibly other factors, such as abnormalities in the growth hormone-insulin-like growth factor axis and/or thyroid function [11, 27]. It is usually associated with a delayed maturation, anemia, or some of its other symptoms and signs. Although it is a frequent sign of non-classical CD, impaired growth is particularly common in younger children with a classical form of the disease [11, 25, 26]. In our group of patients with nonclassical CD, short stature was established in 20 (34.48%) patients. In addition, in 15 of them it was identified delayed maturation and in 10 iron deficiency anemia.

Similar to the experiences of other authors, recurrent abdominal pain, vague loss of appetite with stagnation in body weight, isolated hypertransaminasemia and chronic constipation, either as the only manifestation or with associated anemia, as well as hypoplasia of the dental enamel, were relatively frequent abnormalities in the group of our patients with nonclassical subtype of CD [11, 16, 24].

Other findings, such as alopecia areata, recurrent aphthous stomatitis and dermatitis herpetiformis, were rare manifestations of a nonclassical CD and in a group of our patients [11, 16]. In addition to enteropathy, in three of our patients, lymphocytic gastritis was identified as not-so-rare and on a gluten-free diet reversible finding in the CD [30].

CONCLUSION

Nonclassical CD is characterized by a very heterogeneous and non-specific clinical presentation. According to our

findings, the main features of this subtype of CD are iron deficiency anemia and short stature, and then recurrent abdominal pain, vague loss of appetite with stagnation in body weight and chronic constipation. Although these symptoms and clinical signs occur in many other pathological conditions, as part of their etiological consideration must be borne in mind and nonclassical CD. Timely diagnostics and adequate therapy of nonclassical CD in developmental period has a special significance that is reflected not only in removing immediate problems, but also in the prevention of complications that occur in later stages of life.

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Conflict of interest: None declared.

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Клинички симптоми некласичне целијачне болести код деце и адолесцената

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САЖЕТАК

Увод/Циљ Некласичну целијачну болест (ЦБ) карактерише врло хетерогено и неспецифично клиничко испољавање. Циљ ове студије био је да се утврде основни симптоми и клинички знаци овог подтипа ЦБ код деце и адолесцената.

Методе Студија је базирана на узорку од 58 деце и адолесцената, 38 женског и 20 мушког пола, узраста од 1,75 до 17,75 (10,01 ± 4,62) година, са некласичном ЦБ дијагностикованом у складу са критеријумима Европског удружења за дечју гастроентерологију из 1990. и 2012. године.

Резултати Осим четворо болесника који су били у доби од 1,75 до 2,50 година, сви остали су били старији од три године. Главни клинички симптоми и знаци који су указивали на некласичну ЦБ били су анемија узрокована недостатком гвожђа (48,28%), низак раст (34,48%), повремени болови у трбуху (18,97%), анорексија са застојем или губитком телесне тежине (13,79%) и хронична опстипација (6,90%). Један симптом или знак болести имало је 30 болесника, 15 два и 13 три. Поред тога, 18 болесника су имали сидеропенију без анемије, 12 хипоплазију зубне глеђи и пет благу изоловану хипертрансаминасемију. Дијета без глутена, осим хипоплазије зубне глеђи, резултирала је повлачењем свих показатеља болести.

Закључак Главни симптоми и клинички знаци некласичне ЦБ код деце и адолесцената су анемија узрокована недостатком гвожђа, низак раст и повремени болови у трбуху, а ређе анорексија са стагнацијом или губитком тежине и хронична опстипација. Изузимајући хипоплазију зубне глеђи, дијета без глутена доводи до потпуног опоравка болесника.

Кључне речи: некласична целијачна болест; деца и адолесценти; симптоми и знаци

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Influence of sodium valproate treatment on body mass and insulin resistance parameters in children with epilepsy

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SUMMARY

Introduction/Objective One of the main side effects in patients undergoing valproic acid treatment is weight gain, which might be the reason for drug discontinuation, especially in adolescent girls, and it also has to be considered before introducing the drug.
The main goal of our study is to investigate a possible influence of antiepileptic therapy with sodium valproate on weight and glucose homeostasis in pediatric patients with epilepsy.

Methods The investigation included 49 healthy children with recently diagnosed epilepsy. We measured height, weight, and serum 12-hour overnight fasting glucose and insulin level before initiation and after six- and 12-month valproic acid treatment periods. The body mass index and homeostasis model assessment indexes were calculated for each patient and correlated after the initiation of therapy and after six and 12 months of therapy.

Results We found that children significantly gained weight with statistical significance ($p < 0.01$) even after six months of therapy with a significant glucose metabolism change and statistical difference in average serum glucose and insulin levels ($p < 0.05$).

Conclusion Our results show that a 12-month treatment with valproic acid in children with epilepsy has a great impact on weight gain and glucose homeostasis and metabolism. We strongly recommend that all children with recently diagnosed epilepsy at the initiation of valproate therapy should be closely monitored on a six-month basis. Consultations with a nutritionist is advised especially in children with a preexisting body weight problem.

Keywords: valproic acid; child epilepsy; insulin; weight; HOMA

INTRODUCTION

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [1, 2]. The epilepsy syndrome cluster of features incorporates seizure types, electroencephalogram (EEG), and imaging features that tend to occur together [3]. Factors that contribute to an epilepsy syndrome include the age of onset, remission, triggers, diurnal variation, intellectual and psychiatric dysfunction, EEG findings, imaging studies, family history, and genetics.

Children epilepsy prevalence is estimated to 0.5–4% of children population, depending on countries and world regions. The incidence of epilepsy differs by age and is the highest in the first year of life with a descending trend as the children get older. The data on annual incidence show discrepancies among world regions and vary 33–82 per 100,000 children [4, 5].

The medical approach and treatment of childhood epilepsy differs from epilepsy in adulthood due to different etiology, seizure semiology, existence of specific epileptic syndromes of childhood, comorbidities, child development. Childhood epilepsies that are pharmacoresistant have a great impact on psychomotor development, cognition, and are a great burden for the family of the child. [6]

The aim of epilepsy treatment is to achieve a total or optimal seizure control and to establish a good quality of life for patients with epilepsy [7].

A long-time treatment with antiepileptic drugs in childhood has a great risk of side effects that can cause damage to the child's development and health and can be a burden to health in adulthood. The experience and close monitoring of patients with a long-time antiepileptic treatment is of great importance in the pediatric epilepsy practice.

One of the most widely used antiepileptic drug in children and adults is valproic acid / sodium valproate (VPA). Valproate has multiple mechanisms of action, including γ-aminobutyric acid (GABA) potentiation, blocking of T-type calcium channels, and blocking of sodium channels. One of the most observed side effects in clinical practice of VPA treatment is weight gain [8, 9]. The incidence of this side effect differs 10–70% in child population among authors in the published data [10, 11].

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Transient weight gain can lead to a chronic medical problem – obesity. Childhood obesity is a well-defined independent risk factor for increased morbidity for the cardiovascular disease in adulthood [12]. It is also often related to metabolic and lipid disorders, hypertension, atherogenesis and diabetes. Metabolic syndrome is a nowadays a well-defined entity, which has a high risk of cardiovascular morbidity and diabetes mellitus type 2 [13]. It is defined and diagnosed in case of visceral / central obesity, lipid metabolism disorder (elevated low-density lipoprotein cholesterol, triglycerides, lower high-density lipoprotein cholesterol), glucose intolerance, and hypertension [14].

Therefore, it is of great importance to recognize and identify children with an increased risk of metabolic syndrome, with its impact for comorbidities that are associated with it in adulthood. One of the parameters for metabolic syndrome is insulin resistance, which is a strong prediction factor for the development of diabetes mellitus type 2 [15].

One of the suggested mathematical models in insulin resistance evaluation is the Homeostasis Model Assessment (HOMA) index, developed by Matthews et al. [16]. The HOMA index is calculated according to the following formula: Glycemia (mmol/l) × serum insulin level (μU/ml) / 22.5. The International Diabetes Federation defined a criteria for recognizing groups of patients with a high risk of developing metabolic syndrome in childhood [17].

The aim of the study was to investigate the influence of VPA as monotherapy in children with recently diagnosed epilepsy to body weight and insulin resistance parameters, its impact on glycoregulation, and on insulin resistance development in childhood. The parameters were obtained after six and 12 months of VPA therapy in otherwise healthy children with recently diagnosed epilepsy.

METHODS

The investigation included 49 healthy children with recently diagnosed epilepsy. After the diagnosis of epilepsy was made (two unprovoked events confirmed as seizures and epileptiform EEG changes), a monotherapy with VPA was initiated.

Anthropometric parameters were analyzed – body height and weight and body mass index (BMI) were calculated using the formula BMI = $^{BM}/_{BH^2}$. All the patients were classified for puberty stage using the Tanner method. Pubic and axillary hair was examined, and so was breast development in girls, and genitals and testicle volume in boys. All children were classified according to the Tanner stages 1–4. Prepubertal children had Tanner stage 1 (pubic hair and testicle volume for boys and pubic hair and breast development for girls). The pubertal group included children with any of the sex characteristics of Tanner stage 2. Every child had a blood sample collected at 08:00 am, before the meal, after a 12-hour overnight fasting, and before the morning dose of VPA. Blood samples of glucose, insulin, and valproic acid level were taken. Using the mathematical model, the HOMA index (insulin resistance index) was calculated for each patient. The valproic acid serum level was used in statistical analysis to establish the variability among patients and to evaluate a correlation between the valproic acid serum level and other investigated parameters.

Sampling was made at the initiation of therapy, after six months and 12 months of continuous therapy with VPA. Samples were collected at 08:00 am, after a 12-hour night fasting and before the morning dose of VPA was administered.

The exclusion criteria were as follows: obese children (BMI more than 25 kg/m^2 before the initiation of therapy), children with diagnosed chromosomal anomalies, children with a chronic inflammatory autoimmune disease, children with congenital or chronic heart, lungs, liver and kidney diseases, which can influence glucose and lipid metabolism. Children with chronic neurological conditions (cerebral palsy, congenital neurological disease) and children with any finding other than normal on brain computed tomography or magnetic resonance imaging were also excluded.

Data were collected and analyzed using computer program IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and presented in tables and graphs.

The statistical analysis used the arithmetic mean; for the parametric data and difference testing, the t-test and Fisher ANOVA, χ^2 test were used. For non-parametric data, the Mann–Whitney, the Wilcoxon, and the Freidman and Kruskal–Wallis tests were used. The correlation was investigated using the Pearson and Spearman correlation.

This investigation was approved by the University Children's Ethics Committee – number 017 13/77 on April 9, 2019.

RESULTS

A total of 49 children were investigated. The average age at the time of the VPA therapy initiation was nine years and nine months. The patients were grouped according to their age and presence of sex characteristics (puberty). Statistical analysis of all groups showed no statistical difference between the investigated groups. The distribution of serum concentration of VPA after six and 12 months of therapy showed no statistical difference ($p > 0.05$), which proved that all of the investigated children received the drug in a similar therapeutic range.

The average body mass at the initiation therapy was 40.88 kg. After six months and 12 months of therapy the average body mass increased to 43.53 kg and 47.2 kg, respectively. Statistical analysis showed that there was a highly statistically proven difference between these three groups ($p < 0.01$), which indicates that the children gained weight significantly. This is more obvious when BMI is calculated for each investigated patient (Figure 1). A significant increase in BMI is seen after six and 12 months of therapy, respectively ($p < 0.01$).

The average patient serum glucose level before the initiation of the therapy was 4.66 mmol/l. A significant

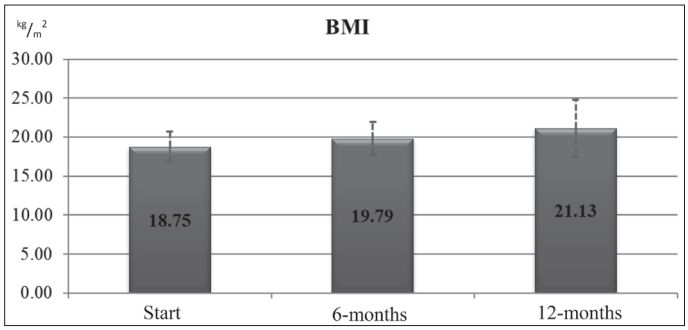

Figure 1. Median values of body mass index distribution of patients at the initiation of therapy, after six and 12 months of continuous anti-epileptic drug therapy

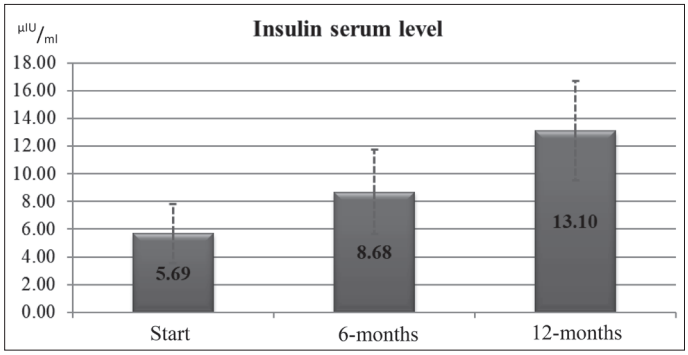

Figure 2. Average serum insulin levels distribution at the initiation of therapy, after six and 12 months of continuous anti-epileptic drug therapy

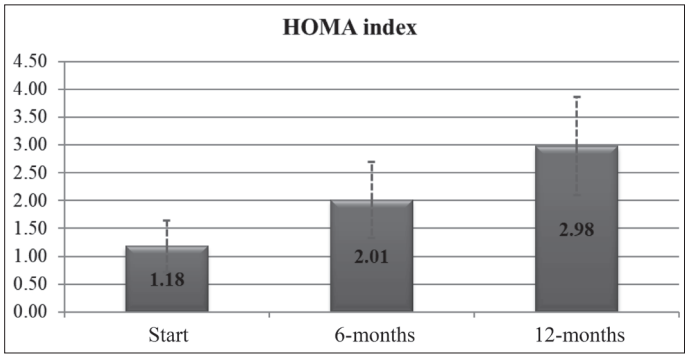

Figure 3. Average homeostasis model assessment – insulin resistance (HOMA) values distribution of patients at the initiation of therapy, after six and 12 months of continuous anti-epileptic drug therapy

increase after six and 12 months of continuous valproic acid therapy was observed, with the average fasting glucose level of 4.94 mmol/l and 4.97 mmol/l, respectively. This difference showed a statistically significant difference between these three groups of parameters ($p < 0.05$).

The average serum insulin level at the initiation of therapy was 5.69 μU/ml. After six and 12 months of continuous anti-epileptic drug, the average serum insulin levels were 8.68 μU/ml and 13.1 μU/ml, respectively. There was a statistically significant difference between these three groups of parameters ($p < 0.05$) (Figure 2).

The calculated average HOMA value at the initiation of therapy was 1.18. After six and 12 months of continuous VPA therapy, the average HOMA values were 2.01 and 2.98, respectively (Figure 3). Analysis shows that there is

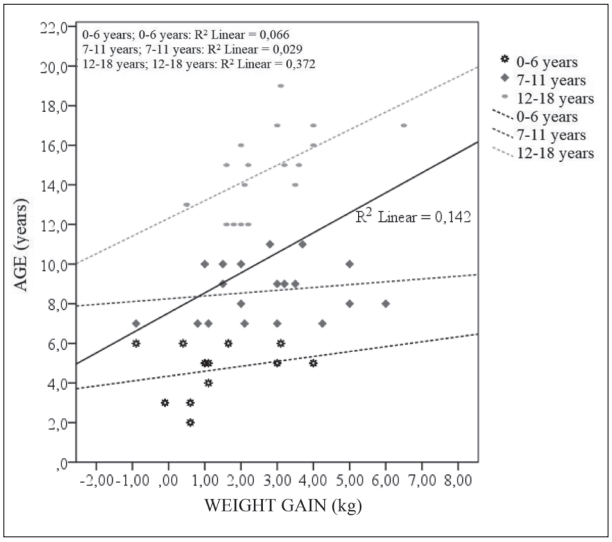

Figure 4. Weight change after 12 months of anti-epileptic drug in correlation to age

a statistically significant difference between these three groups of parameters ($p < 0.05$).

A correlation of weight change after 12 months of anti-epileptic drug therapy between three age groups of patients showed that older children gain weight more than children at a younger age (Figure 4).

When correlating the influence of weight change in correlation to age, a statistically significant difference was shown between these three groups, with the highest statistical difference between the preschool (0–7 years) and the school group (older than seven years) of children ($p < 0.05$) (Table 1). The analysis of sex in relation to weight gain showed that there was no significant difference between boys and girls ($p > 0.05$). Pubertal status analysis also showed that there was no statistical difference in weight gain among pre-pubertal and pubertal children ($p > 0.05$).

Table 1. Correlation of weight change after 12 months of anti-epileptic drug therapy between three groups of patients in correlation to their age

Age group (years)	Age group (years)	Mean Difference	SE	p	95% CI
					Lower boundary
0–6	7–11	-1.36469*	0.56736	0.020	-2.5067
	12–18	-1.33750*	0.57343	0.024	-2.4918
7–11	0–6	1.36469*	0.56736	0.020	0.2227
	12–18	0.02719	0.50610	0.957	-0.9915
12–18	0–6	1.33750*	0.57343	0.024	0.1832
	7–11	-0.02719	0.50610	0.957	-1.0459

SE – standard error;
*the mean difference is significant at the 0.05 level

DISCUSSION

Our investigation included 49 children, with the average age of nine years and nine months. The investigated group of children was cohort in correlation to sex, age (preschool 0–7 years, elementary school 8–12 years, and adolescents 13–18 years) and the puberty status. All of the children received VPA in similar therapeutic doses, with no significant difference between the serum levels of valproic acid for each child. This is important to emphasize, since it excludes the possible bias of VPA doses to investigated side effects.

The investigated group of children was observed over a one-year period. The results showed that the average weight has increased by 2.5 kg after six months, with a further average increase of 6 kg after a year of therapy ($p < 0.01$). The calculated BMI for each patient has shown a statistically significant increase on average after six and 12 months of therapy ($p < 0.01$). Our results are concordant with the results found in other authors' investigations – Sonmez et al. [18], Verrotti et al. [19], Egunsola et al. [20], Masuccio et al. [21], and Ferrara et al. [22] also found a significant increase in weight and BMI in VPA investigational group after six and 12 months of monotherapy. Publications investigating this effect of valproic acid therapy on subsequent weight gain show different findings for children and for adults. Bosnak et al. [23], who investigated a group of 56 children, did not prove significance in calculated Z score for the period of 40 months. Sharpe et al. [10] found a significant increase in body mass in 24% of investigated children. Wirrell et al. [11] found that out of the group of children with significant weight gain 12–19% became obese, with weight more than 95th percentile for age. Among children, the publication data shows increased weight gain in the group of female adolescents [21]. As for the Tanner stage, our results did not show a significant difference in weight gain in prepubertal and pubertal children, although an increased trend of weight gain has been observed in pubertal adolescents ($p > 0.05$). Sex did not play a significant role in weight gain either, since both groups – boys and girls – gained weight at the same pace ($p > 0.05$).

The exact mechanism of the effect of valproic acid on weight gain is still not clearly defined. Sidhu et al. [24] found that a group of patients treated with valproate had a significant increase in HOMA and a decrease in adiponectin levels and proposed that valproate induced hypoadiponectinemia, which correlates with insulin resistance. Kanemura et al. [25] investigated the effect of valproic acid on the serum insulin and glucose level and their correlation and concluded that one of the possible effect was through disturbed glycoregulation. Our results showed that after 12 month of therapy with valproic acid, a significant disruption in glycoregulation appeared and the average serum glucose level (mmol/l) was higher and showed a statistical significance after 12 months as compared to the average glucose level at the initiation of therapy ($p < 0.05$). The average serum insulin level was higher and showed a statistical significance after 12 months of VPA treatment ($p < 0.05$) as compared to the average serum insulin level before valproic acid was initiated.

A well-defined cut-off HOMA values for an increased risk of developing metabolic syndrome in childhood is still not defined. Kurtoglu et al. [26] investigated the HOMA index in obese children and found that the cut-off values for the HOMA index were above 2.67 for prepubertal boys and 2.22 for prepubertal girls, with a higher risk of development of insulin resistance. Their results showed that pubertal boys and girls had a higher cut-off HOMA value for insulin resistance of 5.22 and 3.82, respectively. Our investigation showed that the average HOMA index for our patients had increased after 12 months of VPA therapy, with a high statistical significance ($p < 0.01$) ranging 1.18–2.98.

Although our research showed that VPA had a significant impact to glycoregulation and glucose homeostasis, none of the children developed clinical insulin resistance with the HOMA index above the cut-off values. This concurs with the results by Belcastro et al. [9], Kanemura et al. [25], Masuccio et al. [21], who also did not find statistical significance in VPA monotherapy group regarding insulin resistance parameters at the initiation of VPA therapy and after one year period. The research by Martin et al. [27] showed an increase in body weight in investigated patients, with lower values of serum glycemia after 12 months as compared to the control group of patients without VPA therapy, which contradicts our results. They concluded that his was probably due to an effect of VPA to increased appetite. Rakitin et al. [28] concluded that metabolic changes during VPA treatment were primarily due to a direct primary effect of VPA, with lowering of the glucose level and thus increasing the appetite. They concluded that this effect was not the consequence of increased body weight during VPA treatment. Our results showing significant increase in glucose level after a 12 month of VPA therapy might be due to the initial stage of insulin resistance development.

Another possible explanation of a significant increase of serum insulin and glucose as well as the HOMA index after VPA therapy could be the direct influence of VPA on the GABA receptors in pancreas β cells [29]. Impaired glycoregulation could be the cause of weight increase and metabolic disturbances during VPA therapy.

Research by Zhang et al. [30] suggests a possible influence of VPA on weight gain by upregulation of hypothalamic fat mass and obesity-associated gene (FTO) expression, causing a hypothalamic dysfunction, resulting with enhanced appetite, which contributes to weight gain.

CONCLUSION

Our results have showed that a 12-month VPA treatment in children with epilepsy has a great impact on weight gain and glucose homeostasis and metabolism. Despite significant increase of weight gain and disturbed glucose homeostasis, none of the children became obese nor did they develop clinical signs of insulin resistance. Our

investigation showed that significant number of children increased weight during the initial 12 months of VPA therapy and we strongly recommend that all children with recently diagnosed epilepsy should, at the initiation of VPA therapy, be closely monitored on a six-month basis. Close monitoring of weight, serum glucose, and insulin should be conducted before and after six- and 12-month VPA therapy. In case of a significant weigh gain and glucose metabolism disturbance, pediatric nutritionist and pediatric endocrinologist consultations are suggested. Obese children starting VPA therapy should be closely monitored on a regular six-month basis due to the fact that they are in great risk of developing father glycoregulation disturbance and progression or developing metabolic syndrome.

Conflict of interest: None declared.

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Утицај натријум-валпроата на телесну масу и параметре инсулинске резистенције код деце са епилепсијом

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САЖЕТАК

Увод/Циљ Добитак у телесној маси је један од најчешћих нежељених ефеката примене терапије валпроатима код болесника са епилепсијом. Повећање телесне масе је често главни разлог самовољног прекида терапије, нарочито у групи адолесценткиња.

Циљ рада је био да се испита утицај примене валпроата на телесну масу и гликорегулацију деце са епилепсијом.

Метод Истраживање је укључило укупно 49 здраве деце са новодијагностикованом епилепсијом. Мерена је телесна висина, телесна маса те узорковани гликемија и инсулин наште. Параметри су испитивани пре почетка антиепилептичне терапије валпроатима, а потом после шест и 12 месеци терапије. Индекси *BMI* и *HOMA* су израчунавани коришћењем математичке формуле за сваког болесника на сваком мерењу понаособ.

Резултати Истраживање је показало да постоји статистички значајно повећање телесне масе већ после шест месеци примене терапије валпроатима ($p < 0,01$), те да постоји статистички значајно повећање просечних вредности гликемије и инсулина после 12 месеци терапије ($p < 0,05$).

Закључак Наше истраживање је показало да 12-месечна примена валпроата код деце са новодијагностикованом епилепсијом има значајан утицај на повећање телесне масе и утиче на гликорегулацију и метаболизам глукозе. Препоручујемо да се деца са новодијагностикованом епилепсијом која започну терапију валпроатима редовно прате на шестомесечним контролама.

Кључне речи: валпроат; дечја епилепсија; инсулин; телесна маса; *HOMA*

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The difference between the pain self-perceptions of children with cerebral palsy and those of their caregivers

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SUMMARY

Introduction/Objective Pain is often an underrecognized entity in children with cerebral palsy. The aim of this study was to determine whether there are differences in pain self-perception between children with cerebral palsy and their caregivers.

Methods This retrospective study included 70 children with cerebral palsy and 70 of their caregivers, treated at the Institute of Child and Youth Health Care of Vojvodina, Serbia. Pain intensity ratings on the Visual Analog Scale (VAS) provided by children and/or their caregivers were analyzed.

Results The research involved 70 children with cerebral palsy and the same number of their caregivers. While only 43 (61.4%) of these children were testable, all 70 caregivers participated. Pain was reported by 19 (44.2%) children and 42 (60%) caregivers, while 17 (39.5%) children suffered from musculoskeletal pain, which was noted by 39 (55.7%) caregivers. Average caregiver rating for musculoskeletal pain for children at Level V, I and III on the Gross Motor Function Classification System (GMFCS) was 6.20 ± 2.10, 2.67 ± 2.18, and 2.50 ± 2, respectively. Average self- and caregiver-reported VAS rating for headache/stomachache was 2.73 ± 1.86 and 2.35 ± 1.49, respectively ($p > 0.05$). Statistically significant differences were noted in the musculoskeletal pain VAS scores provided by the caregivers for children at different GMFCS levels ($p < 0.01$).

Conclusion Although no differences in pain perception between children with cerebral palsy and their caregivers have been established, in children with the most severe level of motor disability, caregivers report a statistically higher level of musculoskeletal pain.

Keywords: pain; children; pain intensity; cerebral palsy

INTRODUCTION

Cerebral palsy (CP) is a heterogeneous group of non-progressive neurological disorders caused by brain damage either in utero or in early infancy, adversely affecting the development of posture and movement [1]. It is frequently accompanied by pain of diverse etiology, localization, intensity, and duration, often compromising the quality of life of both children and their caregivers [2]. In extant literature, pain is estimated to affect 27–75% of children with CP [3–6]. Moreover, 25% of children and youth with CP experience moderate to severe pain, and multiple sources of pain are present in more than 12% cases [7]. In CP, pain can have numerous origins, and is often the result of many factors, especially if caused by musculoskeletal deformities, hip dislocation/subluxation, hypertonia, dystonia, constipation, surgical intervention or presence of contractures [3, 7, 8]. In children with CP, headaches can occur for many reasons. Presence of motor disability, especially muscle weakness, muscle contraction, increased muscle tone, and inadequate positioning of the head and neck may lead to impaired sleep quality, increasing the occurrence of headaches, and thus compromising the ability to partake in daily activities, such as playing with peers and completing school assignments, even in children in whom cognitive functioning is not compromised [2, 4–7]. Abdominal pain can be caused by certain medications, as well as by feeding difficulties (those arising due to insufficiently coordinated and inefficient chewing and swallowing in particular), gastroesophageal reflux, slow passage, and constipation, especially in patients who spend a long time in a sitting position and are unable to change body posture on their own [3–7]. Greater understanding of the causes and the severity of pain in children with CP is frequently hindered by the unfeasibility of self-reports in non-verbal children. Although in such cases valuable information can be provided by health care professionals, caregiver-reported pain in children is particularly important [9]. Several single- and multi-dimensional scales and questionnaires have been developed for assessing the pain level in infants, children and adolescents [10, 11], some of which are not applicable to CP,

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or cannot be applied for evaluating chronic pain in children with severe cognitive and motor deficits [12]. Consequently, authors of existing studies tended to rely on a combination of several self-reported questionnaires and the corresponding parent versions, where available, as a means of obtaining more comprehensive data, especially if intended for use in evaluations or when planning rehabilitation interventions [6, 8, 13]. One-dimensional scales, such as Visual Analog Scale (VAS), Numerical Rating Scale (NRS-11), Wong-Baker FACES Pain Rating Scale (FACES) and 6-point categorical Verbal Rating Scale (VRS-6) [11, 14, 15] can be combined with observational data collection instruments, such as FLACC (Face, Legs, Activity, Cry and Consolability) and the revised FLACC (r-FLACC) scale. These scales are reliable and are associated positively with each other, providing a valid framework for the assessment of pain [15–19]. Application of the same questionnaire for assessing pain severity in children with CP may yield inconsistent results, depending on whether the pain is self-reported by the child, or is perceived by caregivers and various healthcare professionals. The differences are particularly pronounced if pain severity is assessed before and after a medical intervention or physiotherapy [20–24].

The aim of the present study was to establish presence of any differences between the pain levels self-reported by children with CP and the ratings given by their caregivers using VAS.

METHODS

This retrospective study was conducted between September 2014 and September 2015 and included 70 children with CP aged < 18 years of both sexes, and 70 their caregivers receiving inpatient and outpatient treatment at the Institute of Child and Youth Health Care of Vojvodina, Novi Sad, Serbia. The study was approved by the institutional Committee on Ethics, and the receipt of written consent from the children's parents/caregivers. Gross motor function was classified using the Gross Motor Function Classification System (GMFCS) [25], and pain intensity was measured using VAS, whereby ratings were provided by the children and/or their caregivers (parents, grandparents, or foster carers). The VAS is a valid and reliable measure for rating pain intensity, requiring participants to mark subjective pain experience on a 10 cm-long line, ranging from 0 (no pain) to 10 (unbearable pain) [14, 26, 27]. In the present study, the scale was used to rate musculoskeletal pain, headache and/or stomachache. Children that underwent a surgical procedure in the preceding month, presented with current trauma or pain related to other pre-established condition were excluded from the study.

Statistical methods

The minimum sample size (68) was determined based on the α error of 0.05 and β error of 0.1 (corresponding to the power of 90%). Numerical variables were expressed as mean (median, arithmetic mean) and variance (standard deviation, range), depending on the data distribution type, whereas frequency and percentage was reported for categorical variables.

Statistical analyses included paired-samples t-test, ANOVA test, and Pearson correlation coefficient, with $p < 0.05$ indicating statistically significant difference. Tukey multiple comparison test was adopted for between-group comparisons. All analyses were performed using the SPSS Version 24.0. (IBM Corp., Armonk, NY, USA) statistical software package.

RESULTS

The study included 70 children with CP, 33 (47.1%) of whom were boys and 37 (52.9%) were girls, aged 8.65 ± 3.66 years. Self-reported data was obtained from 43 (61.4%) children that were testable and capable of providing required information, while their caregivers provided data for all participating children. Most of the caregivers were mothers 58 (82.9%).

In the examined sample, 27 (38.6%) of children had spastic hemiplegia, 19 (27.1%) each had spastic quadriplegia and spastic diplegia, three (4.3%) children had ataxic form of CP, while two (2.9%) children had a dyskinetic form. GMFCS Level I was noted in 26 (37.1%) of participating children, 14 (20%) were at Level II, 10 (14.3%) at Level III, seven (10%) at Level IV, and 13 (18.6%) of children were at Level V (Table 1).

Table 1. Participants' sociodemographic and general characteristics

Variables		n = 70 (100%) M ± SD
Sex	Male	33 (47.1%)
	Female	37 (52.9%)
Age (years) (min–max)		8.65 ± 3.66 (4–17.58)
Self-reported data available	Yes	43 (61.4%)
	No	27 (38.6%)
Participating caregiver	Mother	58 (82.9%)
	Father	2 (2.9%)
	Grandparent	8 (11.4%)
	Foster mother/father	2 (2.8%)
Cerebral palsy type	Spastic hemiplegia	27 (38.6%)
	Spastic quadriplegia	19 (27.1%)
	Spastic diplegia	19 (27.1%)
	Dyskinetic	2 (2.9%)
	Ataxic	3 (4.3%)
Gross Motor Function Classification System level	Level I	26 (37.1%)
	Level II	14 (20%)
	Level III	10 (14.3%)
	Level IV	7 (10%)
	Level V	13 (18.6%)

M ± SD: mean ± standard deviation

Pain was reported by 19 (44.2%) children and by 42 (60%) caregivers, who respectively rated it using VAS at 1.62 ± 0.95 and 1.65 ± 0.94. Musculoskeletal pain was experienced by 17 (39.5%) children (with an average 1.62 ± 0.95 VAS score), whereas it was perceived by 39 (55.7%) caregivers (who rated it at 1.65 ± 0.94 on average). On the other

hand, children and their caregivers rated stomachache/headache at 2.73 ± 1.86 and 2.81 ± 1.86, respectively. For testable children, i.e., those that were capable of rating their subjective pain experience (n = 43), paired-samples t-test was conducted to assess the differences between self- and caregiver-provided VAS scores. For these reasons, the caregiver-provided VAS scores for this subsample do not coincide with those pertaining to the full sample (n = 70). Children in this subgroup self-rated stomachache/headache at 2.73 ± 1.86, while caregiver-rated scores were 2.35 ± 1.49, and this difference was not statistically significant ($p > 0.05$). For this subsample, self- and caregiver-provided musculoskeletal pain VAS scores were 2.94 ± 2.16 and 3.88 ± 2.36, respectively. Once again, this difference failed to reach statistical significance ($p > 0.05$) (Table 2).

Further analyses were conducted to ascertain if the VAS scores differed across the GMFCS levels. Statistically significant differences were noted only in the caregiver-reported musculoskeletal pain ($p < 0.01$). Tukey multiple comparison test was also performed for between- group comparisons, and the results indicated statistically significant differences between children at GMFCS Level V (the most severe CP form) and those at Level I and III. On average, caregiver-reported musculoskeletal pain in the Level V group was 6.20 ± 2.1, while for children at GMFCS Level I and III the caregivers rated musculoskeletal pain at 2.67 ± 2.18 and 2.5 ± 2, respectively (Table 3).

Table 2. Differences between self- and caregiver-rated VAS pain scores

Variable	M ± SD	Pain		p
		Yes	No	
Self-reported pain	43 (100%)	19 (44.2%)	24 (55.8%)	> 0.05[a]
Caregiver-reported pain	70 (100%)	42 (60%)	28 (40%)	
Self-reported musculoskeletal pain	43 (100%)	17 (39.5%)	26 (60.5%)	> 0.05[a]
Caregiver-reported musculoskeletal pain	70 (100%)	39 (55.7%)	31 (44.3%)	
Self-reported headache/ stomachache	43 (100%)	18 (41.8%)	25 (58.2%)	> 0.05[a]
Caregiver-reported headache / stomachache	70 (100%)	30 (42.8%)	40 (57.2%)	
Self-reported headache (min–max)	1.62 ± 0.95 (1–10)			> 0.05[a]
Caregiver-reported headache (min–max)	1.65 ± 0.94 (1–10)			
Self-reported headache/ stomachache VAS score	2.73 ± 1.86			> 0.05[a]
Caregiver-reported headache/ stomachache VAS score	2.35 ± 1.49			
Self-reported musculoskeletal pain VAS score	2.94 ± 2.16			> 0.05[a]
Caregiver-reported musculoskeletal pain VAS score	3.88 ± 2.36			

p – statistical significance; [a] – paired-samples t-test; VAS – Visual Analogue Scale; M ± SD – mean ± standard deviation

Table 3. Self- and caregiver-reported VAS pain scores across five Gross Motor Function Classification System levels

Variables	Self-reported headache/ stomachache VAS score	Caregiver-reported headache/ stomachache VAS score	Self-reported musculoskeletal pain VAS score	Caregiver-reported musculoskeletal pain VAS score
Level I (n = 26) M ± SD	3.17 ± 2.4	2 ± 1.55	3.2 ± 2.59	2.67 ± 2.18
Level II (n = 14) M ± SD	3.20 ± 1.64	3 ± 1.55	2.86 ± 1.95	3.88 ± 1.64
Level III (n = 10) M ± SD	/	2.6 ± 1.67	/	2.5 ± 2
Level IV (n = 7) M ± SD	1.67 ± 0.58	3.33 ± 2.31	4 ± 2.65	5.6 ± 2.79
Level V (n = 13) M ± SD	/	3.29 ± 2.5	/	6.2 ± 2.1**
Full sample (n = 70) M ± SD	2.73 ± 1.86	2.81 ± 1.86	2.94 ± 2.16	4.13 ± 2.53
p	> 0.05a		> 0.05a	

p – statistical significance; VAS – Visual Analog Scale; M ± SD – mean ± standard deviation; [a] – ANOVA test;
**$p < 0.01$[a]

DISCUSSION

Subjective pain experience, which in a wide range of difficulties affecting children with CP often remains unrecognized, adversely affects their quality of life [7, 12]. Speech and language impairments, as well as compromised intellectual functioning, limit the child's ability to self- report the presence of pain. As pain is a subjective experience, it cannot be accurately captured by caregiver reports, but it could be important, especially in non-verbal children [2, 9].

In our study, the majority of respondents was female, which is consistent with the sample composition in several prior studies [14, 20, 28], but does not align with the designed trials based on larger cohorts of children with CP [3–7, 29]. Self-ratings were obtained from 61.4% of the children that took part in the study. In the survey conducted by Penner et al. [7], involving 252 children and youth with CP, only 39.6% of the sample was able to self-report presence of pain, which hinders pain evaluation in this population. More recently, Giray et al. [2] found that children with CP who are dependent and non-verbal are more likely to experience pain.

Similarly, according to Jayanath et al. [9], caregivers of non-verbal children with CP report a high frequency of pain. In our study, caregiver reports were predominantly provided by mothers (82.9%), which is to be expected, as parents are the ones shouldering the greatest burden of care for children with CP. In our sample, all CP forms were represented, concurring with the participant composition in earlier studies [2, 6, 28].

In our study, pain was reported by 19 (44.2%) children and by 42 (60%) caregivers. Based on a survey of 429 children with CP aged 13–17 years and 657 parents conducted by Parkinson et al. [6], pain was self-reported and parent-reported in 74% and 77% of the cases, respectively. Pain prevalence in children with CP, as established by healthcare professionals, tends to be lower compared to the data provided by parents or other close family members. In the study conducted by Badia et al. [21], physiotherapists reported presence of pain in 51.4% of the evaluated children and youth with CP.

In the present study, musculoskeletal pain was self-reported by 39.5% of the children, while the caregivers reported this type of pain in 55.7% cases. According to the respondents, musculoskeletal pain was of a greater severity compared to headache/stomachache. Similar differences between self- and proxy-rated (parent or a health professional) pain levels were noted in other studies where different pain intensity rating scales were employed. For example, in Ramstad et al. [22] study, 62% of the participating 153 children with CP aged 8–18 reported musculoskeletal pain, and its severity was rated higher by their parents compared to self- evaluations. The differences in the results can be attributed to a smaller sample size and younger age of children in our study. More recently, Westbom et al. [28] reported that pain experienced by children with CP tends to be most frequently localized in the lower extremities, feet and knees in particular. Penner et al. [7] assessed the pain experienced by children with CP aged 3–19 using the Health Utilities Index 3 (HUI3) questionnaire, and found that pain is localized in the lower extremities in 82% of respondents that report pain, and is typically attributed to hip dislocation/subluxation, dystonia and constipation. In our study, 39.5% of children reported musculoskeletal pain, while 41.8% reported headache/stomachache. In the study conducted by Parkinson et al. [6], 40% of children with CP complained of lower extremity pain, while 34% reported headaches, and 26% stomachache. Parent- and self-reported pain intensity was significantly correlated (Spearman rank correlation = 0.45; $p < 0.0001$).

All GMFCS levels were represented in our study sample, in line with larger cohort studies [7, 9, 28]. Jayanath et al. [9] conducted their research on a sample of 104 children with CP of both sexes (51% of whom were at GMFCS Level V, and 65% had spastic quadriplegia). Parents reported pain in 65% of these children, which was rated as intense in 17% of the cases, and was noted to occur daily in 28% cases [9]. The VAS was adopted in this study due to its demonstrated reliability and validity as both child self-report and parent-proxy report instrument. It has been employed in a significant number of prior studies involving children with CP, as it is a simple and quick method for assessing spasticity treatment efficacy [11, 14]. Alriksson-Schmidt and Hägglund [4] reported that pain localized in the abdomen and hips was most frequent in children with CP at the GMFCS Level V, while knee pain was most prevalent at Level III and foot pain at Level I.

In the present study, the greatest musculoskeletal pain caregiver-ratings were given for children at GMFCS Level V. Similarly, in a sample of 2777 children with CP aged 1–14 years, Alriksson-Schmidt and Hägglund [4] reported correlations between pain severity and the degree of gross motor impairment. In particular, pain was more frequently reported for children at GMFCS Level III and V compared to those at GMFCS Level I. Similar to our study, in the study conducted by Westbom et al. [28] 37% of children with CP were reported to experience pain, and GMFCS Level V was associated with the highest pain prevalence (50%). Eriksson et al. [5] assessed pain intensity in 3545 children with CP and concluded that it was positively correlated with the GMFCS level. However, no statistically significant difference in pain prevalence was found between self and proxy pain ratings. In an earlier cross-sectional study, Penner et al. [7] found a good agreement between the children's self-reports and parental pain severity/frequency reports. In a sample of 3783 children with CP representing all GMFCS levels, Hägglund et al. [29] parents and children reported presence of pain with comparable frequencies. It is, however, worth noting that changes in pain status are common in children with CP. For example, Christensen et al. [30] followed up 148 children with CP at all GMFCS levels, and found that pain severity tended to decline over time in children with more severe initial pain and higher gross motor function.

Continual monitoring of children with CP (which should include pain assessment) by their healthcare providers is essential for early detection of symptoms. The one-dimensional VAS pain rating scale can be adopted for this purpose, as it allows for rapid evaluation, facilitating longitudinal pain monitoring.

The study limitations include uneven sample distribution in terms of GMFCS levels, as well as failure to account for the influence of pharmacological and non-pharmacological therapy in the analysis.

CONCLUSION

In the present study, no statistically significant differences between self- and caregiver-provided VAS pain ratings were noted. Statistically significantly greater musculoskeletal pain caregiver-ratings were noted for children at GMFCS Level V compared to those at Level I and III. For this reason, it is essential to detect pain in children with CP at all GMFCS levels, as this would ensure that the appropriate treatment is initiated in a timely manner, thus reducing the likelihood of its adverse long-term effects on the child's quality of life.

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Разлика у самоперцепцији бола између деце са церебралном парализом и њихових неговатеља

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САЖЕТАК

Увод/Циљ Бол је често недовољно препознат ентитет код деце са церебралном парализом.

Циљ рада био је утврдити да ли постоје разлике у самоперцепцији бола између деце са церебралном парализом и њихових неговатеља.

Методе Ретроспективна студија је укључивала 70 деце са церебралном парализом лечене на Институту за здравствену заштиту деце и омладине Војводине и исто толико њихових неговатеља. Анализиран је интензитет бола процењен од стране деце и/или њихових неговатеља применом визуелне аналогне скале (ВАС).

Резултати Укупно 43 детета (61,4%) била су тестабилна, као и свих 70 неговатеља. Присуство бола пријавило је 19 деце (44,2%) и 42 (60%) неговатеља. Мускулоскелетни бол имало је 17 деце (39,5%), док је према процени неговатеља бол имало 39 (55,7%) деце. Просечна вредност мускулоскелетног бола према процени неговатеља износила је 6,20 ± 2,10 код деце са нивоом V, за I ниво 2,67 ± 2,18 и III ниво 2,50 ± 2 на скали за процену грубе моторичке онеспособљености (*Gross Motor Function Classification System*). Просечан ВАС за бол глава/стомак по процени детета износио је 2,73 ± 1,86, а по процени неговатеља 2,35 ± 1,49 ($p > 0,05$). Статистички значајна разлика између деце са различитим нивоом церебралне парализе потврђена је на ВАС за мускулоскелетни бол-одговор неговатеља ($p < 0,01$).

Закључак Разлике у перцепцији бола између деце са церебралном парализом и неговатеља нису утврђене, али код деце са најтежим нивоом моторичког онеспособљења неговатељи наводе статистички виши ниво мускулоскелетног бола.

Кључне речи: бол; деца; јачина бола; церебрална парализа

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Otorhinolaryngology emergency department hospitalizations in a secondary medical center

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SUMMARY

Introduction/Objective The overall number of emergency department visits, including otorhinolaryngology, has increased. Due to population growth, industry and traffic expansion, workload of the otorhinolaryngology emergency department is steadily on the rise.
The objective of this study was to determine most common indications for an emergency hospitalization in the otorhinolaryngology department in a secondary medical center. Also, we examined the course of diagnostics and treatment upon admittance, the outcome of hospitalization, and possible referral to a tertiary medical center.

Methods This retrospective study included patients who were urgently hospitalized at the Department of Otorhinolaryngology and Maxillofacial Surgery of the Đorđe Joanović General Hospital in Zrenjanin, Serbia, during a two-year period. The data were obtained by processing the patients' medical charts.

Results The study included 428 patients who were urgently hospitalized at the department of otorhinolaryngology of a secondary medical center during a two-year period. Of the total number, 245 (57.2%) were male and 183 (42.8%) were female, with the average age of 48.5 years. The patients were most frequently hospitalized due to tonsillopharyngitis and its complications, followed by head and neck trauma. Most of the patients were treated conservatively, with medication therapy (72%), and 28% underwent surgical or other invasive intervention. Twenty-seven (6.3%) patients were referred to a tertiary medical center, which correlated significantly with the number of comorbidities and consultative exams.

Conclusion Otorhinolaryngology inflammatory/infectious diseases are the most frequent indication for urgent hospital admission to a secondary medical center. Most of the patients were treated conservatively. Referral to a tertiary medical center significantly correlated with the number of comorbidities and consultative exams.

Keywords: otorhinolaryngology; emergency hospitalizations; secondary medical center

INTRODUCTION

The overall number of emergency department visits, including otorhinolaryngology, has increased [1]. Due to population growth, industry and traffic expansion, workload of otorhinolaryngology emergency departments is steadily on the rise. Facial, orofacial, and cervical trauma and various infections with complications are most frequent causes of emergency hospitalizations [2, 3]. Most otorhinolaryngology emergency cases are not life threatening, but a certain number of patients require hospitalization for further assessment and treatment. During hospitalization, quick and precise diagnosis of these disorders is important in order to preserve functioning organs and, in some cases, the life of the patient.

Some disorders require referral to a tertiary medical center due to the complexity of the disorder, the lack of qualified personnel with surgical expertise or medical equipment in secondary medical centers. Despite a rising need for emergency surgery services globally, there is wide variability in the human and physical resources available. In addition, the number of surgeons, anesthetists, and operating theatres varies significantly by national income [4]. Inappropriate referrals result in an inefficient use of resources and financial burden, not to mention in delaying the diagnosis and potentially endangering the patient. A careful assessment must be made in deciding should a certain emergency disorder be managed in a secondary medical center.

The objective of this study was to determine most common indications for emergency hospitalization at an otorhinolaryngology department of a secondary medical center. In addition, we examined the course of diagnostics and treatment upon admittance, the outcome of hospitalization, and possible referrals to a tertiary medical center.

METHODS

This retrospective study included all the patients who were urgently hospitalized at the Department of Otorhinolaryngology and

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Maxillofacial Surgery of the Đorđe Joanović General Hospital in Zrenjanin, Serbia, from January 1, 2017 to December 31, 2018. This study was approved by the institutional ethics committee (01-273/71/2019). The patients were first examined at the Otorhinolaryngology Emergency Department, and then hospitalized according to their disorder. The data were obtained by processing medical charts of the patients. We analyzed the demographic data (age, sex), diagnosis upon admittance, comorbidities, conducted diagnostic procedures and consultative exams, conducted treatment and invasive or surgical procedures, duration of the hospitalization and further referrals to a tertiary medical center. Patients older than 16 years were considered adults.

Descriptive statistics were calculated for demographic characteristics and other followed parameters and presented as frequencies and proportions. For statistical analysis, χ^2 test, univariate, and multivariate logistic regression methods were used. All test variables with statistical significance of $p < 0.05$ in the univariate model were included in the multivariate model. Statistical significance was considered at $p < 0.05$. Statistical analysis was performed using the IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

Table 1. Characteristics of the patients included in the study

Sex, n (%)	
Male	245 (57.2)
Female	183 (42.8)
Number of comorbidities, n (%)	
None	206 (48.1)
One	130 (30.4)
Two	74 (17.3)
Three or more	18 (4.2)
Additional diagnostics, n (%)	
Consultative examination	247 (57.7)
Radiography imaging	108 (25.2)
Ultrasound imaging	71 (16.6)
CT imaging	48 (11.2)
Number of consultative exams, n (%)	
None	181 (30.6)
One	141 (23.8)
Two	64 (10.8)
Three or more	42 (7.1)
Treatment, n (%)	
Medication treatment	308 (72)
Surgical treatment/intervention	120 (28)
Referral to a tertiary medical center, n (%)	
Yes	27 (6.3)
No	401 (93.7)

Table 2. Indications for hospitalization in patients ≤ 16 years old

Indication for hospitalization	n (%)
Tonsillopharyngitis and complications	9 (2.1)
Digestive tract foreign body	7 (1.6)
Acute suppurative rhinosinusitis without/with complications	5 (1.2)
Head and neck trauma	4 (0.9)
Acute suppurative otitis media without/with complications	4 (0.9)
Head and neck abscess	2 (0.5)
Bleeding after tonsillectomy	2 (0.5)
Allergic reaction to insect bite/medication	1 (0.2)
Total	34 (7.9)

RESULTS

This retrospective study included 428 patients who were urgently hospitalized at the Department of Otorhinolaryngology and Maxillofacial Surgery of the Đorđe Joanović General Hospital in Zrenjanin during a two-year period; 245 (57.2%) patients were male and 183 (42.8%) were female, with the average age of 48.5 years (± 21.8). Patients 40–70 years old were significantly more frequently admitted to the department (χ^2 test, $p < 0.05$). Most of the patients had one, two or more comorbidities (222 patients, 51.9%). Considering additional diagnostics conducted during hospitalization, 51.9% had one or more consultative examinations, 25.2% underwent radiography imaging, 16.6% ultrasound imaging, and 11.2% computed tomography imaging. Twenty-seven patients (6.3%) were referred to a tertiary medical center for further treatment (Table 1). The average duration of hospitalization was 5.6 days (± 4.5 days).

Children and adults were most frequently hospitalized because of tonsillopharyngitis and its complications (in 18.7% of cases). In children, foreign bodies of digestive system were also a frequent indication for hospitalization, followed by otogenic and sinusogenic complications (Table 2). Other frequent reasons for urgent hospitalization in adults were epistaxis, angioedema, head and neck trauma, and head and neck phlegmon or abscess formation (Table 3).

Considering comorbidities, most of the patients were treated for cardiovascular diseases (41.4%), followed by diabetes (10.5%), and pulmonal diseases (7.2%) (Figure 2).

Table 3. Indications for hospitalization in patients > 16 years old

Indication for hospitalization	n (%)
Tonsillopharyngitis and complications	71 (16.6)
Epistaxis	36 (8.4)
Angioedema	36 (8.4)
Head and neck trauma	35 (8.2)
Head and neck abscess/phlegmon	34 (7.9)
Digestive tract foreign body	25 (5.8)
Allergic reaction to insect bite/medication	22 (5.1)
Acute suppurative otitis media without/with complications	21 (4.9)
Perichondritis	17 (4)
Acute suppurative rhinosinusitis without/with complications	16 (3.7)
Malignant head and neck tumors	16 (3.7)
Stridor	13 (3)
Acute laryngitis /laryngotracheitis	11 (2.6)
Dysphagia/aphagia	9 (2.1)
Acute epiglottitis	7 (1.6)
Vertigo	5 (1.2)
Sialoadenitis	5 (1.2)
Neck lymphadenitis	4 (0.9)
Acute idiopathic sensorineural hearing loss	3(0.7)
Bleeding after tonsillectomy	2 (0.5)
Chemical ingestion	2 (0.5)
Respiratory tract foreign body	1 (0.2)
Other	3 (0.7)
Total	394 (92.1)

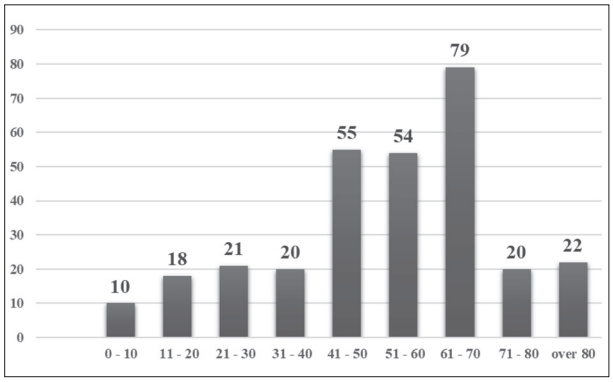

Figure 1. Age groups of patients included in the study

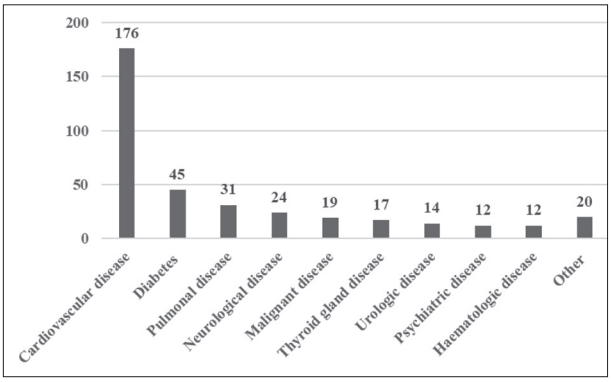

Figure 2. Comorbidities of the patients

Table 4. Surgical and other interventions

Interventions	n (%)
Abscess/hematoma incision and drainage	33 (7.7)
Anterior nasal packing	33 (7.7)
Directoscopy/esophagoscopy with foreign body extraction	26 (6.1)
Tracheotomy	7 (1.6)
Nasal reduction	7 (1.6)
Wound suture	4 (0.9)
Dental extraction	4 (0.9)
Posterior nasal packing	1 (0.2)
Surgical revision of bleeding	1 (0.2)
Other	4 (0.9)

Table 5. Diagnosis on referral to a tertiary medical center

Diagnosis for referral	n (%)
Head and neck malignancy	10 (2.3)
Head and neck trauma	5 (1.2)
Head and neck phlegmon	4 (0.9)
Mastoiditis	3 (0.7)
Failed esophageal foreign body extraction	3 (0.7)
Rhinosinusitis complications	2 (0.5)

Table 6. Univariate and multivariate logistic regression of factors related to the referral to a tertiary medical center

Referral	Univariate log regression			Multivariate log regression		
	Exp (B)	95% CI	p	Exp (B)	95% CI	p
Number of comorbidities	1.517	1.007–1.147	< 0.05	1.249	0.968–1.117	0.326
Number of consultative exams	1.673	1.012–2.275	< 0.01	1.040	0.801–1.948	0.282
Duration of hospitalization	1.075	1.163–2.407	< 0.05	1.445	0.962–2.170	0.76

Most of the patients were treated conservatively with medication therapy (72%), and 28% underwent surgical or other invasive interventions. Abscess or hematoma incision and drainage was most frequently done, as well as anterior nasal packing (in 7.7%). Directoscopy or esophagoscopy due to foreign body extraction was conducted in 6.1% (Table 4).

According to the results of the univariate logistic regression analysis (Table 6), referral to tertiary medical center was significantly related to duration of hospitalization, number of comorbidities and number of consultative exams ($p < 0.05$). Multivariate logistic regression indicated that none of the factors significantly correlated with referral to a tertiary medical center ($p > 0.05$) (Table 6).

DISCUSSION

Otorhinolaryngology emergencies visits are frequent in emergency units, but the number of patients requiring hospitalization is small. There are few published studies describing the structure of otorhinolaryngology emergency hospitalizations [2, 5, 6].

The most common disease responsible for hospital admittance was tonsillopharyngitis and its complications. This does not differ from data obtained from other studies. Multiple secondary medical centers with an otorhinolaryngology department are localized in cities that do not have otorhinolaryngology service at the primary care level. Any application of intravenous therapy is conducted through hospital stay. The lack of resources and logistics leads to attending to patients who would otherwise be treated by their general practitioner. About 25–40% of the medical practice of a general practitioner consists of ear, nose, and throat diseases [3]. This data supports the fact that hospital health services are frequently used instead of primary care centers. Better training and education of general practitioners would allow secondary level healthcare facilities to be more available and effective for more complex cases [7, 8, 9]. On the other hand, in children, admittance was done only in cases where surgical intervention was planned. Children who underwent conservative antibiotic treatment were admitted to the pediatric department.

In Serbia, otorhinolaryngologists also attends to cases of maxillofacial trauma in the emergency department, as the presence of the attending maxillofacial surgeon after working hours is extremely rare, except in tertiary university centers. This directly influences the number of admitted and referred patients, and makes head and neck trauma the second most common diagnosis in hospitalized patients.

One of the prominent data was that computed tomography (CT) diagnostics was done in only 11.2% of the

admitted patients. According to the literature data, CT use in the emergency department increased in the last few decades from 60% to 80% depending on the patients' age, sex, race, and diagnosis [10]. CT can identify patients who can benefit from hospital admission, and aid in determining appropriate disposition and risk assessment. This may be particularly relevant for patients who require major procedures and those with complex clinical presentations (elderly, patients with multiple chronic comorbidities) [11]. One of the main reasons for low percentage of CT use in our patients is poor organization and cooperation with the radiology department, as well as not firmly implemented diagnostics and treatment protocols.

Surgical or other invasive interventions were done in 28% of the cases. The most frequent intervention was abscess incision and drainage. This was also noted as the most frequent ears, nose, and throat surgical emergency in population-based estimates of the global burden [4]. The data was supported with other studies' results [2, 3, 5, 12].

Some authors estimate that less than 10% of emergency otorhinolaryngology cases require middle and high complexity resources in tertiary medical centers [3, 13]. Most common reason for referrals were advanced head and neck malignancies, with cardiovascular and pulmonal complications. Rhinosinusitis and otitis complications were referred when surgical treatment was needed. The lack of equipment and/or experienced surgeons who could treat those patients was also the main reason for referral of trauma patients in need of surgical reduction of facial fractures. Complex patients with advanced neck phlegmons requiring further surgical treatment and postoperative intensive care were also transferred to tertiary medical centers. Further dissemination of the infection such as mediastinitis and sepsis require extensive treatment, which cannot be fully provided in secondary medical centers.

In our study, the number of comorbidities, duration of hospitalization, and the number of consultative exams was proven to be significantly correlated with patients' referral to the tertiary medical center. More than half of the patients had comorbidities (51.9%), cardiovascular diseases and diabetes being the most frequent ones. One or more comorbidities were detected in 21.5% of the patients. Chronic diseases like chronic obstructive pulmonary disease, asthma, cancer, chronic heart failure, liver disease are significantly more frequent in patients who visit the emergency department [14]. There are reports suggesting that infection or trauma could worsen chronic illnesses such as chronic heart disease and chronic obstructive pulmonary disease. These patients are at a greater risk of developing infectious complications and be admitted to hospital care settings [15, 16, 17]. In our study, complications of oropharyngeal infections and neck phlegmons were frequent indications for hospitalization and surgical treatment. Head and neck phlegmons are accompanied by an endogenous intoxication that leads to homeostasis disturbance and vital organs' disorder. In these patients, concomitant pathologies such as cardiovascular insufficiency, diabetes, hepatic and kidney disease significantly influenced the course of the infection and the progression of the disease [18]. Frequent comorbidities in patients result in multidisciplinary approach to a patient's treatment and higher hospitalization rate. The percentage of physician consultations for emergency department patients varies 20–40% [19, 20]. In our study, the number of patients who underwent one or more consultative exams was 247 (57.7%) and was significantly higher compared to the literature data. Complex patients require more consultative examinations and diagnostic procedures, especially if surgical treatment is considered. Higher number of consultative exams was significantly correlated with referrals to a tertiary medical center.

Limitations of the study are those that the data were obtained retrospectively from only one secondary medical center. Multi-centric studies are required to obtain data from other secondary medical centers. The need for precise diagnostic and treatment protocols and their implementation is apparent, in order to define required diagnostics, possible treatment options, and terms of referrals to tertiary centers.

CONCLUSION

The data from this study concluded that otorhinolaryngology inflammatory/infectious diseases are the most frequent indication for urgent hospital admission to a secondary medical center. Most of the patients were treated conservatively. Referral to a tertiary medical center was significantly correlated to the number of comorbidities and consultative exams. Further research is needed to address any need and possible areas of improvement in emergency services in secondary medical centers and in patterns in treatment and referrals to tertiary medical centers.

Conflict of interest: None to declare.

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Ургентна стања у оториноларингологији у секундарној здравственој установи

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САЖЕТАК

Увод/Циљ Свакодневно се у лекарској пракси сусрећемо са хитним стањима из области оториноларингологије. Са порастом броја инфекција респираторног тракта и њихових компликација, као и повреда у саобраћају и индустрији, ургентна стања у оториноларингологији постају све чешћа на секундарном нивоу здравствене заштите.

Циљ рада је био испитати структуру и даљи третман свих хитних пријема обављених у поменутом периоду испитивања у односу на пол, старост, пријемну дијагнозу, обављену интервенцију и третман, упућивање у установу терцијарног ранга, коморбидитете, обављену допунску дијагностику и консултативне прегледе из осталих специјалистичких области.

Методе Ретроспективна студија је обухватила све болеснике који су као хитни случајеви хоспитализовани на Одељењу за оториноларингологију и максилофацијалну хирургију Опште болнице Зрењанин у двогодишњем периоду. Подаци су добијени анализом медицинских историја болесника и адекватном статистичком обрадом.

Резултати Студија је обухватила 245 (57,2%) болесника мушког пола и 183 (42,8%) женског пола просечне старости 48,5 година. Најчешћа пријемна дијагноза је била тонзилофарингитис и његове компликације, потом траума главе и врата. У 72% случајева спроведена је медикаментозна терапија, док је у 28% спроведена хируршка интервенција. У установе терцијарног нивоа упућено је 27 (6,3%) болесника, што је највише зависило од броја коморбидитета и спроведених консултативних прегледа.

Закључак Инфекције и инфламације су најчешће индикације за хитну хоспитализацију у оториноларингологији на секундарном нивоу здравствене заштите. Већина болесника је лечена конзервативно, а упућивање у терцијарну здравствену установу је значајно зависило од броја коморбидитета, броја консултативних прегледа и дужине хоспитализације.

Кључне речи: хитни пријеми; оториноларингологија; секундарна здравствена установа

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Unrecognized tuberculosis in a patient with COVID-19

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SUMMARY

Introduction COVID-19 is responsible for the current global pandemic. Globally, over 15 million people are currently infected, and just over 600,000 have died due to being infected. It is known that people with chronic illnesses and compromised immune systems can develop more severe clinical presentation. Tuberculosis (TB) is still one of the biggest epidemiological problems worldwide. Both of these diseases can be misdiagnosed and can manifest in a similar way. We will present a case study of a patient who was initially treated as a COVID-19 infection, with TB being diagnosed later on. The recovery began only after being treated for both diseases simultaneously**.**

Case report The patient is a 27-year-old male, non-smoker, with no history of any significant diseases. He presented with fever, fatigue and hemoptysis. Computed tomography pulmoangiography had shown massive consolidations and excavations, which could be caused by COVID-19. Despite being treated for COVID-19, there was no clinical improvement. On the follow-up chest X-ray, beside signs of COVID-19, there were also changes that could indicate TB. TB was detected in sputum, using PCR and Mycobacteria Growth Indicator Tube, and only after being treated for both diseases did his condition improve.

Conclusion There are a few reported cases of COVID-19 and TB coinfections, and we believe that there are many more patients with this coinfection being unrecognized.

Keywords: COVID-19; tuberculosis; infection; diagnosis

INTRODUCTION

Corona virus has, until recently, caused only animal infection (feline and bat infections), however, currently it is the most common cause of pneumonia in humans, and can lead to death. Many facts are still unknown regarding this virus, such as transmission, period of incubation, full clinical presentation, radiography, laboratory findings, immune response and specific treatment. Most studies have shown that the respiratory pathway is the most common way of transmission and infection (through coughing, sneezing, talking…). The incubation period varies greatly, between two and 14 days, and can go up to 28 days, but most commonly the incubation lasts for five days [1]. The clinical presentation also varies, and is not specific. The infection can be anything between asymptomatic or mild, which is present in the majority of patients, and severe, with a lethal outcome. The most common symptoms are: fever, cough, difficulty of breathing, fatigue, muscle pain, diarrhea, nausea and headache [2]. Severe forms of the infection manifest with a massive pneumonia followed by acute respiratory failure or sepsis, which in turn demands mechanical ventilation [3]. In the laboratory findings there are leucopenia, thrombocytopenia, increased values of liver enzymes, fibrinogen, D-dimer, LDH, interleukin 6 and presepsin. Inflammation markers (fibrinogen, C reactive protein) can be within reference values; however, they are elevated most of the time [4]. Chest radiography shows interstitial thickening with peripheral consolidation, as well as ground glass changes. Uncommonly, one can find segmental and lobar consolidation and pleural effusion [5]. Specific vaccine has not yet been discovered, and the treatment protocols differ between centers, and is still in early stages of development. Depending on the illness stage, different therapy treatments have shown success: antibiotics, hydroxychloroquine, vitamin, antiviral and systemic corticosteroids. Drugs with immunomodulation have shown promising results in severe forms of the disease [6].

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis spp*. The disease most commonly affects the lungs, although other organs can also be afflicted (nervous, gastrointestinal system, bones, kidneys). The infection does not mean the disease, since only 10% of infected manifest as an active form of the disease. Whether or not the disease will manifest, depends of the infective agent, as well as the immune status of the infected. Risk factors are well known, and almost all of them are related to immunodeficiency (HIV infection, alcoholism, drug abuse…) [7]. The

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symptoms include fever, fatigue, night sweats, loss of body mass, coughing of sputum, pus or fresh blood. In advanced form of the disease, acute respiratory failure is not uncommon, and chest pain is present if the pleura is afflicted. If the extrapulmonary form of the disease is present, the symptoms are organ specific [8]. The clinical presentation varies greatly, from asymptomatic to severe. Radiological findings are specific, and pleural effusion is frequently present. Definitive diagnosis is given when the bacteria is identified, directly, by PCR method or with a pathohistological finding in different tissues, urine, stool or sputum sample. Treatment consists of antituberculotic drugs in standardized protocols [9, 10, 11].

We will present a patient initially treated for COVID-19 infection, as well as tuberculosis, whichang was discovered later on as a coinfection. The recovery began only after being treated for both diseases simultaneously.

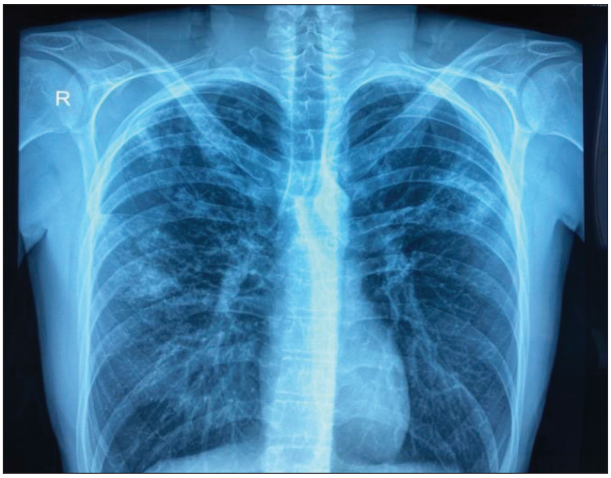

Figure 1. First follow-up chest X-radiography showing both signs of COVID-19 and Tuberculosis infection

CASE REPORT

The patient we present is male, aged 27, with no history of medical illnesses and history. He was first admitted in the Emergency room because of fever (38°C), fatigue and hemoptysis; the symptoms were present for three days prior to admission. Computed tomography angiography was performed, there were no signs of embolism, however it did show massive consolidations of pulmonary parenchyma with excavation which could be caused by COVID-19. Initially, he was hospitalized in regional medical center where COVID-19 was confirmed using PCR method, and was treated using chloroquine (1000 mg/daily) and dual antibiotic therapy (fluoroquinolone and the third generation cephalosporine) with symptomatic support. Despite treatment, no clinical and radiological improvement was achieved, and the patient was transferred to the Clinical Center of Serbia.

On admission patient had fever (37.7°C), was hypotensive (90/60 mmHg), however he maintained oxygen saturation (O_2sat 98%). Hemoptysis was still present. Blood analysis had shown neutrophilia (77.6%), elevated sedimentation rate (20 mm/h), C reactive protein (20.2 mg/l) and presepsin (726 pg/ml). Initially, he was treated with azithromycin.

Chest X ray had findings highly indictive for COVID-19 infection. However, changes in both upper lobes were suspicious for tuberculosis (Figure 1).

Further anamnestic data had shown that six months prior to current infection, the patients' father was diagnosed and treated for active tuberculosis. Our experience so far had shown that hemoptysis is not a sign for COVID-19 pneumonia. Considering that the patient had been in contact with tuberculosis, we have collected patients' sputum. In sputum, using PCR method, *M. tuberculosis* was discovered, and was further confirmed using cultivation on Mycobacteria Growth Indicator Tube. The patient was started on antituberculotic treatment (Isoniazid 300 mg/daily, Rifampicin 600 mg/daily, Pyrazinamide 1200 mg/daily, Ethambutol 1200 mg/daily).

Five days after the beginning of the treatment, the patient was afebrile, with subjective and clinical improvement. Since coughing had stopped, the control sputum was not taken. After receiving two negative PCR tests for COVID-19, the patient was discharged.

DISCUSSION

COVID-19 is responsible for the current global pandemic. As of writing this case report, over 15 million people are infected globally, and over 600,000 people have died due to its' complications [12]. It is known that patients with chronic illnesses and compromised immune system are more susceptible to infection as well as development of more severe forms of the disease. It should be noted that symptoms of pneumonia caused by this virus do not differ from symptoms caused by other pathogens.

Tuberculosis (TB) is still one of the most important epidemiological problems. According to World Health Organization, between eight and ten million people annually get infected, and roughly three million people of tuberculosis. Vaccine and modern therapeutic methods have virtually eradicated TB in developed countries, although the presence of HIV and other causes of immunodeficiency have challenged this claim [13].

Symptoms of both of these diseases are relatively similar: fever, cough and fatigue. Initial computed tomography scan in this patient did show changes indictive for bilateral COVID-19 pneumonia. The diagnosis cannot be based solely on radiographic finding, as both infections can have atypical findings, and can be completely normal. Despite having positive PCR test for COVID-19, which could explain almost all clinical, radiological and biochemical findings, the presence of hemoptysis demanded further testing. Detailed medical, especially socio-epidemiological, history, and the presence of bilateral apical findings on follow-up X-ray were crucial in narrowing of possible diagnosis. After positive PCR and cultivation on Mycobacteria Growth Indicator Tube, it was clear that the patient had COVID-19

and TB coinfection. Only after simultaneously treating both diseases did the patient show signs of improvement, he was no longer febrile and hemoptysis stopped. Follow-up chest X ray, after initiating both treatments, was almost unchanged, which is expected in TB infections after such a short period of treatment. The control of TB infections is still a vital medical problem. The emergence of COVID-19 pandemic has caused that other pulmonary diseases are being taken into consideration significantly less frequent. Tuberculosis is curable in majority of cases, but if left undiscovered and untreated, can lead to serious problems, primarily health related, especially in the wake of the new pandemic. Preventive methods of COVID-19 do not differ significantly, when compared to TB. Mandatory face masks, with special regards to particular masks, which is present in many countries globally, as a tool of combating COVID-19, also reduces the transmission of TB. It is understandable that COVID-19 is priority number one, however, one must not forget the incidence and mortality that TB causes daily [14–17].

The main purpose of this paper is to emphasize the importance of overall approach to the patient despite COVID-19 pandemic. The authors of this paper strongly believe that the number of patients with COVID-19 and TB coinfection is much larger than currently presented, and that many cases are left unrecognized. Regarding our patient, it is still unclear whether the asymptomatic infection with *M. tuberculosis* has caused the compromise of immune system and in turn made the patient susceptible to COVID-19, or that the viral infection was the trigger for reactivation of TB. Regardless, the simultaneous treatment of both diseases has given excellent results.

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Ethical standards: Written consent to publish all shown material was obtained from the patient.

Conflict of interest: None declared

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Непрепозната туберкулоза код болесника са инфекцијом *COVID*-19

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САЖЕТАК

Увод *COVID*-19 је одговоран за пандемију која је присутна широм света. Преко 15 милиона људи је заражено овим инфективним агенсом, а нешто преко 600.000 људи је преминуло због компликација изазваних инфекцијом. Добро је познато да су особе са хроничним болестима и слабијег имунитета подложније инфицирању и развоју тежих клиничких форми болести. Туберкулоза је још увек један од највећих епидемиолошких проблема. Заједничко за ове две заразне болести је то што се могу манифестовати истим симптомима и на време се не дијагностиковати. Приказујемо болесника код кога је иницијално лечена инфекција *COVID*-19, туберулоза је откривена као коинфекција, а опоравак је започео тек после лечења и туберкулозе.

Приказ болесника Болесник је 27-годишњи мушкарац, непушач, без хроничних болести. Због тегоба у виду повишене телесне температуре, малаксалости, кашља са искашљавањем свеже крви у трајању од неколико дана учињена је компјутеризована томографија пулмоангиографија. Налаз је показао масивне консолидације плућног паренхима са знацима екскавације које би могле одговарати пнеумонији коју је изазвао *COVID*-19. Вредност телесне температуре је и даље била повишена, уз повремено искашљавање свеже крви. На радиографији грудног коша осим обостраних мрљастих промена које су вероватно последица инфекције *COVID*-19, уочавају се промене у горњим режњевима, које би могле одговарати специфичном процесу. Туберкулоза је доказана у спутуму, методом *PCR* и *MGIT*, и тек после лечења обе болести стање болесника се побољшало.

Закључак Досад је описано свега неколико случајева истовремене инфекције *COVID*-19 и туберкулозе. Став аутора овог рада је да је инциденца много већа, али су случајеви остали непрепознати.

Кључне речи: *COVID*-19; туберкулоза; инфекција; дијагноза

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Macrophage activation syndrome complicating early course of adult-onset Still's disease

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SUMMARY
Introduction Adult-onset Still's disease is a rare inflammatory disorder of unknown etiology. It can be complicated by macrophage activation syndrome, a potentially life-threatening condition. While macrophage activation syndrome and adult-onset Still's disease share similar features, early recognition is very difficult in clinical praxis.
Case outline We report a young woman, whose illness was presented suddenly, with spiking fever, sore throat, myalgia, arthralgia, and maculopapular rash. In suspicion of sepsis, she received antibiotics, despite no evidence of infection. After two weeks, her condition worsened, which was followed by cytopenia, elevated liver enzymes, and high serum levels of ferritin. She was diagnosed with macrophage activation syndrome in the early course of adult-onset Still's disease. She was treated with high doses of corticosteroids and cyclosporine A and recovered completely.
Conclusion Macrophage activation syndrome can occur at the beginning of adult-onset Still's disease. Early recognition and timely administration of immunosuppressive drugs are important for the successful outcome in this condition.-
Keywords: macrophage activation syndrome; adult-onset Still's disease; hyperferritinemia

INTRODUCTION

Macrophage activation syndrome (MAS) is a severe, hyperinflammatory, life-threatening complication of an inflammatory rheumatic disease, primarily in adult-onset Still's disease (AOSD) and systemic lupus erythematosus. Among children with juvenile idiopathic arthritis (JIA), MAS is most frequent in systemic onset (sJIA). MAS is a secondary form of hemophagocytic lymphohistiocytosis (HLH). HLH is classified into the primary (genetic) and the secondary (reactive) form, which can be induced by an infective, autoimmune, or malign-related disease. MAS is caused by widespread activation and proliferation of cytotoxic CD8+ T cells and macrophages, which express hemophagocytic activity. Immune dysregulation leads to the extensive production of proinflammatory cytokines: interleukin (IL)-2, IL-1, interferon-γ, IL-6, IL-18, and tumor necrosis factor alfa which results in the "cytokine storm" [1]. Clinical presentation is sustained fever, lymphadenopathy, hepatosplenomegaly, dysregulation of the central nervous system, and hemorrhagic manifestation. Blood analysis showed pancytopenia, elevated liver enzymes, falling erythrocyte sedimentation rate (due to hypofibrinogenemia), disturbances of hemostasis, significantly more elevated serum level of ferritin than in other autoimmune diseases [2].

It has been estimated that the incidence of MAS in patients with AOSD ranges 10–25%. MAS can occur any time during the disease and can be activated by an infection or a flare of the basic disease. The mortality rate of MAS in rheumatic diseases is up to 30% [3]. While MAS and AOSD share similar features (fever, hepatosplenomegaly, elevated liver enzymes, hyperferritinemia), in absence of diagnostic criteria for MAS in AOSD, early recognition of this state or condition is very difficult in clinical praxis. If inadequately treated, MAS can result in multiorgan failure and death.

We present a patient with AOSD complication in the early MAS course and successfully treated with high doses of steroids and cyclosporine A.

CASE REPORT

A 33-year-old Caucasian women was admitted to our hospital with suspicion of AOSD. A month before admission, the illness was presented suddenly, with sore throat, spiking fever of 39.4°C, myalgia of arms and legs, and painful knees. Also, she had a salmon-colored rash on arms and legs. She had vesicles in the mouth during one day. She was admitted to a local hospital and initially received antibiotics for 10 days (amoxicillin three days, ceftriaxone seven days), without improvement. Laboratory studies showed erythrocyte sedimentation rate (ESR) 90 mm/h, leukocytes 17.5×10^9/L with neutrophils 91%, serum hemoglobin 111 g/L,

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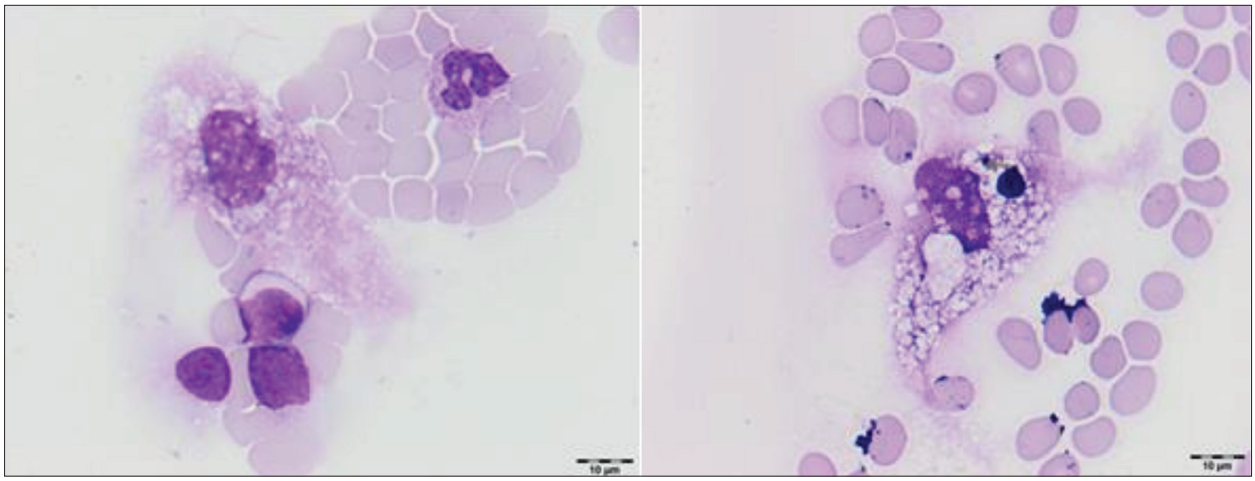

Figure 1. Cytological smear of bone marrow aspiration; in hypocellular bone marrow, a few macrophages were found and only one showed hemophagocytosis, which is not enough for macrophage activation syndrome diagnosis (May–Grunwald–Giemsa, 1000×)

platelets 199 × 10^9/L. In suspicion of sepsis, the patient was treated with empiric widespread spectrum of antibiotics and antimycotics, despite no evidence of infection. After two weeks of treatment, she became febrile continuously (> 40°C). At that time, laboratory findings showed thrombocytopenia 53 × 10^9/L followed by pancytopenia and elevated liver enzymes. Serum ferritin level was extremely high (24,900 μg/L). The suspicious of AOSD and administration of corticosteroids started with a dose of 60 mg per day. The patient's state was deteriorating despite the treatment, and after 25 days she was transferred to our hospital.

On admission to our department, the patient had a fever of 38.3°C, the blood pressure was low (80/60 mmHg), auscultatory method showed heart murmur of the mitral valve 2/6, skin and conjunctivae were icteric. The abdomen was diffusely tender and hepatosplenomegaly was detected. Her knees were tender, with the overall impression of a severely ill patient. Blood test showed ESR of 13 mm/h, C-reactive protein of 20.68 mg/L (< 5 mg/L), leukocytes of 1.37 × 10^9/L (4–10 × 10^9/L), neutrophils of 0.4 × 10^9, erythrocytes of 2.74 × 10^9 (3.8–5.8 × 10^9/L), hemoglobin of 74 g/L (130–180 g/L), platelets of 25 × 10^9 (160–370 × 10^9). Chemistries showed: albumin 23 g/L (32–50 g/L), total bilirubin 74 μmol/L (< 18 μmol/L), aspartate aminotransferase 144 U/L (< 37 U/L), alanine aminotransferase 384 (14–59 U/L), alkaline phosphatase 1161 (70–290 U/L), lactate dehydrogenase 703 (120–246 U/L), γ-glutamyl transferase 968 (< 38 U/L), triglyceride 3.52 mmol/l (< 1.7 mmol/L). Coagulation studies showed fibrinogen 1.5 g/L (2.1–4 g/L), D-dimer 6.98 mg/L (< 0.5 mg/L), international normalized ratio at 1.26, activated partial thromboplastin time 34 seconds. Ferritin was elevated to 14,600 μg/l (20–280 μg/L). Two sets of blood and urine cultures were negative. Aspiration of bone marrow showed hypocellular pattern with macrophages in normal bloodline and only one macrophage, which showed hemophagocytosis (Figure 1). Subsequent serology tests showed negative findings for rheumatoid factor (RF), antinuclear antibodies (ANA), anticardiolipin antibodies, lupus anticoagulant, anti-beta2-glycoprotein I antibodies, antineutrophil cytoplasmic antibody, and antimitochondrial antibodies. Extensive testing for infectious diseases showed that Epstein–Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, hepatitis B, hepatitis C, and human immunodeficiency were negative. Transthoracic and transoesophageal ultrasound of the heart detected mitral regurgitation 2+, without any evidence of vegetation. Computed tomography (body scan) showed only hepato-splenomegaly without any pathologic morphological findings.

Due to the aforementioned findings, the suspicion for MAS was raised. Pulse dosing of methylprednisolone 500 mg daily was started for three days, continued with antibiotics (4.5 g of tazobactam intravenously every eight hours, 1 g of vancomycin every 12 hours, 1 gram of amikacin per day, and 200 mg of fluconazole per day). The patient became afebrile, but moderate bleeding appeared. Analyses showed that hematologic parameters dropped (leukocytes 0.51 × 10^9/L, hemoglobin 74 g/L, platelets 22 × 10^9). She was transferred to an isolation unit. Bone marrow biopsy showed hypoplastic pattern and did not reveal evidence of hemophagocytosis or hematological malignancy. Then we started treatment with dexamethasone of 32 mg in two doses, intravenous immunoglobulin (IVIG) 400 mg/kg per day for three days. Due to the absence of improvement of the hematological parameters, cyclosporine A was introduced in a dose of 5 mg/kg/day (with continuing until 200), continuing with high doses of dexamethasone. Following this kind of regimen, hematological parameters were improved on the seventh day, with fibrinogen normalized as well.

After three weeks, the patient was without complaints and blood tests resolved, except easily elevated γ-glutamyl transferase and ferritin (634 μg/L). The patient was discharged, with prescribed therapy of 0.5 mg of dexamethasone and 5 mg/kg/day of cyclosporine A, with planned gradual reduction. During the follow-up at the outpatient clinic over the next 12 months, the patient was without medical problems. Currently, her therapy is 0.5 mg/kg/day of cyclosporine.

This case report was approved by the institutional ethics committee, and written consent was obtained from the

patient for the publication of this case report and any accompanying images.

DISCUSSION

AOSD is a rare, systemic, inflammatory disease of unknown etiology. Its estimated incidence rate is 0.16–0.4 cases in 100,000 people, and the prevalence is 1–34 cases in one million people [4]. The characteristic triad is a spiking fever, arthralgia and salmon-colored maculopapular rash. Typical blood analyses show leukocytosis (mostly neutrophils), elevated acute phase reactants, high serum levels of ferritin, and negative RF and ANA. Also, elevated liver function tests (enzymes in the blood) can be found. If suspicion for AOSD exists, diagnosis is made by excluding many other diseases with similar presentation including other autoimmune disorders.

In our patient, sepsis was a leading concern at the beginning, and she had received empirical antibiotics. Sepsis and MAS have similar clinical presentations; extensive findings for an infectious disease did not find any cause for concern, and sepsis was excluded. Hence, the initial clinical presentation was the early course of AOSD. Our patient had all four major criteria (fever of 39°C or higher for more than week, arthralgia, skin rash, leukocytosis > 10,000 mm^3 with > 80% granulocytes) and most of the minor criteria (sore throat, splenomegaly, elevated liver enzymes, negative RF and ANA) for AOSD [5]. Two weeks later, the fever became persistent, followed by pancytopenia, hypofibrinogenemia, with an extreme elevation of ferritin level in the blood. This is indicated in the expression of MAS in the initial course of AOSD. At that moment, there are no valid diagnostic criteria for MAS in rheumatologic diseases in adults, and according to the literature data, we apply recommended HLH-2004 diagnostic guidelines [6]. In our patient, based on five of the eight HLH criteria (persistent fever, splenomegaly, 3-line cytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia) the diagnosis of MAS could be done.

Although the finding of hemophagocytosis in bone marrow applies to the gold standard of diagnosis of HLH, it is not determined in 30% of patients [7]. This can be explained with hemophagocytosis in other organs such as the liver, the spleen, and the lymph nodes, which we did not examine in our patient.

Hyperferritinemia is a significant laboratory feature in MAS – it is not only an indicator of the acute inflammatory response, but it also has an immunomodulatory role. Extremely high serum values of ferritin play a role in the high release of cytokines. According to the contemporary findings, four conditions are classified as "hyperferritinemic syndrome": septic shock, catastrophic antiphospholipid syndrome, MAS, and AOSD [8]. There was no evidence of antiphospholipid syndrome or sepsis in our patient.

Treatment of patients with MAS was aimed at eliminating a potential cause of abnormal immune responses and using immunosuppressive drugs for the suppression of a harmful inflammatory response. Traditional therapy in patients with MAS and AOSD includes high-dose corticosteroids and immunosuppressive drug administration, preferably cyclosporine, IVIG, and less methotrexate, cyclophosphamide [9]. In patients refractory to traditional therapy, IL-1 receptor antagonist, anakinra, has a significant effect in interrupting cytokine network, which leads to clinical recovery. This was demonstrated in patients with MAS in sJIA [10]. Another human anti-IL-1β monoclonal antibody, canakinumab, could be used in refractory patients with MAS and AOSD, which is unfortunately not available in all countries [11]. In recent years, several genetic and immunological studies are trying to elucidate the pathogenic mechanism in adult MAS patients and lead to advances in the possible new therapeutic targets in the management of MAS [12]. It is quite clear that IL-1 receptor antagonists in the future may be the main drugs in treating AOSD-associated MAS patients.

In patient with fever of unknown etiology, AOSD should be considered as a possible cause. Postponing the administration of immunosuppressive therapy can be complicated by MAS. The leading findings that support the development of MAS in the AOSD are pancytopenia and hypofibrinogenemia. The timely application of high doses of corticosteroids and early introduction of cyclosporine A lead to an approving outcome of the disease.

Conflict of interest: None declared.

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Синдром активације макрофага као ране компликације Стилове болести код одраслих

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САЖЕТАК

Увод Стилова болест код одраслих је ретко запаљенско обољење непознате етиологије. Може се компликовати синдромом активације макрофага, који може да буде животно угрожавајуће стање. Како синдром активације макрофага и Стилова болест код одраслих имају сличне клиничке одлике, њихово разликовање у клиничком раду је тешко.

Приказ болесника Приказали смо младу, претходно здраву болесницу чија је болест започела наглим порастом температуре, гушобољом, миалгијама, артралгијама и макулозном оспом. Због сумње на септичко стање лечена је антибиотицима, иако није било доказа за инфекцију. После две недеље њено опште стање се погоршало, што је било праћено панцитопенијом, повишеним вредностима ензима јетре и врло високом концентрацијом феритина у крви. Дијагностикован је синдром активације макрофага у раној фази Стилове болести код одраслих. Терапија високим дозама глукокортикоида и циклоспорина А довела је до потпуног опоравка болеснице.

Закључак Синдром активације макрофага се може испољити у раној фази Стилове болести код одраслих. Рано препознавање и правовремена примена имуносупресивне терапије су неопходни за повољан исход болести.

Кључне речи: синдром активације макрофага; Стилова болест код одраслих; хиперферитинемија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Multiple primary synchronous tumors in the lungs

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SUMMARY
Introduction The aim of this paper was to report a case series of three patients diagnosed with multiple primary synchronous cancers (MPSC) in the lungs who were treated multidisciplinary at a single-center institution.
Outline of cases Three male patients were referred to the Clinic for Chest Surgery, at the Military Medical Academy in Belgrade, Serbia for planned surgical treatment of lung cancers. During subsequent diagnostic procedures, second primary synchronous tumors were detected in all presented cases. All patients underwent surgical resection and chemotherapy or a combination of chemo- and radio-therapy. Two out of three patients died with an average survival period of 32 months. One patient is still alive, with current disease-free interval of 21 months.
Conclusion MPSC is a rare condition. The final diagnosis should be based on clinical, radiological, histopathological, and genetic analyses. Treatment modalities of MPSC depend on the clinical staging of the disease, patient's general medical condition, and general assessment of tumor operability and resectability.
Keywords: lung cancer; multiple tumors; synchronous tumor; resection

INTRODUCTION

Epidemiological studies have reported the incidence of multiple primary lung cancers (MPLC) from 5.6–22% [1–4]. Genetic predisposition and environment exposure contribute to the development of MPLC [1]. The increased incidence of MPLC results from advances in screening and diagnostic procedures coupled with higher patient survival rates due to a more sophisticated treatment of the first primary lung cancer [1, 5].

Multiple primary tumors are tumors that arise in different sites and are of different histology and morphology characteristics [1]. The definition of MPLC has changed over time and differs according to different studies and guidelines. Last update of criteria for MPLC comes from American College of Chest Physicians in 2013, while the present most commonly used definitions of multiple primary tumors in general are the ones from the Surveillance Epidemiology and End Results project and International Association of Cancer Registries and International Agency for Research on Cancer [4, 6, 7]. Nowadays, molecular analysis provides precise differentiation between multiple primaries and intrapulmonary metastasis [8, 9, 10]. Comprehensive histologic assessment is another proposed concept which may have advantages over molecular analyses, because it is more rapid and inexpensive [11, 12, 13].

MPLC can be synchronous or metachronous. Synchronous tumors are defined as two or more primary neoplasms detected simultaneously or within an interval of less than six months, while metachronous tumors are diagnosed if the interval of occurrence is longer than six months [6]. Synchronous primary lung cancers (SPLCs) occur less frequently with the incidence of 0.2–8%. It is important to make a distinction between MPLC and metastatic or recurrent primary tumors in order to provide optimal therapy.

The aim of this manuscript is to present a series of three patients diagnosed with MPLC and treated multidisciplinary at a single-center institution. Written informed consent was obtained from all patients or their family member in case of the deceased patients.

CASE REPORTS

Case 1

A 72-year-old male was admitted to the Military Medical Academy in Belgrade, Serbia for planned surgical treatment of adenocarcinoma located in the right lower lobe of the lung. The chest computed tomography (CT) showed a mass lesion of approximately 27 mm in diameter in the right lower lobe and another mass lesion (21 mm in diameter) of unknown etiology in the left lower lobe, without significant lymphadenopathy (Figure 1). Subsequent bronchoscopy revealed normal findings, while the cytological tests showed the presence of adenocarcinoma cells in the right lung. Due to the pathological change in the right lung, the patient underwent right lower lobectomy in February 2017 and histopathological findings confirmed a solid type of infiltrating adenocarcinoma. In June 2017 a control chest CT showed the remaining tumor

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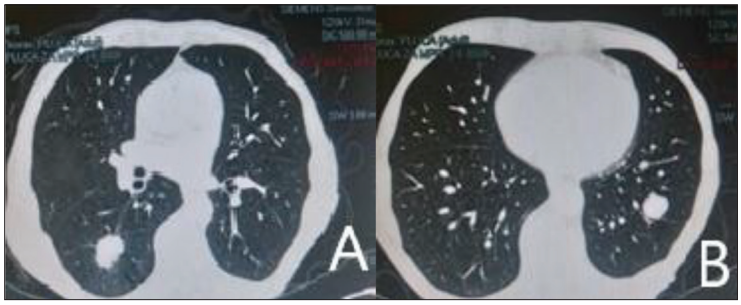

Figure 1. Multi-slice computed tomography findings of pathological masses in (A) the right and (B) left lower lobes of the lung

in the left lung. Six months after the initial surgery the doctors' committee decided to perform atypical resection in the left lower lobe. The final diagnosis of synchronous primary lung typical carcinoid was made based on different morphological features of the tumors. Therefore, adjuvant oral chemotherapy (HT), Vepesida pills, was combined with surgery. Less radical procedure with a delay of six months was chosen for second surgery due to patient's poor general condition. The patient is still alive, 21 months after the second surgery. The characteristics of the present case are given in Table 1.

Case 2

A 56-year-old male was referred to our institution due to productive cough and fever in December 2010. CT of the thorax showed a larger mass (50 mm) in the right upper lobe and a smaller mass (33 mm) in the right lower lobe along with enlarged mediastinal bronchopulmonary lymph nodes (up to 15 mm in diameter) and diffuse bullae. Abdominal CT did not reveal the presence of any pathological changes. Bronchoscopy revealed normal findings, while the cytological tests showed the presence of planocellular malignant cells in the right lung, which was confirmed by needle biopsy and histological analysis of the tumor.

In January 2011 the patient underwent right pneumonectomy with systematic lymphadenectomy.

Table 1. Characteristics of presented cases

Case number	Sex	Age	Smoker	Histopathological diagnosis	TNM classification	Localization	Diameter	Diagnostic procedure	Therapy	Disease-free survival
1	Male	72	Yes	Primary tumor: Adenocarcinoma *Secondary (synchronous) tumor: Typical carcinoid	pT1cN0Mx T1cN0Mx	Right lower lobe Left lower lobe	27 mm 21 mm	Bronchoscopy CT Immunohisto-chemistry	Right lobectomy (02/2017) Lower left atypical resection (08/2017) Adjuvant oral therapy (Vipesid capsules)	Patient is still alive, 21 months after second surgery.
2	Male	56	Yes	Primary tumor: Non-small cell lung cancer (squamous cell carcinoma) **Secondary (synchronous) tumor: Adenocarcinoma (acinar type)	T2bN0M0 T2aN0M0	Right upper lobe Right lower lobe	50 mm 33 mm	Standard Chest X-Ray Bronchoscopy CT Needle biopsy Immunohisto-chemistry	Right pneumonectomy with systematic lymphadenectomy (01/2011) Postoperative radiotherapy Four cycles of gemcitabine and platinum adjuvant therapy	Died in 02/2015 with clinical manifestation of pulmonary thromboembolism
3	Male	58	Yes	Primary tumor: Non-small cell lung cancer (squamous cell carcinoma) *Secondary (synchronous) tumor: Adenocarcinoma	pT1cN2Mx pT2NoMx	Right upper lobe Left upper lobe	23 × 17 mm 22 × 13 mm, tumor infiltrating visceral pleura	Bronchoscopy Transbronchial needle aspiration CT Immunohisto-chemistry	Right upper lobectomy with systematic lymphadenectomy (08/2016) Six cycles of gemcitabine and cisplatin adjuvant therapy Atypical resection (03/2016) Three cycles of Taxol and cisplatin adjuvant therapy	Died in 03/2018 due to liver metastases

TNM – tumor, lymph nodes, and metastasis;
*diagnosed at the same time;
**diagnosed and operated on at the same time

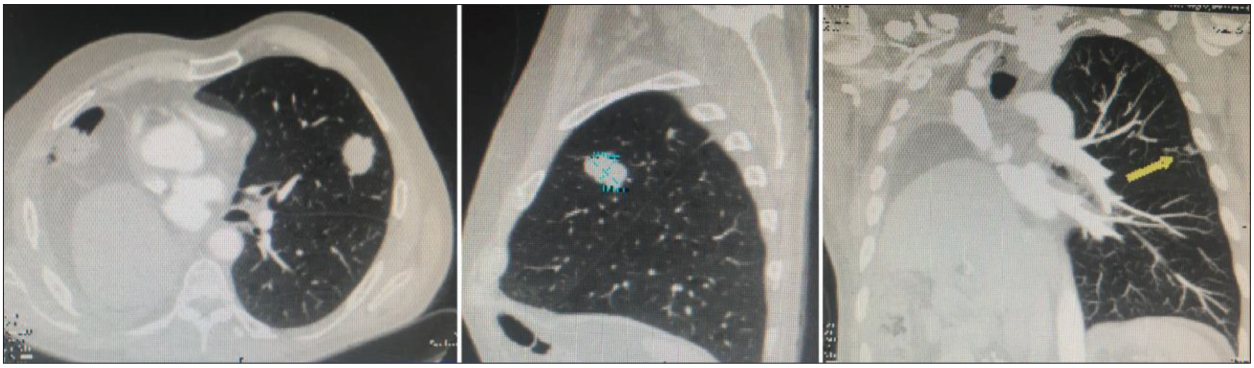

Figure 2. Multi-slice computed tomography finding of secondary deposits in the left lung

Histopathological analysis revealed the diagnosis of planocellular carcinoma in the lesion located in the right upper lobe, and acinar type adenocarcinoma with a formed scar in the tumor in the right lower lobe. Following the decision of the doctors' committee, the patient underwent four cycles of Gemcitabine and Platinum adjuvant HT. In 2012, the patient was reevaluated and control X-ray and CT showed the new nodule in left lung (sized to 12 mm) (Figure 2). Consequently, patient continued with adjuvant HT (III cycles of Paclitaxel – Platinum protocol). Reevaluation in January 2013 showed the enlargement of pathological mass in left lung and patient underwent additional adjuvant therapy with two cycles of Docetaxel. In December 2013 patient presented with the pain under the right rib, loss of appetite and poor general condition. Control chest CT showed the presence of pathological mass in the left lung sized 50 × 50 mm and enlarged local lymph nodes up to 18 mm in diameter. Abdominal CT showed the presence of expansive mass in right liver lobe (70 mm) and nodes in both adrenal glands (up to 20 mm in diameter). The patient received Erlotinib therapy during next four months. After that therapy, the mass in left lung was unchanged and all pathological changes in abdomen were in regression. In February 2015 patient died with clinical manifestation of pulmonary thromboembolism (Table 1).

Case 3

A 58-year-old male was referred to our institution for evaluation of non-microcellular carcinoma in the right lung. The initial chest CT revealed a mass lesion of 23 × 17 mm in the right upper lung lobe along with paratracheal lymphadenopathy (≤ 13 mm) and another mass lesion in the left upper lobe (22 × 13 mm in size) (Figure 3). Subsequent bronchoscopy revealed normal findings Transbronchial needle aspiration of lymph nodes showed no malignant cells, while the cytological analysis of the right bronchus revealed malignant cells of non-microcellular carcinoma. Believing that the change in the left lung might be a metastasis of the previously diagnosed primary carcinoma in the right lung, left atypical resection was performed in March 2016. Intraoperative findings revealed a subpleural tumor mass (22 mm in diameter) affecting the visceral pleura. No lymphovascular or perineural infiltration was observed. Final histopathological analysis confirmed infiltrating estimated glomerular filtration rate (EGFR) wild type adenocarcinoma. After the initial surgery, the patient underwent three cycles of Taxol and Cisplatin adjuvant therapy.

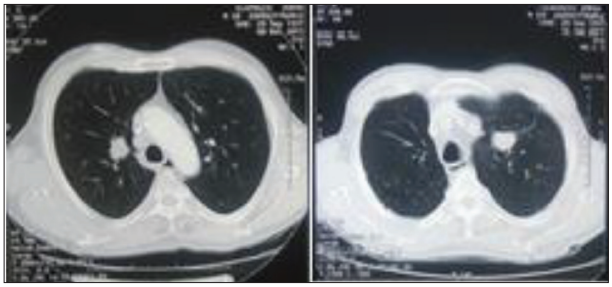

Figure 3. Multi-slice computed tomography findings of pathological masses in the lungs

Follow-up CT showed the remaining pathological mass in the right lung. In August 2016 the patient underwent right upper lobectomy with systematic lymphadenectomy. Histology confirmed infiltrating squamocellular lung carcinoma. Subsequently, the patient received six more cycles of Gemcitabine and Cisplatin adjuvant therapy. The patient lived for 20 months after the second surgery and died in March 2018 due to liver metastasis. The characteristics of present case are given in Table 1.

DISCUSSION

MPLC represents a significant challenge in everyday clinical practice, mostly due to difficulties in diagnosis and treatment of such conditions. To the best of our knowledge, the only report of MPLC in Serbia was published by Kontic et al. [14] in 2011. Therefore, the present article is the largest addressing these tumors in Serbian population.

Adenocarcinoma was reported in all three patients as one of the tumors. Furthermore, typical carcinoid and squamocellular carcinoma, were identified as second primaries. Our findings corroborate the results of a previous study [4]. Namely, Bhaskarla et al. [4] analyzed data of 702,120 patients diagnosed with primary lung cancer and reported that a second primary lung cancer had developed in 1.5% of the investigated population. Adenocarcinoma and squamous cell carcinomas were the most commonly diagnosed second primary lung cancers [4].

The differential diagnosis between MPLCs and a recurrence, metastatic, or satellite lesion arising from the original tumor is difficult. Distinguishing SPLCs and advanced disease is important because their prognosis and treatment are different and a surgical approach to SPLC may result in survival similar to solitary cancers [1, 15]. Sometimes, clinical or radiological evidence is not sufficient to undoubtedly differentiates these conditions. Apart from histopathological reports used as a gold standard, genetic analyses of the clonal origin of tumors are useful because these can help to determine whether MPLC have arisen from the same clone and therefore the same tumor [1, 16]. Song et al. [17] reported a patient with six synchronous invasive adenocarcinomas that were revealed due to whole-exome sequencing and analysis of nonsynonymous mutations. Previous studies have reported that mutations in the p53 tumor suppressor gene, mutation of EGFR and analysis of miRNA expression profiles represent reliable tools for diagnosing MPLC [10, 18, 19]. Therefore, these should be included in diagnosing MPLC [16]. A recent study demonstrated the more frequent disagreement of PD-L1 expression in patients with MPLC in comparison to patients with metastasis [9].

Although recommendations for the management of MPLCs have been published by three major lung cancer research institutes (Union for Inter-national Cancer Control, American Joint Committee on Cancer, and International Association for the Study of Lung Cancer), controversies still exist [5].

In general, the treatment of multiple primaries should cover all identified tumors and be conducted by a multidisciplinary team [1, 5]. According to the guidelines of the American College of Chest Physicians, surgical resection remains the treatment of choice for MPLCs whenever possible [6]. Namely, surgery may be performed if sufficient pulmonary reserve can be obtained after multiple lesions are resected [6]. Surgeons taking characteristics of the tumor and status of patients into consideration mainly decide the extent of resection [5]. For MPLC, which occur in the same lung, anatomical resections (single, bilobectomy, or pneumonectomy) might be recommended [20]. We have included additional HT in all our cases. It was a decision after its presentation to the multidisciplinary team. Chang et al. [21] demonstrated that anatomical resection of the first lesion and limited resection of the second might be safer option for synchronous bilateral lesions. The initial surgery should be performed on the side with the largest tumor [15]. In case of a resectable tumor, but the patient's low intolerance to surgery due to impaired cardiopulmonary function, local therapy is an optional strategy. One of the options is stereotactic body radiation therapy (SBRT) [5]. Varlotto et al. [22] described that the overall survival rate, recurrence rate, and loco-regional control rate of SBRT treatment were acceptable compared with those obtained after surgical treatment. SBRT is limited by respiratory movements, and the complication of radiation pneumonitis. Patients who do not qualify for surgery may also receive percutaneous image-guided tumor radio frequent ablation (RFA) [5]. The advantage of RFA lies in the ability to locally heat tumors to a lethal temperature with minimal damage to surrounding normal lung tissue [23]. The limitations of CT-guided percutaneous RFA in lung tumor therapy is the high incidence of complications, such as pneumothorax, hemothorax, and bronchopleural fistula [24]. A novel option presented in a case report by Teng et al. [25] is percutaneous RFA utilizing an electromagnetic navigation platform.

One of our patients is still alive, 21 months after the second surgery, while the other two died approximately four and two years after surgery. Disease-free interval reported by Bhaskarla et al. [4] was 3.3 years. Longer survival intervals were significantly associated with the lower stage of disease and complete resection of the second carcinoma [4]. Recent studies showed five-year survival rates of 71.3% and 74% [10, 26].

In conclusion, MPLC is a rare condition. The final diagnosis should be based on clinical, radiological, histopathological and genetic analyses. Treatment of MPSC depends on the clinical staging of the disease, patient's general condition, and assessment of tumor operability and resectability.

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Вишеструки примарни синхрони тумори плућа

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САЖЕТАК

Увод Циљ овог рада је да се прикажу три случаја вишеструких примарних синхроних тумора плућа који су мултидисциплинарно лечени.

Прикази болесника Три болесника мушког пола јавила су се на Клинику за грудну хирургију Војномедицинске академије у Београду ради планираног хируршког лечења тумора плућа. Током дијагностичких процедура, које су уследиле у сва три случаја, детектовани су додатни синхрони тумори плућа. Сви болесници су хируршки лечени уз додатну хемотерапију или комбинацију хемотерапије и радиотерапије. Два од три болесника су преминула са временом преживљавања од 32 месеца. Трећи болесник је и даље жив, а период без болести је 21 месец.

Закључак Вишеструки примарни синхрони тумори плућа се ретко јављају. Дефинитивна дијагноза треба да се заснива на клиничким, радиолошким, хистопатолошким и генетичким анализама. Начин лечења наведених тумора зависи од клиничког стадијума болести, општег здравственог стања болесника и опште процене операбилности и ресектабилности.

Кључне речи: карцином плућа; вишеструки тумори; синхрони тумори; ресекција

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Trauma, possible cause of localized unilateral hyperhidrosis of the face?

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SUMMARY

Introduction Localized unilateral hyperhidrosis (LUH) is a rare disorder of unknown origin, with multiple possible triggering factors and unknown pathogenesis. Although there are cases of LUH of the face reported, this is the first to report isolated ipsilateral hyperhidrosis of the face after blunt force trauma.

Case outline A 54-year old Caucasian woman presented with facial LUH of five years' duration. Ipsilateral blunt trauma of the temple that preceded the condition for three months was identified as the most probable cause. For sharp demarcation, the Minor's or starch–iodine test was performed, which revealed the presence and extent of the facial sweating on the left side of the face. Treatment with 20% aluminium chloride hexahydrate sol. (Retrargin sol.) was conducted with partial response.

Conclusion After ruling out underlying diseases as a cause of LUH, a prior trauma should be considered as a potential cause. The possible mechanism could be the lesion of sympathetic chain as a result of cervical traction due to a facial blunt force trauma, although it cannot be positively proven.

Keywords: hyperhidrosis; trauma; unilateral

INTRODUCTION

Localized unilateral hyperhidrosis (LUH) is a rare disorder of unknown origin, with multiple possible triggering factors. LUH is usually located on the forehead or the forearm, characterized by sharply demarcated area of hyperhidrosis, and is secondary in nature. The pathogenesis of LUH remains unclear [1]. Although there are cases of LUH of the face reported, to our knowledge this is the first report of isolated ipsilateral hyperhidrosis of the face after blunt force trauma [2, 3, 4].

CASE REPORT

A 54-year old Caucasian woman presented with a five-year history of hyperhidrosis localized to the left side of the face. Ipsilateral blunt assault trauma of the temple caused by a closed fist strike to the face preceded the condition by three months. The patient was admitted with soft tissue injury only, with significant hematoma and swelling, but no fracture. No treatment was required at the time. The hyperhidrosis is aggravated by physical exercise, but unaffected by emotional triggers, gustative stimuli, or environmental temperature changes.

For sharp demarcation, the Minor's or starch–iodine test is performed [5]. Liquid 10% iodine paint is applied to the skin of the face and neck. Once dry, the area is dusted with corn starch. Sweating is provoked by getting the patient to squat repeatedly for two minutes. The violet-black spots in the starched area constitute a positive test, generated by the formation of iodine–starch complex on dissolution of starch by sweat. In this case, distinctive violet patches were visible on the left side of the face and neck mostly in the mental and infraorbital areas, confirming the presence and extent of the facial sweating (Figure 1).

Physical stimulation was continued for additional two minutes and multiple individual dots 0.5 to 1 mm in diameter appeared on the contralateral side, indicating an intact sweating mechanism, thus excluding anhidrosis of the contralateral side.

The patient's medical history included an eight-year history of hypertension, hyperlipidemia, and spondylosis of the cervical spine. Medications included metoprolol, cilazapril, hydrochlorothiazide, bromazepam, and fenofibrate. There was no history of gastrointestinal, urinary, or vascular disorders indicative of sympathetic nervous system dysfunction, including patterns of defecation and micturition, flushing and migraine headaches.

Physical examination revealed no abnormalities. Blood pressure and pulse rate were within the normal range. Full neurological examination including electrophysiological examination of the face was normal. Psychiatric evaluation

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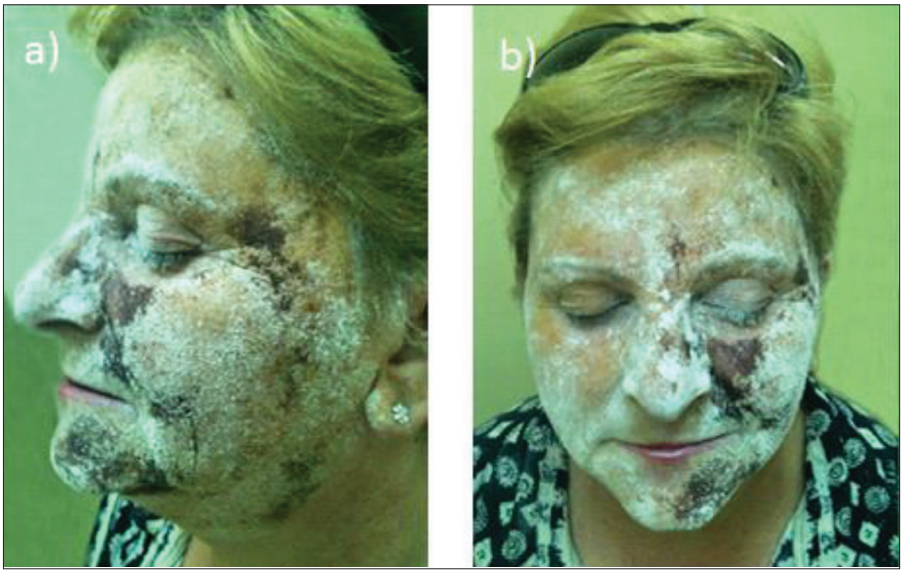

Figure 1. Minor's iodine test, from the (a) profile and (b) straight on views; the starch powder is applied in a patient with localized unilateral hyperhidrosis

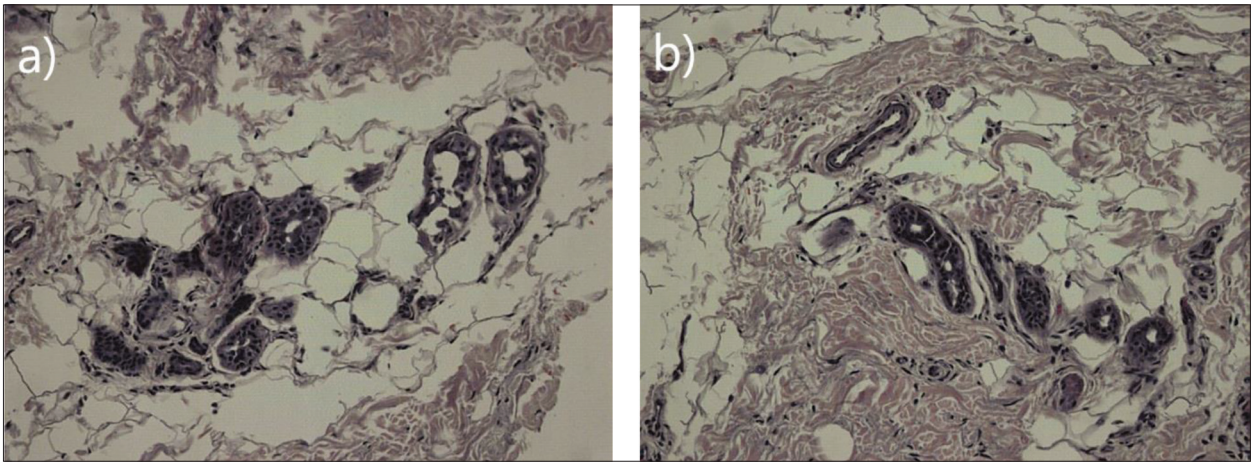

Figure 2. Histopathology of skin biopsies (H&E, 50×); (a) skin biopsy taken from the affected area of the skin and (b) contralateral unaffected area of the skin

revealed no signs of emotional or anxiety disorder. Results of laboratory tests were within normal limits. The computed tomography (CT) scan of the brain, neck, and chest was normal.

Skin biopsies were taken from the affected (Figure 2a) and contralateral unaffected (Figure 2b) areas of the skin.

The histopathology showed the normal number and structure of the eccrine glands, although the diameter of the eccrine duct lumen from the affected area was increased compared to the unaffected side, still within the normal range. These results excluded an eccrine nevoid lesion.

Treatment with daily application of 20% solution of aluminium chloride hexahydrate on the affected area was conducted for five days per week for four weeks and maintained as a three days per week regiment with partial response.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DISCUSSION

LUH is an uncommon condition. The hyperhidrotic area is usually sharply demarcated and measures no more than 10 × 10 cm, and lesions have mostly been reported on the face or forearm of healthy individuals. The reported age of onset varies between seven and 67 years and bouts occur more frequently in the summer than in the winter months. Rarely, LUH is accompanied by contralateral anhidrosis, when hyperhidrosis is generally thought to be compensatory [1]. Pathogenesis of LUH is unclear. Various underlying disorders have been associated with LUH, such as Frey's syndrome, cerebral infarction, Buerger disease, Holmes–Adie syndrome, intra-thoracic malignancies, Riley–Day syndrome, LUH secondary to an eccrine nevus and type 1 neurofibromatosis [6]. As reported by some authors, it can be secondary to trauma or idiopathic [2, 6–11].

Clinical signs of hyperhidrosis are usually visible and Minor's or iodine–starch test is helpful in demarcating the areas of localized hyperhidrosis.

The exact neural pathways of sweating regulated by the autonomic nervous system in humans are not entirely identified and understood. Efferent signals from the primary thermoregulatory center located in the pre-optic hypothalamic regions of the brain travel via the pontine tegmentum and the medullary raphe regions to the intermediolateral cell column of the spinal cord. Neurons from the ventral horn pass through the ramus communicans, combine with peripheral nerves, and travel to sweat glands. In addition, there is also an inhibitory bundle that goes from the frontal operculum, whose lesion at any level can cause hyperhidrosis. Sympathetic system is also responsible for sweating. Sympathetic nerves arise from the intermediolateral nucleus of the lateral grey column, beginning at the first thoracic vertebra of the vertebral column and extend to the second or third lumbar vertebra (Th1–L2, L3). The axons of these neurons travel through the anterior horns and anterior roots of spinal nerves to the sympathetic chain. Cord transection abolishes the supraspinal control of sudomotor function. If someone has impaired sweating above the waist affecting only one side of the body, the lesion is most probably just below the stellate ganglion in the sympathetic chain. The stellate ganglion is located at the level of the seventh cervical vertebrae (C7), anterior to the transverse process of C7, superior to the neck of the first rib, and just below the subclavian artery. Therefore, impaired sweating of the face would probably be due to a lesion of the sympathetic chain at C7–Th1 level [12].

In our case, we speculated that left-sided facial assault injury caused cervical traction (a sort of whiplash injury) in which sympathetic chain was injured, leading to hypohidrosis of the contralateral side (instead of expected anhidrosis) and compensatory hyperhidrosis of the ipsilateral side. Although anhidrosis was clearly excluded by performed tests, hypohidrosis, as a result of partial sympathetic chain lesion (complete transection was never considered for lacking of other symptoms, most prominently Horner's syndrome), could occur with compensatory hyperhidrosis on the side of the trauma, which was the most prominent symptom. Blunt force type of trauma suffered by our patient is known to produce injury of the cervical spine and corresponding structures on both sides. Considering other possible explanations, we must mention Frey's syndrome, in which we have misdirected reconnection of sectioned postganglionic secret motor parasympathetic fibers, which normally innervate the parotid gland to sympathetic receptors, which in turn innervate sweat glands. This results in gustatory sweating. This cannot be an explanation for our case, as in Frey's syndrome "sweating" of the face is exclusively provoked by gustatory stimuli (for example drinking lemon juice), which did not occur in our patient, who had hyperhidrosis continuously [5, 13]. Our patient also did not fulfill criteria for Ross syndrome, a rare condition which consists of Adie's syndrome (myotonic pupils and absent deep tendon reflexes) and segmental anhidrosis typically associated with compensatory hyperhidrosis [14]. A few reported cases were associated with an underlying intrathoracic neoplasm, which has been excluded by thoracic CT scan [1]. It is recorded that strokes affecting the contralateral cerebral hemisphere or its descending connections can result in contralateral hyperhidrosis [15]. However, there are no reasons to believe that our patient had a concomitant stroke. Finally, we must consider a lesion of the peripheral sudomotor nerve fibers. As it was mentioned before, the sudomotor and vasomotor fibers to most of the face separate out at the superior cervical ganglion and anhidrosis or hypohidrosis is often not noticeable in postganglionic lesions. A lesion of local cutaneous small nerve fibers could produce anhidrosis or hypohidrosis on the site of trauma, but the patient had hyperhidrosis on the side of trauma, so this explanation is not applicable and we have to exclude it [12].

LUH can also be associated with emotional or anxiety disorders, and the intensity of symptoms is reported to become tolerable after full de-stress of the patient [16]. In our patient, this etiology was excluded by psychiatric evaluation and follow-up.

There are few reports demonstrating the presence of enlarged sweat glands in the affected skin of patients with localized hyperhidrosis and the lesions have been considered as variants of the pure anatomical eccrine nevi or as functional nevi which showed secondary hypertrophy of the glandular elements, but skin biopsies in our patient failed to reveal such findings [1].

There are no consensus-based criteria for establishing the diagnosis of trauma-based hyperhidrosis, apart for anamnestic data and exclusion of other possible causes of hyperhidrosis or compensatory hyperhidrosis.

There is no standardized therapy for LUH. Treatments are divided into those that work locally on either sweat gland function or on the nervous system that supplies them, and systemic therapy with anticholinergic and anxiolytic drugs. Topical treatment (acids, aldehydes, glycopyrrolate, metal salts e.g. aluminium chloride) is the first choice for localized hyperhidrosis. Botulinum toxin, microwave thermolysis (miraDry®), iontophoresis, systemic medications (anticholinergic and anxiolytic drugs) should be administered if topical treatment is not sufficient or not applicable [17]. Endoscopic thoracic sympathectomy has serious side effects, including compensatory sweating. Considering adverse effects of surgery and systemic therapy, local application of aluminium chloride hexahydrate by the patient is economically acceptable, has satisfactory results, and is a convenient treatment modality [5, 17]. The mechanism of action is postulated to be the induction of eccrine secretory gland atrophy secondary to long-term mechanical obstruction of sweat gland pores by the aluminium salts [5].

The most efficient treatment, with no or few side effects is 6–9 monthly repeated injections of botulinum toxin A, but the cost of this treatment is significant. Medicolegal implications of diagnosing a trauma-caused (compensatory) hyperhidrosis are thus very important. This is one more reason to take a multidisciplinary approach when diagnosing and treating LUH.

CONCLUSION

The approach to a patient with LUH is complex and multidisciplinary. After ruling out an underlying disease, a prior trauma, if present, must be considered as a potential cause. As a possible mechanism of trauma causing LUH in our patient we postulate the lesion of the sympathetic chain induced by a cervical traction after an ipsilateral blunt-assault facial trauma.

Conflict of interest: None declared.

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Повреда као узрок локализоване унилатералне хиперхидрозе лица?

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САЖЕТАК

Увод Локализована унилатерална хиперхидроза (ЛУХ) редак је поремећај непознате етиологије, са многобројним могућим окидајућим факторима, непознате патогенезе. Иако постоје описани случајеви ЛУХ лица, ово је први који илуструје изоловану ипсилатералну хиперхидрозу лица после физичке трауме.

Приказ болесника Приказана је болесница стара 54 године са локализованом унилатералном хиперхидрозом лица која траје пет година уназад. Туп ударац у леву слепоочницу који је три месеца претходио поремећају је идентификован као могући узрок ипсилатералне хиперхидрозе. За јасну демаркацију коришћен је Миноров или тест „јод–скроб", којим је утврђено прекомерно знојење леве стране лица. Спроведена је терапија 20% раствором алуминијум-хлорид-хексахидрата (Ретраргин) са делимичним терапијским одговором.

Закључак После искључења евентуалних постојећих обољења као узрока ЛУХ, трауму која је претходила би требало посматрати као могући узрок. Могући механизам настанка је тракција цервикалне кичме узрокована ударцем у лице и последична лезија симпатичког ланца, иако се наведена тврдња не може са сигурношћу доказати.

Кључне речи: хиперхидроза; траума; унилатерална

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Successfully completed pregnancy after conservative treatment of nonepithelial ovarian cancer

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SUMMARY

Introduction Granulosa cell tumors are rare neoplasms of the ovary with low malignancy potential and late recurrence. They originate from the granulose of the ovary stromal cells and have the ability to produce estrogen. The main treatment is surgical and implies hysterectomy with bilateral salpingo-oophorectomy, omentectomy, taking peritoneal biopsies, and cytological analysis of the peritoneal washing. When found in young women who have not given birth, a conservative approach can be considered. Fertility sparing surgery is safe only for early FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stages IA tumors то IC, where it is necessary to make unilateral salpingo-oophorectomy and complete staging.

Case outline We present a case of young woman with granulosa cell tumor who was accidentally discovered, and after an adequate surgery and chemotherapy she gave a birth to a healthy child.

Conclusion Young women who have not given birth and who have been diagnosed with granulosa cell ovarian tumor can be treated conservatively after adequate disease staging and confirmation that the disease is at an early stage.

Keywords: ovarian granulosa cell tumor; fertility sparing surgery in granulosa cell tumors, treatment; prognostic factors; monitoring

INTRODUCTION

Granulosa cell tumors are rare neoplasms and make up 2–5% of all tumors of the ovary. They belong to the subgroups of the sex cord and are most common in this group (70%) [1]. They originate from the granulose of the ovary stromal cells and have the ability to produce estrogens, and thus lead to a clinical manifestation of disease in the form of vaginal bleeding in postmenopausal or prolonged and irregular bleedings in young patients. There are two types: adult, the most frequent, with a frequency of 95%, occurs in menopausal women, and a juvenile type which is less likely to meet with patients under the age of 30 years. [2]

They are distinguished by the gene mutation at the level of fork head transcription factor 2 (FOXL2) located on chromosome 3q23. This gene is responsible for the normal ovarian function, regulates the proliferation of cellular granuloses, the development of follicles, and the synthesis of ovarian hormone. The mutation of FOXL2 gene leads to dysregulation of TGF-β, resulting in abnormal cell proliferation and tumor formation [3]. Mutations on this gene occurs in more than 97% of the adult tumor granuloses and is rarely detected in other cancers [4].

These tumors are most commonly found in the early stage of the disease. They have good prognosis compared to other ovarian tumors, and five-year survival is over 90% [1]. The main treatment is surgical and implies hysterectomy with bilateral salpingo-oophorectomy, omentectomy, taking peritoneal biopsies, and cytological analysis of the peritoneal washing. When they are discovered in patients in the reproductive period, there is a need to preserve fertility. According to the American National Comprehensive Cancer Network (NCCN) of 2017, a conservative approach is justified in patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IA / IC disease [5].

In the present case, a young patient was diagnosed with a malignant ovarian tumor by accident. Following an adequate disease staging, the patient received adjuvant chemotherapy, and eventually delivered a healthy child.

CASE REPORT

A 27-year-old patient, gravida 0 and para 0 with BMI 17.2 reported to the clinic for surgical treatment of ultrasound diagnostic cysts on the left ovary. The cystic change was 50 × 43 × 20 mm in diameter, with regular Doppler parameters. The patients did not have any discomfort or chronic pain, regular menstrual cycles every 28 days, lasting for five days. In May 2013, a laparoscopic surgery was performed, because there was a cyst with a diameter of five centimeters on the left ovary, partly solid part of the cystic material, the

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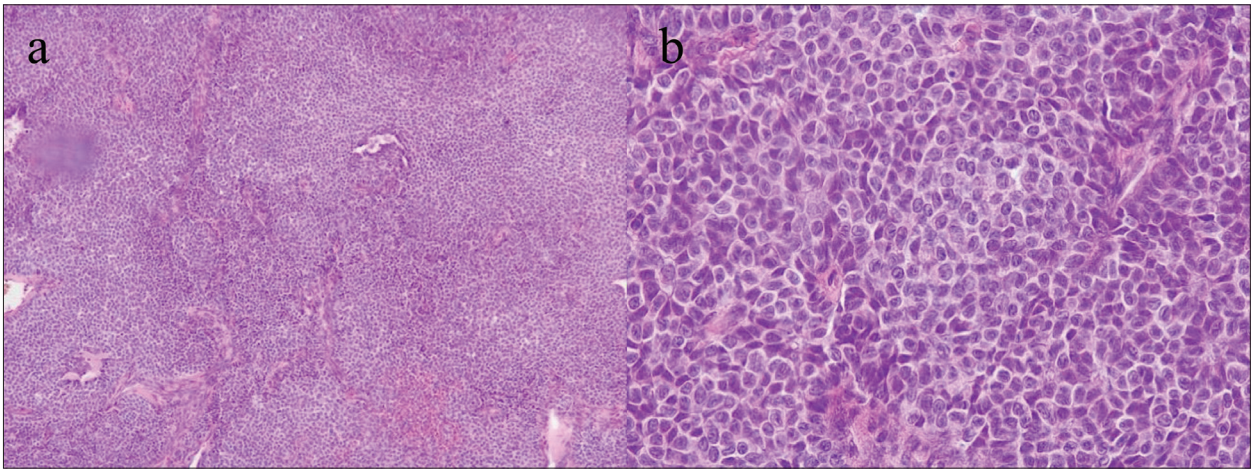

Figure 1. a) The histological features of the tumor: mixed tumor cell population – oval and spindle mononuclear cells with osteoclast-type giant cell (H&E, 100×); b) detail – giant cell soft tissue tumor (H&E, 400×)

uterus, the left ovary, and the fallopian tube were neat and there was no free liquid in the abdomen. A cystectomy of the left ovary was made and the sample was sent in parts to a histopathological examination. The cyst alone had no characteristics indicating malignancy.

Histopathological finding of the cystic ovary involvement indicates that it is a Granulosa cell tumor, an adult type, a medium differentiation, a number of mitosis 3/10, without the involvement of lympho-vascular structures (Figure 1).

Since an inadequate operation was performed for this type of tumor and the stage of the disease was not determined, a month after the first operation, another operation was performed to complete the disease staging according to the FIGO protocol. Lavat, swab paracolic left, right and subdiafragmally were sent to cytological analysis. Left salpingo-oophorectomy, cystectomy and biopsy of the right ovary, and omentum biopsy, were made. Histopathological findings of the left ovary and the fallopian tube are without pathophysiological changes, the biopsy of the right ovary was in order, the removed cyst belonged to the type of paraovarialis cyst and the ometum is also unchanged. The cytological finding was normal without the presence of malignant cells.

Based on this and previous histopathological findings by the multidisciplinary team, the stage of FIGO IC1 disease was identified and it was advised that the patient additionally received three cycles of chemotherapy according to bleomycin, etoposide and cisplatin (BEP) regimen.

After completion of the third cycle of chemotherapy, the repeated magnetic resonance of the small pelvis and abdomen did not show that there were pathological changes and the patient was directed into a regular oncologist regimen.

Three years after the surgery, the patient has undergone in vitro fertilization procedure. An embryo transfer was performed. Pregnancy has passed smoothly without complications. The value of the tumor of the inhibitor B marker that was in order, and was observed the whole time. In July 2017, the patient has undergone a caesarean section, and gave birth to a male child, weighing 3550 grams and 52 cm in length, Apgar score 9/10. Multidisciplinary team advised the patient to undergo a radical surgical procedure of the primary illness after giving birth, which the patient refused.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

Tumors of the sexual cord that belong to granulosa cell tumors are rare ovarian neoplasms with low malignant potential and significantly better prognosis compared to much more common tumors of the ovary of epithelial origin. It is significant that in most cases (about 81%) are detected in the early stage of the disease. Their main characteristic is increased estrogen production. This leads to the occurrence of bleeding in women in postmenopausal, or prolonged menstrual or irregular bleeding as well as amenorrhea in young patients, and these are the main symptoms that cause them to visit a doctor [6, 7]. The second common symptom is abdominal pain caused by the size of the tumor, as it is shown that in about 73.5% of cases, the size is over 10 cm, causing pressure on the surrounding organs and distension of the abdomen [8].

An adequate approach in treating patients with this type of tumor involves total hysterectomy with bilateral salpingo-oophorectomy, peritoneal sprains, peritoneal biopsies of the susceptible sites, a biopsy and infracolic omentectomy. Removing the lymph nodes is not recommended unless they are enlarged. Brown et al. [9] in their work involving 262 female patients with a sexual tape tumor showed that none of the 58 patients who underwent lymphadenectomy had any positive metastases in them. A large study involving 1156 patients, of which 572 were subjected to lymphadenectomy in only 3% of cases, the presence of metastases was confirmed. It is further demonstrated that survival is not significant in relation to patients in whom lymphadenectomy has not been conducted [10].

Conservative treatment may be advisable in patients in whom the disease is detected in the early stage of FIGO IA / IC. Preservation of fertility is possible at this stage, as it has been shown that there is no difference in survival in conservative versus radical access, and a total of five years of survival is 97% [11].

Secondary surgical treatment in patients who did not have staging of a disease in the first act is obligatory It implies salpingo-oophorectomy on the side of the tumor, multiple peritoneal biopsies of the suspected sites, blind biopsies, omental biopsy, and cytological analysis of the peritoneal flushing. [12]. The main prognostic factors are the age of a patient, tumor size, mitotic activity, nuclear atypia, but in many studies, it has been found the disease stage is the most reliable prognostic factor [1]. Biopsy of the other ovary is not necessary because this tumor is unilateral in 98% of cases, and on the other hand, we erase the appearance of the progenitor and preserve the ovarian function of the remaining ovarian tissue [13].

It is important to emphasize that due to increased production of estrogen, it can cause changes in endometrium and the appearance of hyperplasia and endometrial carcinoma, and in the case of a conservative approach it is necessary to perform endometrial biopsy to exclude endometrial cancer [14].

The recurrent disease in these tumors is late and amounts to 32–44%. In about 60% of cases, it occurs in the form of local appearance in the small pelvis [1]. Due to this feature, the question arises when it is necessary to perform a complete surgical removal of the uterus and the remaining ovaries, whether after the end of the birth or the occurrence of relapse can be expected. Some authors suggest that it is safe to do with the onset of recurrent disease as some propose radicalization of surgery at the end of birth to reduce the risk of disease spread and increased survival [15].

The use of adjuvant chemotherapy did not improve survival, and its application continues to be controversial, but according to NCCN recommendations it is advised to use adjuvant chemotherapy in a poorly differentiated type, tumor FIGO stage IC, which implies random or spontaneous rupture capsules, as well as in tumors larger than 10 cm [16]. The first line of therapy is combination of BEP, which our patient also received [17].

Studies have shown the high incidence of pregnancy among patient with diagnosed and treated granulose cell tumors. The pregnancy rate is 86.4% and the live-birth rate is 95%.

In managing these data and the fact of a patient's high survival rate when the tumor is detected at an early stage of the disease, we can conclude that a conservative approach to achieve progeny is justified and safe. An adequate staging of disease is the most important approach when making such a decision.

Conflict of interest: None declared.

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Успешно завршена трудноћа после конзервативног третмана неепителног малигног тумора јајника

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САЖЕТАК

Увод Тумори гранулозних ћелија су ретке неоплазме оваријума са ниским малигним потенцијалом и касним рецидивом. Потичу од гранулозних ћелија строме јајника и имају способност да производе естрогене. Главни третман је хируршки и подразумева хистеректомију са билатералном салпингоофоректомијом, оментектомијом, узимањем перитонеалних биопсија и цитолошком анализом перитонеалног испирка.

Када се нађе код младих жена које нису рађале, може се размотрити конзервативни приступ, који је безбедан само за ране стадијуме ФИГО *IA* до *IC*, при чему је неопходно учинити унилатералну салпингоофоректомију и комплетно стадирање болести.

Приказ болесника Представљамо случај младе жене са тумором гранулозних ћелија који је случајно откривен. После адекватне операције и хемиотерапије рођено је здраво дете.

Закључак Младе жене које нису рађале и којима је дијагностикован тумор гранулозних ћелија јајника могу се конзервативно лечити после адекватног стадирања болести и потврде да се болест налази у раној фази.

Кључне речи: тумори гранулозних ћелија јајника; очување фертилитета, лечење; прогностички фактори; праћење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Uncommon severe blunt ocular injury associated with large retinal dialysis caused by a fishing sinker

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SUMMARY

Introduction Severe ocular injuries caused by fishing equipment are relatively rare. The visual prognosis for fishing-related injuries depends on the involved ocular structures, the presence of complications, and surgical techniques applied.

Case outline A 40-year-old man reported a sudden severe sharp pain and a loss of vision in his left eye while he was pulling the fishing rod during recreational fishing. At admission, his best corrected visual acuity (BCVA) of the left eye was 1/60. Clinical examination revealed a laceration in the temporal quadrant of the bulbar conjunctiva 0.2–0.3 mm in size and a dark tumefaction under the conjunctiva in the same region. It was identified during primary surgical exploration as a fishing sinker 1 cm in size lodged under the lateral rectus muscle. The bulbar wall was intact and the fishing sinker was safely removed. Phacoemulsification with the implantation of an artificial foldable intraocular lens and 23G pars plana vitrectomy were performed. During vitrectomy, subretinal hemorrhage in the macular region and large retinal dialysis in the temporal segment were revealed. Vitrectomy was finished with silicone oil tamponade. One week later, the patient's BCVA of the left eye was 2/60. Eight months after surgery, spontaneous resorption of subretinal hemorrhage in the macular region and the attached retina was observed. The patient's BCVA was 3/60 due to the destruction of photoreceptors and retinal pigment epithelium and the formation of epiretinal membrane.

Conclusion To our knowledge, this is the first case report of a severe blunt ocular injury associated with large retinal dialysis caused by a fishing sinker.

Keywords: ocular trauma; fishing sinker; subretinal hemorrhage; retinal dialysis; vitrectomy

INTRODUCTION

Ocular injury is the main cause of visual morbidity and blindness in the adult-age population worldwide [1]. Numerous causes of eye trauma exist and sport-related injuries have been described in the literature. Fishing is a popular activity and usually no particular safety measures are undertaken. However, ocular traumas ranging from simple to severe can occur during recreational fishing. Severe eye injuries caused by fishhooks and other parts of fishing equipment are relatively rare. Cases of ocular injuries caused by fishhook are mostly reported and the severity of ocular injuries depends on the involved ocular structures. Various structures of the eye including the lid, conjunctiva, cornea, sclera, anterior chamber, lens, and the posterior segment structures may be affected in fishhook ocular injury. Possible complications of these injuries may involve the anterior and the posterior segment with partial or complete loss of vision and even loss of the eye in certain circumstances. Treatment of these injuries depends on the location of the injury, the involved ocular structures, and the type of fishhook or other parts of fishing equipment [2]. In cases when a metal foreign body is suspected, detailed examination of anterior and posterior segment structures of injured eye is required, including X-ray or computed tomography of orbits, as well as ultrasound examination [3].

We present an uncommon, very severe blunt eye injury associated with large retinal dialysis caused by a fishing sinker. We describe the unusual mechanism, severity, treatment, and clinical outcome of an injury that occurred during recreational fishing.

CASE REPORT

A 40-year-old man was admitted at the Clinic for Eye Diseases after suffering trauma to his left eye during recreational fishing. On initial presentation, the patient reported a sudden severe sharp pain in his left eye and a loss of vision with a sensation of dark curtain coming down across his left eye that occurred while he was pulling the fishing rod.

The patient's best corrected visual acuity (BCVA) was 1.0 in the right eye and 1/60 in the left eye. Intraocular pressure in both eyes was 16 mmHg. Slit lamp examination of the anterior and posterior segment of the right eye was normal. Slit lamp examination of the left eye anterior segment showed suffusion and hyperemia of the bulbar conjunctiva with the presence of small laceration in the temporal

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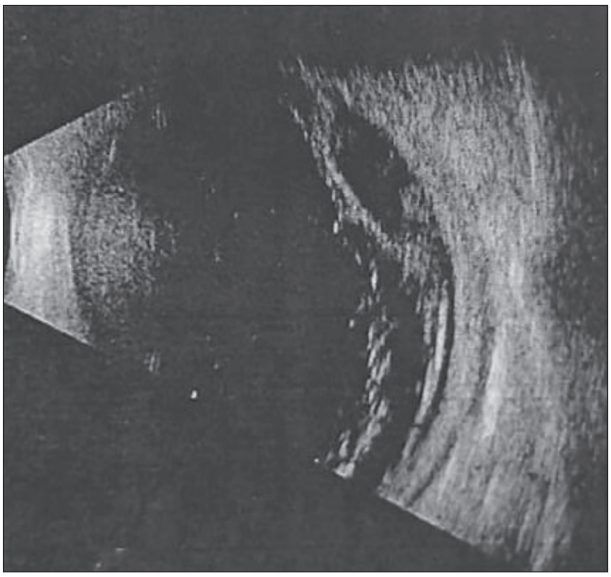

Figure 1. Ultrasound of the left eye shows the presence of mobile vitreous opacities of low to medium reflection (hemophthalmos), no echo signs of an intraocular foreign body, and the zone of high reflection of the detached retina

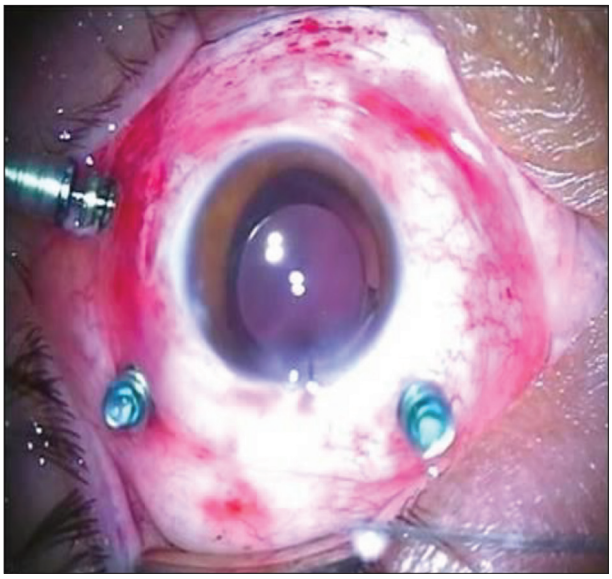

Figure 3. Implanted, artificial foldable intraocular lens and 3-port pars plana vitrectomy 23G system with the infusion line

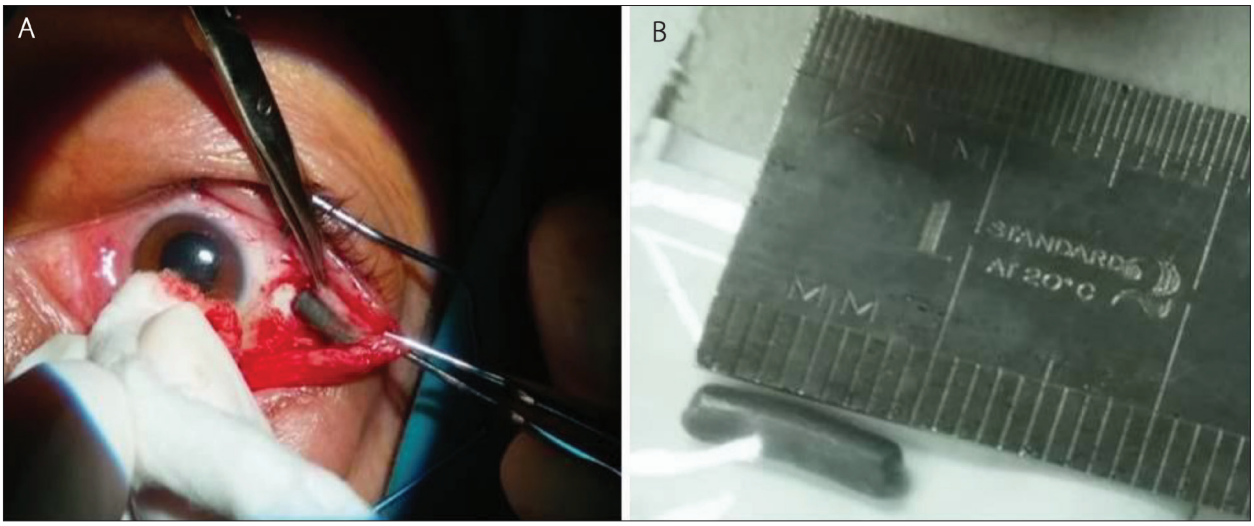

Figure 2. Intact bulbar wall and extracted fishing sinker during the primary surgical exploration (A); dimensions of the fishing sinker (B)

quadrant 0.2–0.3 mm in size. A dark tumefaction under the bulbar conjunctiva in the region of the small laceration in the lateral rectus muscle zone was observed. The cornea was intact, the anterior chamber was deeper and clear with traumatic mydriasis and slightly irregular pupil, with clear lens in the physiological position. The eye fundus examination demonstrated hemophthalmos. Ultrasound examination of the left eye revealed the presence of mobile vitreous opacities of low to medium reflection, the findings consistent to hemophthalmos, no echo signs of intraocular foreign body, and the zone of high reflection of the detached retina (Figure 1).

The presence of dark tumefaction in the zone of the lateral rectus muscle under the bulbar conjunctiva raised the suspicion of globe rupture with the prolapsed uveal tissue. Primary surgical exploration was done under local anesthesia. Intact bulbar wall and unexpected presence of a metal foreign body, a fishing sinker, under the lateral rectus muscle, 1 cm in size, were revealed. The fishing sinker was extracted (Figure 2). Phacoemulsification of the natural lens with the implantation of an artificial foldable intraocular lens (Figure 3) and 23G pars plana vitrectomy with silicone oil tamponade were performed. Following three-port sclerotomies at pars plana, at 3.5 mm from the limbus and the placement of the infusion line, "core" vitrectomy and removal of hemophthalmos were performed enabling the visualization of the fundus. Several pre-retinal hemorrhages, subretinal hemorrhage in the macular region and large retinal dialysis in the temporal segment were observed (Figure 4). In this segment, the retina appeared wrinkled, immobile, with irregular posterior border with attached vitreous and small quantity of subretinal fluid. Triamcinolone acetonide (Kenalog®) was applied in the vitreous for better visualization, especially in the zone of

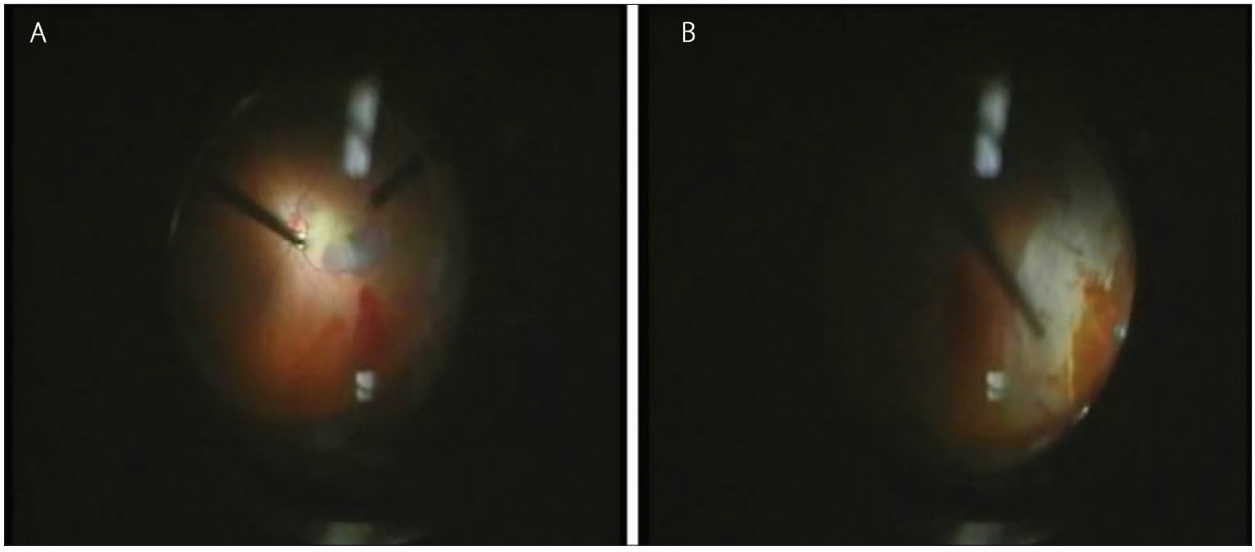

Figure 4. Several pre-retinal hemorrhages and subretinal hemorrhage in the macular region (A); a large retinal dialysis in the temporal quadrant (B)

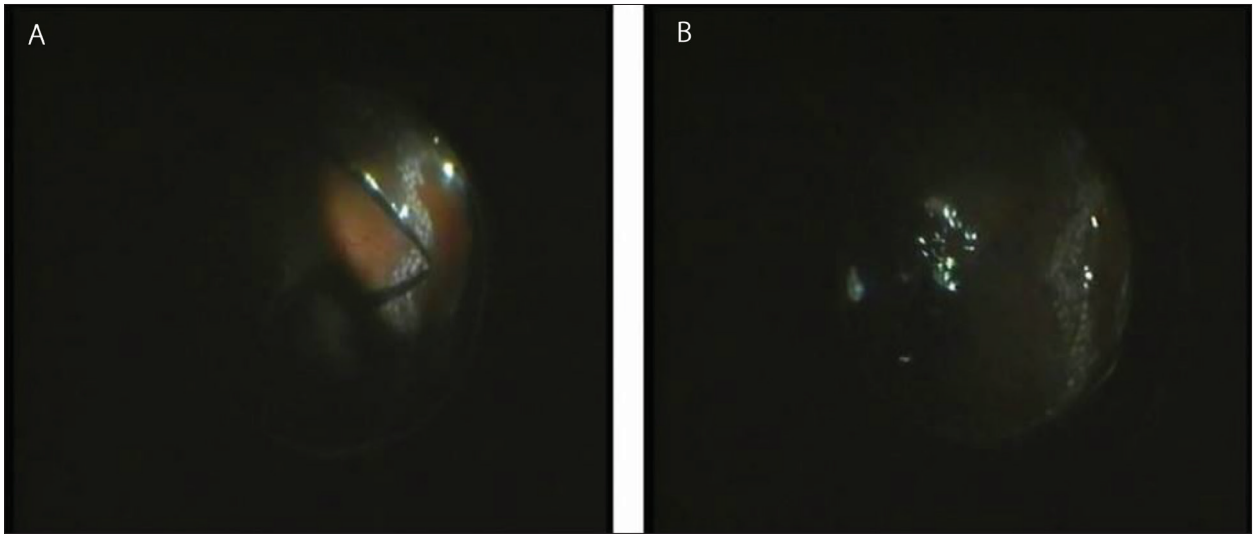

Figure 5. Perfluorocarbon–air exchange and laser spots in several rows along the posterior border of the dialysis (A); surgical treatment was finished with air–silicone oil exchange (B)

the posterior border of dialysis and at the vitreous base. The posterior border of the dialysis was relaxed from vitreal traction and the retina became mobile. The vitreous base was cleared along the complete circumferention. Perfluorocarbon (decalin) was installed and the retina was stabilized and attached in the zone of damage. Laser photocoagulation was applied in several rows along complete circumferention of the peripheral retina and in the zone of the posterior border of dialysis. Perfluorocarbon–air exchange was done and surgical treatment was finished with air–silicone oil exchange (Figure 5). During hospitalization, the patient received antibiotics, corticosteroids, and a mydriatic drug locally, as well as systemic antibiotics and corticosteroids. In the early postoperative period, the mild increase of intraocular pressure of 26 mmHg was noticed and treated locally with antiglaucomatous therapy. He was discharged from the hospital and at the control visit one week later, the patient's left eye BCVA was 2/60, with intraocular pressure of 15 mmHg. At eight months after surgery, the patient's BCVA was 3/60. At the same control visit, fundus photography showed spontaneous resorption of the subretinal hemorrhage in the macular region, attached retina under the silicone oil with scar tissue at the posterior border of the dialysis (Figure 6). Macular optical coherence tomography findings showed thinning, photoreceptors and retinal pigment epithelium destruction, and epiretinal membrane (Figure 7).

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

The majority of reported cases of fishing-related ocular injuries have been caused by fishhooks. These reports

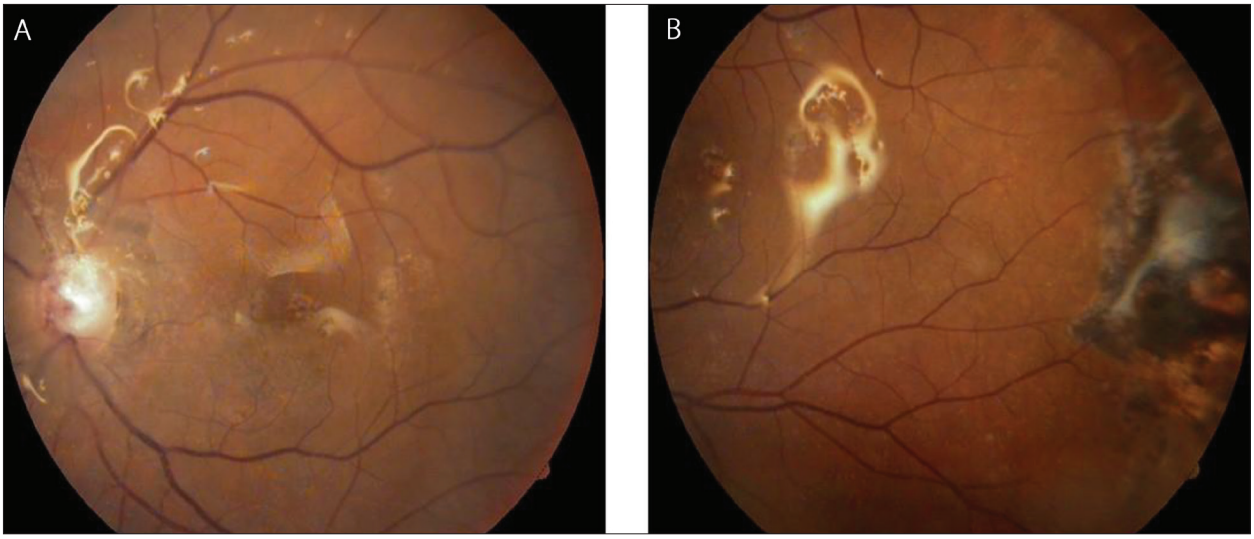

Figure 6. Fundus photography shows the spontaneous resorption of the subretinal hemorrhage in the macular region (A) with attached retina under the silicone oil and the scar tissue at the posterior border of the dialysis (B)

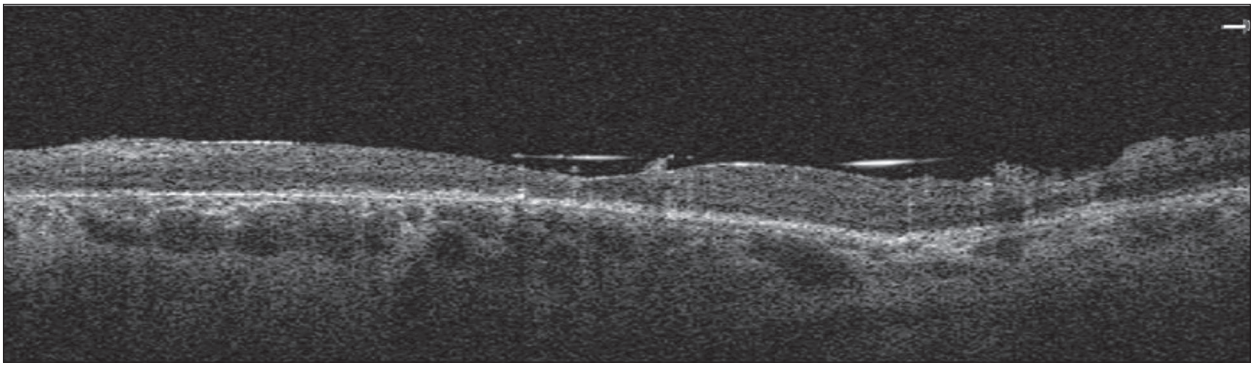

Figure 7. Optical coherence tomography of the macula shows thinning, photoreceptors and retinal pigment epithelium destruction, and epiretinal membrane

describe the types and severity of injuries, and the surgical techniques applied for fishhook removal [4, 5]. To our knowledge, this is the first case report of a patient with a severe blunt ocular injury caused by a fishing sinker during recreational fishing. The eye injury was caused by a metal fishing sinker 1 cm in length, which penetrated bulbar conjunctiva leaving a laceration of 0.2–0.3 mm in size. The fishing sinker was revealed during the primary surgical exploration of the eye globe and it was embedded under the lateral rectus muscle and removed. During vitrectomy, a large retinal dialysis was observed in the temporal quadrant in the projection of the contusion scleral wall injury caused by the fishing sinker. The large retinal dialysis, subretinal hemorrhage in the macular region, and hemophthalmos determined the severity of the eye injury in this patient.

In a retrospective analysis using United States Eye Injury Registry, Alfaro et al. [6] reported that 19.54% of sport-related ocular traumas occurred during fishing. Corneal laceration, globe rupture, and hyphema are the most frequent eye injuries caused by fishhooks, fishing lures, or sinkers. In a study by Hoskin et al. [7], fishing-related eye injuries were found in 7% of sport-related injuries in a Western Australian pediatric population. Purtskhvanidze et al. [2] reported nine patients who experienced eye injury caused by a fishhook. Five patients had only eyelid injuries (55%) and four patients suffered open globe injuries (45%). Among those, one patient had eye trauma limited to cornea (25%), one patient had scleral injury (25%), and two patients had injuries of the lens, the iris, and the posterior segment (50%). Surgical treatment described in this report included primary pars plana vitrectomy performed for endophthalmitis and for retinal detachment with the giant retinal tear and choroid hemorrhage. Choovuthayakorn et al. [4] described primary wound management, the "back-out" technique of removing a fishhook from the upper eyelid embedded during fishing. The fishhook penetrated the cornea and the iris and was lodged in the ciliary body behind the clouded natural lens. The patient underwent lensectomy with pars plana vitrectomy and silicone oil tamponade for the treatment of the local retinal detachment. Uncommon mechanism of eye injury and the surgical treatment was reported by Iannetti and Tortorella [5] in patients who suffered fishhook injury that penetrated through the sclera 2 mm from the corneal limbus and the trabeculum and was lodged in the anterior chamber. Nakatsuka et al. [8] described the "cut-out" technique for the removal of a large fishhook that caused full-thickness

corneal penetration at the nasal limbus and was lodged in the anterior chamber angle of the eye.

We describe a severe blunt eye trauma associated with hemophthalmos, subretinal hemorrhage in the macular region, and a large retinal dialysis in the temporal quadrant. Retinal tears in the region of the ora serrata and peripheral retina are typically caused by blunt trauma [9]. A retinal dialysis is a tear in the retina whose anterior edge is at ora serrata and whose posterior edge is attached to the vitreous base [10]. Retinal dialysis has been described as the most common complication after ocular contusion injury [11]. The incidence of rhegmatogenous retinal detachment caused by a dialysis is 8–17% and the retinal dialyses are most often seen in younger men following trauma [12]. In contrast to eye trauma-related giant retinal tears, which are caused by vitreal traction, in a retinal dialysis vitreous base is firmly attached to the posterior border, but an avulsion of the vitreous base may occur and it represents the pathognomonic sign of a blunt eye injury [11]. A blunt injury causes a retinal dialysis by the compression of the eye in the anteroposterior plane, which results in the expanding in the equatorial plane and causes pressure in the vitreous base [11]. Retinal dialyses are most often located in the inferotemporal quadrant. However, multiple dialyses, small dialyses, and dialyses in several quadrants may exist [13].

In conclusion, to our knowledge, this is the first case report of a severe blunt ocular injury associated with a large retinal dialysis caused by a fishing sinker. Accidents due to fishing equipment are rare and may result in serious ocular injuries and significant visual loss. The outcome of a fishing-related ocular injury depends on affected eye structures, the mechanism of injury, the presence of complications, and surgical techniques applied. We report treatments that were applied in a patient with a severe ocular trauma caused by a fishing sinker that involved the posterior segment, including subretinal macular hemorrhage and retinal dialysis, which enabled satisfactory visual and anatomical outcomes. However, to reduce the occurrence of fishing-related eye injuries, preventive measures should be undertaken, such as the use of protective eyewear during this activity.

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Неуобичајено тешка контузиона повреда ока удружена са великом дијализом ретине настала металним тегом за пецање

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САЖЕТАК

Увод Тешке повреде ока настале опремом за пецање су релативно ретке. Функционална прогноза по вид код повреда насталих опремом за пецање зависи од захваћених окуларних структура, присуства компликација и хируршких техника које се примењују код различитих типова повреда.

Приказ болесника Мушкарац, узраста 40 година, током рекреативног пецања је, повлачећи штап, одједном осетио веома оштар бол и губитак вида на левом оку. Најбоље коригована видна оштрина на левом, повређеном оку, на пријему је износила 1/60. Клиничким прегледом уочена је лацерација булбарне конјунктиве величине 0,2–0,3 *mm*, као и тамна тумефакција испод конјунктиве у истом, темпоралном сегменту. Тамна тумефакција испод конјунктиве је током примарне хируршке експлорације идентификована као метални тег за пецање величине 1 *cm*, који се налазио испод спољашњег правог мишића. Булбарни зид је био интактан, а метални тег пажљиво уклоњен. Затим је урађена факоемулзификација природног сочива са уградњом савитљивог, вештачког, интраокуларног сочива као и 23Г *pars plana* витректомија. Током витректомије откривено је присуство субретиналне хеморагије у макули, као и велика дијализа ретине у темпоралном квадранту. Витректомија је завршена тампонадом силиконским уљем. На првој постоперативној контроли, недељу дана касније, најбоље коригована видна оштрина на левом оку је износила 2/60. Осам месеци после операције контролни налаз је показао спонтану ресорпцију субретиналне хеморагије у макули са налегнутом ретином. Најбоље коригована видна оштрина је износила 3/60 као последица деструкције фоторецептора и ретиналног пигментног епитела у макули и формирања епиретиналне мембране.

Закључак Према нашим сазнањима, ово је први приказ тешке контузионе повреде ока удружене са великом дијализом ретине настале металним тегом за пецање.

Кључне речи: траума ока; метални тег за пецање; субретинална хеморагија; дијализа ретине; витректомија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Non-invasive approach in the treatment of temporomandibular joint osteoarthritis

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SUMMARY

Introduction Temporomandibular dysfunction (TMD) is a set of disorders that involve the masticatory muscles, the temporomandibular joint (TMJ), and its associated structures. Osteoarthritis (OA), as one of the forms of TMD, leads to permanent changes in the bone structures of TMJ. These changes can be the cause of serious functional disorders of the TMJ.

Case outline This article describes a case of a 24-year-old female patient who sought help due to pain and swelling in the area of the right and left TMJ, accompanied by muscular tension, severe headaches, which did not respond to medication. After establishing the diagnosis, we applied a therapy in the treatment of the bilateral OA of the TMJ, where we used non-invasive methods. Six months later, the patient reported the absence of pain, swelling, headache, and muscle tension in the orofacial region.

Conclusion There is no "gold standard" for the management of OA of TMJ. In our study, non-invasive therapy was successful in eliminating pain, increasing the range of motion of the lower jaw, stopping the progression of the disease, and advancing the quality of life.

Keywords: temporomandibular joint dysfunction; temporomandibular joint osteoarthritis; stabilization splint; cone beam computed tomography

INTRODUCTION

Temporomandibular dysfunction (TMD) is a set of disorders that involve the masticatory muscles, the temporomandibular joint (TMJ), and its associated structures [1].

Ostheoarthritis (OA) as a form of TMD leads to a permanent chage in bone structures. OA of the TMJ is a degenerative disease of the TMJ structures, followed by inflammatory changes causing pain, crepitus, and limited mouth opening [2].

The etiology is multifactorial. It most commonly occurs unilaterally as the possession of trauma, unbalanced dental occlusion, parafunction, systemic diseases, and functional overloading of the TMJ [3]. Some studies have not found an association between age, sex, and prevalence of OA of the TMJ, but others have shown that the mean age in women, with more frequent occurrence (84.5%), is 48.09 years, and 48.18 years in men [4, 5].

The most reliable diagnostic method that can confirm a clinical diagnosis of OA of the TMJ is radiological. Cone-beam computed tomography (CBCT) is a reliable three-dimensional (3D) method that can detect the radiological characteristics of this disease by the presence of one or more bone changes such as surface erosion, osteophyte, subcortical pseudocyst, articular surface flattening, and subcortical sclerosis [6].

Therapy involves a multidisciplinary approach, it can be non-invasive, minimally-invasive, and invasive. Non-invasive therapy includes patient education, physical, pharmacological, and splint therapy. Minimally-invasive therapy includes injections, arthrocentesis, arthroscopy, while invasive modalities include surgical interventions [3, 7].

The aim of this study is to prove by appropriate diagnostic methods that OA of the TMJ lies behind TMD, and to show the possibility of successful application of non-invasive therapy of this disease in the progressive case of the younger population.

CASE REPORT

This report was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac, Serbia.

A 24-year-old female patient contacted the Faculty of Medical Sciences, University of Kragujevac, due to severe pain and swelling in the area of the right and left TMJ. The intensity of pain increased during the night, chewing, sneezing, mouth opening, and lateral movements of the lower jaw. Pain existed in the lower two-thirds of the face with severe muscular tension and headaches, which often did not respond to medication. The period of onset of pain in the right and left TMJ and the right leg coincided with the period of a stressful life situation.

Analysis of the anamnestic data revealed that she was born with a deformity of the right foot, which was rehabilitated with the use of

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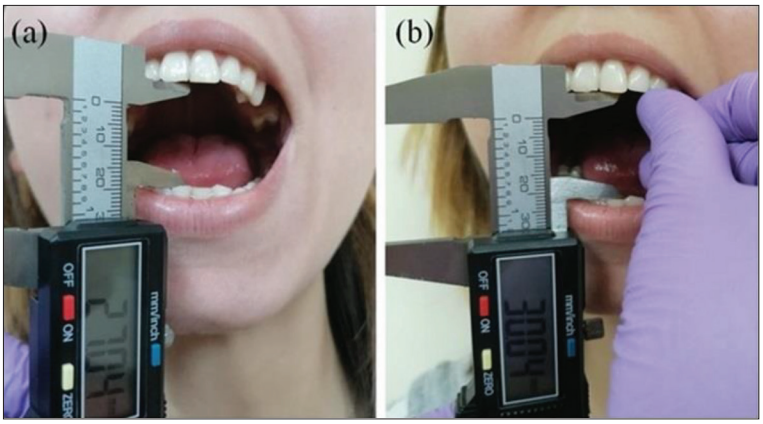

Figure 1. Assisted and non-assisted mouth opening at the beginning of therapy; non-assisted (a); assisted (b)

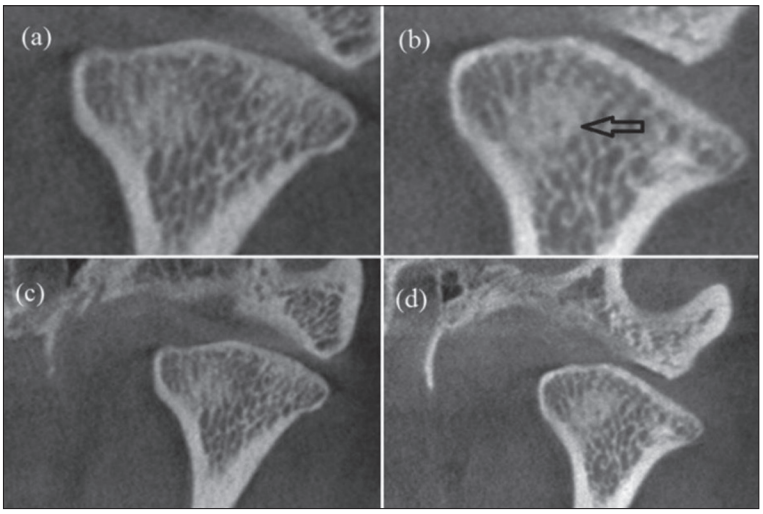

Figure 2. Osteoarthritis changes of the left and right temporomandibular joint (TMJ) on CBCT; the right TMJ without subcortical pseudocyst (a); subcortical pseudocyst of the left TMJ (b); ero-sion of the right (c) and the left (d) TMJ

surgical and physical therapy (*Dg. Pes equinovarus lat.dex, Th. Operatio: Plastica sec. Mc Kay*). Physical therapy lasted up to 18 years, the symptoms were in remission until the end of the 24th year, after which the onset of problems in the right leg occurred again. She was born with a visual impairment (nearsightedness, diopter -11), wherewith an adequate physical therapy the disorder was reduced by the time she was 18 years old (diopter -5.5). The patient denied the existence of the same or similar illness in the immediate and extended family.

By extraoral examination, non-assisted mouth opening without the onset of painful sensations was 27.04 mm, while the assisted mouth opening, regardless of the onset of pain, was 30.04 mm (Figure 1). In the TMJ, the pain occurred with a protrusive movement of 6 mm. During the right (5 mm) and left (7 mm) lateral movement of the lower jaw, the pain occurred in the area of both TMJs. Opening the mouth, the deviation of the mandible to the left was detected. The middle line of the face did not coincide with the middle of the dental arch. On a visual analogue scale (VAS = 0–10), the patient registered a painful sensation VAS = 9. Palpation of the masticatory and neck muscles showed no painful sensitivity, whereas palpation of the lateral pole of both condyles showed severe pain with the presence of crepitus.

Intraoral examination and analysis of the orthopantomogram (OPG) showed the presence of a bilateral interrupted dental row of the upper jaw (missing teeth 16, 25, 26) and the presence of all teeth of the lower jaw. The teeth that were present were conservatively repaired, with no prosthetic replacement. The presence of skeletal class II was observed, the vertical overbite of the tooth amounted to 2 mm and horizontal overjet was 9 mm. The occlusion of the posterior teeth was normal. The periodontal condition of the teeth was preserved.

The radiological diagnostics of the patient's right and left TMJ was made with an Orthophos XG 3D apparatus (Sirona Dental Systems GmbH, Bensheim, Germany). The work area covered by the imaging was 8 × 8 cm. Analysis and 3D reconstruction was performed with the help of GALAXIS v1.9.4 software (Sirona Dental Systems GmbH). Analysis of 3D radiograms showed the articular surface of the temporal bone in the right joint was of the usual morphological structure, with slight erosion in the middle part of the articular surface of the temporal bone. The right articular extension of the lower jaw was of normal ovoid shape, with slight erosion near the medial pole of the condyle. The articular surface of the temporal bone in the left joint was of the usual morphological structure, with slight erosion in the middle and posterior part of the articular surface of the temporal bone. The left articular extension of the lower jaw was of a normal ovoid shape, with the presence of a single subcortical pseudocyst oval in shape (0.64 mm × 0.81 mm) (Figure 2). The mediolateral dimensions of the head of the left condyle were significantly larger than those of the condyle on the opposite side, as were other measurements as well (Figure 3, 4).

The first therapeutic procedure in the treatment of the bilateral OA of the TMJ was to refer the patient to appropriate physical and psychological therapy. After satisfactory results were obtained, the patient underwent reversible occlusal therapy in the form of applying a stabilization splint (SS) in the position of the centric relation with the aim of raising the vertical dimension of the occlusion by 2 mm. The clinical and laboratory phases during the fabrication of the SS are shown in Figure 5. Wearing the splint overnight and for two hours a day, four to six weeks, was recommended. The patient also received anti-inflammatory medication (NSAID ibuprofen pills 0.4 g, 2 × 1, four weeks) and muscle relaxants [tolperison pills 0.15 g, 3 × 1 (first five days), 2 × 1 (next five days), and 1 × 1 (by the end of the month)]. Six months after wearing the SS, at the check-up, the patient reported the absence of pain, swelling in both TMJs, cessation of the headache and muscle tension in the

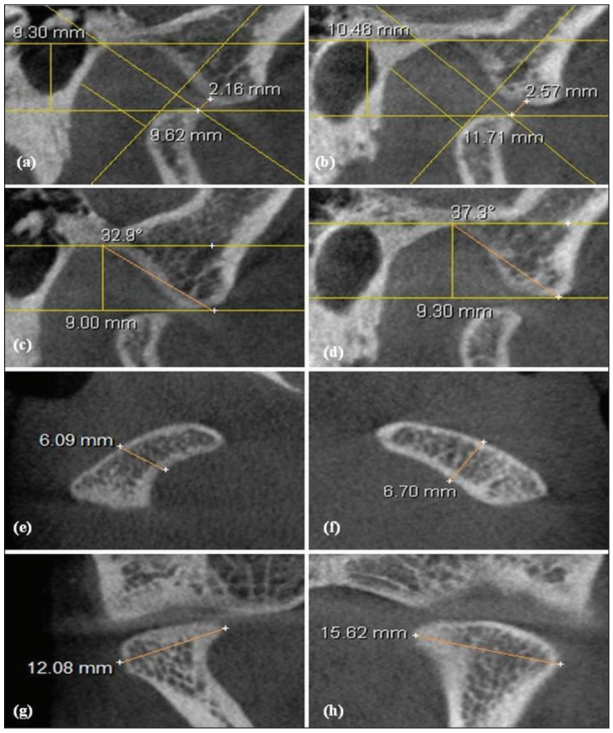

Figure 3. Dimensions of anatomical structures, right and left temporomandibular joint (TMJ) on CBCT; height of joint space of the right (front, posterior and upper joint space) (a), and the left (b) TMJ; sagittal condylar angle and depth of mandibular fossa of the right (c), and the left (d) TMJ; anterior–posterior dimension of a condyle head of the right (e), and the left (f) TMJ; medi-olateral dimension of a condyle head of the right (g), and the left (h) TMJ

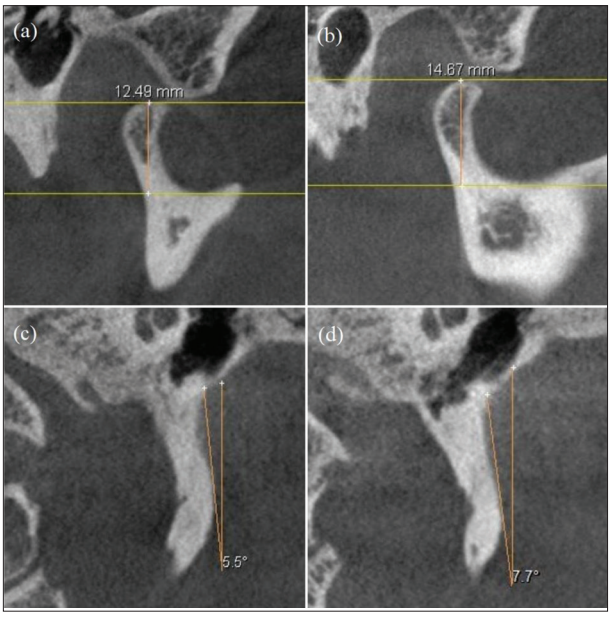

Figure 4. Dimensions of anatomical structures, right and left temporomandibular joint (TMJ) on CBCT; condyle height of the right (a), and the left (b) TMJ; Bennett angle of the right (c), and the left (d) TMJ

orofacial region. She stated that low-intensity pain in the right and left TMJs, that did not interfere with normal life activities (VAS = 3) occurred during chewing of hard food. Maximal mouth opening improved with an intermaxillary separation of 39.09 mm (unassisted) and 46.22 mm (assisted) (Figure 6). When opening the mouth, there was still a mild deviation of the mandible to the left, and crepitus in both TMJs were still felt. The palpation of the lateral pole of both condyles did not result in painful sensitivity. Lower jaw movements during the opening, protrusion, and left and right lateral movement did not cause pain.

Based on the achieved positive therapeutic effect, in order to maintain the remission of the disease, it was proposed to apply irreversible therapy in the form of fixed prosthetic dental replacement in the upper jaw, which would permanently correct the existing spatial relationship of the upper and the lower jaw and normalize relations within the masticatory system.

DISCUSSION

TMD are heterogeneous musculoskeletal disorders that result in the presence of chronic pain that significantly

Figur 5. Wax model and the definitive form of the stabilization splint (SS); wax model of the SS in centric relation (a), protrusive position (b); undisturbed guidance of the wax model of the SS in the left (c), and the right (d) lateral position; SS in centric relation (a1), protrusive position (b1); undisturbed guidance of the SS in the left (c1), and the right (d1) lateral position

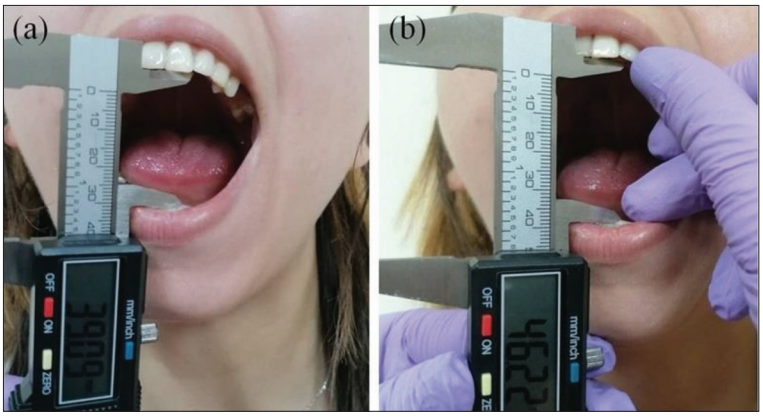

Figure 6. Assisted and non-assisted mouth opening after six months of therapy; non-assisted (a); assisted (b)

affects the quality of life, socio-psychological status, and inability to perform daily activities [6]. OA of the TMJ, as one of the subtypes of TMD, is a degenerative disease characterized by destructive changes of the TMJ structures and a condition that is still being researched [3].

In order to make an accurate diagnosis, it is necessary to detect the signs and symptoms of the disease through medical history, clinical examination, laboratory, and radiographic procedures [7]. The most common symptoms of TMD by extraoral examination are sound in the TMJ, painful sensitivity of the muscles on palpation, and lateral turning of the mandible during the mouth opening [8]. These symptoms were also present in our patient, except for the representation of painful sensitivity of the masticatory and neck muscles on palpation, whereas palpation of the lateral pole of both condyles showed severe pain with the presence of crepitus.

Computed tomography (CT) and CBCT are 3D TMJ imaging methods reliable in visualizing the bony contours of the mandibular condyle and mandibular fossa. In our study, the patient was diagnosed with the presence of OA of the TMJ by detecting symptoms and signs of the disease with the help of medical history, clinical examination, and radiographic methods (OPG, CBCT). Ahmad et al. [6] stated that the CBCT method in clinical practice has emerged as more acceptable and can be said to be a reliable tool in the diagnosis of OA by being able to perfectly detect the bone changes of the mandible condyle and mandibular fossa, including the presence of one or more changes such as osteophyte, surface erosion, subcortical pseudocyst, flattening, and subcortical sclerosis.

Therapy is multidisciplinary, aimed at reducing pain and inflammation in the TMJ, which improves the function of the orofacial system, prevents further development of the disorder, and partly eliminates the etiological factors that lead to the onset of the disorder [2, 7]. In our study, the patient was treated with non-invasive methods that included patient education, physical, medical, psychological, and SS therapy, which was a successful procedure, in the form of complete painlessness and range of motion of the lower jaw within the physiological limits, while avoiding invasive methods. There are different modalities of pharmacotherapy in the treatment of OA of the TMJ, but one of the most widely used, which we also used in our study, are NSAIDs, which play a role in reducing pain, inflammation and thus slow down the degenerative process, and muscle relaxants which have a role in regulation the reflex masticatory muscle spasm [7, 3]. SS therapy has a significant effect on reducing the intensity of pain, improving the quality of life, and the comfortable mouth opening of patients, which is consistent with the results of our study [9, 10]. Kuzmanovic Pficer et al. [11] have indicated that SS can play a significant role in the treatment of TMDs in the short term (≤ 3 months), while in our study, the full positive effects of SS showed after six months, where in the third month of using SS, a significant improvement of the disease state appeared in our patient, but not the maximum positive effect of therapy. Ok et al. [12] have shown that SS treatment could be a successful therapy option for the reduction of bone resorption in the mandibular fossa of OA of the TMJ patients. The researchers indicate that the most appropriate method is the one that will achieve the best results with a less invasive approach with the aim of eliminating symptoms, stopping the progression of the disease, and improving the quality of life of the patient [3]. Kalladka et al. [7] agree that invasive techniques, if necessary, must be preceded by attempts to reduce OA of the TMJ symptoms by non-invasive methods, with surgical methods being considered only if non-invasive methods are in no way capable of eliminating the symptoms. Future research on this subject using an appropriate sample size would be of great value.

Based on the described case of a young patient's OA of the TMJ, the task of medical workers is primarily to recognize the symptomatology of the disease. As medical history and clinical diagnosis are not always characteristic, it is important to supplement the findings with adequate radiographic imaging techniques. Based on a proper diagnosis, the most acceptable therapeutic method will be the one that will achieve the best results with a less invasive approach. In our study, non-invasive therapy had a positive effect as a form of therapeutic modality.

Conflict of interest: None declared.

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Неинвазивни приступ у терапији остеоартритиса темпоромандибуларног зглоба

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САЖЕТАК

Увод Темпоромандибуларне дисфункције представљају скуп поремећаја који укључују мастикаторне мишиће, темпоромандибуларни зглоб (ТМЗ) и његове придружене структуре. Остеоартритис, као једна од форми темпоромандибуларне дисфункције, доводи до трајних промена на коштаним структурама ТМЗ. Ове промене могу бити узрок озбиљних функцијских поремећаја ТМЗ.

Приказ болесника Описује се случај 24-годишње болеснице која је затражила помоћ због болова и отока у пределу десног и левог ТМЗ, праћених мишићном напетошћу, јаким главобољама, које нису реаговале на фармакотерапију. После успостављања дијагнозе, у лечењу остеоартритиса билатералног ТМЗ примењивали смо неинвазивну терапију. Шест месеци касније болесница није имала бол, отицање у оба ТМЗ, главобољу и напетост мишића у орофацијалној регији.

Закључак Не постоји „златни стандард" у терапији остеоартритиса ТМЗ. У овом приказу неинвазивна терапија је имала позитиван ефекат; постигнут је успех у уклањању бола, повећању опсега кретњи доње вилице, заустављању прогресије болести и побољшању квалитета живота.

Кључне речи: дисфункција темпоромандибуларног зглоба; остеоартритис темпоромандибуларног зглоба; стабилизациони сплинт; компјутеризована томографија конусног зрака

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Correction of a post-traumatically scarred upper lip with hyaluron filler

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SUMMARY

Introduction It is generally known that dermal fillers are widely used in anti-aging medicine, to provide volume in healthy skin and mucous tissue. Fillers can also be successfully used with concave scars in order to lift the tissue and to give third dimension to the retracted skin surface.

The aim of this case report was to show successful non-surgical treatment with hyaluron filler of the post-traumatically deformed upper lip.

Case outline We report a case of a woman with asymmetric partly incompetent upper lip, after trauma and primary surgical reconstruction. After almost 12 years, reconstruction with hyaluron filler was performed, using linear retrograde and bolus technique.

Conclusion Presented case correction of the posttraumatic scar of the upper lip illustrates that good aesthetic results could be achieved with hyaluron fillers.

Keywords: hyaluron; filler; scar tissue

INTRODUCTION

With more or less success, many techniques, such as pulsed dye laser, scar excision, dermabrasion and steroid injections, are used to improve post-surgical scars. Scars can be concave, depressed, and convex – hypertrophic [1, 2, 3]. Dermal fillers are used for esthetic purposes, to give volume to healthy skin and mucous tissue [2, 4]. Also, their use with concave scars in order to lift the tissue and to give the third dimension to the retracted skin surface showed much success [1, 2]. Hyaluron filler is a sterile, biodegradable, viscoelastic, isotonic, transparent injectable gel implant, which was approved by the United States Food and Drug Administration (FDA) in 1996. It is used for face reconstruction and remodeling [4]. In clinical practice, hyaluron fillers give good esthetic results in post-surgical scars and tissue lacking. After excessive trauma of the maxillofacial region, scars and lack of the tissue (skin, mucosa, muscle, fat, bone) could produce some degree of disfiguration and functional disturbances [1, 3]. The use of hyaluron, in order to increase volume and replace the missing tissue, could be successful, especially by applying adequate filler combined with suitable technique for each case [5]. Different fillers have various indications for scar treatment and provide variable, longer or shorter lasting results, depending on properties of cross-linked hyaluron [1, 6, 7]. With hyaluron fillers, it is possible to make scar less noticeable, to provide symmetric appearance-reshaping lips according to the patient's wishes.

The objective of this case report was to show successful, non-surgical treatment with hyaluron filler of the post-traumatically deformed upper lip.

CASE REPORT

We report a case of a 30-year-old woman who underwent primary surgical treatment of the upper lip traumatic wound sustained in a car accident12 years previously (2008). Before the trauma, her lips were symmetric, competent, normal in size, with slightly thinner upper vermilion. After the surgical treatment, the right part of the upper lip remained incompetent due to the neglected hypotrophic scar. Her teeth were slightly visible showing incisal part of the right upper central and lateral incisor. Over the years, this asymmetry was even more obvious due to scar tissue contraction (Figure 1A). As a consequence, the function was compromised due to lips incompetence. Moreover, the patient was unable to pronounce labial consonants correctly. She was admitted to the Eterna Polyclinic for Plastic and Reconstructive Surgery, in order to correct the posttraumatic scar using minimally invasive esthetic treatment with hyaluron filler. The aim of the correction was to give symmetric appearance to the lips, make scar less noticeable, and to reshape the lips according to the patient's wishes. After anamnesis and clinical examination, the patient was prepared for the application of the hyaluron filler. Disinfection of the operative field – the vermilion, surrounding skin and mucosa – was done with Povidon jodid® (10% iodine solution, Hemofarm A.D., Vršac, Srbija), and local infiltrative plexus anesthesia 2% lidocaine – epinephrine

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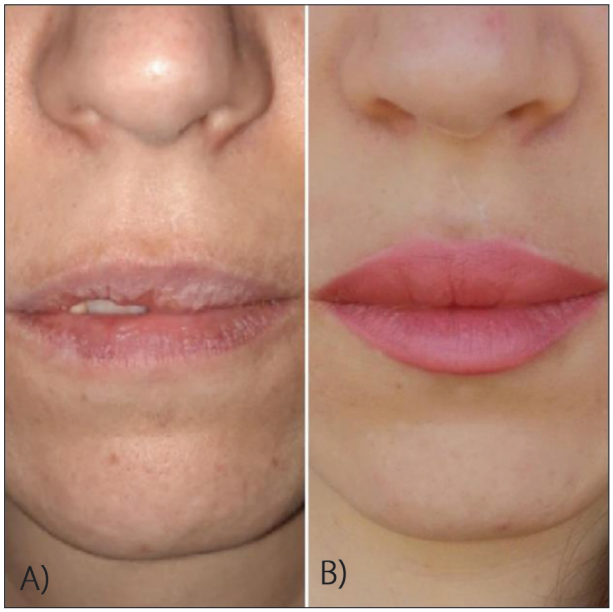

Figure 1. (A) Before and (B) after non-surgical lip reconstruction

(lidocaine 40 mg / 2 ml + epinephrine 0.025 mg / 2 ml, Galenika a.d., Belgrade, Serbia), for the terminal branches of the maxillary nerve was applied. A gel with cross-linked hyaluronic acid (sodium hyaluronate) concentration of 20 mg/g with the addition of antioxidant (mannitol) Stylage M (Laboratoires VIVACY, Paris, France) was used. The hyaluron filler is of non-animal origin, sterile, and non-pyrogenic, physiological pH and osmolality. For injecting the filer, a 27G needle was used, 12 mm in length, factory packed with the hyaluron filler. Soft tissue reconstruction of the right side of the upper lip, by application of hyaluronic acid injection, was administered with retrograde linear and bolus technique. One-stage application of the filler was performed. Initial application of the hyaluronic acid was deposited via perpendicular approach to the volume-lacking tissue, with a gradual product deposition as the needle was withdrawn. A series of linear columns were created, to give the third dimension and more volume. These columns serve as support structures for the next phase, when bolus technique vas applied. In parts of the upper vermilion, where more volume was needed, small boluses of the product were injected. Overall, 0.5 ml of the filler was administrated to reconstruct the lacking volume of the upper lip. The rest of the product (0.5 ml) was used to contour and refresh the left side of the upper lip, the lower lip, and to provide an even and natural look, regarding the patient's wishes (Figure 1B). In addition, after treatment, the patient regained the ability to pronounce labial consonants correctly.

This case report was approved by the institutional ethics committe, was done according to the Helsinki declaration, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

After an excessive trauma, injuries can be severe, and sometimes it is complicated to reconstruct or to replace the lacking tissue. Scars can be irregular, complex, and disfiguring. With the help of reconstructive surgery, consequences can be diminished. However, this type of surgery sometimes leaves unsatisfactory esthetic results, and patients do not want to undergo another surgical procedure. Over the recent decades, cosmetic surgery has become an important and challenging area, and in combination with minimally invasive procedures such as dermal filler application it can give good, natural-looking results [1, 8]. In addition, esthetic dissatisfaction impacts self-esteem and the quality of life, it is a cause for moderated social behavior, camouflage of the defect and self-awareness. [8, 9]. In the presented case, trauma despite primary reconstruction left an unsatisfactory esthetic result. The patient had psychological traumas, awareness of her appearance, and fear of any further esthetic procedures. Function of the lips was compromised, causing the inability to pronounce labial consonants due to air leakage on the side where the scar was contracted. Asymmetry, neglected scar, and long time period between the trauma/surgery and this esthetic treatment of nearly 12 years made this task even more challenging. In the literature the lips are often presented with linear scars, after cleft lip surgery or resection, with satisfactory results after esthetic treatment with hyaluron fillers [1, 2, 4]. We must emphasize the difference – in this case there was an old, irregularly shaped scar, which is much more difficult to treat. Primary use of hyaluron fillers is an esthetic improvement of healthy dermal tissue, but with corrections and reconstructions like this one we suggest that it can be successfully used in the treatment of scar tissue.

The presented correction of the posttraumatic scar of the upper lip illustrates that good esthetic results can be achieved with hyaluron fillers.

Conflict of interest: None declared.

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Корекција посттрауматског ожиљка горње усне хијалуронским филером

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САЖЕТАК

Увод Опште је познато да се дермални филери често користе у естетској медицини да би се обезбедио волумен здраве коже и слузокоже. Филери се могу успешно користити код конкавних ожиљака, како би се подигло ткиво и дала трећа димензија удубљеној површини коже.
Циљ овог приказа био је да се покаже успешан нехируршки третман посттрауматски деформисане горње усне применом хијалуронског филера.

Приказ болесника Приказује се пацијенткиња са асиметричном, делимично инкомпетентном горњом усном, након трауме и примарне хируршке реконструкције. После скоро 12 година изведена је реконструкција хијалуронским филером линеарном ретроградном и болус техником.
Закључак Приказан случај коригованог посттрауматског ожиљка горње усне илуструје да се добри естетски резултати могу постићи хијалуронским филером.
Кључне речи: хијалурон; филер; ожиљно ткиво

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Myalgic encephalomyelitis – enigma at the medicine's crossroads

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SUMMARY
Myalgic encephalomyelitis is a complex, multisystem disease with chronic course significantly affecting patients' quality of life. Physical and mental exertion intolerability, muscle pain, and sleep problems are the main features accompanied often with cognitive inefficacy and vegetative symptoms. Prevalence is 7–3000 per 100,000 adults. It is estimated that 90% of the patients are misdiagnosed. Pathogenesis is still only speculative but current research points to disturbances in the immunological system, inflammatory pathways, autonomic and central nervous system, muscle and mitochondria, as well as alterations of gut microbiota and gut permeability. The onset is typically acute, following an infectious disease. Exertional intolerance lasting for more than six months is an important diagnostic factor. The core features must be moderate to severe and present at least 50% of the time. Diagnostic criteria should be fulfilled and differential diagnosis should be made to exclude other potential pathological conditions or to diagnose comorbidities. Brain magnetic resonance imaging morphometry has shown gray matter atrophy in occipital lobes bilaterally, right angular gyrus, and the posterior division of the left parahippocampal gyrus, consistent with memory problems and potentially with impairment of visual processing. Treatment is still symptomatic and of partial benefit. Symptomatic treatment can include medications for controlling pain and sleep problems, graded exercise and cognitive behavioral therapy. Larger controlled trials are needed to shed more light on this challenging condition.
Keywords: myalgic encephalomyelitis; chronic fatigue syndrome; post-exertional malaise

INTRODUCTION

Myalgic encephalomyelitis (ME) with chronic fatigue syndrome (CFS) (ME/CFS) or systemic exertion intolerance disease (SEID)is a multifaceted condition involving muscular, nervous, hormonal, and immune systems [1, 2]. Patients have difficulties with sleep and attention, experience pain and dizziness, and have extreme fatigue not accountable to any other medical condition [3]. ME can be incapacitating and often affects activities of daily living, sometimes making patients immobile (up to 25%). Syndrome is typically chronic, with the onset between 40 and 60 years, but it can begin at any age. Women are prone to ME/CFS more than men. This is an overlapping domain of rheumatology, neurology, and psychiatry. Prevalence of ME/CFS is 0.1–2.2% [4]. It is estimated that 90% of the patients are misdiagnosed. Physicians are often not educated in ME/CFS and there is no confirmatory test.

CLINICAL PICTURE

Symptoms of ME/CFS can develop suddenly or gradually [5]. Sometimes it starts as a flu-like disease or after an infection (viral, bacterial, or parasitic) [6]. Involved clinical domains are multiple and can be neurological, cognitive, immune, autonomic, post exertional malaise, and pain [7]. These patients also face an increased risk for developing diabetes, cardiovascular disease, and thyroid disease.

Patients are fatigued, do not improve with rest and are worse on attempt of physical or mental activity (post-exertional malaise – PEM; SEID). There is often working incapacity, secondary alcoholism, and inability to participate in family and social life. Before the onset of CFS/ME, most patients are healthy and active [1].

Typically, there are muscle or joint pains, memory, concentration, and information processing speed problems. Perception, speech, motor functions, and intelligence are not involved. Patients complain of sore throat, headaches, unrefreshing sleep, feeling dizzy, and are generally unwell. Some patients have digestive problems, night sweats, or may be intolerant to some foods, chemicals, or noise [5].

People can have difficulties to sit or walk, and some might be bedridden (up to 25%). The other group of patients, in contrast, have preserved functional capacities, but the majority have at least some difficulty at work, in family life and/or at school. Approximately 75% of the patients are unable to participate in their

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professional activities. Symptoms often fluctuate during the day or on various days, last more than six months, and cannot be explained by any other disease [1]. Objectively enlarged lymph nodes can be found in the neck or armpits. Sometimes there are palpitations and irregular heart beat. ME/CFS often lead to depression, social isolation, impairment of activities of everyday living and incapacity for work.

Younger children with ME/CFS have a more equal sex representation compared to adolescents and adults, shorter duration of symptoms, less distinct disability and fatigue, and are less prone to cognitive symptoms, but more often complain of a sore throat [8]. Adolescents less often have palpitations, dizziness, malaise, pain, anxiety, and tender lymph nodes, but more often headaches and comorbid depression than adults [8].

ETIOLOGY

Etiology of ME/CFS is not known but known risk factors are age (40s and 50s), female sex, psychological stress, childhood trauma, lower middle education, low physical fitness, preexisting psychological illness (depression, anxiety), and allergies [1]. Epstein–Barr virus or human herpesvirus-4 (HHV-4) can cause infectious mononucleosis that causes syndrome that fulfills criteria for ME/CFS in substantial number of affected individuals [9]. Other viral infections that can lead to chronic fatigue are HHV-6 and mouse leukemia viruses. Also, there is a possibility of some bacterial infections.

The patients with ME/CFS have slight impairment of the immune system: changes in cytokine and immunoglobulin levels, T- and B-cell phenotype, and a decrease of natural killer cell cytotoxicity, but also increased certain autoantibodies' levels [10, 11]. Some authors hypothesize about the possibility of ME/CFS being an autoimmune disease as there are autoantibodies to some neurotransmitter receptors [10]. Autoimmunity can be triggered by infectious agents and/or stress, and immune deficiencies leading to other pathological mechanisms. Increased permeability of intestinal and blood–brain barriers can lead to the penetration of antibodies from the general circulation into the brain, with potential brain tissue autoimmune lesions [9].

So far, many autoantibodies have been detected, mainly those targeting nuclear structures (antinuclear antibodies, nuclear envelope, reticulated speckles, etc.), membrane structures (phospholipids, cardiolipin, phosphatidylserine, gangliosides), neurotransmitter receptors and neurotransmitters (MAchR, M1 AChR, M3/4 AchR, 5-hydroxytryptamine) and other antigens [10]. Immunological activation forces change to aerobic glycolysis in order to keep necessary energy levels, leading to maintenance of chronic inflammation with mitochondrial dysfunction and extreme fatigue.

Some hormonal imbalances can be found in function of hypothalamus, pituitary, and adrenal glands, but its significance is not known. Many deficiencies of the B complex vitamins are manifested by malaise and cognitive decline and are of substantial prevalence, but these etiological possibilities need large studies [12, 13].

Genetic factors may play some role in the etiology of ME/CFS. Twin studies show increased predisposition for the condition and there are also studies linking genetic factors and infection [14].

ME/CFS is also characterized by increased measures of oxidative stress while antioxidant potential is decreased. This process leads to impaired lipid-based signaling systems of S-palmitoylation and of omega-3 polyunsaturated fatty acids [15]. Nitric oxide/superoxide cycle is also involved in cardiac failure and might be the crucial mechanism of increased fatigue [16]. Overproduction of nitric oxide leads to increased levels of superoxide with consequent depletion of adenosine triphosphate (ATP) and activation of excitatory neurotransmitter N-methyl-D-aspartate, which is followed by an increase of intracellular calcium that continues the vicious cycle with increased activity of nitric oxide. Chronic activation of nuclear factor kappa B (NFκB) is supposed to be present in ME/CFS, and vitamin D_3 supplementation could suppress the activation of NFκB [16].

PATOGENESIS

Pathogenesis of ME/CFS is still only speculative but current research points to disturbances in immunological system, inflammatory pathways, autonomic and central nervous system, muscles, mitochondria, gut microbiota, and permeability [1, 17]. Infectious mechanisms also may play a role in ME/CFS as well as other factors that can initiate similar pathological cascades [17].

Extreme fatigue in ME/CFS might be the result of energy production disturbances leading to exertion intolerance [2]. Some evidence leads to autonomic nervous system dysfunction, such as orthostatic hypotension or tachycardia, at least in some ME/CFS patients [18]. Metabolic syndrome might not be the cause but the result of fatigue and the lack of physical activity [2].

One study recognized nine biochemical factors common to both male and female ME/CFS patients but not to healthy controls with an apparent diagnostic accuracy of more than 90% [19]: a decrease in sphingolipid, glycosphingolipid, phospholipid, purine, microbiome aromatic amino acid, branched-chain amino acid metabolites, flavine adenine nucleotide, and lathosterol. These changes constitute the hypometabolic profile of ME/CFS.

ME/CFS has been linked with mitochondrial dysfunction, damage of adenosine monophosphate-activated protein kinase, oxidative stress, and skeletal muscle cell acidosis, which correlate with core symptoms such as fatigue, exercise intolerance, and myalgia [2]. Contrary to known mitochondrial diseases, in ME/CFS there is no mutation in either nuclear or mitochondrial DNA [20]. Also, there is no ATP reduction. Findings of muscle biopsies from subjects with ME/CFS have shown signs of mitochondrial degeneration and oxidative damage [2].

There are some indications of impaired function of hypothalamic–hypophyseal–adrenal axis [21]. Microglia

probably have an important role in ME/CFS. It has been proposed that microglia might be activated by various factors such as immune changes, stress, etc., via the stimulation of hypothalamic mast cells with consequent focal neuroinflammation and disturbed homeostasis with mitochondrial dysfunction [2].

Some studies advocate for a role for microglia and astrocytes of immunologically induced CFS, so that the infection causes sequential signaling such as increased blood–brain barrier permeability, secretion of IL-1β, upregulation of the serotonin transporter (5-HTT) in astrocytes, reducing extracellular serotonin (5-HT) levels and less activation of 5-HT_{1A} receptor subtype [22]. This etiopathogenetic assumption has found clinical confirmation in achieving positive therapeutic effects using antidepressants from the group of selective serotonin reuptake inhibitors.

Neuroimaging in ME/CFS shows more diffuse activation patterns than controls on attention tests, sometimes structural abnormalities in the brain stem with signs of inflammation, reduction in the serotonin 1A receptor binding, particularly in the hippocampus bilaterally, and reduced serotonin transporters density in the rostral anterior cingulate [23]. Some studies also showed regional abnormalities but with inconsistent locations and widespread disruption of the autonomic nervous system [24].

Clinical pictures of ME/CFS and d-lactic acidosis are overlapping and there is evidence of d-lactate-producing bacteria dysbiosis [25]. Both conditions have neurological disturbances caused by microbiota–gut–brain system dysfunction. D-lactic acidosis is an acute condition causing encephalopathy, while ME/CFS is a chronic state with possible subclinical levels of d-lactate, making the two entities possibly the parts of the same continuum [25].

DIAGNOSIS

Diagnosis of ME/CFS is made on the clinical grounds and by exclusion of other medical conditions with no specific diagnostic test [1]. Current diagnostic criteria for ME/CFS proposed by the United States Centers for Disease Control and Prevention are presented in Table 1 [5]. The onset of ME/CFS is typically acute following an infectious disease. Exercise intolerance lasting more than six months is an important diagnostic factor. Fatigue is not alleviated with rest. Sleep problems are always present. Optional symptoms are orthostatic intolerance and/or memory and concentration problems. Core clinical features must be moderate to severe and present at least 50% of the time.

Table 1. Current diagnostic criteria for myalgic encephalomyelitis with chronic fatigue syndrome proposed by the Centers for Disease Control

1	Significantly lowered ability to participate in activities that were routine before the onset of the condition, and persisting more than six months
2	Physical or mental activity causing worsening symptoms that would not have been problematic before the onset of the condition, (post-exertional malaise)
3	Sleep problems; Additionally, one of the two: • Difficulty with thinking and memory • Worsening of problems with standing or sitting

Documenting PEM is very important and is defined as a "collapse" after previously tolerated physical and psychic exertion, sometimes during even mild everyday activities [26]. Recommended additional investigations in ME/CFS depending on the symptoms are the following: chest X-ray, electrocardiogram, tilt table test for autonomic function, ACTH challenge test or cortisol stimulation test, parathyroid hormone, estradiol, follicle-stimulating hormone, gastroscopy, colonoscopy, gliadin, endomysial antibodies, infectious disease screen including HIV, hepatitis, Lyme disease, Q fever, microbiology of stools, urine, genitals and respiratory tract, antinuclear antibodies, immunoglobulins, functional antibodies and subsets of lymphocytes, magnetic resonance imaging of the brain, overnight polysomnography with multiple sleep latency test, and cystoscopy [6].

There is still not a unique set of biomarkers that would help in diagnosing ME/CFS. There are many proposed and studied compounds but with yet uncertain significance – precise measures of potentially elevated d-lactic acid [25]. Human herpesviruses (HHV-1–8, including HHV-6A and HHV-6B) and Epstein–Barr virus are associated with ME/CFS, but studies have not shown significant differences between patients and healthy controls [27].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of ME/CFS is quite wide and consists of the following [5, 26]:

- **Infectious diseases**: tick-borne diseases – Lyme disease (including neuroborreliosis) etc., mononucleosis i.e. Epstein–Barr virus, parvovirus, HIV infection and AIDS, influenza, tuberculosis, hepatitis B and C, *Giardia*, West Nile virus, Q fever, Valley fever, syphilis;
- **Psychiatric disorders**: anxiety, depression and bipolar disorder, alcohol and substance abuse, schizophrenia, delusional disorders, dementia, anorexia/bulimia nervosa; sleep apnea;
- **Rheumatological diseases**: fibromyalgia, polymyalgia rheumatica, Sjögren's syndrome, giant-cell arteritis, polymyositis, dermatomyositis, systemic lupus, rheumatoid arthritis;
- **Neurological diseases**: parkinsonism, multiple sclerosis (MS), myasthenia gravis, vitamin B_{12} deficiency, cerebrospinal fluid leak, Chiari malformation, sleep apnea, narcolepsy, periodic limb movement disorder, malformation, traumatic brain injury, spinal stenosis, craniocervical instability, seizures;
- **Endocrine/metabolic diseases**: diabetes mellitus, hypothyroidism, hyperthyroidism, thyroiditis, Addison's disease, adrenal insufficiency, Cushing's disease, hypercalcemia;
- **Cardiovascular disorders:** cardiomyopathy, congestive heart failure, coronary artery, disease, pulmonary hypertension, valvular heart disease, arrhythmias;

- **Gastrointestinal disorders:** coeliac disease, food allergy or intolerances, inflammatory bowel diseases, small intestinal bacterial overgrowth, chronic hepatitis;
- **Miscellaneous**: anemia, iron overload, various malignancies (primary and secondary), sinusitis, allergic rhinitis, the effect of some drugs, chronic obstructive pulmonary disease, asthma, end-stage kidney disease, severe obesity (BMI > 40), overwork / burnt out syndrome, athletic overtraining, heavy metals toxicity (e.g. lead, mercury), etc.

ME/CFS can have remitting course that must be distinguished from MS as they have some overlapping symptoms [28]. These are fatigue, cognitive problems, physical disability, etc. However, MS patients do not have, unlike those with ME/CFS, tender lymph nodes and flu-like symptoms, are younger, more likely to be married, less Caucasian, and with less disability [28]. Contrary to depression, ME/CFS does not have anhedonia, low motivation, and guilt.

A closely related problem are comorbidities, so diagnostic procedure is not a mere excluding process. Various diseases can coexist with ME/CFS, so they also have to be diagnosed and treated [26].

TREATMENT

There is no causal cure for ME/CFS. Symptomatic treatments can include medications for controlling pain and sleep problems, graded exercise therapy, which is controversial, and cognitive behavioral therapy (CBT) [26]. Many medications have been tried but without proved therapeutic effects, so they are used off label [29]. Anticonvulsants, mostly gabapentin and pregabalin, are prescribed to alleviate pain and sleep disturbances, but are most effective for neuropathic pain [1]. Antidepressants (nefazodone, mirtazapine, sertraline, amitriptyline, and others) can be administered in cases of depression, anxiety and sleep problems, but have a plethora of side effects and interact with many other drugs, so one should be very careful in prescribing these medications [30]. Alternative to antidepressants is CBT. In patients with most severe and therapy-resistant pain, narcotic medicines are prescribed, usually tramadol, codeine, etc., for a short period to avoid risk of addiction [31].

In line with the proposed immune and viral etiology, immunomodulatory drugs are given, such as rintatolimod and rituximab, which supposedly improve exercise capacity, cognition, and the quality of life, but the studies are of insufficient quality and with equivocal proof of the drug's efficacy and safety [1]. Steroid treatment is known for its immunosuppressive properties but studies did not show any substantial benefit [32].

Important aspect of CFS/ME treatment is the use of nutritional supplements in patients with biochemically proven deficiencies [1]. Multivitamin/multimineral tablets containing antioxidant compounds (e.g. alpha-lipoic acid, vitamin C, and vitamin E) showed some promise in a study in women with ME/CFS [33]. In prescribing some supplements, laboratory follow up is necessary [34, 35]. General fatigue is one of the main symptoms in vitamin B_{12} deficiency [34, 35, 36]. There is substantial difference in determining "normal" levels of vitamin B_{12} in the blood among studies, and blood levels are not a good measure of tissue B_{12} status [34]. Also, different preparations and administration routes further complicate assessment of B_{12} supplementation in such a controversial entity as CFS/ME. Experience with injections of methylcobalamin in patients with CFS/ME in combination with folic acid is positive [37].

Combination of coenzyme Q10 and nicotinamide adenine dinucleotide is an antioxidant treatment that also improves mitochondrial function in CFS/ME due to increased ATP production [38]. Essential fatty acids administration in CFS/ME showed improvement in only one study, while others did not find any improvement [39].

Treating gut dysbiosis i.e. antibiotics targeting *Streptococcus* genus is a hypothetical therapy for neurological symptoms in ME/CFS, not much explored so far [40]. Treatment protocol of a recent study included a four-week treatment with alternate weeks of erythromycin as ethyl succinate salt 400 mg twice daily and probiotic (d-lactate free multistrain probiotic, 5 × 1010 cfu) twice daily [40]. Significant improvement was noted in sleep, attention, speed of processing information, cognitive flexibility, verbal memory and fluency, with more impact in males. Level of fatigue, mood, and urine d:l lactate ratio did not change with medication.

PROGNOSIS

A systematic review described improvement and occupational outcomes of people with CFS found that the median full recovery rate was 5% with the range 0–31%, and the median proportion of patients who improved during follow-up was 39.5%, range 8–63% [41]. Return to work at follow-up ranged 8–30% in relevant studies. In five studies, a worsening of symptoms during the period of follow-up was detected in 5–20% of participants. A good outcome was associated with less fatigue severity at baseline. Other factors occasionally, but not consistently, related to the outcome, included age at onset, and attributing illness to a psychological cause and/or having a sense of control over symptoms [41]. Although clinical picture is chronic, most people get better over time with some rest symptoms. Younger age is a favorable prognostic factor.

CONCLUSION

CFS/ME is a complex, multisystem disease of chronic course with serious consequences on patients' quality of life. Physical and mental exertion intolerability, muscle pain, and sleep problems are the main features often accompanied by cognitive inefficacy and vegetative symptoms. Etiology and pathophysiology are not known but there are many theories based on multiple findings of involvement of immune, endocrine/metabolic, biochemical,

and other mechanisms. There are numerous comorbidities, and differential diagnosis is often complicated. Treatment is still symptomatic and of partial benefit, with many drugs of various classes and nonpharmacological measures routinely used. Larger controlled trials are needed to shed more light on this challenging condition.

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Мијалгични енцефаломијелитис – енигма на раскршћу медицине

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САЖЕТАК

Мијалгични енцефаломијелитис је сложено, мултисистемско обољење са хроничним током које значајно утиче на квалитет живота болесника. Слаба толеранција на физички и ментални напор, болови у мишићима и проблеми са спавањем главне су одлике и често су праћене когнитивном неефикасношћу и вегетативним симптомима. Преваленција је 7–3000 на 100.000 одраслих. Процењује се да је 90% ових болесника погрешно дијагностиковано. Патогенеза је и даље само спекулативна, али тренутна истраживања указују на поремећаје у имунолошком систему, инфламаторном одговору, аутономном и централном нервном систему, мишићима и митохондријама, као и промене микробиоте и пропустљивости црева. Почетак болести је типично акутан и прати инфективну болест. Нетолеранција напора која траје дуже од шест месеци важан је дијагностички критеријум. Основне карактеристике морају бити умерене до тешке и присутне најмање 50% времена. Искључивање других могућих патолошких стања или коморбидитетних дијагноза захтева задовољавање дијагностичких критеријума и диференцијално дијагностичко сагледавање. Морфометријска снимања мозга магнетном резонанцом показала су атрофију сиве масе у окципиталним режњевима билатерално, десном ангуларном гирусу и постериорном левом парахипокампалном гирусу, што може довести до проблема са памћењем и оштећења визуелне обраде информација. Лечење је и даље симптоматско и само делимично успешно. Симптоматски третман може да укључује лекове за контролу бола и проблема са спавањем, дозирану физичку активност и когнитивно-бихевиоралну терапију. Потребне су веће студије да би се разјаснило ово медицинско стање.

Кључне речи: мијалгични енцефаломијелитис; синдром хроничног умора; слабост после напора

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Over-time work of part-time health care professionals – case study of the General Hospital of Valjevo

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SUMMARY

Introduction/Objective In practice, for more than 10 years there has been ongoing litigation between healthcare institutions and healthcare workers, who have found that reduced working hours may be payment compensation for overtime work (on-call time, on-call duty, stand-by time).
The objective of this paper was to analyze the problem and propose a solution in order to stop disputes and eliminate uncertainty.

Methods A case study method, comparative method and normative method were used in this article. Court practice has been analyzed in relation to a number of civil proceedings, as well as the opinion of the State Audit Institution of the Republic of Serbia and the Ministry of State Administration and Local Self-Government on a specific case.

Results Healthcare workers and healthcare institutions have different legal views about the right to salary supplement based on overtime work of healthcare workers who work reduced working hours. Although the court has taken a stand on the side of healthcare workers, disputes do not stop because healthcare institutions do not change their calculation method.

Conclusion The solution is to amend legal regulations that need to regulate in detail and unequivocally the manner of payment of salary supplements for healthcare workers in order to avoid any doubts and contentious situations.

Keywords: healthcare worker; overtime work; reduced working hours; salary supplements

INTRODUCTION AND BACKGROUND OF THE STUDY

The Labor Law of the Republic of Serbia stipulates that full-time job equals a 40-hour-week, with that a collective agreement may specify working hours of less than 40 hours but not shorter than 36 hours [1]. In this case, there is a legal fiction about the existence of a full-time position, so that employees fulfill all their employment rights, as well as employees who work 40 hours a week.

Working time means the period from the beginning to the end of daily work perfomance during which an employee effectively carries out work, that is, they are at the disposal of their employer, performing their duties in a workplace or other place designated by employer, in accordance with applicable law [2]. Directive 2003/88/EC of the European Parliament and of the Council of November 4, 2003, Concerning Certain Aspects of the Organisation of Working Time, within the concept of working time implies the period during which the worker performs work, is available to the employer and carries out his activities and duties in accordance with the national law [3]. As a rule, the duration of an employee's work time is prescribed as full time during working day and during the working week [4].

An employee must have sufficient time to rest, to renew his/her physical and intellectual potential, for quality time with family, education and cultural uplift. "All the well-being a person possesses includes current consumption, future consumption (savings), possession of property and enjoyment of leisure" [5]. Long working hours on regular bases not only adversely affect health and safety of employees, but also affect productivity. Researches indicate detrimental effect of performing work of particular occupations on health, especially jobs in healthcare as well as overtime work [6–9]. An employer who does not respect the obligations regarding working hours becomes a "silent killer" of free time and private life of his employees [10].

Overtime is work longer than full time which is generally paid more [definition by the Organisation for Economic Co-operation and Development (2001)] [11]. As a rule, this work is forbidden. The Constitution of the Republic of Serbia stipulates that employees are entitled to a limited working time and this right cannot be denied or waived [12, 13]. Overtime should be understood as a "necessary evil" and avoided in situations where the jobs for which it is introduced can be done by rational organization, redistribution of working hours or employment of new workers [14].

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Overtime work of healthcare professionals is regulated by the Law of Healthcare, such as on-call time, on-call duty and stand-by time [15]. Healthcare institution can introduce on-call time work as overtime (on-call time is one of the widespread forms of overtime work [16]) only if it is not able to ensure continuity in providing healthcare by organizing shift work and scheduling working hours of employees. During on-call time, healthcare worker must be present at the healthcare facility. According to the Court of Justice of the European Union, on-call time where a worker is required to be physically present at a place determined by his employer must be considered working time regardless of the fact that the person does not perform continuous professional activity during the on-call period. This conclusion is not changed by the fact that the employer provides the doctor with a rest room in which he can stay as long as his professional services are not needed. [17, 18]. Also, the Court of Justice of the European Union has taken the position that time spent on stand-by time should be recognized as working time, if a doctor is required to come to work during the stand-by period. Otherwise, if the doctor was not called, despite the obligation to be available to the employer, he enjoys a greater degree of freedom than the worker in the workplace, i.e., he can use his time in his own interest, with fewer restrictions [19]. The average weekly working time, with overtime work, i.e., on-call time and on-call duty, at the four-month level, cannot last more than 48 hours per week for a healthcare professional. Directive 2003/88/EC of the European Parlaiment and of the Council of 4 November 2003 Concerning Certain Aspects of the Organisation of Working Time provides an opportunity for Member States to be excluded from the 48-hour working week limit, provided that safety and health at work are respected and with the express consent of the employee [11]. Collective agreement may stipulate that the average working time is tied to period longer than four months and maximum of nine months. Healthcare facility can introduce on-call work as overtime work and stand-by time. On-call work is a special form of overtime work where a healthcare professional comes on-call to provide healthcare outside of his fixed hours and can be introduced for employees who are at stand-by time. Exceptionally, on-call work may also be introduced for off-duty employees in the event of natural and other major incidents, traffic accidents, crises and emergencies, in accordance with the law. During stand-by time, healthcare provider is not present in healthcare facility, but must be available to provide emergency medical care in healthcare facility and respond to a call from a competent person. According to the standards of the International Labor Organization, stand-by time can be considered working time only if the restrictions imposed on him during that period prevent the employee from actually using this time for personal purposes [20].

The legislator indicates by work what does not represent work (on standby and on-call work), but such a qualification should be conditionally understood, in terms of work as a potential possibility. These types of overtime work eliminate the risk of possible non-provision of health services by health care institutions [21]. Healthcare professionals must not leave workplace until they are provided with a replacement during working hours or after expiry of working hours, if this would impair the performance of healthcare and endanger health of a patient. An employee who has resumed work after expiry of working time, which is considered as overtime work, is obliged to notify the immediate supervisor in writing at latest on the next working day.

A special question is the possibility of working overtime on a reduced working hours basis. Reduced working hours work, unlike part-time work, is legally equated from the point of view of the employee's right to a salary and other rights of full-time employees – legal fiction about exercising employment rights as well as full-time employees [10]. An employee working on jobs to which reduced working hours are asigned, cannot be assigned overtime work as well, unless otherwise provided by law [1]. The Law of Healthcare defines it otherwise: an employee who does reduced working hours jobs, in accordance with the law which governs labor, may be assigned to overtime in those jobs, in the cases we cited, as well as in cases where healthcare provision cannot be otherwise organized.

In modern labor legislation, working time regulations generally have protective characteristcis. Thus, in the world of work, there is a general tendency for shortening working time [16]. Although there is a tendency in the world for the introduction of a four-day work week [22], due to lack of healthcare workforce in Serbia the overtime work of employees who work reduced working hours is widespread [23].

Due to increased risks during overtime work, the legislator prescribes compensation in the form of a salary supplement. An employed healthcare worker who works overtime is entitled to a salary supplement for overtime work, which is stipulated by the Special Collective Agreement [24]. Upon the employee's written request, overtime work is converted into free hours on the quarterly basis instead of the right to a salary supplement. For every hour of overtime work, an employee is entitled to one and a half hours of free time. For time spent on stand-by time, when employed healthcare workers do not work, they are entitled to a salary supplement. Stand-by time on weekdays can last up to maximum 16 hours, and on Saturdays, Sundays and public holidays 24 hours. On-call time, on-call duty and stand-by time hours are mutually exclusive. An employed healthcare worker is entitled to overtime pay bonuses (on-call time and on-call duty) – 26% of the basic salary. During stand-by time, an employee is entitled to a supplement for each hour spent on stand-by time in the amount of 10% of the value of the basic salary's working hour. All of the above also applies to health workers employed by the Ministry of Justice, in the system of execution of criminal sanctions, given that the right to health care is one of the basic rights listed in the provisions of the Law on Execution of Criminal Sanctions [25, 26]. However, labor regulations do not apply to health workers who practice the profession as self-employed (private practice) as they have the status of self-employed. When entrepreneurs perform the activity personally and have no employees, they maintain the

status of a self-employed person and the Labor Law does not apply to them [27, 28]. A natural person registered in a special register, who performs the activity of a free profession regulated by special regulations, is considered an entrepreneur. Free profession is a profession that is qualified as such and defined by law – practice of law, notary and health services, engineering, auditing, tax and actuarial consulting, art, journalism, veterinary medicine, etc. [29].

In practice, for over 10 years, the litigations between healthcare institutions and healthcare workers regarding salary supplement for overtime work (on-call time, on-call duty, stand-by time) have been conducted, that is to say, the healthcare workers who have been assigned reduced working hours, which is why healthcare institutions have large court costs. The aim of this paper is to analyze the problem and propose a solution in order to stop disputes and eliminate uncertainty.

METHODS

Case study method, comparative method and normative method were used in this paper. The legal solutions and court practice regarding a large number of litigation procedures related to the payment of overtime salary supplements to reduced working hours of healthcare workers have been analyzed. Judgments of courts of all levels were analyzed, namely the Basic Court in Valjevo, the Court of Appeal in Belgrade, the Supreme Court of Cassation of Serbia and the Constitutional Court of Serbia and Court of Justice of the European Union. Therewith, the opinion of the State Audit Institution of the Republic of Serbia and the Ministry of State Administration and Local Self-Government on the specific issue were analyzed.

CASE STUDY

A large number of employed healthcare workers at the General Hospital in Valjevo, who have been assigned reduced working hours in accordance with Law, have filed lawsuits against their employer for less paid supplement based on overtime work, as well as on-call work and stand-by time, citing that hourly price of their overtime work is not equal to hourly price of healthcare workers who have not been assigned reduced working hours. For example, a psychiatrist healthcare professional at the Neurology Department is assigned working time of 36 hours per week which is considered a full-working time. Aforementioned believed that his hourly work price should be determined by dividing basic salary on a weekly basis by 36 rather than 40, so consequently the price of his overtime hour was higher than the price of working hour of an employee who does not work reduced working hours.

The defendant emphasized that it is stipulated that when calculating employees' salaries, one starts from the average working hour fund of 174 hours a month, hence in this way of calculating value of working hours as the basis on which salaries and supplements are calculated, it is multiplied by the number of working days, that is to say, of working hours in a particular month, and salary supplements are calculated according to the number of recorded hours spent on-call time, stand-by time, etc. It was pointed out that the fact that the plaintiff works shorter does not affect the amount of the value of his working hour, because the value of the working hour is fixed and based on a 40-hour working week. Reduced working hours work is a protective measure aimed at protecting an employee working in jobs with increased risk from exposure to the harmful effects of the working environment and working conditions. The purpose of this protective measure is fulfilled by the shortening of working hours.

The Basic Court upheld the claimant's claim, stating that the defendant was under an obligation to calculate salary on a fixed basis, pursuant to Art. 4 and 6 of the Law on Salaries in State Bodies and Public Services while accepting allegations made by the Claimant [30, 31]. In the aforementioned factual and legal situation, the Court of Appeal in Belgrade first, by one judgment, quashed the judgment of the Basic Court of Valjevo and remitted the case for retrial, taking the stand that unique price of a working hour, both for regular work and for salary supplement is determined on the basis of a full fund of hours, that is, 40-hour working week, because basic salary is paid for full-time work and work which is considered full-time, while percentages of the increase based on the salary supplement are applied to basic salary [32]. It further cited that the claimant is paid a full-time salary as if he worked 40 hours rather than 36 hours, and for salary supplements price of working hours is increased in proportion to the time spent at work, and since one base cannot be used for full working time, and the other for salary supplements aforemetioned overturned the first-instance judgment and ordered the removal of ambiguities. However, in the judgments given later, the Court of Appeal affirmed the judgments of the Basic Court, which upheld the claims [33, 34].

Ruling on a separate revision as an extraordinary remedy, the Supreme Court of Cassation of Serbia issued a decision dismissing it as an impermissible revision against the judgment of the Court of Appeal in Belgrade [35]. In the reasoning of the decision, the court stated that it considered that conditions to allow a decision on revision were not fulfilled since there was no need to harmonize case law or to decide on a revision in order to consider a legal issue of general interest.

Constitutional appeals were also decided by the Constitutional Court of Serbia. By the same decision, it rejected the constitutional complaint of the Valjevo General Hospital against the judgment of the Belgrade Court of Appeal, stating that the reasoning of the Belgrade Court of Appeal contained a constitutionally acceptable application of substantive law [36]. The aforementioned estimated that when calculating increased earnings on the basis of overtime work, night work and work on non-working days, it should start from the fact that the claimant's full time work is 36 hours per week, which is the basic parameter for determining value of working hours.

At the request of Valjevo General Hospital, the Ministry of State Administration and Local Self-Government of the Republic of Serbia gave an opinion that reduced working hours is an issue of protective character applicable to specific categories of jobs (high-risk jobs) and that additional privileges cannot be extracted from that special regime in terms of calculating the base on a weekly basis of less than 40 hours per week, but not less than 36 hours per week and in a situation when a reduced working hours at the certian position was introduced by a risk assessment act [37].

The whole problem is complicated by different interpretations of salary supplement calculation base. In this regard, the opinion of the State Audit Institution, which stated in its report on the audit of the final account and regularity of operations of the Valjevo General Hospital for 2016 that based on the insight into the program for the calculation of salaries, bonuses and employee benefits and payroll of employees, it is determined that the parameters set in the payroll program are incorrectly defined in the calculation of all salary supplements, except past work, in such a way that employees who have an additional management coefficient do not take its value, if stated in the base separately from the basic coefficient, but only the value of the coefficient first entered into the system (usually this is the basic one) [38].

DISCUSSION

From the presented case, it can be concluded that the main problem is that in practice there are two different legal positions on method of calculating salary supplement for employed healthcare workerss who have fixed reduced working hoursing hours.

By analyzing a specific case, we are giving our opinion on the legality and regularity of salary calculation. At first glance, the logic of the courts and the Constitutional Court of Serbia. On the other hand, in practice, it means that two doctors who have the same salary under a contract of employment, where one works reduced working hours and the other full time, will not receive the same compensation when calculating 10% salary supplement even though they both do not work. A reduced working hours doctor will also have a higher salary bonus on stand-by time than a full-time doctor, even though they do not work, which is not fair given that they have the same basic salary.

Firstly, we should start from legal provisions, namely the provisions of Art. 2 par. 3 of the Law on Salaries in State Bodies and Public Services, which stipulates that the basic salary of employees in public services shall be the product of base and coefficient and the provisions of Art. 4. which stipulates that the coefficient expresses complexity of work, responsibility, working conditions and qualifications [39]. Then the provision of Art. 5th par. 4. stipulates that the basis for calculating the salary supplement is the basic salary established by this law. The provision of Art. 6 of the same law stipulates that salary determined for the purposes of Article 2 of this Law shall be paid for full-time work, or the work which is considered full time work. Bearing in mind opinions expressed, the most correct position was taken by the Court of Appeal in Belgrade in judgment Gž1 3149/13 of 20 June 2014 in which it cited that the uniform price of working hour for both regular work and salary supplements is determined on the basis of the full fund of hours, that is, 40-hour work week, since the basic salary is paid for full-time work and work which is considered full-time, while percentages of pay increase are applied to the basic salary. A reduced working hours employee cannot be paid a full-time salary as if he works 40 hours rather than 36 hours, and for salary supplements price of working hours should be increased in proportion to time spent at work, that is, one base cannot be used for full-time work and the other for salary supplements. In this regard, we believe that the stated opinion of the State Audit Institution is correct, since the basic salary includes managerial supplement for, i.e., the base used for calculation of salary must also be used for calculation of salary supplement.

In comparative law, for example in Croatia, the Collective Agreement for Health and Health Insurance stipulates that for workers who have a position allowance contained in the job complexity coefficient or receive that allowance based on the provisions of this Agreement, on-call and stand-by time benefits are calculated in relation to the basic salary of the job where the employee is on standby (Articles 51–52) [40]. This specification is the result of numerous court disputes on the occasion of which the Supreme Court of Croatia took a stand at the session of the Civil Department on December 9, 2019, in which it is said: "Healthcare workers during the validity of the Collective Agreement for activities of healthcare industry and health insurance (The People's Newspaper, 143/13 and 96/15) who, in regular work, are entitled to an increase in salary for special working conditions referred to in Art. 57 of the Collective Agreement and the right to increase salary for exceptional responsibility for life and health referred to in Art. 59. are entitled to supplements (cumulatively) and to overtime hours" [41].

In the Republic of Slovenia, for each hour of stand-by, the employee is entitled to payment in the amount of 30% of the basic salary of the job for which he is on standby. For each hour on duty, the employee is entitled to a payment in the amount of 90% of the value of the basic salary for the job for which he performs his duty. If on-call hours coincide with a Sunday, holiday or night hour, the employee is also entitled to an allowance of 30% of the basic salary [42].

Finally, we will consider percentage increase of salary based on overtime work which in Serbian law is minimum 26%. Considered by comparative law in the Republic of Croatia, the basic salary of a healthcare worker is increased by 50% for overtime work [40] and the same percentage increase is in the Republic of Slovenia [42]. The solutions of some collective agreements in Serbia are also significant. For example, the Collective Agreement for State-owned enterprise "Pošta Srbije" (Serbian Postal Service) in Belgrade stipulates a 45% increase in salary for overtime work [43]. The Special Collective Agreement for Police Officers stipulates the right to an overtime work supplement of 28.6% of the basic salary [44]. The Special Collective Agreement for Electric Power Industry of Serbia stipulates a 45% increase in overtime work salary [45].

CONCLUSION

Overtime work is extremely permissible because it represents an exception to the rule that an employee is entitled to limited working hours. An even bigger exception is overtime work of employees who have been assigned reducing working hours job, which is why every effort should be made to minimize this work.

Regarding the problem of paying salary supplement for overtime work of healthcare workers, we believe that the solution to the problem is to change legal regulations that need to regulate in detail and unequivocally the method of payment of supplements for healthcare workers in order to avoid any doubts and controversy situations. Healthcare providers would have to adjust their salary calculations in accordance with court decisions in order to avoid damages caused by conducting court proceedings.

In addition, increase of salary for overtime work of 26% of the base should be revised in the light of comparative law solutions as well as solutions of some collective agreements in Serbia.

Conflict of interest: None declared.

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Прековремени рад здравствених радника – студија случаја Опште болнице Ваљево

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САЖЕТАК

Увод/Циљ У пракси се већ више од десет година воде судски спорови између здравствених установа и здравствених радника којима је утврђено скраћено радно време поводом исплате додатака на плату за прековремени рад (дежурства, рад по позиву, приправност).

Циљ рада је анализа проблема и предлог решења како би се обуставили спорови и отклонила неизвесност.

Методе У раду је коришћен метод студије случаја, упоредни метод и нормативни метод. Анализирана је судска пракса поводом већег броја парничних поступака као и мишљења Државне ревизорске институције Републике Србије и Министарства државне управе и локалне самоуправе по конкретном случају.

Резултати Здравствени радници и здравствене установе имају различите правне ставове о праву на додатке на плату по основу прековременог рада здравствених радника који раде са скраћеним радним временом. Иако је суд заузео став на страни здравствених радника, спорови не престају јер здравствене установе не мењају свој начин обрачуна.

Закључак Решење проблема је у измени правних прописа којима треба детаљно и недвосмислено уредити начин исплате додатака на плату за здравствене раднике како би се избегле све недоумице и спорне ситуације.

Кључне речи: здравствени радник; прековремени рад; скраћено радно време; додаци на плату

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Modern radiotherapy in the treatment of localized prostate cancer

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SUMMARY
Prostate cancer (PC) is one of the most prevalent cancers in men and the second leading cause of cancer-related deaths, after lung cancer. The incidence and mortality from PC worldwide are correlated with increasing age.
The treatment of patients is multidisciplinary, with radiotherapy being an integral part, whether applied as an independent method or in combination with surgery or systemic therapy. The technological progress in the middle of the last century, opened up new possibilities in the planning and conducting radiotherapy started the new era of radiotherapy called modern radiotherapy. Today, highly conformal external beam techniques such as intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT) are used as the gold standard in PC radiotherapy. They enable the precise definition of tumor volume based on modern diagnostic procedures, with maximum sparing of the surrounding organs. Advanced conformal techniques have also led to an escalation of the tumor dose, thus achieving better local control of the disease with significant reduction of early and late complications of treatment, the quality of life of PC patients is preserved.
In addition to technological progress, modern radiotherapy includes monitoring the side effects of radiotherapy, and assessment of clinical and individual parameters that affect sensitivity and response to radiation. This should enable personalized radiotherapy with optimization of the treatment for each patient, which is one of the goals of modern oncology.
Keywords: prostate cancer; IMRT; VMAT

INTRODUCTION

In men, prostate cancer (PC) is the second most frequent cancer diagnosed, and the second leading cause of cancer-related deaths [1]. In Serbia, it ranks third in both incidence and mortality, behind lung and colorectal cancer [2]. The incidence rate is almost 60% in men over 65 years of age [3]. It is believed that global aging of population and prolonged life expectancy increase the incidence of PC in the future, and it is anticipated that by 2030 there will be 20.3 million new cases, with 13.2 million deaths [1, 4].

Multidisciplinary approach in the treatment of PC includes radiotherapy (RT) as an important treatment modality in both localized and metastatic disease. It can be applied as a stand-alone method or in combination with other forms of treatment – surgery, or systemic therapy [5, 6].

Since the clinical behavior of PC range from indolent to highly aggressive, it is important to know prognostic factors to determine the appropriate treatment as well as possible benefits and side effects of each of the therapeutic options. The main prognostic factors include prostate-specific antigen value (PSA), Gleason score (GS) and tumor stage. Based on these three factors, according to the European Association of Urology (EAU), patients are divided according to the risk of biochemical recurrence after local treatment in three risk categories (Table 1).

The optimal management for localized PC remains controversial due to various forms of therapy that have different and specific impact on the quality of life and sexual function of long-term PC survivors. When comparing treatment options for localized PC, there are no significant differences in biochemical recurrence-free survival and disease-free survival between the patients treated with active

Table 1. The European Association of Urology risk categories for biochemical recurrence of localized and locally advanced prostate cancer [6]

Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/ml	PSA 10–20 ng/ml	PSA > 20 ng/ml	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)
and cT1–2a	or cT2b	or cT2c	cT3–4 or cN+
Localized	Localized	Localized	Locally advanced

GS – Gleason score; ISUP – International Society for Urological Pathology; PSA – prostate-specific antigen

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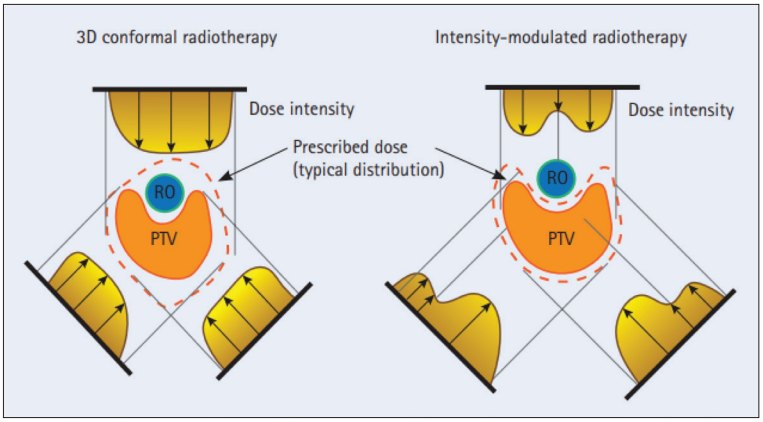

Figure 1. Intensity-modulated radiotherapy improves the conformity of the total dose delivered to the planning target volume (prostate and seminal vesicles) while reducing the dose to the risk organ – rectum, compared to conformal radiotherapy; the dotted line represents the applied dose delivered to the planning target volume [5];
RO – rectum; PTV – planning target volume

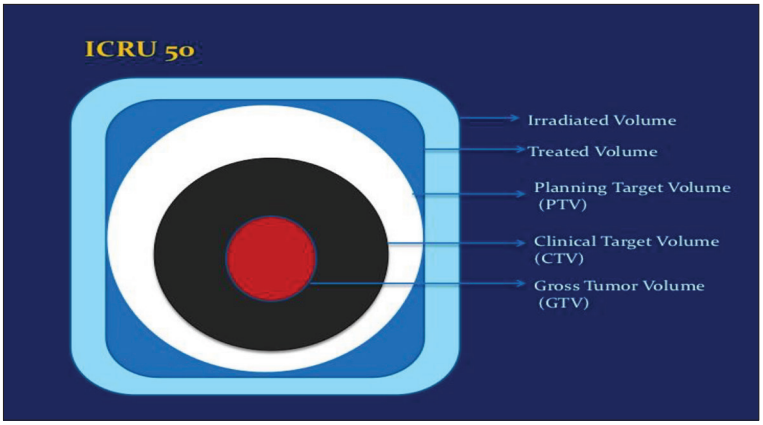

Figure 2. Schematic diagram of radiotherapy irradiation volumes – ICRU 50 [14]

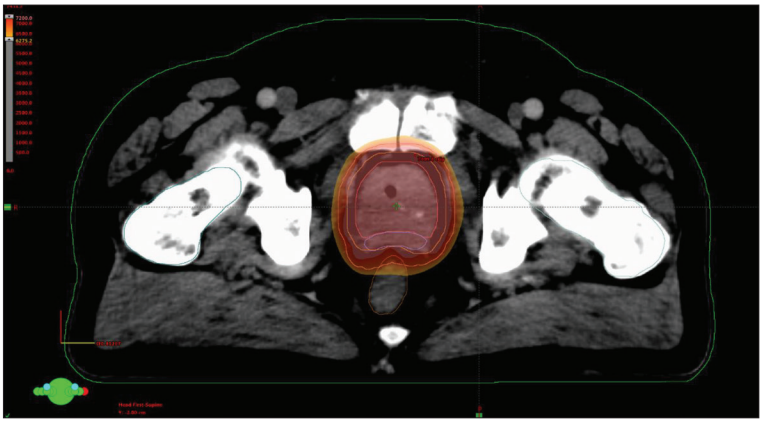

Figure 3. Isodose distribution in a patient with intermediate-risk prostate cancer (property of the Institute of Oncology and Radiology of Serbia)

surveillance, radical prostatectomy, or high-dose external beam radiotherapy (EBRT). In addition to the age of the patient, the presence of comorbidities, socioeconomic status of the patient, and trends in the personal practice of clinical centers play an important role in choosing the appropriate therapy [6, 7].

MODERN RADIOTHERAPY

The first reports of radiation usage in the treatment of PC appeared in the early 20th century. EBRT was initially used only as an addition to interstitial radium treatment because kilovoltage radiation systems were not adequate to allow definitive treatment of deeply localized tumors such as PC. With the discovery of androgen-deprivation therapy (ADT) in the early 1940s, radiotherapy lost its popularity in PC treatment. In the late 1950s, the pioneering work of an American radiologist, Malcolm Bagshaw, introduced the possibility of treating PC using megavoltage radiotherapy [8]. Today, more than one third of men with localized PC are treated with only EBRT [9].

Improved diagnostic data processing, such as computerized tomography (CT) and magnetic resonance imaging (MRI), have resulted in three-dimensional conformal radiotherapy treatment (3D-CRT) with accurate visualization of the geometric positions of tumor and normal tissue [10].

Today, highly conformal EBRT such as intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT) are used as the gold standard in the treatment of PC. Both techniques provide a complex dose distribution within the target volume (TV) and enables:

1. dose-escalation
2. better sparing of surrounding healthy tissue
3. better local disease control
4. lower morbidity rate

Radiotherapy treatments require a careful balance between adequate therapeutic tumor doses but not causing irreparable damage to normal tissues. Known as the "therapeutic ratio", ongoing technological advances and research continue to develop techniques to maximize this balance [5, 11].

Intensity-modulated radiotherapy

Worldwide, IMRT is most commonly used in PC. IMRT is a more advanced form of 3D-CRT. It is a technologically complex radiotherapy option developed to deliver the appropriate radiation dose to irregular and inhomogeneous TV with maximum sparing of the surrounding organs. IMRT uses dynamic multileaf collimators, which automatically and continuously adjust to the TV. This is achieved by subdividing each radiation beam into smaller beamlets and varying the individual intensities of these beamlets [5, 11]. In the treatment of PC, IMRT uses five to seven beams which reduce the dose to adjacent structures. A

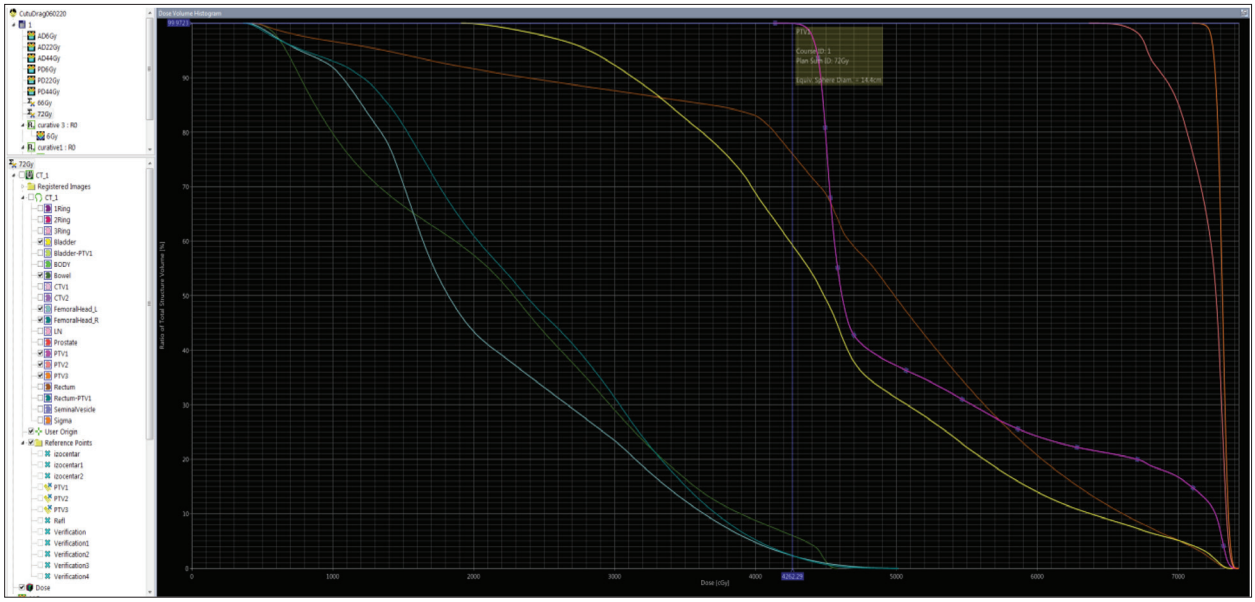

Figure 4. Dose Volume Histogram (graphical representation of target volumes and radiation doses, property of the Institute of Oncology and Radiology of Serbia)

standard IMRT plan often requires multiple fixed angle radiation beams, which can increase treatment delivery time. However, IMRT compared with 3D-CRT leading to a larger volume of normal tissue receiving low radiation doses which could be associated with an increased risk of secondary malignancies [11, 12].

Volumetric modulated arc therapy

In recent years, there has been a development of IMRT with the addition of rotating fields, to overcome a limit of IMRT with fixed fields. VMAT is a novel radiation technique which involves treatment of the whole TV using one or two arcs of beams from a machine that rotates around the patient continuously while delivering therapy. The main advantage over static fixed-gantry IMRT is reduced treatment delivery time and reduction of radiation dose to the rest of the body. With dose escalation using IMRT and VMAT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualized and corrected in real time. IGRT involves the incorporation of imaging before and/or during treatment to enable more precise verification of treatment delivery and allow for adaptive strategies to improve the accuracy of treatment [6, 13].

Target volumes

Delineation of TV and organs at risk, in both IMRT and VMAT, is performed by using some imaging method (CT, MRI). Accurate determination of TV is the most important and most difficult part of PC radiotherapy. In the context of radiotherapy delivery, the International Commission on Radiation Units and Measurements (ICRU) has been developing guidelines for prescribing, recording and reporting dose for radiation therapy. TV is defined following the recommendations of ICRU, the most recent of which is ICRU 83.

TVs include:

- GTV (gross tumor volume) – represents the tumor mass visible on the planning CT scan. In PC, the tumor within the prostate itself is not visible on the CT image, thus entire prostate is defined as GTV.
- CTV (clinical target volume) – the volume around the visible tumor mass which includes possible microscopic zones of tumor spread such as seminal vesicles and pelvic lymph nodes. In postoperative setting, this volume includes the tumor bed and the surrounding zones of possible microscopic spread of malignant cells.
- PTV (planning target volume) – represents the TV to which the prescribed therapeutic dose is applied. They are obtained by the delineation of the appropriate margin on the CTV, which represents an additional safety zone, having in mind the inaccuracies of immobilization and physiological movements of organs.
- OAR (organs at risk) – represent organs receiving significant RT dose, such as intestine, rectum, bladder [11, 14].

Dose prescription

Up to now, using conventional RT, doses was in the range of 65–66Gy. Recent advances in RT, such as IMRT and VMAT, have significantly reduced irradiation-related toxicities, which makes dose intensification possible. Recommended treatment for the low-risk group of PC patients is in the range of 72Gy to over 80Gy, with a standard fractionation regiment (1.8–2Gy daily, five days a week). In the intermediate-risk group, doses are in the same range as in the low-risk group, with the addition of ADT for

4–6 months. Dose-escalation in this group leads to better treatment results, and by the EAU the lowest recommended dose is 76Gy. For the high-risk group for localized disease, dose-escalation and long-term use of ADT are recommended, usually 2–3 years [6, 11].

RADIATION TOXICITY

Modern radiotherapy includes monitoring of radiotherapy side effects. Side effects result from the damage of healthy tissues near the treatment area. Therefore, in assessing the overall effect of radiotherapy, it is necessary to assess the complications of the treatment. The side effects can be divided into:

a) Acute (early) complications – occur during radiation or a few weeks after it. These reactions are sometimes very severe, usually transient and less likely to lead to permanent damage.
b) Subacute complications – occur in the period from several weeks to several months after radiation.
c) Late complications – usually manifest after several months, even several years after the radiation. These changes are usually permanent (irreversible). Oncogenesis with the appearance of the so-called secondary malignancy caused by radiation is late damage.

With the use of modern RT (IMRT, VMAT), greater precision was achieved compared to the conventional RT, which results in less pronounced acute and late complications [15].

Small bowel and the rectum are two important dose-limiting structures in PC radiotherapy. Symptoms experienced during treatment include a change in bowel habits, bowel frequency, urgency, and fecal incontinence. The most commonly reported late toxicities were chronic diarrhea, proctitis, or rectal bleeding. Several factors have been associated with increased gastrointestinal toxicity and these include larger bowel volume receiving high doses of radiation, the patient's age, comorbidities such as diabetes, and concomitant use of ADT. Hemorrhoids, previous gastrointestinal diseases, and abdominal surgery, as well as the use of antiplatelet drugs, had a significant impact on the occurrence of acute toxicity grade ≥ 1 of the lower gastrointestinal tract [15, 16].

Bladder damage resulting from acute radiation toxicity is primarily manifested as radiation cystitis (frequent urination and dysuric disorders). Smoking, previous abdominopelvic surgeries and the use of diuretics significantly affect the occurrence of acute genitourinary toxicity grade ≥ 2. Risk factors for the development of late genitourinary complications (i.e., cystitis, hematuria, urethral stricture, or bladder contracture) are higher radiation dose, previous urinary problems, transurethral interventions, and acute genitourinary complications [15, 17].

The increased radiation dose for patients with localized PC has now become an established standard of practice. However, a few retrospective studies confirmed the increased risk of late complications when higher radiation doses are delivered using conventional RT. With IMRT the rectal and bladder volume receiving 95% of the prescribed dose was significantly reduced, by shaping the high-dose volume to the prostate, with an absolute reduction of 23% and 80%, respectively [15, 18].

In general, if IMRT with IGRT is used for dose escalation, rates of severe late side effects (≥ grade 3) for the rectum are 2–3% and for the genitourinary tract 2–5%. Several retrospective and prospective studies have shown that IMRT reduces the radiation dose in the OAR with diminished rates of acute and late toxicity, even with higher doses (> 74 Gy). Zelefsky et al. [18] compared treatment outcomes in two groups of patients, first treated with 3D-CRT, and the second treated with a higher dose using IMRT. The use of IMRT significantly reduced the risk of late gastrointestinal toxicities compared with conventional 3D-CRT yet the incidence of late urinary morbidity did not seem to be diminished [6, 18, 19].

CONCLUSION

Severe late complications significantly reduce the quality of life (QOL) of PC survivors. It is essential to strike a balance between the therapeutic benefits and radiotherapy side effects. Early detection and proper evaluation of complications as well as personalized therapy approach are especially important in increasing the patient's QOL. With the use of modern RT (IMRT, VMAT), greater precision achieved compared to conventional RT, allowing dose escalation, which has been shown to improve clinical outcomes while simultaneously reducing toxicity. This is particularly significant in long-term PC survivors.

Conflict of interest: None declared.

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Савремена радиотерапија у лечењу локализованог карцинома простате

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САЖЕТАК

Карцином простате један је од најчешћих малигнитета код мушкараца а други по смртности узроковане раком, одмах после карцинома плућа. Учесталост и морталитет од карцинома простате широм света су у корелацији са повећањем старосне доби.

Лечење болесника је мултидисциплинарно, при чему је радиотерапија његов неизоставан део, било да се примењује као самостална метода или у комбинацији са хирургијом или системском терапијом. Технолошки напредак средином прошлог века отворио је нове могућности у планирању и спровођењу радиотерапије и почетак нове ере радиотерапије, коју можемо назвати савремена радиотерапија. Данас се као златни стандард у радиотерапији карцинома простате користе висококонформалне транскутане технике као што су интензитетом модулисана радиотерапија (*IMRT*) и запремински модулисана ротациона терапија (*VMAT*). Оне омогућавају да се на основу савремених дијагностичких процедура прецизно дефинише волумен тумора уз максималну поштеду околних органа. Напредне конформалне технике довеле су и до ескалације туморске дозе, чиме је постигнута боља локална контрола болести. Овакав напредак је био услов да се знатно смање ране и касне компликације лечења и тиме очува квалитет живота онколошких болесника.

Дакле, савремена радиотерапија поред технолошког напретка подразумева и праћење нежељених ефеката радиотерапије и процену клиничких и индивидуалних параметара који утичу на осетљивост и реакцију на зрачење. Све ове активности треба да омогуће персонализовану радиотерапију са оптимизацијом плана лечења за сваког болесника понаособ, што представља један од циљева модерне онкологије.

Кључне речи: рак простате; *IMRT*; *VMAT*

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 објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и 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.

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