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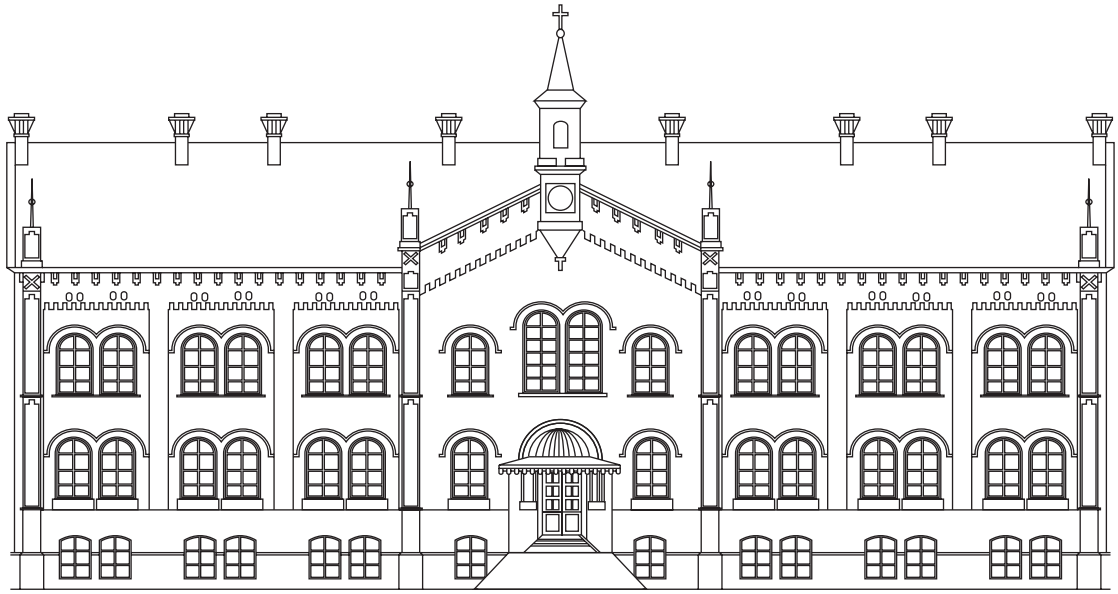

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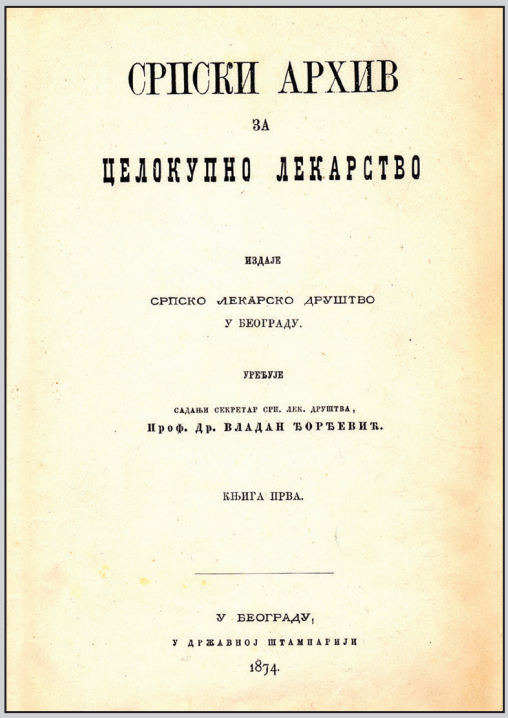

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ЗА

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1874.

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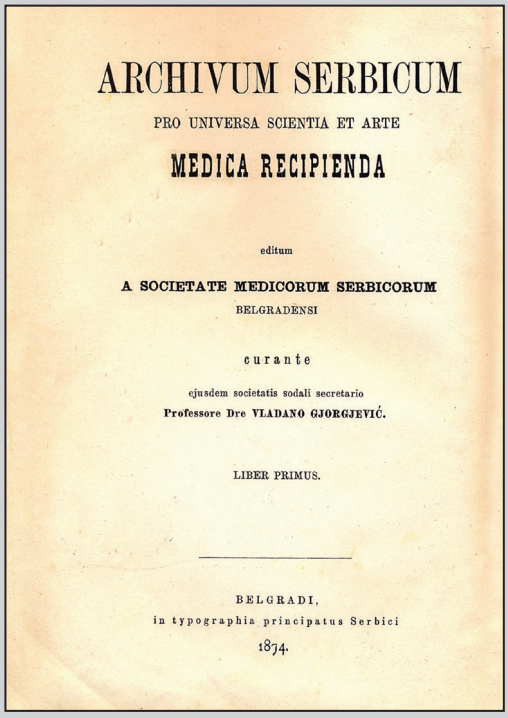

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1874.

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Impact of the COVID-19 pandemic on pre-hospital and in-hospital time-dependent performance measures of treatment of patients with acute ischemic stroke – experience of a tertiary healthcare center

Lana Macura[1], Rea Mikulan[1], Višnja Pađen[1,2]

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SUMMARY

Introduction/Objective The outbreak of the COVID-19 pandemic has posed major challenges to the process of urgent care of patients with acute ischemic stroke (AIS) that requires optimal and well-coordinated pre- and in-hospital chains in order to enable recanalization therapy commencement at the earliest possible opportunity. The objective of the study was to compare time-dependent performance measures and treatment results of patients with AIS hospitalized at a tertiary healthcare center before and during the COVID-19 pandemic.

Methods A retrospective analysis was performed on AIS patients treated with recanalization therapy at the Emergency Neurology Department of the University Clinical Centre of Serbia, during the March–June period of 2019, 2020, and 2021. Besides demographic and clinical characteristics, the following were calculated for each patient: time elapsed from stroke onset to hospital arrival ("onset-to-door"), time elapsed from hospitalization to the beginning of recanalization therapy ("door-to-needle"), and total time elapsed from symptoms' onset to treatment initiation ("onset-to-needle"). The patients' functional outcome was assessed after three months by using modified Rankin Scale score.

Results A total of 84 patients were included [25/2019, 30/2020, and 29/2021; (p = 0.512)]. No statistical significance was detected regarding the age, sex, severity of stroke symptoms at hospital admission, or the type of received recanalization therapy. Our study showed no statistical difference regarding time needed to reach the hospital (p = 0.441), "door-to-needle" time (p = 0.549), nor overall times elapsed from symptoms' onset to therapy (p = 0.481) among three groups of patients. Furthermore, comparison of the patients' three-month functional outcomes did not show statistical significance (p = 0.922).

Conclusion The experience of this tertiary healthcare system has shown notable resilience to the side-effects of the COVID-19 pandemic.

Keywords: acute ischemic stroke; recanalization therapy; pandemic; impact

INTRODUCTION

Acute ischemic stroke (AIS) is a clinical term that refers to the sudden onset of an infarcted area in the brain due to thrombotic or embolic occlusion of a blood vessel [1]. The infarcted zone implies irreversible necrotic changes of parenchyma and it is the most severely affected brain area by stroke. It is surrounded by the penumbra zone, in which the neuronal tissue is functionally altered, due to reduced perfusion, but still structurally preserved [2]. Neurons from the penumbra zone have the ability to restore their function if the circulation is re-established in a short period of time, otherwise, their necrosis and expansion of the infarct area will occure. Recovery of penumbra tissue is the main focus of recanalization therapy, and time is the most important factor of treatment success [3, 4]. It has been shown that administration of intravenous thrombolytic therapy (IVT), performed with alteplase, within the first 4.5 hours of symptoms reduces mortality and disability by 10–30% in the first six months after the stroke [3]. Furthermore, several recent studies showed a clear benefit of endovascular mechanical thrombectomy (EVT) in patients with large vessel occlusion [4]. As a result, the use of EVT (in the first six hours, or in clearly defined cases even 24 hours after the stroke onset), along with drug therapy, has become a standard method of treatment for patients with AIS and large vessel occlusion [4]. Patients with AIS require urgent treatment, optimal and well-coordinated pre- and in-hospital chains in order to receive recanalization therapy at the earliest possible opportunity.

Cases of pneumonia of unclear etiology were reported in Wuhan, China at the end of 2019 [5]. Soon after, viral causative agent was identified and named *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2*)* [6]. Since then, interhuman transmission of this newly discovered type of virus reached global proportions within a few months, and the World Health Organization declared a pandemic in March of 2020 [7]. The pandemic has seriously challenged healthcare systems due to the large number of COVID-positive patients and has disrupted the normal functioning of the

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remaining healthcare centers that treat acute and chronic conditions of non-COVID patients. This study focused on assessing the quality of treatment patients with AIS by recanalization therapy in a non-COVID tertiary institution under pandemic circumstances.

METHODS

A retrospective data analysis was conducted on AIS patients treated with recanalization therapy at the Department of Emergency Neurology, Neurology Clinic of the University Clinical Center of Serbia. The analysis was performed for the March–June of 2020 period (immediately after the pandemic proclamation and during the declared state of emergency in Serbia) compared to the same period in 2019 (when pandemic and consequential measures did not exist) and 2021 (when the healthcare system already adapted to functioning in pandemic circumstances).

Inclusion criteria for the study were as follows: implementation of recanalization therapy in acute stroke treatment, as well as known time of symptoms onset, arrival to the hospital, and commencement of reperfusion therapy. At admission, all patients were examined by a senior neurologist. The stroke diagnosis was made based on clinical criteria and stroke severity was assessed by using the National Institutes of Health Stroke Scale (NIHSS) score [8]. The clinical stroke diagnosis was confirmed by CT examination, analyzed by a neuroradiologist. The patient's arterial blood pressure was measured, electrocardiogram and complete laboratory analyses were done on admission. All the patients included in the study were treated with recanalization therapy, whose type (IVT, EVT, or both) was determined after consideration of clinical and neuroimaging parameters by a multidisciplinary team (neurologist, neuroradiologist), and according to current European and North American guidelines of stroke treatment [9]. Patients who did not meet the criteria for recanalization therapy administration were not included in the study. During hospitalization, patients underwent additional CT examinations 12–72 hours after admission, or earlier in case of clinical deterioration. The neurologist assessed the patient's clinical status seven days after, on discharge, and three months after the stroke. For all the patients, basic clinical and demographical characteristics were analyzed. Furthermore, the assessment of pre-hospital and in-hospital time-dependent performance measures were performed. We considered time of symptoms' onset, time of admission to the hospital, and time when the reperfusion therapy started. Therefore, for each patient we calculated and expressed in minutes time they needed to reach the hospital after the stroke onset ("onset-to-door"), time that elapsed from hospitalization to the beginning of recanalization therapy ("door-to-needle"), and overall time-period that elapsed from the onset of symptoms to the onset of treatment ("onset-to-needle"). The final outcome of stroke was assessed after three months by using modified Rankin Scale (mRS) score.

For statistical data analysis, IBM SPSS Statistics, Version 28.0 (IBM Corp, Armonk, NY, USA) was used. Patients' demographic and clinical characteristics were analyzed by descriptive methods and represented by average values or frequencies. Time intervals are represented by median and interquartile range. Patient group sizes and age variables were compared using the ANOVA test. The category variables, represented by frequencies, were compared by the χ^2 or Fisher test. The numerical variables presented by medians were compared using the Mann–Whitney test, or in case of looking for a difference among data from all three years at the same time, the Kruskal–Wallis test.

This research was approved by the Ethics Board of the University Clinical Centre of Serbia.

RESULTS

The study included a total of 84 AIS patients treated with recanalization therapy [25 patients treated in 2019, 30 patients treated in 2020, and 29 patients treated in 2021; (p = 0.512)]. There were no statistically significant differences regarding age, sex, severity of clinical presentation of stroke (assessed by using NIHSS score on admission), nor the type of recanalization therapy applied. The patients' demographic and clinical characteristics are presented in Table 1.

Among patients from 2019, 52% were male (13 patients); comparing to 60% (18 male patients) from 2020 and 44.8% (13 male patients) from 2021 (p = 0.506). The mean age of patients in all three groups was 64 ± 15 years. From other hospitals, we admitted two patients with AIS (8% of admissions) in 2019, four patients (13.3%) in 2020, and nine patients (31%) in 2021 (p = 0.064). The median (IQR) NIHSS score was 13 (7–18) for patients treated in

Table 1. Demographic and clinical characteristics of the study population

Characteristics	2019 n = 25	2020 n = 30	2021 n = 29	2019/2020/2021 p-value
Age, mean (x ± sd)	64.28 ± 15.38	64. 13 ± 14.25	64.72 ± 15	0.988
Sex: male (%)	13 (52%)	18 (60%)	13 (44.8%)	0.506
Severity of stroke presentation – NIHSS, median (IQR)	13 (7–18)	11 (5–16.25)	11 (8–14)	0.728
Patients transferred from other hospital, n (%)	2 (8%)	4 (13.3%)	9 (31%)	0.064
Type of reperfusion (%) IVT EVT IVT + EVT	 13 (52%) 11 (44%) 1 (4%)	 15 (50%) 11 (36.7%) 4 (13.3%)	 11 (37.9%) 14 (48.3%) 4 (13.8%)	 0.52 0.66 0.455

IQR – interquartile range; NIHSS – National Institutes of Health Stroke Scale; EVT – endovascular treatment; IVT – intravenous thrombolysis

Table 2. Time-dependent treatment performance measures (prehospital and intrahospital)

Performance measures	2019	2020	2021	2019/2020/2021 p-value
Stroke onset – hospital arrival, minutes, median (IQR)	120 (75–162.5)	95 (61.5–177.3)	135.5 (68.3–193.8)	0.441
Stroke onset – treatment commencement minutes, median (IQR)	180 (162.5–285)	175.5 (158.3–277)	235 (168.5–296.3)	0.481
Door-to-needle minutes, median (IQR)	75 (55–117.5)	83 (69.3–123.5)	99.5 (65.8–131.8)	0.549

IQR – interquartile range

2019; 11 (5–16) in 2020, and 11 (8–14) among those treated in 2021 (p = 0.728). Intravenous thrombolysis, as the only method of reperfusion, was conducted in 13 patients (52%) from 2019, in 15 patients (50%) from 2020, and in 11 patients (37.9%) from 2021 (p = 0.52). Endovascular thrombectomy, without previous IVT, was conducted in 11 patients (44%) in 2019, also 11 patients (36.7%) in 2020, and 14 patients (48.3%) in 2021 (p = 0.66). Both types of recanalization therapy (IVT + EVT) were performed in one patient in 2019 (4%), compared to four patients in 2020 (13.3%) and also four in 2021 (13.8%) (p = 0.455).

The analysis of time-dependent performance measures was conducted in two steps: the first step was comparison of data from all three years at the same time in order to detect possible statistical difference; then we separately compared results from each year (2019/2020, 2019/2021, 2020/2021). These results are shown in Table 2. There were no statistically significant differences among the analyzed data. After the symptoms' onset, the patients needed 120 minutes (75–162.5) to arrive to the hospital in 2019; 95 minutes (61.5–177.25) in 2020, and 135.5 minutes (68.25–193.75) in 2021 (p = 0.441). From the patients' arrival to the hospital to the beginning of therapy ("door-to-needle" time), 75 minutes (55–117.5) passed in 2019; 83 minutes (69.25–123.5) in 2020; and 99.5 minutes (65.75–131.75) in 2021 (p = 0.549). The overall time period elapsed from symptoms onset to the beginning of recanalization amounted to 180 minutes (162.5–285) in 2019; 175.5 minutes (158.25–277) in 2020, and 235 minutes (168.5–296.25) in 2021. Although the average time needed to start therapy is obviously longer in 2021, statistical significance has not been reached (p = 0.481).

Stroke outcome was assessed three months later by using mRS: median (IQR) in 2019 was 3 (0–5), in 2020 it was 4 (0.75–5), and also 4 (1–4.5) in 2021 [p = 0.922]. Detailed results are presented in Figure 1.

Table 2a. The resulting p-values obtained by comparing the data listed above (results from every year versus other two years)

Compared data	2019/2020	2019/2021	2020/2021
Onset of symptoms – hospital arrival	0.548	0.301	0.286
Onset of symptoms – onset of treatment	0.787	0.345	0.272
Door-to-needle	0.253	0.417	0.840

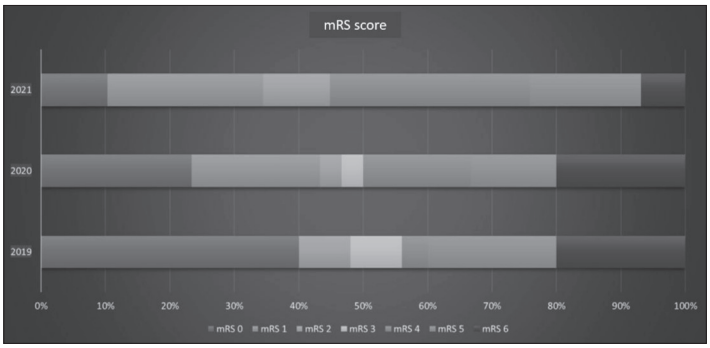

Figure 1. Three-month functional outcomes of patients with acute ischemic stroke treated with recanalization therapy [presented by modified Rankin (mRS) score]

DISCUSSION

Stroke, as a thromboembolic event, has been recognized as one of the possible complications of coronavirus infection [10, 11, 12]. Elderly patients with pre-existing comorbidities are at greater risk of developing this rare but severe complication [13]. Therefore, the incidence of AIS is expected to be higher during a pandemic. However, the conclusion of numerous studies [14–18] as well as the World Stroke Organization [19] is a paradoxical decline in the number of stroke hospitalizations and administered recanalization therapies during the pandemic, at the expense of fewer diagnosed transient ischemic attacks and minor strokes. The probable reason for this apparent drop in incidence is the patient's neglect of milder stroke symptoms in fear of COVID-infection in hospitals [20].

Regarding timely-dependent performance measures worldwide, results of studies published thus far are somewhat discrepant. Studies conducted in Canada and the USA showed a prolongation of admission and diagnosis of patients with AIS during the pandemic, which affected the delayed initiation of recanalization therapy [21, 22]. In a USA multicenter study, faster access to CT scanners was registered upon admission to the hospital, during the pandemic: median (IQR) times in 2019 and 2020 were 37 (15–101) and 29 (14–77) minutes, respectively (p < 0.01); the time required to start recanalization therapy after CT diagnosis was significantly extended: the median (IQR) in 2019 was 22 (13–37) *vs.* 29 (18–47) minutes in 2020 (p = 0.02) [21]. Overall, this led to a statistically significant delay in recanalization therapy in 2020 compared to 2019: the 2019/2020 median is 42/46 minutes (p = 0.03). A Canadian study found a delay in starting IVT upon arrival at the hospital (medians from 2019 and 2020 were 35 and 61 minutes, respectively, p = 0.005), which was caused by delayed CT diagnostics [from hospital arrival to CT usually 7.5 minutes elapsed in 2019, and 19 minutes in 2020 (p = 0.004)] [22].

In Hong Kong, at the very beginning of the pandemic (January–March of 2020), an average delay of 60 minutes was noted in the inception of recanalization therapy compared to the period immediately before the pandemic [23]. Also, lower percentage of patients arrived to hospital within the "golden hour" (4.5 hours from the onset of the symptoms) for intravenous thrombolysis.

Although we did not find statistical significance when comparing "door-to-needle" time in our study (p = 0.549), the observed delay in recanalization upon arrival at the hospital during the pandemic cannot be ignored (2019/2020/2021 medians were 75/83/99.5 minutes), which, as in the case of the Canadian study, could be explained by implementation of "covid-screening" protocols in emergency rooms – each patient is evaluated for possible symptoms of respiratory infection or tested with a rapid antigen test prior to hospitalization [22]. These necessary procedures certainly postpone diagnostics and therapy actions. Patients from our study reached the hospital faster in 2020 (median of 95 minutes) than in 2019 or 2021 (medians of 120 and 135.5 minutes, respectively), probably due to the lockdown and curfew proclaimed in Serbia from March to May of 2020.

On the other hand, a recent European multicenter study that involved 20 centers, including the UCCS Emergency Neurology Service, noticed that the number of recanalization therapies was 7% lower in the first wave of the pandemic than in the reference period (March–June) of 2019, but the quality of treatment remained the same – prehospital and intrahospital time-dependent performance measures of treatment did not differ [2019/2020 in the minutes elapsed from the onset of symptoms to hospital admission: 145/133, (p = 0.777), and the minutes elapsed from admission to hospital to the beginning of therapy: 48/51, (p = 0.653)] [24]. Equal success of treatment before and during the pandemic was proven by comparing the values of NIHSS 24 hours after hospital admission: medians (IQR) in 2019 and 2020 were, respectively, 5 (2–13) and 6 (2–14), (p = 0.674) [24]. These results are in line with the conclusions of our study. Our center, as well as other European centers participating in this multicenter study, are experienced centers with many years of practice in caring for patients with AIS, which may be an explanation for such results [24].

A small number of studies have analyzed the performance of emergency neurological services in 2021 and their long-term adaptations to pandemic operating conditions. The state of emergency in Serbia lasted from March to June of 2020, during which an occasional ban on movement and strict anti-epidemic measures were proclaimed. At that time, the health service was able to respond well to the new situation due to the small number of COVID-positive hospitalized patients. After that period, anti-epidemic measures were periodically introduced and abolished, and, as a result, the number of those infected increased. During most of 2021, the burden on the health system in Serbia was incomparably higher than at the pandemic's beginning, due to the large number of COVID-positive cases, overcrowding of hospital capacities, fewer non-COVID institutions, and the overall lack of staff (because of redistribution to COVID-hospitals or easy possibility of infection and consequent absence from work) [25]. Chinese studies published recently showed a significant delay in door-to-needle time during the pandemic period, compared to prepandemic 2019 [26, 27]. A study from Chongqing also found that patients had higher NIHSS score, and that hospital mortality was higher during the pandemic period [26]. A Beijing study, besides lower quality of stroke care service during the pandemic, noticed a drop in admissions of AIS patients in that period [27]. In the future, we will probably have many studies that analyze the newly created way of functioning of all health institutions, including performance measures for the pandemic ending period, which could be a future target for our study project as well.

Possible limitations of this study are reflected in the relatively small sample of patients and the retrospective nature of the study. Additional interpreting of the results of this study is necessary because this center is the largest in the country and has many years of experience in dealing with severe cases of stroke, so it is very possible that it is not a representative sample for the country's smaller centers, since they have been more severely affected by pandemic due to the lack of staff and capacity to care for urgent patients.

CONCLUSION

The study showed that the new pandemic conditions in 2020 and the necessary adaptation of the health system to a new way of functioning, which was still taking place in 2021, did not significantly affect the effective implementation of recanalization therapy for AIS and that time-dependent parameters and treatment results of AIS were similar to those from the prepandemic year of 2019. The results are important and encouraging and prove that the emergency neurology service of this tertiary center successfully resists the challenges of the current global situation. Still, the main focus is to further reduce time needed for patients to receive therapy and thus get a chance for fuller recovery and less disability, now with maximum respect for all recommended preventive epidemic measures during the admission and diagnosis of patients in the emergency rooms.

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Утицај пандемије ковида 19 на мере прехоспиталног и интрахоспиталног лечења акутног исхемијског можданог удара – искуство терцијарног центра

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САЖЕТАК

Увод/Циљ Појава пандемије ковида 19 поставила је велике изазове при процесу збрињавања болесника са акутним исхемијским можданим ударом (АИМУ), који захтева оптимално функционисање свих служби у ланцу ургентног збрињавања како би се омогућило започињање спровођења реканализационе терапије што је пре могуће. Циљ рада је анализа учинка временски зависних мера прехоспиталног и интрахоспиталног збрињавања болесника са АИМУ лечених реканализационом терапијом у терцијарном здравственом центру у периоду пре и током пандемије ковида 19.

Методе Спроведена је ретроспективна анализа података о болесницима са АИМУ леченим реканализационом терапијом на Одељењу ургентне неурологије Универзитетског клиничког центра Србије, у периоду март–јун током 2019, 2020. и 2021. године. Уз демографске и клиничке карактеристике, за сваког болесника је процењено време протекло од појаве симптома до доласка у болницу, период од доласка у болницу до почетка примене реканализационе терапије и укупно време од јављања симптома до започињања лечења. Процена функционалног исхода је вршена после три месеца применом модификоване Ранкинове скале.

Резултати У студију су укључена 84 болесника [25/2019, 30/2020. и 29/2021; (p = 0,512)]. Није утврђено постојање статистички значајне разлике према старости, полу, тежини клиничке презентације АИМУ, као ни типу примењене реканализације. Није утврђена статистички значајна разлика када је реч о периоду потребном да се дође до болнице (p = 0,441), нити је идентификовано значајно кашњење у спровођењу терапије (p = 0,549). Није доказана статистички значајна разлика у поређењу тромесечних функционалних исхода болесника (p = 0,922).

Закључак Упркос великим изазовима у функционисању здравственог система, лечење болесника са АИМУ реканализационом терапијом у систему терцијарне здравствене заштите је показало релативну отпорност на ефекте актуелне пандемије ковида 19.

Кључне речи: акутни исхемијски мождани удар; реканализациона терапија; утицај; пандемија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Urinary stasis in a transplanted kidney – 20 years of experience of one transplant center

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SUMMARY

Introduction/Objective Urinary stasis in a transplanted kidney occurs due to ureteral obstruction caused by intrinsic or extrinsic etiological factors. The aim of this study was to determine the prevalence, time of occurrence, and etiopathogenetic factors of urinary stasis and their distribution according to the type of kidney donor. And to analyze the success of different types of surgical and conservative treatment.

Methods The retrospective-prospective randomized study included 580 patients transplanted in the Transplant Center, Clinic of Urology, University Clinical Center of Serbia, for a period of 20 years. After diagnosing urinary stasis, minimally invasive or open surgical interventions were performed, while for one group of patients the definitive treatment was non-surgical with observation and active monitoring. The main control parameters during non-surgical treatment were the diameter of pyelon, serum creatinine values, and urine culture findings.

Results Urinary stasis was found in 15% of transplanted patients. The largest number of transplanted patients had early urinary stasis, within three months of transplantation (68%). The most common etiological factors of urinary stasis were intrinsic factors (66%), which were significantly more frequent in transplant patients from a living donor. Non-surgical treatment with observation and active monitoring was successfully performed in 22% of the patients.

Conclusion The largest number of transplanted patients with urinary stasis has been successfully treated surgically, most often with open surgery. Surgical correction is advised in cases of pronounced dilatation of the canalicular system with a tendency to increase, in progressive decrease in renal function, and recurrent complicated urinary infections refractory to antibiotic therapy.

Keywords: kidney transplantation; urinary stasis; surgical treatment; conservative treatment

INTRODUCTION

Urinary stasis in a transplanted kidney occurs due to obstruction of the ureter caused by intrinsic or extrinsic etiological factors. The cause of intrinsic etiological factors where the pathological process involves the wall of the ureter is most often ischemia, and less often edema and technical factors in reimplantation of the ureter into the bladder. Ischemia occurs as a result of extensive dissection around the ureter with a lesion of the blood vessels that vascularize the ureter and denudation of the adventitia of the ureter, which contains small blood vessels, during kidney explantation or kidney preparation for transplantation [1]. Therefore, the vascularization of the ureter should be preserved by a minimal peri-urethral dissection and especially by the preservation of the so-called "golden triangle," the space between the ureter, the lower half of the kidney, and the renal vascular pedicle. Stenting of the ureter protects against ureteral ischemia shortly after transplantation [2]. Extrinsic etiological factors can be extraureteral, which compress the ureter (hematoma, lymphocele), and intraureteral, which are in the lumen of the ureter (blood clot, calculus, tumor).

Early obstruction occurs within three months of transplantation and is most often caused by ischemia of the ureter, and less often by technical errors when performing ureterocystoneostomy, and compression from the outside [3]. Late obstruction, three months after transplantation or later, occurs due to ischemic fibrosis caused by deficient vascularization of the ureter, vasculitis in the context of episodes of acute rejection, vasoconstriction caused by immunosuppressive therapy, and chronic infection [4]. Viral and bacterial infections, acute rejection, and toxicity of immunosuppressive therapy can cause occasional transient obstruction due to ureterocystoneostomy edema and a loss of ureteral tone, due to denervation and impaired ureteral peristalsis. Ureteral tumors and urolithiasis are rare causes of late ureteral obstruction in transplanted patients [5].

Urinary stasis in a transplanted kidney most often requires surgical treatment in order to preserve renal function, prevent graft loss and death of the recipient. Any surgical intervention on a transplanted kidney is extremely precarious due to the possibility of further damage and loss of graft function and endangering the life of the patient [6, 7]. Therefore, it is justified to consider the possibility of a non-surgical expectant approach in the treatment of this complication [8].

The aim of this study was to determine the occurrence, time of development, and

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etiopathogenetic factors of urinary stasis in the transplanted kidney and their distribution according to the type of kidney donor; to assess the success of different types of surgical treatment: open and minimally invasive endoscopic and percutaneous interventions, and non-surgical approaches to the treatment of urinary stasis; and to analyze the most important parameters in the observation and active monitoring of transplanted patients with urinary stasis who are treated non-surgically, i.e., the parameters based on which the indication for surgical treatment will be set.

METHODS

The research was conducted as a retrospective-prospective randomized cohort study. The study included 580 patients transplanted over a period of 20 years, from 1999 to 2018, at the Transplantation Center, Clinic of Urology, University Clinical Center of Serbia. In all living donor kidney transplant patients, the donors were close relatives of the recipient. All cadaveric kidney donors were heart-beating (brain-dead) donors. In most cases, cadaveric uniorgan explants of only kidneys, were performed. Multi-organ cadaveric explants with kidney and liver explants were extremely rare. In the selection of a living donor, while determining the suitability of a cadaveric donor, as well as determining suitable recipient for a kidney transplant, all immunological and clinical criteria were met.

In all the patients, a standard operative technique was used during kidney explantation, from both living and cadaveric donors, and kidney transplantation. In all cases of transplantation from a living donor, termino-terminal arterial anastomosis of the renal artery and hypogastric artery was performed, while termino-lateral anastomosis of the renal artery and external iliac artery was performed in cadaveric transplantation. Urethrocystoneostomy was performed extravesically according to the Lich–Gregoir technique with mandatory placement of a "double J" stent within three weeks. In all cases of kidney transplantation, whether from a living or cadaveric donor, the left kidney was transplanted into the right iliac fossa, and the right kidney into the left. In most transplants, graft perfusion was performed using the Collins solution, and extremely rarely, only in multiorgan explantation, using histidine-tryptophan-ketoglutarate. All the patients were on a standard protocol of triple conventional immunosuppressive therapy. Induction immunosuppression was performed in all the patients. In kidney rejection, with or without previous biopsy, standard immunosuppressive treatment was applied.

The following diagnostic procedures were used in the diagnosis of urinary stasis: ultrasonography, antegrade pyelography, multislice computed tomography (MSCT), cystography, intravenous urography, nuclear magnetic resonance (NMR), and dynamic scintigraphy. As part of the diagnosis of urinary stasis in the transplanted kidney, the existence of an associated urinary fistula was ruled out in all the subjects.

In all the patients undergoing surgical treatment, percutaneous nephrostomy was initially performed. The initial surgical therapeutic procedures were minimally invasive endoscopic or percutaneous, and some of the open surgical interventions were performed in case of their failure. The group of patients whose definitive treatment was non-surgical was under observation and active monitoring with frequent ultrasonography controls, as well as repeated laboratory and microbiological analyses. The main observed control parameters in accordance with the data from the literature were as follows: the diameter of the pyelon of the transplanted kidney (measured ultrasonographically), serum creatinine values and urine culture (positive result was a bacterial count > 10^5) [8]. The values are presented as initial (value at the beginning of the observation), maximum (highest value during the observation) and final (value at the end of the observation).

Written consent was obtained from all the patients, the study has been approved by the relevant ethics committee, and conforms to the legal standards.

RESULTS

Out of 580 transplanted patients, a slightly higher number were from a living donor (306; 53%) (Figure 1). The largest number of transplantations from a living donor was performed in the first half of the study, from 1999 to 2008 (259), and from a cadaveric donor in the second half, from 2009 to 2018 (216). The difference in the number of transplants performed in the first and second half of the study in relation to the type of kidney donor is statistically significant ($p < 0.05$).

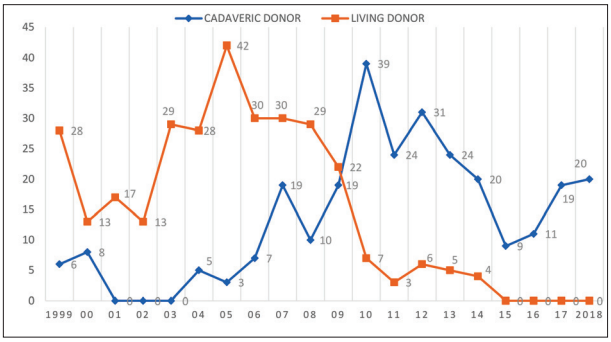

Figure 1. Annual distribution of kidney transplants according to donor type (n = 580)

The average age of the transplanted patients was 39.6 ± 10.6 years (range 18–62 years). The largest number of transplanted patients, 412 of them (71%) were between the ages of 30 and 50 years, 110 (19%) were under 30 years old, and 58 (10%) were older than 50 years. Among the transplanted patients, there were slightly more female patients (348; 60%).

In 87 (15%) transplanted patients, urinary stasis was found on the transplanted kidney. Approximately the same incidence of urinary stasis was registered in transplants from living (51; 17%) and cadaveric donors (36; 13%). The

difference in the number of patients with urinary stasis among transplanted patients from living and cadaveric donors is not statistically significant ($p > 0.05$). There was also no statistically significantly higher frequency of urinary stasis in older recipients. The largest number of transplanted patients had early urinary stasis, within three months of transplantation (59; 68%). No statistically significant difference was found in the prevalence of early and late urinary stasis in transplanted patients from different types of kidney donors ($p > 0.05$).

Of the etiological factors of urinary stasis, intrinsic factors were more frequent (57; 66%). Urinary stasis in patients transplanted from living donors was more often caused by intrinsic factors (42; 48%), and in cadaveric donors by extrinsic factors (21; 25%) (Figure 2). The difference in the prevalence of intrinsic and extrinsic etiological factors of urinary stasis, in transplantation from living and cadaveric donors is statistically significant ($p > 0.05$). Of the extrinsic etiological factors that led to urinary stasis in the transplanted kidney, the extraureteral factors were the following: lymphocele (14; 47%), hematoma (10; 33%), and compression of the funiculus on the ureter (5; 17%); the only intraureteral factor was calculosis (1; 3%).

The largest number of patients with urinary stasis required surgical treatment (68; 78%). In all cases of surgical treatment, percutaneous nephrostomy was initially performed. The majority of transplanted patients with urinary retention required treatment with open surgery (43; 63%). The following types of open surgical treatment were performed: replacement of the ureteral graft with a native ureter and ureteropyeloanastomosis (22; 32%), revision of ureterocystoneostomy (8; 12%), deliberation of the ureter with probe placement (4; 6%), hematoma drainage (4; 6%), marsupialization of lymphocele (3; 4%), and nephrectomy of the transplanted kidney (2; 3%). Minimally invasive endoscopic and percutaneous procedures were performed in 25 (37%) patients: percutaneous drainage with sclerotherapy (11; 16%), retrograde endoscopic placement of the probe (7; 10%), antegrade percutaneous placement of the probe (4; 6%), percutaneous hematoma drainage (2; 3%), and extracorporeal lithotripsy (1; 2%) were performed (Figure 3). Due to an unsuccessful previous intervention, 42 (62%) patients underwent two or more interventions until successful surgical treatment was achieved. The treatment was unsuccessful and ended with nephrectomy of the transplanted kidney in only two (3%) patients.

Non-surgical treatment involving observation with active monitoring was successfully performed in 19 (22%) transplanted patients with urinary retention. The average duration of observation was 8.3 ± 4.1 months (range 3–18 months). Non-surgical treatment led to the complete

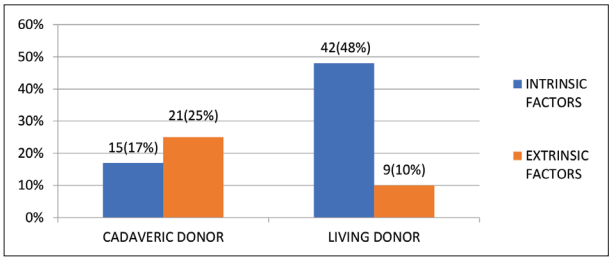

Figure 2. Etiological factors of urinary stasis in a transplanted kidney according to the type of kidney donor

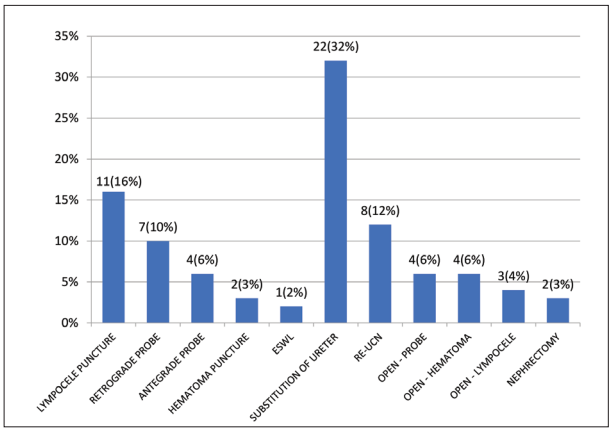

Figure 3. Surgical treatment of urinary stasis (n = 68) with a representation of minimally invasive endoscopic and percutaneous (n = 25) and open surgical procedures (n = 43)

resolution of urinary stasis in five patients (26%). The parameters observed during the conservative treatment of urinary stasis in the transplanted kidney are presented in Table 1. Statistically significant difference was found in the initial and maximum values of serum creatinine in relation to the end creatinine values ($p < 0.05$). No statistically significant difference was found between the initial, maximum, and final values of the pyelon diameter ($p < 0.05$). The frequency of positive urine culture initially and during observation is statistically insignificant ($p > 0.05$), while all patients had a negative urine culture at the end of observation.

In the majority of patients, one or more associated pathological conditions were treated during conservative treatment: cytomegalovirus infection (4; 22%), BK virus infection (8; 44%), acute graft rejection (7; 39%), toxicity of immunosuppressive therapy (10; 55%), and urinary infection (11; 66%).

Finally, successful treatment of urinary stasis in the transplanted kidney was achieved in 85 (98%) patients. In two (2%) patients, the graft was lost, explanted, and the patient was returned to dialysis. There were no fatalities.

Table 1. Parameters of conservative treatment of urinary stasis in a transplanted kidney (n = 19)

Parameters	Initial value	Maximal value	End value	p
Pyelon (mm)	22 ± 10 (10–30)	28 ± 9 (15–35)	20 ± 12 (0–30)	$p > 0.05$
Serum creatinine (μmol/L)	197 ± 89 (120–287)	236 ± 75 (130–325)	118 ± 18 (70–138)	$p < 0.05$
Positive urine culture (%)	50	61	0	$p > 0.05$

The values are presented as initial (at the beginning of the observation), maximum (highest during the observation), and final (at the end of the observation period).

DISCUSSION

Etiopathogenetic factors that lead to urological complications in a transplanted kidney are of donor or recipient origin and of medical or technical nature. Damage to the transplanted kidney is the result of ischemia, inflammation, infection, toxicity of immunosuppressive drugs, clinical condition of the donor and recipient, or technical errors during kidney explantation and transplantation [9]. The incidence of urinary stasis in a transplanted kidney is highly variable according to different studies, and ranges 3–20% [4, 10, 11, 12]. In older studies, it is registered more often than in today's researches. This may be related to advances in the technical factors of explantation and transplantation and new, improved perfusion solutions and the use of continuous mechanical hypothermic perfusion. In addition, new, more effective and less toxic immunosuppressive drugs and revised immunosuppressive protocols with lower doses of immunosuppressive drugs lead to a reduction in complications. In our study, urinary stasis in the transplanted kidney was detected in 15% of transplanted patients and occurred twice as often in the first 10 years of the study.

The most common etiological factors of urinary stasis are intrinsic factors due to ischemia, technical errors, or edema localized in the distal part of the ureter, most often on ureterocystoneostomy. It has been stated that ischemia is the most common cause of obstruction [7]. In our study, intrinsic factors as a cause of urinary stasis were registered in 66% of patients and were statistically significantly more common in patients transplanted from a living donor. Extrinsic etiological factors were significantly more frequent in cadaveric donors, and lymphocele was the most common among them.

Increasingly high-quality dialysis and improved drugs for chronic renal failure lead to an older age of the recipients. The data on the association of the age of the recipient with the onset of complications are controversial. In our study, 71% of the transplanted patients were between the ages of 30 and 50 years, and only 10% were older than 50 years. Irdam et al. [12] showed that older donor and recipient age are risk factors in developing urinary stasis after kidney transplantation. In our study no statistically significantly higher frequency of urinary stasis was found in older recipients.

The technical factor is important in causing urinary stasis in the transplanted kidney, because interruption of the ureter vascularization leads to ischemia and finally stricture of the ureter. Preservation of normal ureter vascularization by minimal periureteral dissection reduces the possibility of ureteral complications. Even with all the measures to preserve ureteral vascularization employed, the distal ureter is prone to ischemia due to its location and distance from the renal blood vessels (Figure 4). Furthermore, technical factors such as the type of ureterocystoneostomy and prophylactic stent use may also influence the higher incidence of urinary stasis in the transplanted kidney [3]. Today, ureterocystoneostomy is most often performed according to the modified Lich–Gregoir extravesical technique. It is performed easily and quickly on the front-lateral wall of the bladder. It includes a short muscular tunnel across the end of the ureter to prevent vesicoureteral reflux and development of compressive ischemia and subsequent stricture [13]. There are controversies about the necessity of stenting the transplanted ureter. In most studies, the prophylactic use of stents significantly reduces the incidence of urethral strictures [14]. In our study, all transplanted patients underwent ureterocystoneostomy according to the Lich–Gregoir technique using the extravesical route, and the ureter was routinely stented by placing a double J probe within three weeks.

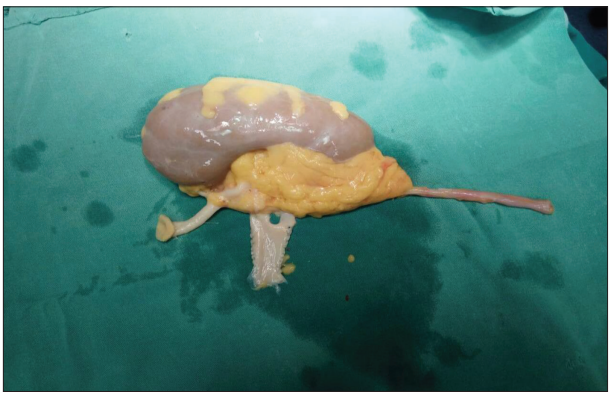

Figure 4. Right kidney explanted from cadaver and ready for transplantation; the renal artery has an aortic "Carrel patch," and the vein is lengthened by the reconstruction of part of the vena cava; fatty tissue is preserved in the hilus of the kidney and around the ureter ("golden triangle") to preserve ureteral circulation

Urinary stasis is most often described as a complication of kidney transplantation during the first year after transplantation [10]. In our study, we found a more frequent occurrence of early obstruction, during the first three months after transplantation (68%), which is consistent with the results of similar studies [4, 15].

The connection between episodes of acute rejection and the toxicity of immunosuppressive therapy in the occurrence of urinary stasis in a transplanted kidney is well known [16]. Vasoconstriction during kidney rejection and vasculitis caused by toxic immunosuppression therapy lead to ischemia and further complications in ureter. Immunological complications in the occurrence of urinary stasis are less common in transplants from living relatives and in transplants from cadaveric donors with standard immunological risk. In our study, urinary stasis occurred statistically insignificantly more often in transplantations from living kidney donors.

Today, the main goal of surgical treatment of urinary stasis in a transplanted kidney is the use of minimally invasive surgical techniques due to lower accompanying morbidity. Most patients with urinary stasis in a transplanted kidney can be treated with a percutaneous and endoscopic approach [17]. Short ureteral strictures on the distal ureter or on ureterocystoneostomy can be treated by antegrade percutaneous dilatation and placement of the probe into the ureter, or less often by a retrograde approach. In our study, surgical treatment was performed in 78% of patients, and among them, open surgery was

performed more often in 63% of patients, that is in accordance with similar studies [18]. In all cases of surgical treatment, percutaneous nephrostomy was initially performed as a temporary measure to establish urinary drainage, improve renal function, and treat infection [19]. Of the minimally invasive procedures, percutaneous drainage and lymphocele sclerotherapy were performed most often. Open surgical intervention is indicated after previously unsuccessful endoscopic or percutaneous treatment [20]. In our patients, ureter graft replacement with native ureter and ureteropyeloanastomosis of native ureter with pyelon of graft was most frequently performed open surgical treatment.

The non-surgical approach in treatment of urinary stasis in transplanted patients involves observation with active monitoring [8]. Successful non-surgical treatment in our study was performed in 22% of the patients. Repeated and periodic ultrasonographic examination, monitoring of renal function through serum creatinine levels, and monitoring of presence of urinary infection are crucial before making the decision to perform surgical intervention on the transplanted kidney [14]. Surgical correction is advised in cases of pronounced dilatation of the canalicular system with a tendency to increase, in cases of progressive decrease in renal function, and recurrent urinary infection refractory to antibiotic therapy [8]. Progressive elevation of serum creatinine is a strong indicator of graft dysfunction, while there is no standard threshold value of pyelon diameter in predicting the need for surgical intervention. It must be in conjunction with other parameters, especially with serum creatinine values, but also with the presence of a urinary infection refractory to antibiotic therapy [8, 21]. In our study, in successfully conservatively treated patients, a significant reduction in serum creatinine was achieved with improvement or normalization of graft function, followed by the absence of urinary infection with sterile urine culture. In one-quarter of patients, the dilatation of the canalicular system of the graft disappeared spontaneously, while in the others, functionally insignificant residual stasis remained without the need for surgical correction (Figure 5). Possible causes for residual stasis are a transient disturbance of peristalsis with blockage of the transmission of peristaltic waves through the wall of the ureter due to edema and ischemia, as well as transient vesicoureteral reflux [22].

Adequate treatment of associated pathological conditions on the transplanted kidney with urinary stasis can lead to an improvement in graft function and at the same time to a reduction or complete disappearance of stasis on the transplanted kidney. Therefore, a detailed exploration of all possible factors of deterioration of graft function is required. There is a causal relationship between cytomegalovirus, BK virus, and bacterial infection and stasis in a transplanted kidney [23, 24, 25]. Infections can cause edema, spasm, and ischemic damage to the ureter

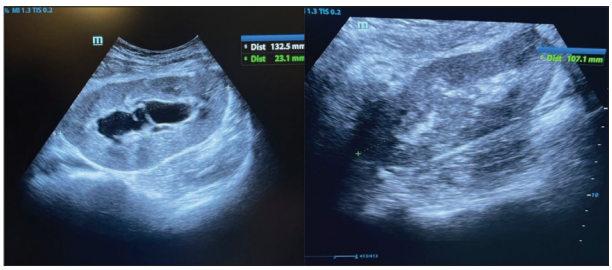

Figure 5. Complete spontaneous resolution of urinary stasis in the transplanted kidney during observation and active follow-up over a period of six weeks

leading to urinary stasis. The toxicity of immunosuppressive therapy is accompanied by ischemic damage to the ureter based on vasoconstriction and edema formation. Therefore, minimizing the negative effects of immunosuppressive therapy is very important. Renal rejection can be accompanied by obstruction due to local inflammation and vasculitis-induced ischemia of the ureter, which results in decreased tonus of the ureter due to denervation, and leads to edema and later fibrosis [26]. It is important to focus on the etiopathogenesis of urinary retention and to recognize and treat associated pathological conditions that may lead to graft dysfunction. Because of the unpredictable clinical course, individual evaluation of each transplant patient with urinary retention is crucial. In our study, the majority of patients under observation with active monitoring were treated for associated pathological conditions.

CONCLUSION

Urinary stasis in the transplanted kidney was found in 15% of transplanted patients without significant differences in representation according to the type of kidney donor. Most often, urinary stasis in the transplanted kidney occurred early, during the first three months after transplantation, and the most common etiological factors were intrinsic factors, significantly more common in transplantation from a living donor. The largest number of patients with urinary stasis were treated surgically with open surgery, most often by replacing the graft ureter with a native ureter with ureteropyeloanastomosis. Nonsurgical treatment was successful in 22% of transplant patients with urinary retention. Non-surgical treatment with active monitoring requires repeated ultrasound examinations with monitoring of renal function and the presence of urinary infection. Surgical correction is advised in cases of pronounced dilatation of the canalicular system of the transplanted kidney with a tendency to increase, in cases of progressive decrease in renal function and accompanying recurrent complicated urinary infection refractory to antibiotic therapy.

Conflict of interest: None declared.

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Уринарни застој на трансплантираном бубрегу – двадесетогодишње искуство једног трансплантационог центра

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САЖЕТАК

Увод/Циљ Уринарни застој трансплантираног бубрега настаје због опструкције уретера изазване интринзичним или екстринзичним етиолошким факторима.

Циљ рада је био утврдити заступљеност, време настанка и етиопатогенетске факторе уринарног застоја на трансплантираном бубрегу и њихову дистрибуцију према врсти донора бубрега, као и анализирати учесталост и успешност различитих врста хируршког и конзервативног лечења.

Методе У ретроспективно-проспективној рандомизованој студији обухваћено је 580 болесника са трансплантираним бубрегом у Центру за трансплантацију Клинике за урологију Клиничког центра Србије у периоду од 20 година. По дијагностиковању уринарног застоја на трансплантираном бубрегу, урађене су минимално инвазивне или отворене хируршке интервенције, док је за једну групу болесника дефинитивно лечење било нехируршко са опсервацијом и активним праћењем. Главни контролни параметри у току нехируршког лечења били су дијаметар пијелона трансплантираног бубрега, вредности серумског креатинина и налаз уринокултуре.

Резултати Код 15% болесника са трансплантираним бубрегом нађен је уринарни застој на трансплантираном бубрегу. Највећи број болесника имао је рани уринарни застој, у току прва три месеца од трансплантације (68%). Најчешћи етиолошки фактори уринарног застоја су били интринзични фактори (66%), који су се значајно учесталије јављали код болесника са трансплантираним бубрегом од живог донора. Нехируршко лечење са опсервацијом и активним праћењем је успешно спроведено код 22% болесника.

Закључак Највећи број болесника са уринарним застојем лечен је хируршки. Хируршка корекција се саветује у случајевима изражене дилатације каналикуларног система са тенденцијом повећања, код прогресивног снижења реналне функције и рецидивне компликоване уринарне инфекције отпорне на антибиотску терапију.

Кључне речи: трансплантација бубрега; уринарни застој; хируршко лечење; нехируршко лечење

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Perioperative outcomes of laparoscopic and open retropubic radical prostatectomy

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SUMMARY

Introduction/Objective Radical prostatectomy (RP) is a treatment option with high curative potential in patients with prostate cancer of moderate-risk.
The aim of the study is to assess perioperative results of laparoscopic RP (LRP) and open retropubic RP (ORRP).

Methods From 2016 to 2020, a total of 244 patients undergone RP, as follow: 145 patients LRP and 99 patients ORRP. Demographic data, preoperative parameters, perioperative and pathological outcomes were analyzed and compared among LRP and ORRP groups.

Results In regard to demographic data and preoperative parameters (BMI, mean age, median pretreatment prostate-specific antigen, clinical stage and Gleason score from biopsy), there are no differences between the observed groups. Patients from ORRP group had significantly shorter operative time ($p < 0.05$). Patients from LRP group had major advantages in regard to estimated blood loss (EBL) (550 ml for LRP *vs*. 1450 ml for ORRP), hospitalization time (six days for LRP *vs*. nine days for ORRP), catheter removal (6.5 days for LRP *vs*. 12 days for ORRP), overall complication rates (29% for LRP *vs*. 48.4% for ORRP) and blood transfusion rates (22.7% for LRP and 37.4% for ORRP).

Conclusion Both LRP and ORRP provide favorable operative results in terms of efficacy, safety and oncologic outcome. However, patients undergoing LRP were more likely to have less EBL, shorter length of hospital stay, earlier catheter removal and lower rates of overall perioperative complications.

Keywords: prostate cancer; laparoscopic radical prostatectomy; open retropubic radical prostatectomy

INTRODUCTION

Current epidemiological data show that prostate cancer is the second most common cancer affecting the male population, with the increasing incidence in recent years [1, 2]. Radical prostatectomy is a treatment option with high curative potential in patients with prostate cancer of moderate-risk [3, 4]. Nowadays, operative techniques include open, laparoscopic and robotic-assisted RP. Open RP (ORRP) has been in use for the longest time, but is associated with certain disadvantages, including intraoperative hemorrhage and length of hospital stay [5]. Minimally invasive RPs including laparoscopic (LRP) and robot-assisted (RARP), are designed as technically innovative operative techniques and had been introduced into clinical practice in the late 20th and early 21st centuries [6, 7]. Regardless of the type of operative technique, the basic goal of RP remains the same – removal of cancer while achieving good functional results in terms of continence and sexual function [6]. Published results of numerous studies on the effects of the aforementioned operative techniques on the oncological and functional outcomes are still not completely consistent [5, 7]. Herein, we present the results of our prospective study regarding the perioperative surgical outcomes and complications of LRP and open retropubic radical prostatectomy (ORRP).

METHODS

From January 2016 to June 2020, a total of 244 study patients, mean age 67.2 years (61–74; SD = 10.72) had undergone radical prostatectomy at the University Clinic of Urology in Skopje. Depending on the applied operative technique, the patients were divided into two groups, as follows:

1) Group LRP – 145 patients who had undergone laparoscopic radical prostatectomy;
2) Group ORRP – 99 patients who had undergone radical retropubic radical prostatectomy.

All applied procedures on the examined groups of patients were carried out in accordance with the ethical principles of the Declaration of Helsinki, with guaranteed discretion in regard to personal data.

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Ethical Committee of the Mother Teresa University Clinical Center in Skopje aproved the study (Number of Approval 03-116/4).

We applied for ORRP the operative technique described by Walsh [8]. Surgical technique of laparoscopic prostatectomy was performed by the same surgical team, according to Heilbronn technique [9]. Both techniques were performed without pelvic lymph node dissection, since only patients with pretreatment prostate-specific antigen (PSA) levels ≤ 10 ng/mL were included in the study. All patients underwent standardized preoperative procedure of our clinic, including: complete blood count, biochemical analysis, urine, urine culture, serum PSA, multislice computerized abdomino-pelvic tomography, histopathological result of transrectal ultrasound guided prostate biopsy, cardiac and anesthesia evaluation, urological evaluation, decision for the operative treatment by the Council for uro-oncology and patient informed consent form. Demographic data and preoperative parameters included the following: mean age, body mass index (BMI), median pretreatment prostatic specific antigen (PSA) values (ng/ml), clinical stage and Gleason score (GS) from biopsy. Perioperative and pathological outcomes included the following: operation time, estimated blood loss (ml), pathological stage, pathologic GS, prostate volume and positive surgical margins (PSM). Operative complications have been classified and recorded according to Clavien–Dindo classification [10].

Statistical analysis was performed using R Studio. Two-proportions z-test was used to conduct a hypothesis test about the difference between the proportions of the observed two groups of patients. A p-value of < 0.05 was deemed statistically significant.

RESULTS

Basic demographic and preoperative data are listed in Table 1.

Table 1. Demographic data and preoperative parameters

Parameters	LRP	ORRP	p-value
No. of patients	145	99	
Mean age	67 (61–74)	67.5 (63–73)	0.3685
BMI (kg/m^2)	23.2 (21.7–26.8)	23.6 (22.1–27)	0.3043
Median pretreatment PSA (ng/ml)	10.6 (6.3–18.6)	10.9 (7.1–17.5)	0.3870
Clinical stage, No. (%)			
T1	128 (88.3)	90 (90.9)	0.5157
T2	2 (1.4)	1 (1.02)	0.7949
T3	14 (9.6)	8 (8.08)	0.6745
T4	1 (0.7)	0 (0)	0.4065
GS from biopsy	6.77 ± 1.1	6.85 ± 1.33	0.6091
GS ≤ 6, n (%)	65 (44.8)	42 (42.4)	0.7114
GS = 3+4, n (%)	30 (20.7)	20 (20.2)	0.9283
GS = 4+3, n (%)	26 (18)	14 (14.2)	0.4295
GS = 8, n (%)	15 (10.3)	12 (12.1)	0.6672
GS = 9, 10, n (%)	9 (6.2)	11 (11.1)	0.1707

LRP – laparoscopic radical prostatectomy; ORRP – open retropubic radical prostatectomy; BMI – body mass index; PSA – prostate-specific antigen; GS – Gleason score

In regard to mean age, BMI and median PSA before treatment, no statistically significant differences were found among the analyzed groups (p = 0.3685 *vs.* 0.3043 *vs.* 0.3870, respectively). In relation to each of the clinical stages, there are no statistically significant differences between the observed groups (p = 0.5157 for T1, p = 0.7949 for T2, p = 0.6745 for T3, p = 0.4065 for T4, respectively). There is no statistical difference between the groups in the prevalence of GS from biopsy (p = 6091).

Regarding the representation of each of the mentioned values of GS biopsy samples (GS ≤ 6, GS = 3 + 4, GS = 4 + 3 GS = 8), there are no statistically significant differences between the examined groups.

The most common pathological stage was T2c with 40% (in the LRP group), while the least represented stage was T4 with 0%, but in relation to the representation of all the stages shown, no statistically significant differences were found between the observed groups.

GS of biopsy samples did not differ significantly, both between the two groups (6.77 ± 1.1 for LRP *vs.* 6.85 ± 1.33 for ORRP; p = 0.6091), and between each of the analyzed intervals, respectively (Table 2).

Table 2. Perioperative and pathological outcomes

Parameters	LRP	ORRP	p-value
Operation time (min), median (IQR)	207 (173–250)	151 (127–220)	0.0021
EBL (ml), median (IQR)	550 (250–850)	1450 (500–2400)	0.0000
Hospitalization time (day)	6 (5–8)	9 (6–12)	0.0000
Catheter removal (day)	6.5 (5–8)	12 (10–14)	0.0000
Nerve-sparing, No. (%)	84 (58)	64 (65)	0.2937
Unilateral nerve-sparing, No. (%)	33 (23)	27 (27)	0.4237
Bilateral nerve-sparing, No. (%)	68 (47)	58 (57)	0.0735
Pathological stage, No. (%)			
T2a	22 (15.2)	8 (8.1)	0.0969
T2b	7 (4.8)	8 (8.1)	0.2983
T2c	58 (40)	38 (38.3)	0.8026
T3a	32 (22)	19 (19.2)	0.5892
T3b	26 (18)	26 (26.3)	0.1188
T4	0 (0)	0 (0)	-
Pathologic GS			
2–6	34 (23.4)	27 (27.3)	0.4965
7	76 (52.4)	48 (48.5)	0.5485
8–10	35 (24.2)	24 (24.2)	0.9840
Prostate volume (g), median (IQR)	38.2 (29.1–49)	39.1 (28.8–50)	0.3675
PSM, n (%)	58 (40)	35 (35.3)	0.4654

LRP – laparoscopic radical prostatectomy; ORRP – open retropubic radical prostatectomy; IQR – interquartile range; GS – Gleason score; PSM – positive surgical margins

The average operative time was shorter in the ORRP group and this difference was statistically significant in favor of the ORRP group (207 for LRP *vs.* 151 for ORRP; p = 0.0021). However, the average estimated blood loss (EBL) was lower in the LRP group (550 ml) compared to the ORRP (1450 ml) and this difference was statistically significant in favor of the LRP group (p = 0.0000). Hospitalization time was longer in the ORRP group compared to LRP (nine days *vs.* six days, p = 0.0000) and this

difference is statistically significant in favor of the LRP group. Patients from the ORRP group had a urinary catheter longer than patients from the LRP group (12 days *vs*. 6.5 days; p = 0.0000) and this difference is statistically significant in favor of the LRP group. When analyzing the overall frequency of the nerve-sparing procedure, it was more frequent in the ORRP group compared to the LRP group (65% *vs*. 58%, p = 0.2937), but this difference between the observed groups was not statistically significant. Both unilateral and bilateral nerve-sparing procedures were applied more often in the ORRP group compared to the LRP group (27% *vs*. 23%, p = 0.4237; 57% *vs*. 47%, p = 0.0735, individually), but neither in the first nor in the second case is this difference between the observed groups statistically significant.

Regarding the pathological stage, stages T2a, T2c and T3a were more often represented in the LRP group compared to the ORRP group, respectively (15.2% *vs*. 8.1%, p = 0.0969; 40% *vs*. 38.3%, p = 0.8026; 32 *vs*. 19%, p = 0.5892, respectively) and that difference between the observed groups is not statistically significant. Stages T2b and T3b, respectively, were more prevalent in the ORRP group than in the LRP group (8.1% *vs*. 4.8%, p = 0.2983; 26.3% *vs*. 18%, p = 0.1188, respectively) but the difference in favor of the ORRP group is not statistically significant. Stage T4 was not detected in both observed groups. Among the observed groups, there are no statistically significant differences in relation to the representation of each of the categories of pathological GS, respectively. GS 2–6 was more prevalent in the ORRP group compared to the LRP group (27.3% *vs*. 23.4%, p = 0.4965); GS7 was more prevalent in the LRP group compared to the ORRP group (52.4% *vs*. 48.5%, p = 0.5485), while GS 8-10 was equally represented in both observed groups (24.2% *vs*. 24.2%, p = 0.9840). The average prostate volume was higher in the ORRP group compared to the LRP group (38.2g *vs*. 39.1 g; p = 0.3675) and this difference between the observed groups is not statistically significant. Among the observed groups, no statistically significant difference was found in terms of PSM representation either (40% for LRP *vs*. 35.3% for ORRP, respectively, p = 0.4654).

Table 3. Operative complications

Perioperative and early postoperative complications, < 30 days, n (%)	LRP No. (%)	ORRP No. (%)	p-value
Overall	42 (29)	48 (48.4)	**0.0083**
Grade I	6 (4.1)	5 (5.055)	0.7279
Grade II	28 (19.3)	40 (40.4)	**0.0030**
Grade IIIa	2 (1.4)	4 (4.055)	0.1868
Grade IIIb	5 (3.4)	8 (8.08)	0.1141
Grade IVa	1 (0.8)	1 (1.01)	0.7872
Grade IVb	0 (0)	0 (0)	-
Grade V	0 (0)	0 (0)	-
Blood transfusion, n (%)	33 (22.7)	37 (37.4)	**0.01314**

LRP – laparoscopic radical prostatectomy; ORRP – open retropubic

The total share of perioperative and early postoperative complications was higher in the ORRP group (80.8% for ORRP *vs*. 29% for LRP, p = 0.0000) and this difference is statistically significant in favor of the ORRP group (Table 3). The share of these complications in all analyzed categories (according to the Clavien–Dindo classification) respectively was higher in the ORRP group, but this difference compared to the LRP group is statistically significant only for the Grade 2 category (62.6% for ORRP *vs*. 19, 3% for LRP, p = 0.0000). No Grade IVb and Grade V complications were recorded. Transfusion rates were higher in the ORRP group (69.6% for ORRP *vs*. 22.7% for LRP, p = 0.0000), and that difference is statistically significant.

DISCUSSION

Radical prostatectomy is the usual curative treatment for localized prostate cancer. The operative technique of radical prostatectomy developed from open surgery to laparoscopic procedure, and the latest robot-assisted technique (RARP), which is today the most common technique in developed countries, with a growing trend of popularity [11]. Laparoscopic surgery gained great popularity at the beginning of the 21st century. The basic motives and reasons for the development of this technique are contained in its minimal invasiveness, which creates the conditions for improving operative results in terms of complications, bleeding and length of hospitalization [12]. Open radical retropubic prostatectomy has its own qualities, including availability of performing in smaller centers, short duration of the procedure, financial profitability, relatively low invasiveness, possibility of performing quality lymphadenectomy and relatively quick recovery. The presented results of randomized controlled studies on the oncological results of operative treatment of patients with localized prostate cancer show high rates of cancer-specific survival, namely: 80.4% after 23 years, 91.5–95.9% after 19.5 years, and 99% after 10 years of follow-up [13]. When it comes to the results achieved by applying each of the aforementioned operative techniques respectively, several systematic analyzes have been presented to date comparing the results of open versus laparoscopic robot-assisted radical prostatectomy, and the results were inconsistent [14].

The results of our study show that there are no statistically significant differences among the observed groups in terms of demographic and preoperative parameters, which makes the examined sample consistent for objective comparison.

Analyzing the perioperative results of robotic-assisted laparoscopic radical prostatectomy, laparoscopic radical prostatectomy and open radical prostatectomy, Sirisopana et al. [14] stated an average operative time of 160, 210 and 200 minutes, respectively, and that the difference was statistically significant in favor of the ORRP group. Similarly, the results of our study show that the average operative time in the ORRP group was statistically significantly shorter compared to the LRP group (151 minutes for ORRP *vs*. 207 minutes for LRP, p < 0.05). The results of several large studies, including a systematic review and meta-analysis by Cao et al. [15], as well as by Forsmark et al. [16], whose study was included in the LAPRO trial,

are consonant with our results regarding operative time, favoring the ORRP group. On the other hand, our results show that EBL is statistically significantly higher in the ORRP group compared to the LRP group, which is in line with the experiences of other authors [12, 14, 15, 16]. The literature also states that the reduction of EBL is directly correlated with the quality of visualization, which is one of the advantages of the laparoscopic technique compared to the open [14]. In our series, the average hospitalization time was nine days in the ORRP group and it was statistically significantly longer than in the LRP group with six days. The average duration of catheterization in the ORRP group was 12 days, statistically significantly longer than in the LRP group (6.5 days). The results of many studies confirm our findings regarding the duration of hospitalization and catheterization, favoring the laparoscopic operative technique [14, 15, 17].

In our series, the nerve sparing technique was applied more often in the ORRP group, but without a statistically significant difference compared to the LRP group. This technique certainly contributes to the quality of the preservation of the bladder neck and to the preservation of potency and continence, which primarily depends on the operator's skills [15, 18]. However, in our study we did not study the effects of this technique on the rate of potency and continence, but this will certainly be the subject of future consideration. Differences between pathological GS categories among the observed groups are not statistically significant, which confirms clear inclusion criteria and good selection of our study patients.

PSM is an indicator of the oncological outcome of surgery, but also a predictor of biochemical relapse [19]. In our study, the PSM rate was higher in the LRP group (40%) compared to the ORRP group (35.3%), but without statistical significance. In a recent meta-analysis by Cao et al. [15], the overall PSM rate for LRP/RARP was 22.3% and for ORRP 28.6%, with no statistical differences. Analyzing RARP, Wang et al. [20] reported variations in PSM rates from 12.1% to 41.3%. Our results are in the range of values shown by other authors, but we are convinced that this result can be improved by using a unique operative technique for all operators participating in the study [21]. Prostate volume was slightly higher in the ORRP group, but this difference compared to the ORRP group is not statistically significant. Prostate volume along with GS has been reported to be the most reliable predictor of PSM [15].

Perioperative and early postoperative complications (< 30 days), classified according to the Clavien–Dindo system were detected in a total of 122 patients, namely: 42 in the LRP group and 48 in the ORRP group. The relative share of 48.4% of complications in the ORRP group is higher than the relative share of 29% in the LRP group, and the difference is statistically significant ($p = 0.0083$). Among the analyzed complications, Grade 2 complications dominated in both examined groups, in a total of 68 patients. Relative share of these complications is higher in the ORRP group (40.4% for ORRP *vs.* 19.3% for LRP, $p = 0.0030$) and this difference is statistically significant in favor of the ORRP group. Relative share of complications of the other categories (Grade I, Grade IIIa, Grade IIIb and Grade IVa) was higher in the ORRP group compared to the LRP group, but this difference is not statistically significant for any individual category. Complications of Grade IVb and Grade V were not determined. There are few head-to-head studies in the literature comparing the operative complications of LRP versus ORRP. Pompe et al. [22] reported that in their series of 13924 RPs, the average operative complication rate was 20.6%, with Grade I and Grade II predominating. Analyzing the operative complications of ORRP and LRP in a series of 4592 patients, Rabbani et al. [23] reported an average rate of 30.3%, which did not include the relative share of blood transfusion in the ORRP group, which was 55% and was higher than the share in the LRP group. Sirisopana et al. [14] reported an overall complication rate of 81.25% for ORRP and 29.05% for LRP, among which Grade 1 and 2 complications predominate, with blood transfusions of 69.35% for ORRP and 23.4% for LRP [14]. The presented rates of perioperative and early postoperative complications in our series are in compliance with the results presented in the literature. Blood transfusions were significantly more frequent in the ORRP group (22.7% for LRP *vs.* 37.4% for ORRP, $p = 0.01314$). We want to emphasize that blood transfusions are included into Grade II complications, and they are also separately compared in relation to the studied groups. There is no doubt that the outcome of operative treatment is influenced by the experience of the operative team, as well as the number of operations performed annually. A recently published study by Ploussard et al. [24] states that 10 cases per year represents the lower limit of the number of operative interventions, which is associated with an unfavorable operative outcome. The results of our research show that in the mentioned period we performed an average of 61 radical prostatectomies per year, which ranks our hospital among high-volume institutions, and this certainly contributes to the improvement of perioperative results.

CONCLUSION

For patients with moderate-risk prostate cancer, both LRP and ORRP provide favorable operative results in terms of efficacy, safety and oncologic outcome. However, patients undergoing LRP were more likely to have less EBL, shorter length of hospital stay, earlier catheter removal and lower rates of overall perioperative complications.

Conflict of interest: None declared.

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Перипоративни исходи лапароскопске и отворене ретропубичне радикалне простатектомије

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САЖЕТАК

Увод/Циљ Радикална простатектомија је опција лечења са високим куративним потенцијалом код болесника са карциномом простате умереног ризика.

Циљ рада је процена перипоративних резултата лапароскопске (ЛРП) и отворене ретропубичне радикалне простатектомије (ОРРП).

Методе Од 2016. до 2020. године укупно 244 болесника подвргнута су радикалној простатектомији, и то: 145 болесника ЛРП и 99 болесника ОРРП. Демографски подаци, преоперативни параметри, перипоративни и патолошки исходи анализирани су и упоређени између група ЛРП и ОРРП.

Резултати У погледу демографских података и преоперативних параметара (индекс телесне масе, средња старост, средња вредност простатичног специфичног антигена пре третмана, клинички стадијум и биопсијски Глисонов скор) није било статистички значајних разлика између анализираних група. Болесници из групе ОРРП имали су значајно краће време операције ($p < 0,05$). Међутим, болесници из групе ЛРП имали су велике предности у поређењу са болесницима из групе ОРРП у погледу процењеног губитка крви (550 *ml* за ЛРП наспрам 1450 *ml* за ОРРП), времена хоспитализације (шест дана за ЛРП наспрам девет дана за ОРРП), уклањања катетера (6,5 дана за ЛРП наспрам 12 дана за ОРРП), укупне стопе компликација (29% за ЛРП наспрам 48,4% за ОРРП) и трансфузије крви (22,7% за ЛРП и 37,4% за ОРРП).

Закључак И ЛРП и ОРРП обезбеђују повољне оперативне резултате у погледу ефикасности, безбедности и онколошког исхода. Међутим, вероватније је да ће болесници који су били подвргнути ЛРП-у имати мањи процењени губитак крви, да ће краће боравити у болници, да ће им се раније уклонити катетер и да ће имати ниже стопе укупних перипоративних компликација.

Кључне речи: карцином простате; лапароскопска радикална простатектомија; отворена ретропубична радикална простатектомија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Novel inflammatory markers and prognostic importance of platinum-sensitive ovarian carcinoma relapse

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SUMMARY

Introduction/Objective Ovarian carcinomas are the deadliest gynecological tumors. Despite advances in treatment options, survival rates are still not at the desired level. Since clinical signs are not typical in early-stage disease, two-thirds of patients are diagnosed late. Carbohydrate Antigen 125 (CA125) does not have sufficient sensitivity and specificity in early-stage disease and early post-relapse progression. There is a need for a simple and cost-effective marker that correlates with CA125. For this purpose, we aimed to evaluate the potential of systemic inflammatory markers' as diagnostic aids.

Methods Patients with platinum-sensitive recurrent ovarian carcinomas were preferred because the treatment options were more diverse than the resistant group. Using retrospective data collection, 105 patients with platinum-sensitive recurrent ovarian carcinoma, admitted in the last four years were included in the study. Complete blood count data was recorded based on recurrence and progression periods.

Results When the systemic immune inflammatory index (SII) values were evaluated in combination with CA125 in terms of progression during the control visits after platinum-sensitive disease recurrence treatment, progression detection proportions increased to 97.5%, which was 82.9% when only CA125 was used. On the other hand, false positivity, which was 18.5% for CA125 alone, decreased to 2.5% when combined with SII. Furthermore, neutrophil lymphocyte ratio, white blood cells, and neutrophil values showed correlations with high CA125 values.

Conclusion The SII value could be used together with CA125 because it is easy to use, accessible, and has low cost in clinical practice, as well as to increase the accuracy rate and make precise corrections in the false positivity rate.

Keywords: ovarian cancer; CA125; relapse; inflammatory biomarkers; platinum sensitivity

INTRODUCTION

Ovarian cancer has the fifth-most cancer-related mortality in women in developed countries and is the deadliest gynecological tumor [1]. Although personalized treatment modalities, chemotherapeutic agents, and the addition of drugs such as bevacizumab (anti-vascular endothelial growth factor) to combination therapies in relapsed disease have positively contributed to progression-free survival in recent years, there has still not been enough contribution to overall survival [2]. While the five-year survival rate is 90% in patients detected in the early stage, this rate regresses to 20% in advanced-stage patients [3]. Approximately two thirds of the cases are diagnosed at later stages because of early onset, non-specific, and mostly constitutional complaints [3].

CA125 has low sensitivity and specificity, especially in ovarian cancers' earlier stages [4]. Furthermore, CA125 levels can elevate in benign situations such as endometriosis, menstruation, and coronary artery disease. As a result, high false-positivity may cause significant psychological problems in women who do not have ovarian cancer, leading to unnecessary additional treatment burdens [5]. Additionally, approximately 20% of epithelial ovarian cancer cases have typical CA125 measurements [6]. Considering these circumstances, CA125 alone cannot support the diagnosis during ovarian cancer recurrences. For this purpose, we aimed to evaluate biomarkers for recurrences in platinum-sensitive ovarian cancers that are simple, can be evaluated in correlation with CA125, and can be measured in any health institution without the need for additional laboratory expenses or a special infrastructure. Therefore, we analyzed inflammatory markers' contribution such as neutrophil lymphocyte ratio (NLR) and systemic immune inflammatory index (SII) in ovarian cancer patients' diagnosis and relapse periods.

METHODS

Using a retrospective database search, 105 patients with platinum-sensitive recurrent ovarian carcinoma, admitted in the last four years were included. The study was prepared per the declaration of Helsinki and was approved by the ethics committee of Health Sciences University, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, dated August 24, 2022, and numbered 2022-08/1930.

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Recurrence and progression timestamps were taken as a basis in processing the hemogram parameters. In addition, platelet-to-lymphocyte ratio (PLR), NLR, and Systemic immune inflammation index (SII) (with a formula of platelet × neutrophil / lymphocyte) were calculated.

Analyses were performed using the Statistical Package for the Social Sciences program [SPSS for Windows, Version 25.0, (IBM Corp., Armonk, NY, USA)]. Normality analises were performed to show the distribution of the variables. Continuous variables were reported using the median (interquartile range) and mean (SD), and categorical variables using the Pearson χ^2 or Fisher's exact test. ROC analysis was performed to calculate the best SII cut-off value. Finally, Spearman correlation analysis was performed for evaluating numerical variable relationships. A p-value of < 0.05 was accepted as significant.

RESULTS

A total of 105 patients with platinum-sensitive recurrent ovarian carcinoma were included. The median age was 55.81 (34–78). When evaluated for menopausal status, 34 (32.3%) patients were premenopausal, while 65 (67.6%) were postmenopausal. Progression developed in 16 (47%) of 34 premenopausal patients and 25 (35.4%) of 65 postmenopausal patients. When the patients were categorized according to their histopathological subtype, there were 90 (85.7%) high grade serous, six (5.7%) low grade serous, five (4.7%) endometrioid, two (1.9%) clear cell, and two (1.9%) other types.

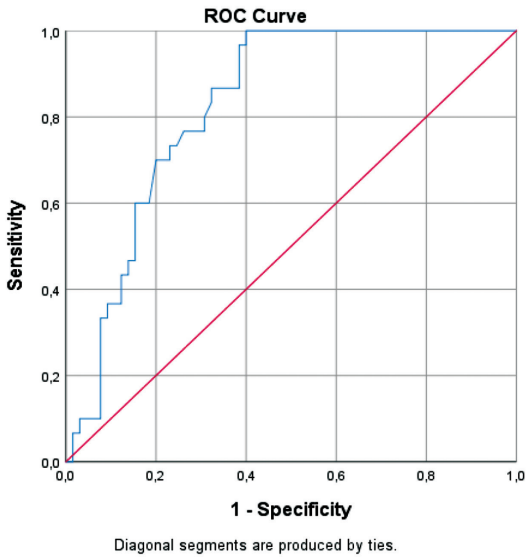
The relationship between laboratory parameters and progression is given in Table 1. Serum CA125 was converted into two separate categorical variables as 35 and below and above 35. CA125 cut-off value was taken as 35. NLR was higher in the group with CA125 > 35 U/ml compared to the group with CA125 ≤ 35 U/ml (p = 0.002) (Table 1). Also, white blood cells had been substantially elevated in CA125 > 35 U/ml cases compared to CA125 ≤ 35 cases (p = 0.05).

Table 1. Relationship of laboratory parameters to CA125

Parameters	CA125 ≤ 35 U/ml (n = 29) Median (range) (95% CI)	CA125 > 35 U/ml (n = 39) Median (range) (95% CI)	p-value
NLR	1.92 (1.47–2.26)	2.95 (3.12–4.52)	**0.002***
SII	722 (877–1999)	810 (580–1138)	0.621*
PLR	161 (134.91–216.35)	144 (141.48–211.77)	0.459*
WBC	6 (4.5–10.2) (x 10^3)	8.1 (7.9–9.7) (x 10^3)	**0.050***
Lymphocyte	1.7(1.57–2.14) (x 10^3)	1.48 (1.42–1.99) (x 10^3)	0.111*
CRP	4.0 (0.82–16)	6 (5.2–20)	0.986*

NLR – neutrophil lymphocyte ratio; SII – systemic immune inflammation index; PLR – platelet lymphocyte ratio; WBC – white blood cells; CA125 – Carbohydrate Antigen 125
*Mann Whitney U

Of our patients, 41 (39%) developed progression after relapse treatment. Serum CA125 was elevated in 34 (82.9%) of 41 patients with this progression. Measurements of CA125 and SII values were planned for these patients.



Progression	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p
SII	0.825	0.744–0.906	929.5	73.3	75.4	**< 0.001**

AUC – area under the receiver operating curve; CI – confidence interval

Figure 1. Roc analysis results in determining the progression of the systemic immune inflammation index variable

As a result of the ROC analysis performed, the value of 929.5 was accepted as the best cut-off (Figure 1), and disease progression was detected in 40 (97.5%) patients when CA125 and elevated SII were evaluated simultaneously. There were five patients (18.5%) with CA125 > 35 and no recurrence on imaging. When CA125 was evaluated together with SII, one (2.5%) of 41 patients with progression was marked as "no progression" (Table 2).

Table 2. Relationship between age, CA125, SII, and performance status with progression

Progression				
Parameters		Present n = 41 (%)	Absent n = 64 (%)	p-value
Age	≤ 50	14 (34.1)	15 (23.4)	0.23[1]
	> 50	27 (65.8)	49 (76.5)	
CA125*	≤ 35	7 (17.1)	22 (81.5)	0.35[2]
	> 35	34 (82.9)	5 (18.5)	
(SII ≥ 929.5 + CA125 > 35)*		40 (97.5)	1 (2.5)	
Eastern Cooperative Oncology Group Performance Status	0	4 (20)	16 (80)	0.13[2]
	1	30 (44.7)	37 (55.2)	
	2	7 (38.8)	11 (51.1)	

CA125 – Carbohydrate Antigen 125; SII – systemic immune inflammation index
[1]Pearson's χ^2; [2]Fisher's exact test;
*Measurement values in patients with progression after relapse treatment

According to Figure 1, the SII parameter estimation was significant in differentiating additional parameters in progression development (p < 0.001). The area under the ROC curve (AUC) for SII to diagnose the presence of progression was 0.825 (95% [CI], 0.744–0.906). For predicting progression, the SII at a cut-off value of ≥ 929.5 had a sensitivity of 73.3% and a specificity of 75.4%.

The Spearman correlation analysis for interactions between the laboratory parameters' numerical variables

Table 3. Correlation between laboratory parameters

Parameters	p	Lymphocyte	Neutrophil	SII	NLR	PLR	CA125 (recurrence)
Lymphocyte	r	1					
	p						
Lymphocyte	r	0.125	1				
	p	0.226					
Lymphocyte	r	-0.266**	0.134	1			
	p	**0.009**	0.196				
Lymphocyte	r	-0.540**	0.637**	0.351**	1		
	p	**< 0.001**	**< 0.001**	**< 0.001**			
Lymphocyte	r	-0.319**	-0.098	0.393**	0.318**	1	
	p	**0.002**	0.343	**< 0.001**	**0.002**		
Lymphocyte	r	-0.152	0.233	-0.005	0.262*	-0.130	1
	p	0.250	**0.076**	0.972	**0.045**	0.325	

CA125 – carbohydrate antigen 125; SII – systemic immune inflammation index; NLR – neutrophil lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; *Spearman correlation analysis

showed a significant and low relationship among NLR and CA125 (r = 0.26, p = 0.045). Besides, serum neutrophil and CA125 values were also evaluated as having a significant relationship (r = 0.23, p = 0.076) (Table 3).

DISCUSSION

Despite many efforts to find the most appropriate biomarker for ovarian cancers, early detection methods still rely on serum CA125 level measurement [7]. CA125 is elevated in 83% of ovarian cancers, but it has low sensitivity and specificity in very early-stage ovarian cancers, and this rate drops to 50–60%. The premenopausal ages had a sensitivity of 50–74%, and a specificity of 69–78%. Additionally, the postmenopausal ages had a sensitivity of 69–87%, and a specificity of 81–93% [8, 9]. Due to various factors, there is a need for biomarkers that can increase the sensitivity and specificity of CA125. To address this issue, Ke Huang et al. [10] have shown that the combination of CA125 with biomarkers such as NLR and PLR is more effective than using CA125 alone in detecting the subgroup of borderline epithelial ovarian tumors that can potentially become malignant. In our study, we aimed to fill this gap by examining the contribution of NLR, PLR, and SII values. While we found that all three biomarkers provided significant contributions, unlike the study by Ke Huang et al. [10], we observed that the SII value, which combines neutrophil, lymphocyte, and platelet values, further enhances the sensitivity and specificity of CA125 when used in combination. Our study observed progression in 47% of premenopausal patients and 35.4% of postmenopausal patients.

CA125 can elevate in benign situations like endometriosis, menstruation, and pregnancy, in addition to ovarian carcinomas. However, it is also used as a marker in hematological malignancies such as lymphoma [11, 12, 13]. Therefore, it is not recommended for population screenings because of its low reliability [14]. Gschwantler et al. [15] in 2017 evaluated leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitor factor, and HE4 together in addition to CA125, and their 94.3% sensitivity and 92.3% specificity rate are important for the combined evaluation of several biomarkers to yield more reliable results, even in a highly complicated tumor. However, it takes work to measure these parameters and causes an additional cost burden. Therefore, evaluating the markers should be accessible and cost-effective in all health institutions. Our study aims to shed light on this gap and to obtain easily accessible biomarkers to be used in earlier diagnosis and progression detection.

There was a total of 47 patients with disease progression with CA125 > 35, and when the imaging and clinical findings were evaluated together, six patients (18.5%) were not considered to have progression. On the other hand, only one (2.5%) of the patients with high CA125 + SII values did not show any progression. Therefore, it was determined that our CA125 false positive rate decreased from 18.5% to 2.5%. Furthermore, when SII values of recurrence patients' progression were evaluated in combination with CA125, the rate of progression detection increased to 97.5%, which was 82.9% compared to the evaluation of CA125 alone.

Patients with ovarian cancers whose first recurrence timing (platinum-free follow-up interval-PTA) occurs within six months are considered to have a platinum-resistant disease, and platinum-based regimens are not preferred in the treatment options of these patients. In the follow-up of patients after adjuvant therapy, using CA125 in combination with other biomarkers will increase the reliability of recurrence detection, thus providing earlier recognition and reducing the additional platinum exposure of the patients.

CONCLUSION

Considering all these data, the SII value could be used together with CA125 because it is easy to use, accessible, and has low cost in clinical practice, as well as to increase the accuracy rate and make precise corrections in the false positivity rate. Furthermore, in the analyses performed, it was determined that NLR, white blood cells, and Neutrophil values were parallel with high CA125 values.

Conflict of interest: None declared.

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Нови инфламаторни маркери и прогностички значај релапса карцинома јајника осетљивог на платину

Фатих Таj, Мустафа Бујукор, Озтурк Атеш

Болница за обуку и истраживање онкологије у Анкари „Абдурахман Журтаслан", Одељење за медицинску онкологију, Анкара, Турска

САЖЕТАК

Увод/Циљ Карциноми јајника су најсмртоноснији гинеколошки тумори. Упркос напретку у опцијама лечења, стопе преживљавања још увек нису на жељеном нивоу. Пошто клинички знаци нису типични у раној фази болести, 2/3 болесница се дијагностикује касно. Антиген угљених хидрата 125 (*CA*125) нема довољну осетљивост и специфичност у раној фази болести и раној прогресији после релапса. Постоји потреба за једноставним и исплативим маркером који корелира са *CA*125. У ту сврху, желели смо да проценимо потенцијал системских инфламаторних маркера као дијагностичких помагала.

Методе Болеснице са рекурентним карциномом јајника осетљивим на платину су биле у предности јер су опције лечења биле разноврсније од резистентне групе. Користећи ретроспективно прикупљање података, у студију је укључено 105 болесница са рекурентним карциномом јајника осетљивим на платину, примљених у последње четири године. Подаци комплетне крвне слике су снимљени на основу периода рецидива и прогресије.

Резултати Када су вредности системског имунолошког инфламаторног индекса процењене у комбинацији са *CA*125 у смислу прогресије током контролних посета после третмана рецидива болести осетљиве на платину, пропорције откривања прогресије су порасле на 97,5%, што је било 82,9% када је био коришћен само *CA*125. С друге стране, лажна позитивност, која је била 18,5% само за *CA*125, смањена је на 2,5% када се комбинује са системским имунолошким инфламаторним индексом. Штавише, однос вредности неутрофила и лимфоцита, вредности белих крвних зрнаца и неутрофила показале су корелацију са високим вредностима *CA*125.

Закључак Вредност системског имунолошког инфламаторног индекса би се могла користити заједно са *CA*125 јер је лака за употребу, приступачна и има ниску цену у клиничкој пракси, као и за повећање стопе тачности и прецизне корекције у стопи лажне позитивности.

Кључне речи: рак јајника; *CA*125; релапс; инфламаторни биомаркери; осетљивост на платину

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence and clinical forms of celiac disease in siblings of children with verified disease

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SUMMARY

Introduction/Objective Celiac disease (CD) is the result of a polygenic predisposition and gluten-containing diet. The aim of this study was to determine the prevalence and clinical forms of CD in siblings of children with verified disease.

Methods The study included 83 siblings, aged 1.5–27 (11.77 ± 6.2) years, of 64 children with CD diagnosed according to ESPGHAN criteria (1990/2012). In addition to a detailed history and clinical examination, serum levels of IgA and antibodies to tissue transglutaminase (AtTG) IgA and IgG classes were determined in all subjects. All with elevated AtTG levels underwent multiple duodenal enterobiopsy. The diagnosis of CD was confirmed by the finding of characteristic histological changes.

Results The diagnosis of CB was made in 13 of 83 subjects (15.67%). Nine of them had an asymptomatic form of the disease, while in the others the disease was clinically manifested – in three the form was classical, in one it was accompanied by severe malnutrition (-26.80%), and in one the manifestation was nonclassical (only short stature). Except for sideropenia and hypoferritinemia in four patients, of which two with hemoglobin below the reference value, standard laboratory findings were within normal limits.

Conclusion Our research shows that the prevalence of CD in siblings of children with verified disease is 15.67%. It is mostly detected in its asymptomatic form. In accordance with this, routine application of serological screening for CD in this population group is necessary for its timely diagnosis and treatment.

Keywords: celiac disease; children; siblings; prevalence

INTRODUCTION

Celiac disease (CD) is a multisystem autoimmune disease that occurs in genetically predisposed individuals on a gluten-containing diet [1]. It occurs in all population groups, and most often in members of the white race (~1%) [2, 3, 4]. In relatives of the first and second order, as well as in patients with other autoimmune diseases, selective IgA deficiency and some of the chromosome abnormalities (Down, Turner, and Williams–Beuren syndromes), the incidence of the disease is many times higher [1, 2, 4–8]. The basis of the disease and the key finding in its diagnostics is nonspecific inflammation of the small intestinal mucosa that is resolved by gluten-free diet [1].

The pillar of hereditary predisposition to CD is the presence of genes encoding HLA DQ2 and HLA DQ8, which are registered in over 99% of patients [2]. DQ2 is registered in 85–95% of subjects, and HLA DQ2 in 5–15% [2, 9]. However, in addition to having HLA DQ2 or HLA DQ8 and exposure to gluten, the presence of non-HLA genes is necessary for the disease to occur [2, 5, 10]. In addition, non-gluten external factors have a, to date, unclear role in the appearance of the disease [5, 10, 11].

The aim of this study was to determine the prevalence and clinical form of CD in siblings of children with verified disease.

METHODS

The study included 83 siblings, 46 male and 37 female, aged 1.5–27 (11.77 ± 6.2) years, of 64 children (18 boys and 46 girls) with CD diagnosed according to the criteria created by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1990 and 2012 [12, 13]. All patients with verified CD and their siblings subjected to the examination originated from the same parents. One of the study participants, a 14-year-old girl, had verified type 2 diabetes mellitus. The research was performed in accordance with the current ESPGHAN recommendations [1]. The study protocol was approved by the local ethics committee.

In addition to a detailed history and clinical examination, serum levels of IgA and antibodies

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to tissue transglutaminase (AtTG) IgA and IgG classes were determined in all siblings. Also, blood tests and standard biochemical analyses (serum iron and ferritin concentrations, total proteins, albumin, urea, total cholesterol, 3-glyceride, calcium, phosphorus, alkaline phosphatase, and the liver function test) were performed in all of them. The obtained findings were compared with reference values [14, 15]. The diagnostic criterion for anemia was the level of hemoglobin (Hb) for children up to 5 years old below 110 g/l, for those 5–11 years old below 115 g/l, and for those older than 11 years the diagnostic criterion was below 120 g/l [15].

Although three subjects (two boys and one girl) had an AtTG IgA titer over 10 times the upper reference value and clinical signs of classical CD, all underwent multiple duodenal enterobiopsy for reliable disease verification [1, 5, 13]. Classification of pathohistological damage of the small intestinal mucosa was performed according to modified Marsh criteria on infiltrative (I), infiltrative-hyperplastic (II), destructive (III), and hypoplastic (IV) type [16]. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb), and total (IIIc).

Oslo definitions for CD were used for differentiation of the clinical types of the disease [17]. According to these criteria, CD is classified into two basic types: symptomatic and asymptomatic (subclinical). Symptomatic disease is further differentiated into classical and nonclassical. Classical CD is characterized by poor appetite, chronic diarrhea, failure to thrive, muscle wasting, abdominal distension and irritability, while nonclassical type of the disease are dominated by atypical (nonclassical) digestive and/or various extraintestinal manifestations, either single or combined, such as constipation, recurrent abdominal pain, short stature, delayed puberty, chronic fatigue, iron deficiency anemia, isolated hypertransaminasemia and others.

RESULTS

The diagnosis of CB was found in 13 of 83 siblings (15.67%), seven females and six males, aged 2.58–20 (10.58 ± 5.49) years. The type of the disease in nine was asymptomatic and in four it was clinically manifest, in three classical and in one nonclassical. All three subjects with classical CD were younger than three years. One of them also had severe malnutrition, i.e., a body weight deficit of 26.8% compared to normal. In patients with non-classical disease, only short stature was noted. Except for sideropenia and hypoferritinemia in four patients, of which two with hemoglobin below the reference value, both with clinical classical disease, other standard laboratory findings were within normal limits. In one of them, aged 1.5 years, a selective IgA deficit (0.06 g/l) was found. Histological examination of the small intestinal mucosa in one subject revealed infiltrative-hyperplastic enteropathy, while in others it was destructive, of which in six it was partial, in five subtotal, and in one total. In two subjects with classical CD, subtotal enteropathy was found, and in one, the most severe case among them, total enteropathy. The patient with short stature, a 13-year-old boy, had subtotal enteropathy. In siblings with asymptomatic CD, enteropathy was subtotal in two cases, it was partial in six cases, and infiltrative-hyperplastic in one case. In patients with the classical type of the disease, gluten-free diet resulted in the withdrawal of symptoms within a week or two and complete recovery after 3–6 months. Also, the patient with short stature normalized his body height after two years of dietary treatment.

DISCUSSION

CD is a gluten-induced autoimmune disease of polygenically predisposed individuals [1, 5]. Accordingly, it is characterized by a high prevalence in close relatives, especially first-degree relatives, as well as in patients with other autoimmune diseases [1, 5]. Additionally, the disease is highly present in people with selective IgA deficiency and patients with Down, Turner, and Williams syndromes [1, 5]. Given this fact, as well as the much more frequent asymptomatic compared to clinically recognizable CD expression, as part of the ESPGHAN diagnostic guide published in 2020, it was recommended that these groups should be tested for its presence [1]. The basis of an active approach in the diagnosis of CD in these high-risk groups is that timely detection and adequate treatment of the disease prevents its immediate and far-reaching complications, which can sometimes be very serious [1]. As part of this diagnostic protocol, subjects should undergo total IgA and AtTG-IgA testing as an initial screen. If total IgA concentrations are low, the second step should consist of an IgG-based test (deamidated gliadin peptide, anti-endomysial, or tissue transglutaminase). In cases where AtTG-IgA serum concentration is greater than 10 times above the reference value for a diagnosis of CD, enterobiopsy is not necessary. As part of our study, all the above criteria were consistently met. Although three subjects had an AtTG IgA titer over 10 times the upper reference value, in order to reliably verify the disease, all subjects underwent multiple duodenal enterobiopsy.

According to data from the literature, the prevalence of CD among the first-degree relatives is 3–22%, on average about 10%, which fits our finding [9, 10, 18–25]. In addition, two siblings in our group of subjects also had additional disorders, one type 2 diabetes mellitus, and the other selective IgA deficiency [5, 7, 8].

The basis of the CD and the key finding in its diagnostics is gluten-sensitive enteropathy, i.e., a nonspecific inflammation of the small intestinal mucosa, resolved by gluten-free diet [1]. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by different extraintestinal manifestations, which can sometimes be the only sign of the disease [5, 26, 27, 28]. From the clinical aspect, CD is divided into two basic types: symptomatic (classical and nonclassical) and asymptomatic [17]. The classical CD form is most often seen at the age of 9–36 months, and non-classical in later childhood,

adolescence, and in adulthood [5]. Of the 13 siblings with CD detected in our study, nine had the asymptomatic type of the disease, one had an atypical manifestation (short stature as the only manifestation), and three had the classical type. All nine with asymptomatic CD and the patient with short stature were in adolescence, while all three with clinically classical CD were younger than three years. In addition, four subjects, three with classical and one with asymptomatic CD, had iron deficiency, of which two, both with classical CD, and low Hb. In the group of siblings with asymptomatic CD, infiltrative-hyperplastic enteropathy was registered in one case, partial enteropathy in six, and subtotal enteropathy was registered in two patients. Subtotal enteropathy was found in boys with short stature and in two siblings with classical CD, and total enteropathy was found in subjects with the most severe form of the disease. Although the degree of damage to the small intestinal mucosa obtained by enterobiopsy does not correlate with the clinical expression of CD, in the group of our subjects this association was quite convincing [29, 30].

All siblings with diagnosed CD are advised to follow a permanent gluten-free diet [1]. In addition, four subjects requested oral correction of iron deficiency. Respondents with classical CD also received folic acid for 2–4 months. Strict adherence to the elimination diet in patients with classical CD resulted in rapid withdrawal of symptoms and consequent complete recovery, and in boys with short stature normalization of body height after two years of treatment.

CONCLUSION

According to our findings, the prevalence of CD in siblings with verified disease is 15.67%, or more than 15 times that of the general population. It is mostly detected in its asymptomatic form. Having in mind this fact, it is clear that it is necessary to test this group of children for CD in order to achieve its timely diagnosis and treatment and thus prevent both immediate and far-reaching complications.

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Преваленција и клинички облици целијачне болести код браће и сестара деце са верификованом болешћу

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САЖЕТАК

Увод/Циљ Целијачна болест (ЦБ) резултат је полигенске предиспозиције и исхране са присуством глутена.
Циљ рада је био да се утврди преваленција ЦБ код браће и сестара деце са верификованом болешћу.

Методе Студијом је обухваћено 83 браће и сестара, старости 1,5–27 (11,77 ± 6,2) година, 64-оро деце са ЦБ дијагностикованом у складу са *ESPGHAN* критеријумима (1990/2012). Поред детаљне анамнезе и клиничког прегледа, код свих испитаника одређени су серумски нивои *IgA* и антитела на ткивну трансглутаминазу (*AtTG*) *IgA* и *IgG* класе. Сви са повишеним нивоом *AtTG* подвргнути су мултиплој дуоденалној ентеробиопсији. Дијагноза ЦБ је потврђивана налазом карактеристичних хистолошких промена.

Резултати Дијагноза ЦБ је постављена код 13 од 83 испитаника (15,67%). Девет њих су имали асимптоматски облик болести, док је код осталих болест била клинички манифестна, код три класична, код једног праћена тежом малнутрицијом (-26,8%) и код једног некласична (само низак раст). Сем сидеропеније и хипоферитинемије код четири болесника, од чега код два са хемоглобином испод референтне вредности, стандардни лабораторијски налази су били у граници нормале.

Закључак Наше истраживање показује да преваленција ЦБ код браће и сестара деце са верификованом болешћу износи 15,67%. Претежно се открива у асимптоматском облику. У складу са тим, неопходна је рутинска примена серолошког скрининга на ЦБ у овој популационој групи у циљу њене правовремене дијагностике и третмана.

Кључне речи: целијачна болест; деца; браћа и сестре; преваленција

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Assessment of diagnostic value of *HLA-DQ2/DQ8* typing and anti-tissue transglutaminase antibodies as an alternative to duodenal biopsy in pediatric celiac disease

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SUMMARY

Introduction/Objective The objective of the paper is to assess the applicability of serum anti-tissue transglutaminase (tTG) antibodies IgA and IgG concentration and *HLA-DQ2/DQ8* typing as a non-invasive alternative to duodenal biopsy in diagnosing celiac disease (CD) in pediatric population.

Methods A prospective cohort study included a total of 179 pediatric patients aged 1–18 years. Determination of tTG IgA and tTG IgG antibodies and human leukocyte antigen (*HLA*) *DQ2/DQ8* typing was performed for all patients. Histology of duodenal biopsies was interpreted by the modified Marsh scoring system.

Results The diagnosis of CD was confirmed in 101 (56%) patients of the studied population. In cases of CD, *HLA-DQ2/DQ8* was positive in 100 patients (99%). The tTG IgA antibodies in concentration higher than 100 U/ml were detected in 77 (76.2%) of the CD patients and in significantly smaller number for tTG IgG [29 (28.7%)] ($p < 0.001$). Statistically highly significant association of duodenal lesions Marsh grade 3 with concentration of tTG IgA 10-fold higher than the upper level of normal (ULN) was established ($p < 0.001$)

Conclusion Concentration of tTG IgA 10-fold higher than ULN is significantly positively correlated with Marsh grade 3 histopathology findings. Specific antibodies determination in combination with *HLA-DQ2/DQ8* typing proves to be sufficient for a diagnosis of CD, supporting the fact that duodenal biopsy may be avoided in a significant majority of patients – 75%.

Keywords: celiac disease; tissue transglutaminase antibodies; *HLA-DQ2/DQ8* typing; non-invasive

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that primarily affects the small intestine, and is caused by the ingestion of gluten in genetically susceptible individuals. Prevalence in the general population ranges 0.5–2%, with an average of about 1% [1, 2]. The development of the coeliac enteropathy depends on a complex immune response to gluten proteins. Clinical presentation of CD is highly variable and includes classical and non-classical gastrointestinal symptoms, extraintestinal manifestations, and subclinical cases. Familial occurrence was found to be present in 5–15% of patients, more often female in ratio 2–3:1, usually disclosing in children; however, up to 20% of cases may be diagnosed in patients over 60 years of age [3, 4, 5].

The reasons for the rising number of CD cases in recent decades are unknown, but may be related to environmental factors that may promote loss of tolerance to dietary gluten. Therefore, the quantity of early-life gluten exposure has been a major focus of prevention efforts.

The criteria for the diagnosis of CD are changing, but in adults, diagnosis still depends on the presence of duodenal villous atrophy, along with findings from serology analysis. Although guidelines in the United States continue to mandate a biopsy at all ages, some children receive a diagnosis of CD without a biopsy [6].

A strong association of CD with *HLA-DQ2* and *HLA-DQ8* genetic haplotypes has been well documented. In general population, *HLA-DQ2/DQ8* phenotype is present in 30–40% of individuals, but only 3% develop CD [7]. Globally, 95–99% of CD patients carry *HLA-DQ2* and/or *HLA-DQ8* haplotypes. Prevalence of *HLA-DQ2* phenotype ranges 90–95% among CD patients from European Caucasian population [8]. The presence of at least 1 of these haplotypes is necessary but insufficient for development of CD. Two twin studies have found concordance rates of only 49–83% among monozygotic twins,

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indicating the existence of environmental risk factors [6, 9]. Therefore, human leukocyte antigen (*HLA*) typing could not be recommended as the sole marker for diagnosis of CD since positive predictive value reaches only 57%, while sensitivity does not exceed 63% [10]. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) proposed in 2012 and 2020 that it might be possible to avoid intestinal biopsy in children who meet the following criteria: have characteristic symptoms of CD, levels of tTG IgA greater than 10-fold the upper limit of normal, confirmed with a positive serologic result for anti-endomysial antibodies (EMA) [10, 11]. According to guidelines from 2012/2020, *HLA-DQ2/DQ8* typing was also recommended as a useful tool for CD diagnosis exclusion as well as for adding strength to the diagnosis of CD [11].

Considering the invasive nature of endoscopy and its potential complications, it has been postulated that an increase of both tTG IgA and/or IgG antibodies is predictive of the grade of small intestine villous atrophy, thus making intestinal biopsy unnecessary in two-thirds of the patients [10].

Presence of tTG IgA in different concentrations has been described in several autoimmune disorders, such as autoimmune hepatitis (AIH), inflammatory bowel disease (IBD), autoimmune thyroiditis and systemic lupus erythematous. However, elevation of tTG IgA in autoimmune disorders is not always associated with CD. Therefore, in this particular clinical setting determination of EMA was reported as a better choice [12].

The aim of our study was to estimate the accuracy of non-invasive diagnostic methods in pediatric patients with CD proposed by the ESPGHAN criteria. Our approach included a determining both IgA tTG and IgG tTG serum concentrations and correlating these values to the Marsh histology. The other goal of our study was to determine the usefulness of *HLA-DQ2/DQ8* typing in adding diagnostic accuracy to the aforementioned serologic analysis for confirmatory diagnosis of CD [11].

METHODS

This prospective study was conducted at Dr. Vukan Čupić Mother and Child Health Care Institute, Belgrade, Serbia during an observational period between January 2017 and December 2020. A total of 179 patients, aged from 12 months to 18 years, were included. The study group consisted of two major subgroups: a) children with at least one clinical or laboratory finding suggestive of CD: chronic diarrhea, bloating, chronic constipation, dyspepsia, failure to thrive, chronic weight loss, anemia and elevated serum transaminases, and b) asymptomatic children with positive family history for CD or previously diagnosed conditions associated with an increased risk for CD: immunoglobulin A deficiency (IgAD), AIH, Crohn's disease, diabetes mellitus type 1, Down syndrome.

Inclusion criteria of our study were the following: a) status of tTG IgA and tTG IgG antibodies determined before initiation of treatment; b) determined *HLA-DQ2/DQ8* typing; c) duodenal biopsy done within four weeks before the initiation of treatment.

Prior use of gluten-free diet (GFD) or the presence of IgAD (serum concentration of IgA ≤ 0.07 g/l) were considered to be the exclusion criteria. IgA antibodies in IgAD are not a reliable parameter due to their abnormally low concentrations, which would disrupt statistical analysis, and were excluded from this study [13].

Serum concentrations of the tTG IgA and tTG IgG antibodies were measured by using ELISA kit ORG 540 (Organon, USA) with recommended cut-off concentrations of tTG IgA and IgG antibodies > 10 U/ml (maximum operating range, 200 U/ml).

HLA typing for *DQ2* and *DQ8* haplotypes and was performed by the standard Complement Dependent Cytotoxicity assay [14].

Histological evaluation of intestinal forceps biopsies consisted of at least four specimens: three from the D2 section and one from a bulb of the duodenum. The results of histologic evaluation were classified using the Marsh scoring system modified by Oberhuber: Marsh 0 – normal mucosa; Marsh 1 – infiltrative lesions with at least 25 lymphocytes per 100 examined epithelial cells; Marsh 2 – hyperplastic lesions; Marsh 3 a, b, c stages were interpreted as partial, subtotal, and total villous atrophy, respectively [15, 16].

All statistical data were analyzed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY). The data are presented as frequencies and median values depending on the type. The χ^2 test and the Mann–Whitney U test were used to assess the difference between the groups. Spearman correlation analysis was used to test the association between two variables. Diagnostic accuracy was presented with sensitivity, specificity, positive predictive value, and negative predictive value. We used receiver operating characteristic (ROC) analysis to find the optimal cut-off values. All p-values below 0.05 were considered statistically significant.

The study was conducted with the approval of the institutional ethics committee.

RESULTS

In the study cohort of 179 patients, the diagnosis of CD was established in 101 (56.4%). Basic demographic characteristics of the study subjects along with *HLA-DQ2/DQ8* typing profiles are presented in Table 1. In patients younger than two years (n = 35), CD was confirmed in 60% (n = 21), while in older than two years (n = 144), the same diagnosis was established in 63% (n = 91). Statistical analyses showed that *HLA-DQ2/D8* typing provided high negative predictive value of 99% for the diagnosis of CD, with specificity of 56%, positive predictive value of 75%, with test accuracy estimated at 82%.

Diagnostic accuracy of tTG IgA and IgG at different values of interest (10, 50, and 100 U/ml) was tested (Table 2), while optimal cut-off value was determined by ROC: for tTG IgA at 13 U/ml, and for TTG at IgG 5 U/ml, as

Table 1. Basic demographic data and status of *HLA-DQ2/DQ8* typing in the studied group

Demographic data	CD		p
	Yes (n = 101)	No (n = 78)	
Age (years)	7 (3–13)	7.5 (3–11)	0.984
Sex, male (n, %)	29 (28.7%)	41 (52.6%)	0.001
Positive *HLA-DQ2* and/or *DQ8* (n, %)	100 (99%)	33 (42.3%)	< 0.001
Positive *DQ2* (n, %)	97 (96%)	27(35%)	
Positive *DQ8* (n, %)	3 (3%)	6 (7%)	
Negative *HLA-DQ2* and *DQ8*	1 (1%)	45 (58%)	

Table 2. Serological and histopathological features of the studied group; all data were calculated without patients with IgA deficiency (tTG IgA is 0)

Features	CD		p
	Yes (n = 101)	No (n = 78)	
tTG IgA (U/ml)			
0–10	1 (1%)	70 (89.7%)	< 0.001
11–50	10 (9.9%)	5 (6.4%)	
51–100	12 (11.9%)	1 (1.3%)	
> 100	77 (76.2%)	2 (2.6%)	
tTG IgG (U/ml)			
0–10	27 (26.7%)	68 (87.2%)	< 0.001
11–50	32 (31.7%)	8 (10.3%)	
51–100	13 (12.9%)	2 (2.6%)	
> 100	29 (28.7%)	0	
Marsh histopathology	95 (94.1%)	10 (12.8%)	< 0.001
Marsh grade			
0	3 (3%)	62 (79.4%)	< 0.001
I	2 (2%)	6 (7.7%)	
II	1 (1%)	2 (2.6%)	
IIIa	15 (14.9%)	6 (7.7%)	
IIIb	18 (17.8%)	2 (2.6%)	
IIIc	62 (61.4%)	0	

Table 3. Determination of the cut-off values of tTG IgA and tTG IgG concentrations optimal for diagnosing celiac disease

Test	p	AUC	Cut-off	Sn	Sp
tTG IgA	< 0.001	0.984 (0.968–1.000)	13	99.9%	91%
tTG IgG	< 0.001	0.832 (0.771–0.892)	5	74.3%	87.2%

Sn – sensitivity; Sp – specificity; AUC – area under the curve

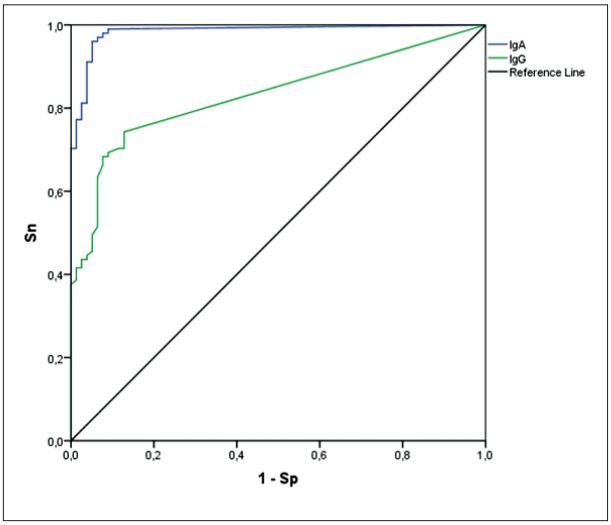

Figure 1. Receiving operating curve and area under the curve determine the best cut-off value for both tTG IgA and tTG IgG

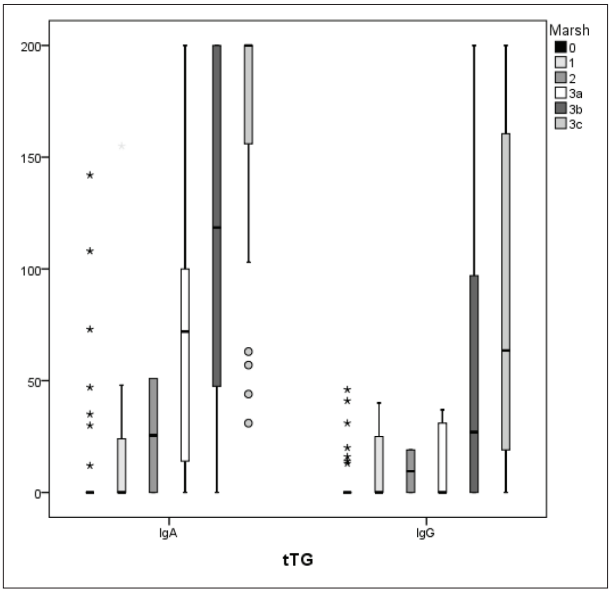

Figure 2. Correlation of tTG IgA (left) and tTG IgG (right) levels, with lesions of enteral mucosa graded by Marsh criteria (p > 0.001)

presented in Figure 1 and Table 3. As shown in Table 4, the highest sensitivity of tTG was found at IgA > 10 and IgG > 50, respectively. On the other hand, the highest specificity was detected both for tTG IgA and tTG IgG at levels higher than 50 U/ml.

There is statistically significant correlation of tTG IgA and tTG IgG concentrations with the extent of enteric mucosa lesions graded by the Marsh criteria ($p < 0.001$). The most significant association was observable for Marsh grade 3a lesions and tTG IgA concentration and also for Marsh grade 3b and tTG IgG concentration. Concentration of tTG IgA above 100 U/ml (10-fold higher than the ULN)

Table 4. Diagnostic accuracy of anti tTG IgA and tTG IgG for celiac disease at different concentration values of interest (10, 50, and 100 U/ml)

	Sn	Sp	PPV	NPV
IgA > 10	99 (93.8–99.9)	89.7 (80.3–95.1)	92.6 (85.5–96.5)	98.6 (91.3–99.9)
IgG > 10	73.3 (63.4–81.3)	87.2 (77.2–93.3)	88.1 (78.7–93.8)	71.5 (61.2–80.1)
IgA > 50	89.1 (80.9–94.2)	96.1 (88.4–99)	96.7 (90.2–99.2)	87.2 (77.8–93.1)
IgG > 50	41.6 (31.9–51.8)	97.4 (90.2–99.5)	95.4 (83.3–99.2)	56.3 (47.5–64.7)
IgA > 100	77.2 (67.6–84.7)	97.4 (90.2–99.5)	97.5 (90.4–99.5)	76.7 (67.0–84.4)
IgG > 100	28.7 (20.4–38.7)	1 (94.1–1)	1 (85.4–1)	52 (43.7–60.2)

Sn – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value

was present in CD patients with enteric mucosa lesions Marsh 3c, with few exceptions (Figure 2 left). Although statistically significant, tTG IgG variation in relation to Marsh grade was lower (Figure 2 right).

DISCUSSION

Our study reiterated female predominance in the population of CD patients, as demonstrated by previous studies [5].

The age at the onset of CD did not affect the accuracy of the final diagnosis. It has been reported that tTG has limited diagnostic value in children younger than two years of age in establishing the CD diagnosis, suggesting that the concentration of antibodies on deamidated gliadin peptide could be of higher accuracy [11]. We should consider two possible causes of lower sensitivity of tTG in younger age. Namely, children under two years of age tend to have lower values of total IgA, which impacts the levels of tTG IgA. On the other hand, tTG antibodies could be less sensitive to gluten stimulation in younger age. Additionally, lower amount of gluten in an infant diet represents weak stimulus for tTG rise, but nevertheless causes abnormal gut histopathology [17]. Since we have excluded children with IgA deficiency from the statistical analysis, our study found that the diagnostic value of tTG should be considered reliable, without any effect of the age ($p = 0.984$). Therefore, we may assume that tTG in very young children is not inferior to AGA.

Our results in regard to *HLA-DQ2/DQ8* typing in CD patients showed almost complete correspondence to the similar study from 2014 conducted on a Serbian population [8]. Namely, both studies show that above 94% of patients diagnosed with CD carry the *HLA-DQ2* haplotype. In comparison with other studies in our geographic regions, there is also high degree of data similarity: e.g., in Croatia, 93.7% children with diagnosed CD carry *DQ2* [8]. In other parts of Europe, the prevalence of *HLA-DQ2* among CD patients may vary from nearly 85% in Greece and 87% in France to 92% in Scandinavia [8, 18]. In other parts of the world, *HLA-DQ* types in affected population are distinctly different, as shown in a Brazilian study: *HLA-DQ2* at 68.5%, *HLA-DQ8* at 17.8%, and both *DQ2* and *DQ8* at 6.8% [19]. The negative predictive value of *HLA* typing of 99% is in full accordance to the results of previous studies [8]. In the group of patients without confirmed CD, 42% were positive for *HLA-DQ2/DQ8*. This result is slightly exceeding the prevalence of aforementioned haplotypes of 30–40% in the general population, and it could be attributed to familial aggregation [7].

As shown in our results, the concentration of tTG IgA antibodies above 100 U/ml was highly suggestive of CD. Total serum IgA, tTG IgA and IgG antibodies as well as EMA antibodies all correlate to intestinal villous atrophy. Sensitivity of tTG IgA in the diagnosis of CD has been found to range 71–100%, while for EMA it is estimated at 86–100%; specificity is similar in both, ranging 90–100%. American College of Gastroenterology recommended the tTG IgA antibody as the most cost-effective and reliable screening test to identify CD. Obtaining a total serum IgA level at the initial testing is also recommended to identify those with selective IgAD in whom a tTG IgG-based test should be used [17]. In our study, tTG IgA above 100 U/ml (10 × ULN) showed high sensitivity (77.2) and specificity (97.5), with the optimal cut-off value at 13 U/ml. In contrast, tTG IgG above 100 U/ml (10 × ULN) showed significantly lower sensitivity of only 28.7, with absolute specificity and cut-off value optimally estimated at 5 U/ml. This observation could be explained by immunogenity of different isotypes: tTG IgG shows slower kinetics after gluten challenge especially if the stimulus contained a low gluten concentration. Moreover, tTG IgA and IgG share affinity for the same epitopes, and competition between these favors IgA antibodies. Circulating tTG IgG falls very slowly, and could be positive for over two years, which could be of importance in prolonged monitoring of patients with CD and associated IgAD [17].

We determined EMA antibodies only in special situations, such as the following: a) a finding of low concentration of the IgA tTG antibody with positive *HLA-DQ2/DQ8* typing; b) positive IgA tTG antibodies associated with negative *HLA-DQ2/DQ8* typing; c) patients with comorbid autoimmune diseases. At the time of our study, the determination of EMA IgA and IgG antibodies was not available at our hospital. Therefore, for 59 of our patient, the EMA were analyzed in different laboratories (by operator dependent methods). Due to this shortcoming, EMA antibodies status was excluded from statistical analysis. The analysis of EMA antibodies status in patients with clinical signs of CD is required by ESPGHAN recommendations [11]. However, our study demonstrates that the lack of EMA availability did not significantly affect the yield of non-invasive approach combining tTG serology and HLA typing.

False positive serology for tTG was reported in approximately 10% of the patients with food intolerance, post-infectious enteritis syndrome, sprue and kwashiorkor, and without evidence of CD [20, 21]. We found false positive results for tTG IgA in 3% of our patients, and in 12.9% for tTG IgG. In these cases, the importance of HLA typing is reflected in selecting patients in need of further investigation, such as EMA antibody testing and duodenal biopsy.

By contrast, false negative serology for tTG antibodies is only rarely described (~1%) in CD patients, especially in those with sufficient total IgA activity [21]. In our study, only one patient (1%) had false negative both tTG IgA and tTG IgG, with normal total serum IgA, positive *HLA-DQ2/DQ8*, and subsequent Marsh 3c histopathology; in the same patient, six months of GFD resulted in the resolution of histopathology findings to Marsh grade 0.

In our cohort of patients with confirmed CD, tTG IgA above 100 U/ml was found in 71% ($n = 73$) of the patients. Nevertheless, the tTG IgA concentration above 100 U/ml (10 × ULN) should be considered a good predictor of Marsh lesion grade 3, and especially of 3c (Figure 2, left).

The presence of duodenal damage, even Marsh 3 lesions, is not strictly correlated to the CD diagnosis, especially in children younger than two years [10]. Differential diagnosis in these cases is broad and includes other conditions, such as milk protein allergy, immune enteropathy,

Giardia infestation, post-infectious enteritis, malnutrition, etc. It should also be noted that in 13% of our patients Marsh 3a and 3b lesions were not associated with final diagnosis of CD. However, all Marsh 3c patients had definitive CD. Thus, only Marsh 3c lesions could be accepted as the "gold standard" in the histopathologic diagnosis of CD.

Crohn's disease and CD are two immune disorders with diverse genetic background. There is a strict correlation between *HLA-DQ2/DQ8* and CD, but this correlation is lacking in Crohn's disease [19]. However, patients with comorbidities of CD and Crohn's disease are expected to be *HLA-DQ2/DQ8*-positive. The prevalence of CD is not increased in children with IBD when compared to the general population [22]. False positive tTG antibodies' values can occur in children with IBD. Some patients with IBD, especially with Crohn's disease, show tTG IgA positivity in the absence of CD. In these patients, positivity of tTG antibodies may be a consequence of induced apoptosis and undergoing tissue damage in the bowel [23].

In our study, two patients had comorbidities of CD and Crohn's disease. One of them was diagnosed by the finding of increased tTG (IgA and IgG > 200 U/ml) antibodies, positive EMA antibodies, *HLA-DQ2/DQ8*-positive typing, and Marsh 3c score on histopathology; GFD resulted in a significant decrease of tTG. However, a single patient from our study had Crohn's disease and slightly positive tTG IgA (51–100 U/ml), negative both tTG IgG and EmA, as well as negative *HLA-DQ2/DQ8* typing and Marsh 0 histopathology. In this non-CD patient, tTG IgA gradually fell to normal levels after three months of follow-up, without GFD.

The correlation of AIH and chronic liver disease with CD seems to be complex as well. Some data demonstrated that CD prevalence does not differ significantly between the general population and patients with chronic liver disease such as AIH (comorbidity with CD in about 4–6% of cases) [24]. Furthermore, similarly to other autoimmune conditions, AIH could be associated with nonspecific positivity of tTG antibodies. In such a scenario, it would be important to determine EMA and rely on high sensitivity and specificity of this marker [25]. Interestingly, in our study, two of the patients with AIH had tTG IgA above 100 U/ml, with negative tTG IgG, EMA, *HLA-DQ2/DQ8* typing, and Marsh 0 histology. Also, the same two patients failed to demonstrate a decrease of tTG IgA during GFD, so the CD diagnosis could be excluded. In the third patient with AIH from our cohort, high concentrations of both tTG IgA and IgG antibodies (> 200 U/ml), positive EMA antibody, and positive *HLA-DQ2/DQ8* typing correlated to Marsh 3 histopathology. This CD patient responded to GFD and his tTG gradually decreased.

CONCLUSION

We confirmed previous findings that positive *HLA-DQ2/DQ8* typing combined with tTG IgA in concentration 10-fold higher than ULN should be regarded as sufficient for the diagnosis of CD. Furthermore, we showed that a duodenal biopsy may not be necessary in approximately 75% of pediatric patients with suspected CD. An increased concentration of tTG IgA antibodies significantly correlated with the grade of Marsh histopathology lesions. We report that the concentration of tTG IgA higher than 100 U/ml (10-fold higher than ULN) is a good predictor of more extended Marsh lesions (grade 3a, 3b or 3c) in children. By contrast, the measurement of tTG IgG antibodies was found to be of weaker sensitivity, although it remains an important diagnostic tool in special conditions such as IgAD or certain autoimmune diseases. Finally, EMA concentration was of particular importance for confirmation of CD diagnosis in challenging patients, but the pitfall of our study was the incomplete testing of the whole group. Therefore, determination of EMA should be regarded as an important part of the diagnostic algorithms for CD based on non-invasive approach.

Conflict of interest: None declared.

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Процена дијагностичке вредности *HLA-DQ2/DQ8* типизирања и антитела на ткивну трансглутаминазу као алтернативе дуоденалној биопсији код целијачне болести деце

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САЖЕТАК

Увод/Циљ Циљ рада је да се процени применљивост серумских антиткивних трансглутаминаза (*tTG*) концентрације антитела *IgA* и *IgG* и *HLA-DQ2/DQ8* типизације, као неинвазивне алтернативе биопсији дуоденума у дијагностици целијачне болести (ЦБ) у педијатријској популацији.

Методе Проспективна кохортна студија обухватила је укупно 179 педијатријских болесника узраста 1–18 година. Код свих болесника одређена су антитела *tTG IgA* и *tTG IgG* и извршена је типизација хуманог леукоцитног антигена (*HLA*) *DQ2*/*DQ8*, као и биопсија дуоденума. Хистопатологија биопсије дуоденума је интерпретирана модификованим Маршовим системом бодовања.

Резултати Дијагноза ЦБ је потврђена код 101 (56%) болесника, док је *HLA-DQ2/DQ8* био позитиван код 100 болесника (99%). Антитела на *tTG IgA* у концентрацији већој од 100 *J/ml* откривена су код 77 (76,2%) болесника са ЦД и у значајно мањем броју за *tTG IgG* 29 (28,7%) ($p < 0,001$). Утврђена је статистички високо значајна повезаност атрофије дуоденума (Маршовог степена 3 *a*, *b*, *c*), са концентрацијом *tTG IgA* 10 пута већом од горњег нивоа нормале ($p < 0,001$).

Закључак Концентрација *tTG IgA* 10 пута већа од горњег нивоа нормале је у значајној позитивној корелацији са хистопатолошким налазима Маршовог степена 3. Одређивање ових специфичних антитела у комбинацији са *HLA-DQ2/DQ8* типизацијом показало се довољним за дијагнозу ЦБ, што говори у прилог чињеници да се биопсија дуоденума може избећи у значајној већини болесника – 75%.

Кључне речи: целијакија; антитела на ткивну трансглутаминазу; *HLA-DQ2/DQ8* типизација; неинвазивна дијагностика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Can pre-treatment dysfunctional voiding and incontinence scoring system score predict treatment outcome in children with dysfunctional voiding – a randomized trial

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SUMMARY

Introduction/Objective Dysfunctional Voiding and Incontinence Scoring System (DVISS) was created to help diagnose functional voiding disorders in children based on their clinical symptoms. However, its role in prognosticating treatment outcome in dysfunctional voiding (DV) was not explored.
The aim was to analyze the pre-treatment DVISS score's ability to predict treatment outcomes in a pediatric population with DV.

Methods A total of 86 patients were divided into two groups at random. In addition to standard urotherapy, group A also received pelvic floor and diaphragmatic breathing exercises, while group B only received standard urotherapy. Initial and final DVISS scores for the 12-month treatment period were recorded. Both before and after the treatment, uroflowmetry with pelvic floor electromyography were performed together with residual urine volumes measurement. The treatment outcome (non-, partial and full response) was defined according to the objective improvement in daytime and nighttime wetting, constipation, urinary infections and uroflowmetry findings. The cut-off values, sensitivity, and specificity of the pre-treatment DVISS score in predicting non/partial and full response in group A and B were determined using Receiver Operating Characteristic (ROC) curve analysis.

Results Pre-treatment DVISS score could not predict full response in both groups (the area under the ROC curve < 0.50) nor non-/ partial response in A group ($p = 0.127$). In B group, sensitivity and specificity of the initial DVISS score (cut-off value 9.5) in prediction of non-/partial response was 73.1% and 33.3%, respectively ($p = 0.043$).

Conclusion DVISS cannot be used in the treatment result prediction in DV.

Keywords: dysfunctional voiding; children; urotherapy; The Dysfunctional Voiding and Incontinence Scoring System; diaphragmatic breathing exercises; pelvic floor exercises

INTRODUCTION

Neurologically healthy children with dysfunctional voiding (DV) are described as having "an intermittent and/or fluctuating uroflow rate due to involuntary intermittent contractions of the striated muscle of the external urethral sphincter or pelvic floor during voiding" [1]. These patients have urination difficulties, and some of them may show urgent, frequent urination, daytime and nighttime wetting because of insufficient bladder emptying and the existence of residual urine (RU) after voiding [2]. Recurrent urinary tract infections (UTI), persistent constipation and vesicoureteral reflux (VUR) are strongly linked to DV [3].

In order to assess lower urinary tract symptoms (LUTS), bowel disorders, quality of life issues and behavioral problems in children with functional voiding problems, several scoring systems and questionnaires have been created [4–8]. Akbal et al. [6] examined the validity of the Dysfunctional Voiding and Incontinence Scoring System (DVISS), and found that a median score was significantly different in children with functional voiding problems in relation to the healthy population.

To our knowledge, there are no published studies that have explored the accuracy of the DVISS in children with DV. The purpose of this research was, therefore, to determine the accuracy of pre-treatment DVISS score in prediction of treatment results of two different urotherapy programs. Our hypothesis was that children who continued to manifest LUTS and abnormal voiding pattern after treatment (non- and partial responders) would have pre-treatment DVISS ≥ 9.5 (a cut-off score indicating the presence of voiding dysfunction).

METHODS

Study design

A prospective, controlled, and randomized clinical trial in children with DV was conducted at the Physical and Rehabilitation Medicine Clinic of the University Clinical Center. This study includes secondary analysis of data from

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1. Da li je Vaše dete mokro u toku dana?	Ne	Ponekad	1–2 puta dnevno	Uvek
	0	1	3	5
2. Koliko se Vaše dete umokri u toku dana?	Vlaži donji veš	Malo navlaži pantalone	Dosta navlaži pantalone	
	1	3	5	
3. Da li je Vaše dete mokro tokom noći?	Ne	1–2 noći nedeljno	3–5 noći nedeljno	6–7 noći nedeljno
	0	1	3	5
4. Koliko se Vaše dete umokri u toku noći?	Malo navlaži posteljinu kreveta		Dosta navlaži posteljinu kreveta	
	1		4	
5. Koliko puta Vaše dete mokri?	Manje od 7 puta dnevno		Više od 7 puta dnevno	
	0		1	
6. Moje dete se napreže tokom mokrenja.	Ne		Da	
	0		4	
7. Moje dete oseća bol prilikom mokrenja.	Ne		Da	
	0		1	
8. Moje dete mokri isprekidano.	Ne		Da	
	0		2	
9. Moje dete ima potrebu da ide da mokri ubrzo po završetku prethodnog mokrenja.	Ne		Da	
	0		2	
10. Moje dete ima iznenadan osećaj za potrebom da odmah mokri.	Ne		Da	
	0		1	
11. Moje dete zadržava mokrenje tako što prekrsti noge.	Ne		Da	
	0		2	
12. Moje dete se umokrava na putu ka toaletu.	Ne		Da	
	0		2	
13. Moje dete nema pražnjenje creva svaki dan.	Ne		Da	
	0		1	
14. Pitanje o kvalitetu života	Ne	Ponekad	Malo utiče	Mnogo utiče
Ukoliko Vaše dete ima neki od gore navedenih simptoma, da li to utiče na njegov porodični, socijalni i školski život?	0	1	2	3

Figure 1. Serbian version of the Dysfunctional Voiding and Incontinence Scoring System

a previously published randomized controlled clinical trial (registered with CinicalTrials.gov under the code NCT04981340).

After the inclusion criteria were met, parents were asked to complete the translated and culturally adapted DVISS [8] in the presence of their child at the Clinic (Figure 1). Randomization was carried out by a child drawing an envelope containing an assignment. All children (group A and B) received standard urotherapy, while group A additionally received pelvic floor muscle (PFM) retraining and diaphragmatic breathing exercises. Therapy in both groups was conducted at the Clinic during the first week (four visits); it was then continued at home until the subjective and objective improvements were accomplished.

All the children were followed 12 months after the beginning of the treatment, after which the DVISS was again completed at the Clinic. Scheduled clinic visits were arranged once a month.

Participants

Inclusion criteria were: age 5–18 years, met DV criteria established by the International Children's Continence Society (ICCS) [1] as well as unsuccessful prior therapy by primary care pediatricians for three months. All children were toilet trained with dry period lasting for six months. Parents provided written informed consent on study entrance. Exclusion criteria included neurological disorders, monosymptomatic nocturnal enuresis, cognitive disorders, the lower urinary tract structural anomalies and UTI verified four weeks before the study entry.

Interventions

Baseline evaluation included medical history, the DVISS, physical examination, a two day-daytime frequency and volume chart, a seven day-bladder and defecation diary, urine culture and urinalysis, ultrasonography of kidneys and bladder and uroflowmetry with pelvic floor electromyography and measurement of post-void RU. Uroflowmetry was performed twice when the child felt the need to urinate. Maximal flow rate (Qmax), average flow rate (Qavg), estimated Qmax, flow index (FI) Qmax, voided volume (VV), RU and total bladder capacity (TBC) (TBC = VV + RU) were obtained for every patient. Normal void included VV > 50 ml, TBC < 115% of age estimated bladder capacity (EBC) and RU < 20 ml [9]. EBC was calculated in milliliters using the following equation till the age of 12: 30 + (age in years × 30) [1]. After that age, it was assumed to be 390 ml. FI was calculated using the formula actual Qmax/estimated Qmax [9]. Male (plateau 0.659, bell 0.659–1.253, and tower > 1.253) and female (plateau 0.683, bell 0.683–1.071, and tower > 1.071) flow shapes were defined using the Qmax FI [9]. Fractionated uroflowmetry curves (staccato/interrupted) were determined according to the ICCS criteria [1].

Using the Rome IV criteria, functional constipation was identified [10]. All males underwent X-ray voiding cystourethrography to rule out structural abnormalities of the lower urinary tract, and all patients with recurrent UTIs underwent the procedure to detect VUR.

The research interventions (diaphragmatic breathing, PFM exercises, urotherapy, chronic constipation and recurrent UTIs management) have been previously described in detail [11]. The goal of diaphragmatic breathing exercises, relaxation of lower abdominal muscles, was explained to group A, after which exercises were performed in supine and sitting positions under the supervision of a physiotherapist. Following diaphragmatic breathing, pelvic floor exercises were introduced after a child learned how to recruit the PFM correctly without activating the accessory muscles. The emphasis was placed on a longer relaxation phase following a brief PFM contraction. Children were required to exercise every day during the course of the treatment under the supervision of their parents.

In both groups, standard urotherapy consisted of child's and parental education, regular voiding and fluid intake, as well as an optimal voiding position and pattern.

Constipation management

Child and parental education, toilet training, proper defecation position and pattern, and nutritional and drinking adjustments were all part of the treatment in both groups. During the treatment, laxatives (lactulose 1 ml/kg bodyweight daily in 1–3 doses) were given to achieve 1–2 milkshake-like stools per day.

Pharmacotherapy

Oxybutynin chloride (0.3 mg per kg body weight daily) was provided to all patients with reduced bladder capacity (maximum VV on a daytime frequency and volume chart < 65% of age EBC) [1] without RU. Desmopressin 0.2 mg oral formulation was prescribed in all patients with nocturnal urine production exceeding 130% of age EBC [1].

Antibiotic prophylaxis (nitrofurantoin in a nightly dose of 1ml per kg bodyweight) was given to children with symptomatic UTIs who had positive urine cultures on monthly assessments for three months.

The dysfunctional voiding and incontinence scoring system

This questionnaire consisted of 14 questions (Figure 1). Parents were asked to rate the frequency and severity of nighttime and daytime wetting while their child was present in the first four questions, and the subsequent eight questions required a yes or no response. With the exception of the final question regarding quality of life, each response was given a score. Total score ranged from 0 to 35. The Receiver Operating Characteristic (ROC) curve analysis was used in both groups to establish a cut-off score indicating the presence of voiding dysfunction (excluding quality of life score).

Follow-up

All children were re-evaluated on a monthly basis during the 12-month period at the Clinic by clinicians. With each clinic appointment, changes in LUTS were noted and the diaries and charts were analyzed. Both groups underwent uroflowmetry with pelvic floor electromyography and RU measurement.

On the last visit and one year after the start of the program, all the patients were re-evaluated. Their parents were asked to complete the final DVISS in the presence of their child at the Clinic. After that, uroflowmetry was performed twice and RU was measured immediately after urination using ultrasonography.

Treatment result evaluation

Treatment result was defined as full, partial and non-response according to the ICCS propositions [1]. The treatment outcome was determined as "full response" in children who were cured of daytime and nighttime wetting as well as UTIs; "partial response" when wetness and UTIs improved by more than 50%, and "non-response" when wetting and UTIs did not change. The term "full response" was used to refer to children who had constipation and had more than three defecations per week, two episodes of fecal soiling per month, and no abdominal cramps for more than a month.

Depending on whether a patient had a full, partial, or no response to treatment, each patient group was separated into three subgroups. For each subgroup of patients, the mean pre- and post-treatment score was determined and the values were compared in each group and between the A and B groups. Children in each group were divided into two subgroups in order to assess the sensitivity and

specificity of the baseline DVISS score in predicting treatment outcome. One subgroup consisted of children with full response (children who were cured), while the second consisted of children with partial and non-response (children who continued to manifest LUTS). The results of the treatment were contrasted with each patient's pre-treatment total scores.

Statistical methods

SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA) was used for all statistical research. While categorical variables are represented by absolute numbers and percentages, continuous variables are given as means and SD. The initial DVISS score's sensitivity and specificity in predicting non-/partial and full response in groups A and B were all determined using ROC curve analysis. To determine the significance of differences in continuous variables between the two independent groups, the Student's t-test for normally distributed data was applied. The Mann–Whitney U-test was used for non-normally distributed data. The significance of differences in continuous variables between two dependent groups was examined using paired sample t-test statistics for normally distributed data and a Wilcoxon signed-rank test for non-normally distributed data. To compare categorical variables between groups, Fisher's exact test and Pearson's χ^2 test were also used. In order to evaluate statistical significance, a p value < 0.05 was utilized.

This study was done in accord with standards of the institutional committee on ethics.

RESULTS

This trial included 86 children between 5 and 15 years old, with a 7.17 ± 2.52-year average. Due to non-attendance at scheduled appointments, 11 children in group B withdrew from the study. Treatment compliance was 100% in A group, and 66% in B group. There were 51 (68%) female patients among 75 children remained for the final analysis (Table 1). Out of 43 patients in group A, 65.12% were female, while in group B (32 patients), 71.88% were girls. Age and gender did not significantly differ between the groups. Children in group A had higher percentage of full responses (60.46%) than patients in group B (18.80%). Just one patient was a non-responder in group A compared to 17 (53.1%) in group B.

No statistically marked difference in mean scores between groups A and B for non-responders, partial responders, and complete responders were noticed at the beginning of the study (Table 2). Children with non-response in both groups had higher initial mean score compared to children with full response. This difference was statistically significant in group B (20.29 ± 10.51 *vs.* 10.00 ± 3.40) (p < 0.05). In both groups, post-treatment mean score as well as scores in group A children with full and partial response and group B children with non- and partial response were significantly lower compared to pre-treatment values.

Table 3 represents ROC curve analysis results. Initial DVISS score could not predict full response in both groups (AUC < 0.5). Using a cut-off value of 9.5 of the initial DVISS score, sensitivity was 88.2% and specificity 11.5% in prediction of non-/ partial response in A group (p = 0.127). Sensitivity and specificity of the initial DVISS score (cut-off value 9.5) in prediction of non-/partial response was 73.1% and 33.3%, respectively in group B patients (p = 0.043).

Table 1. The patients' characteristics

Patients' characteristics	Group A	Group B	p	Total
No. of patients	43	32		75
Mean age years (SD)	7.51 (2.49)	6.72 (2.53)	0.152	7.17 (2.52)
Gender female (%)	28 (65.12)	23 (71.88)	0.535	51 (68)
Pharmacotherapy				
Anticholinergics (No. of patients, %)	11 (25.58)	7 (21.87)	0.711	18 (24)
Desmopressin (No. of patients, %)	11 (25.58)	8 (25)	0.955	19 (25.33)
Antibiotic prophylaxis (No. of patients, %)	15 (34.88)	13 (40.62)	0.611	28 (37.33)
Vesicoureteral reflux (No. of patients, %)	4 (9.3)	5 (15.62)	0.484	9 (12)
Treatment outcome				
Non-response (No. of patients, %)	1 (2.33)	17 (53.1)	< 0.001	18 (24)
Partial response (No. of patients, %)	16 (37.21)	9 (28.19)		25 (33.33)
Full response (No. of patients, %)	26 (60.46)	6 (18.80)		32 (42.66)

Continuous variables are given as means and standard deviation and categorical variables as absolute number and in %; χ^2 test, Mann–Whitney test

Table 2. Comparison between treatment outcome and mean Dysfunctional Voiding and Incontinence Scoring System score

Outcome	Group A			Group B		
	Before therapy	After therapy	p	Before therapy	After therapy	p
Non-response	31	17	-	20.29 (10.51)*f	18.41 (10.80)	< 0.05
Partial response	18.25 (7.35)	6.87 (3.81)	< 0.001	16.77 (7.88)	11.88 (5.30)	< 0.05
Full response	14.80 (5.60)	1.96 (2.32)	< 0.001	10 (3.40)	6.50 (1.76)	0.083
Mean score	16.46 (6.78)	4.14 (4.26)	< 0.001	17.37 (9.50)	14.53 (9.45)	< 0.01

Data are given as mean value and standard deviation, paired sample t-test /Wilcoxon signed-rank test
* – p < 0.05 (Mann–Whitney test), ^{f} – *vs.* full response in Group B

Table 3. Receiver operating characteristic curve analysis results of the initial Dysfunctional Voiding and Incontinence Scoring System (DVISS) score and treatment outcome

Treatment outcome	AUC	Standard error	95% CI	Sensitivity	Specificity	p
GROUP A						
Initial DVISS score (cut-off value 9.5)						
Non-/partial response	0.639	0.090	0.462–0.816	0.882	0.115	0.127
Full response	0.361	0.090	0.184–0.538	0.885	0.118	0.127
GROUP B						
Initial DVISS score (cut-off value 9.5)						
Non-/partial response	0.768	0.087	0.598–0.940	0.731	0.333	0.043
Full response	0.231	0.087	0.060–0.402	0.667	0.269	0.043

AUC – area under the curve

Table 4. Clinical manifestations and uroflowmetry findings in 7/26 (26.92%) patients with pre-treatment score < 9.5 in Group B with partial and non-response to the treatment

Group B	Before treatment	After treatment	p
Patients No. (%)	7 (100)	7 (100)	1.000
Daily urinary incontinence	0 (0)	0 (0)	1.000
Nocturnal enuresis	0 (0)	0 (0)	1.000
Urinary tract infections	3 (42.9)	3 (42.9)	1.000
Constipation	2 (28.6)	1 (14.3)	0.515
Vesicoureteral reflux	2 (28.6)	2 (28.6)	1.000
Uroflowmetry parameters (mean ± SD)			
Voided volume (ml)	347.14 ± 127.28	298.71 ± 157.24	0.195
Qavg (ml/s)	10.51 ± 3.63	9.30 ± 7.02	0.416
Qmax (ml/s)	22.95 ± 14.68	23.58 ± 15.50	0.816
Estimated Qmax (ml/s)	21.48 ± 1.93	19.43 ± 1.75	0.058
Flow index Qmax	1.07 ± 0.72	1.18 ± 0.73	0.406
Post-void residual urine (ml)	24.14 ± 13.56	22.78 ± 16.60	0.655
Total bladder capacity (%/EBC)	168.91 ± 32.73	130.45 ± 29.93	0.029*
Fractionated uroflowmetry curve (No., %)	7 (100)	6 (85.71)	1.000
Bell-shaped (No., %)	0 (0)	0 (0)	1.000
Plateau-shaped (No., %)	0 (0)	1 (14.29)	1.000
Tower-shaped (No., %)	0 (0)	0 (0)	1.000

Fisher's exact test, paired sample t-test;
*p < 0.05;
Qavg – average flow rate; Qmax – maximal flow rate; EBC – estimated bladder capacity

In group B, 7/26 (26.92%) partial and non-responders with pre-treatment total score of less than 9.5 were evaluated (Table 4). These children did not manifest daytime and nighttime incontinence, 3/7 (42.90%) had UTIs, and 2/7 (28.60%) were constipated. They all had fractionated uroflowmetry curve, increased RU and TBC. Two children had VUR. After the treatment, only TBC was improved ($p < 0.05$).

DISCUSSION

This study has shown that only in 73.1% of group B patients with the initial DVISS score ≥ 9.5, non-/partial response could be correctly predicted.

In children with functional voiding disorders several scoring systems were developed to enable to establish a diagnosis based on clinical symptoms, as well as an assessment of the effectiveness of various therapeutic modalities [6, 12, 13, 14]. The first was published in 2000 by researchers in Toronto [12]. The Dysfunctional Voiding Scoring System (DVSS) is a modification of the scoring system used in adults with benign prostatic hyperplasia (International Prostate Symptom Score). In order to use the ICCS terminology, its name was changed to The Pediatric Lower Urinary Tract Scoring System [13]. Akbal et al. [6] examined the validity of the DVISS which was based on the scoring system used in 1992 in The International Reflux Study in Children. It has been shown that it can be used in everyday clinical practice as an objective scoring system in the diagnosis, treatment and monitoring of children with functional voiding disorders. The DVSS and the DVISS have been translated and adapted to Serbian language and their validity and reliability have been tested in Serbian children with voiding dysfunction [7, 8]. It has been shown that these scoring systems have high reliability and concurrent validity for assessing voiding dysfunction in Serbian pediatric population.

Altan et al. [15] investigated the diagnostic properties of three scoring systems (the DVSS, the DVISS and the Incontinence Symptom Index-Pediatric for children older than 11 years) and found that the DVISS had the highest accuracy in distinguishing the patients with various LUTS from healthy controls with an 81% sensitivity, 97.6% specificity and 89% accuracy.

Before the children entered the trial, oxybutynin and desmopressin were prescribed in nearly 50% of patients in both groups. In total, 11/43 (25.5%) children in group A and 8/32 (25%) children in group B were taking desmopressin due to nocturnal polyuria. The ratio of treated children did not differ significantly between the groups which goes to say that its impact on the treatment result in each group was almost the same. In a study by Hoebeke et al. [16], 50% of children with DV wet during the night while Jacobsen et al. [17] noticed nocturnal enuresis in 22/46 (48%) of children. In the last study, of eight children who became dry, three had taken desmopressin. It can be hypothesized that nocturnal polyuria, which is one of the main reasons for nocturnal enuresis, is linked to DV.

To our knowledge, there have been no data about DVISS accuracy in the evaluation of children with DV. Mean initial DVISS in our study was 17.01 which is comparable with the score in children with functional voiding disorders in other studies [6, 14, 18]. In both groups with children with non-response, mean pre-treatment score was higher than initial mean score in children with full and partial response although significantly only in group B. However, as we had only 18 patients with non-response, we cannot draw any final conclusion whether initial higher score would predict poorer treatment outcome.

After therapy, mean total score in group A as well as in the full response subgroup was significantly lower compared to initial values. Children with partial response had also significantly lower post-treatment DVISS score. These children improved daytime and nighttime wetting and therefore scored less on DVISS, but they continued to manifest UTIs and abnormal voiding pattern. In group B, mean post-treatment score, as well as scores in partial and non-responders were significantly lower compared to initial values although these children continued to have UTIs, increased RU and fractionated uroflowmetry curve. These findings can be partly explained by the subjective nature of the questionnaire. Children and their parents were receiving more attention by the clinicians as clinical visits were arranged once a month in both groups, and perhaps scored better on DVISS.

The role of the DVISS in prognosticating treatment effect in children with voiding disorders was explored by

Tuygun et al. [19]. A total score ≥ 9 marked the presence of voiding dysfunction. In the group with children who were wetting, the DVISS specificity in the full response prediction was 80%, while in the group of children with UTIs and wetting, it was 88%. In both groups the sensitivity was 100%. The authors concluded that in children with voiding disorders, the DVISS could be an additional diagnostic tool.

In our study, in group B, the sensitivity of 73.1% of the initial DVISS score ≥ 9.5 was achieved in the non-/partial response subgroup. This implies that only 73.1% of children who continued to manifest LUTS after treatment, had initial DVISS score ≥ 9.5. Almost 27% of children had initial DVISS score < 9.5. Therefore, we suggest the DVISS be used in the assessment of the treatment result and follow-up of children with DV only as an adjunct to more objective diagnostic procedures such are voiding and defecation diaries and charts, uroflowmetry and RU measurement.

We further analyzed initial LUTS and uroflowmetry parameters of 7/26 (26.9%) children in group B with non- and partial response who had initial score < 9.5. These children did not demonstrate wetting problems (daily urinary incontinence and nocturnal enuresis) and therefore scored less on questions regarding daytime and nighttime wetting (they scored zero points on first four questions). Their frequency of voiding during the day was low (less than four times but scored zero points on that question) and they complained of intermittency and/or straining during voiding (scored six points on questions six and eight). They were also postponing voiding (scored two points on question 11). Although their pre-treatment score was < 9.5, they had severe DV. They demonstrated staccato or interrupted uroflowmetry voiding pattern with increased PFM activity during voiding. This implies that some questions of the present DVISS should be differently scored, particularly the question five regarding the number of voiding per day (the score is zero if the frequency of voiding is less than seven times per day). Infrequent voiding is a relevant clinical finding which should be adequately scored. Besides, there was only one question on constipation but its severity and fecal incontinence were not assessed [20]. There is a need for re-evaluation of existing DVISS in children with DV.

The study's main restriction is the low number of participants in the subgroups which could have negative impact on statistical results. In this context, our findings should be supported by prospective, randomized, multicenter studies with larger study population.

CONCLUSIONS

In addition to traditional urotherapy, dysfunctional voiders whose regimen included diaphragmatic breathing and PFM exercises, had significantly more full response patients compared to children who had standard urotherapy as monotherapy. However, in both groups, mean post-treatment DVISS score as well as scores in group A children with full and partial response and group B children with non- and partial response were significantly lower compared to pre-treatment values.

Initial DVISS could not predict full response in both groups. Only in group B, initial DVISS score ≥ 9.5 could predict in 73.1% of patients non-/partial response to the treatment. Therefore, the DVISS cannot be used in the treatment outcome prediction in DV.

Conflict of interest: None declared.

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Да ли се Упитник о дисфункционалном мокрењу и уринарној инконтиненцији може користити у предвиђању резултата лечења деце са дисфункционалним мокрењем – рандомизовано испитивање

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САЖЕТАК

Увод/Циљ Упитник о дисфункционалном мокрењу и уринарној инконтиненцији креиран је да помогне у постављању дијагнозе функционалних поремећаја мокрења код деце на основу њихових клиничких симптома.
Међутим, његова улога у предвиђању исхода лечења код деце са дисфункционалним мокрењем није истражена.
Циљ рада је био да анализира да ли се на основу иницијалног Упитника о дисфункционалном мокрењу и уринарној инконтиненцији може предвидети резултат лечења у педијатријској популацији са дисфункционалним мокрењем.
Методе У једну од две групе насумично је распоређено 86 пацијената. Поред стандардне уротерапије, у групи А су примењиване вежбе релаксације мишића карличне пречаге и дијафрагмалног дисања, док је група Б имала само стандардну уротерапију. Упитник је попуњен на почетку (иницијални резултат) и на крају 12-месечног периода лечења. Урофлоуметрија са електромиографијом мишића карличне пречаге и ултразвучно мерење постмикционог урина вршени су пре и на крају третмана. Исход лечења (без одговора, парцијални и пун одговор) дефинисан је према објективном побољшању дневног и ноћног влажења веша, опстипације, уринарних инфекција и налаза урофлоуметрије. Анализом *ROC* криве одређиване су граничне вредности, сензитивност и специфичност иницијалног резултата Упитника о дисфункционалном мокрењу и уринарној инконтиненцији у предвиђању терапијског одговора у групи А и Б.
Резултати Иницијалним резултатом Упитника нису се могли предвидети риспондери у обе групе (површина испод криве < 0,50), као ни нон/парцијални риспондери у групи А (p = 0,127). У групи Б, сензитивност и специфичност иницијалног резултата Упитника (гранична вредност 9,5) у предвиђању нон/парцијалних риспондера износила је 73,1% и 33,3%, респективно (p = 0,043).
Закључак Упитник о дисфункционалном мокрењу и уринарној инконтиненцији не може се користити у предвиђању исхода лечења деце са дисфункционалним мокрењем.

Кључне речи: дисфункционално мокрење; деца; уротерапија; Упитник о дисфункционалном мокрењу и уринарној инконтиненцији; вежбе дијафрагмалног дисања; вежбе карличне пречаге

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The relationship between internet use and depressive symptoms among high school students

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SUMMARY

Introduction/Objective Problematic internet use has been associated with various mental health problems. The objective of this study was to investigate the internet use and its relationship with depressive symptoms among high school students.

Methods This cross-sectional observational study included 620 students from the first to the fourth grade of four high schools in Požarevac, Serbia. The research data were obtained from an *ad hoc* designed questionnaire on socio-demographic data, health habits, and the internet use, Internet Addiction Test (IAT) and Center for Epidemiological Studies Depression Scale for Children (CES-DC).

Results Out of 620 students (66.9% girls) there were 389 respondents (62.7%) who reported normal (n = 40), or average internet use (n = 349) with a mild level of addiction, while 226 (36.5%) subjects belonged to problematic internet use group, and five students (0.8%) showed a high level of internet addiction. A CES-DC score ≥ 15, considered indicative of clinically significant depressive symptoms, was found significantly more frequent among internet addicts compared to internet normal users (78.4% *vs.* 46.5%, respectively). Among internet addicts there was a significantly higher percentage of those who used psychologist/psychotherapist help compared to internet normal users (29.4% *vs.* 12.1%, respectively). The logistic regression analysis showed that internet addiction (IAT score ≥ 50) was the strongest independent predictor of clinically significant depressive symptoms (OR = 3.32; 95% CI = 2.24–4.91), after adjusting for confounders (female gender, urban living, Tik Tok and Twitter use, sports activities, and the use of the internet for learning or for aimless "surfing").

Conclusion We show that internet addiction is positively related to clinically significant depressive symptoms among high school students. Health education focused on the proper use of the internet may be regarded as mental health promotion.

Keywords: internet; behavior; addiction; depressive symptoms

INTRODUCTION

In recent years, over 40% of the world's population has gained access to the internet, and the use of mobile devices in this regard is increasing, especially the use of smartphones [1]. The portability of the internet through smartphones enables rapid access and widespread use of the global network [2]. According to the research of the Statistical Office of the Republic of Serbia for 2021 in Serbia, 81.2% of the population use the internet, 95.5% use a mobile phone, and 64% use a computer every day, or almost every day. Over 74% of the internet population have social media accounts [3].

Although life without the internet and its possibilities have become unimaginable, excessive use can also have harmful consequences [4]. It is very important to distinguish functional internet use that does not pose a significant health risk and is beneficial for most users, from an excessive, uncontrolled, and dysfunctional use, accompanied by preoccupation and the experience of loss of control. This attitude towards the internet can have various negative consequences, including neglecting social activities, communication, health, demands at work or school, as well as changes in eating and sleeping habits [1, 2].

The concept of internet addiction was originally introduced by an American author Kimberly Young [5] in the mid-90s of the 20th century. Young [5] described signs and symptoms like other psychological addictions that fit the definition of internet addiction later offered by Kuss and Griffiths [6]. They conceptualized internet addiction as a specific psychological addiction with similar signs as other psychological addictions such as loss of control, withdrawal symptoms, disruption of daily functioning, and loss of interest in other activities [6].

Numerous studies have examined the role of various psychological factors in the excessive use of the internet. Internet addiction has been positively associated with social isolation, but also with dissatisfaction with peer interactions. On the other hand, parental care and emotional support seem to provide protection against problematic internet use, while family dissatisfaction and lack of emotional support

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predict the emergence of internet addiction symptoms [7, 8]. Earlier research found a positive correlation between problematic internet use and depression [9]. Internet users find social and emotional support in the virtual world, and a sense of belonging while communicating online with other people [7]. Excessive internet use in children can lead to sedentary lifestyles and health problems such as obesity, poor posture, psychological issues and other health disorders and is also associated with attention deficit hyperactivity disorder and major depressive episodes [9–13].

In our opinion, there is not sufficient research to draw definitive conclusions about the connection between internet use and mental health of adolescents.

The aim of this study was to investigate the relationship between internet use and depressive symptoms among of high school students.

METHODS

This research was designed as a cross-sectional observational study, which included 620 students from the first to the fourth grade of four secondary schools in Požarevac, Serbia. The research included students of a Gymnasium, a Medical School, Economic and Commercial Schools, and an Agricultural School in Požarevac. The research instrument was an *ad hoc* designed questionnaire consisting of the following three parts.

1. Socio-demographic data, data on student school success, health habits, and data related to internet use [gender, age, place of residence (urban or semiurban), average mark, engaging in physical activity, consumption of psychoactive substances, average length of sleep, visit to a psychologist or psychiatrist, time spent on the internet, the purpose of using the internet, accounts on social networks].

2. The Internet Addiction Test (IAT), a reliable and valid test developed by Dr. Kimberly Young, is used to measure internet addiction. The test measures the level of internet addiction, consisting of 20 questions rated on a five-point Likert scale (1 = almost never, 2 = rarely, 3 = sometimes, 4 = often, 5 = almost always). The total score of the questionnaire has a range of 0–100 points and indicates four levels of internet use: normal level (0–30), average online use with a mild level of addiction (31–49), problematic use with a moderate level (50–79), and pathological, with a high level of internet addiction (80–100). A higher final score indicates more internet use and a higher level of addiction. A score ≥ 50 points indicates that the use of the internet creates problems in the normal social functioning of an individual [14, 15].

3. The Center for Epidemiological Studies Depression Scale for Children (CES-DC) is a 20-item self-report test used to quantify depressive symptoms in children and adolescents. The CES-DC is considered to have high reliability and validity for age groups between 12 and 18 years. In the CES-DC scoring system, each item has four possible responses: "not at all" = 0, "a little" = 1, "fairly" = 2, and "very much" = 3. Based on the scoring of all items, a final score can range 0–60. A higher score indicates a higher level of depressive symptoms. A score of 15 and above is considered indicative of clinically significant depressive symptoms [16].

All students voluntarily participated in the research. The research was conducted in accordance with ethical principles and with the informed consent of school leaders, school principals, class teachers, and students (we got written approval from the management of the four high schools). We previously gave verbal instructions for filling out the questionnaire. Completing the questionnaire took about 30 minutes.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). The parametric test used in this study is Student's t test. The non-parametric tests used in this study are Pearson's χ^2 test and Mantel–Haenszel χ^2 test for trend. Regression models with depressive symptoms as dependent and IAT adjusted for variables significant in the univariate model were tested by Nagelkerke's R^2.

RESULTS

There were 620 students who participated in the study, of which 415 (66.9%) were girls and 205 (33.1%) were boys. Based on the categorization of the IAT score, all respondents were divided into two groups: normal internet users (IAT score 0–49) without pronounced symptoms of addiction, and problematic and pathological users of the internet, i.e., with addictive behavior (IAT scores ≥ 50%). There were 40 respondents (6.5%) who reported normal use of the internet, 349 students (56.3%) belonged to average internet users with a mild level of addiction, while 226 (36.5%) reported problematic use of the internet and five students (0.8%) showed a high level of internet addiction.

Table 1 shows the distribution of respondents according to demographic characteristics. The average school achievement was significantly worse among students addicted to the internet compared to normal internet users (4.19 *vs.* 4.30, respectively). The percentage of students from urban areas among internet addicts was significantly higher than those from semiurban areas (64.1% *vs.* 35.9%, respectively). The distribution of internet addicts in relation to grade was different than expected in terms of a significantly lower percentage of fourth-graders in comparison to other grades, but, overall, the downward trend was not significant. Female students were more frequently addicted to the internet compared to males (borderline statistical significance), while age and type of high school were not significantly related to problematic internet use.

The largest percentage of students used a smartphone with internet access (96.1%), and 81.5% of students used a desktop computer or laptop with internet access. Only 0.2% of students declared that they did not have any of these devices and did not use the internet.

Table 1. Distribution of respondents per demographic characteristics

Characteristic		Subject groups in relation to IAT score						p
		Total		0–49		50–100		
		N	%	N	%	N	%	
Gender	Male	205	33.1	139	35.7	66	28.6	0.067[a]
	Female	415	66.9	250	64.3	165	71.4	
Place of living	Semiurban	270	43.5	187	48.1	83	35.9	0.003[a]
	Urban	350	56.5	202	51.9	148	64.1	
School	Gymnasium	135	21.8	92	23.7	43	18.6	0.394 [a]
	Medical High School	229	36.9	145	37.3	84	36.4	
	Economic and Commercial High School	166	26.8	98	25.2	68	29.4	
	Agricultural High School	90	14.5	54	13.9	36	15.6	
Grade	1	153	24.7	84	21.6	69	29.9	0.042[a] 0.070[b]
	2	207	33.4	139	35.7	68	29.4	
	3	193	31.1	118	30.3	75	32.5	
	4	67	10.8	48	12.3	19	8.2	
		AS	SD	AS	SD	AS	SD	
Age		16.12	1.06	16.18	1.07	16.02	1.03	0.071[c]
Average mark		4.26	0.64	4.30	0.64	4.19	0.64	0.027[c]

[a]Pearson's χ^2 test;
[b]Mantel–Henschel χ^2test for trend;
[c]Student's t-test

Table 2. Distribution of respondents in relation to time spent on the internet

Variables		Groups of respondents in relation to IAT score						p
		Total		0–49		50–100		
		n	%	n	%	n	%	
Hours spent browsing the internet for learning	0	28	4.5%	12	3.1%	16	6.9%	0.082
	1/2 h	102	16.5%	58	14.9%	44	19%	
	1/2 – 1 h	138	22.3%	87	22.4%	51	22.1%	
	1–2 h	201	32.4%	137	35.2%	64	27.7%	
	2–3 h	93	15%	60	15.4%	33	14.3%	
	3 h–4 h	32	5.2%	22	5.7%	10	4.3%	
	> 4 h	26	4.2%	13	3.3%	13	5.6%	
Hours a day spent on social networks	0	2	0.3%	1	0.3%	1	0.4%	< 0.001
	1/2 h	13	2.1%	10	2.6%	3	1.3%	
	1/2 – 1 h	24	3.9%	22	5.7%	2	0.9%	
	1–2 h	101	16.3%	87	22.4%	14	6.1%	
	2–3 h	148	23.9%	111	28.5%	37	16%	
	3–4 h	141	22.7%	80	20.6%	61	26.4%	
	> 4 h	191	30.8%	78	20.1%	113	48.9%	
Hours spent playing computer and video games	0	303	48.9%	214	55%	89	38.5%	0.001
	1/2 h	97	15.6%	51	13.1%	46	19.9%	
	1/2 – 1 h	42	6.8%	27	6.9%	15	6.5%	
	1–2 h	75	12.1%	46	11.8%	29	12.6%	
	2–3 h	33	5.3%	19	4.9%	14	6.1%	
	3–4 h	29	4.7%	14	3.6%	15	6.5%	
	> 4 h	41	6.6%	18	4.6%	23	10%	
Using the internet for learning	No	206	33.2%	103	26.5%	103	44.6%	< 0.001
	Yes	414	66.8%	286	73.5%	128	55.4%	
Using the internet for aimless "surfing"	No	411	66.3%	276	71%	135	58.4%	0.001
	Yes	209	33.7%	113	29%	96	41.6%	
Tik Tok	No	259	41.8%	196	50.4%	63	27.3%	< 0.001
	Yes	361	58.2%	193	49.6%	168	72.7%	
Twitter	No	457	73.7%	298	76.6%	159	68.8%	0.033
	Yes	163	26.3%	91	23.4%	72	31.2%	

Pearson's χ^2 test

Table 3. Distribution of respondents in relation to the need for professional help and the occurrence of depressive symptoms

Variables		Groups of respondents in relation to IAT score						p
		Total		0–49		50–100		
		N	%	N	%	N	%	
Help of psychologist/ psychotherapist	No	410	66.1	291	74.8	119	51.5	<0.001[a]
	Thinks about it	81	13.1	42	10.8	39	16.9	
	Used once	73	11.8	32	8.2	41	17.7	
	Used several times	42	6.8	15	3.9	27	11.7	
	Still use	14	2.3	9	2.3	5	2.2	
Help of psychiatrist-child psychiatrist	No	500	80.6	329	84.6	171	74.0	0.002[a]
	Thinks about it	18	2.9	5	1.3	13	5.6	
	Used once	74	11.9	43	11.1	31	13.4	
	Used several times	23	3.7	10	2.6	13	5.6	
	Still use	5	0.8	2	0.5	3	1.3	
CES DC score - depressive symptoms	No	258	41.6	208	53.5	50	21.6	< 0.001[b]
	Yes	362	58.4	181	46.5	181	78.4	

[a]Mann-Whitney U test
[b]Pearson's χ^2 test

Table 4. Logistic regression model with CES-DC total score of 15 and more as dependent variable

Variables	OR	95% CI		p
IAT score (≥ 50 = 1; < 50 = 0)	3.317	2.242	4.907	< 0.001
Place of living (Semiurban = 1; Urban = 2)	1.164	0.814	1.665	0.404
Gender (Male = 1; Female = 2)	2.075	1.408	3.058	0.000
Using the internet for learning (Yes = 1; No = 0)	0.611	0.413	0.902	0.013
Using the internet for aimless "surfing" (Yes = 1; No = 0)	1.224	0.839	1.788	0.294
Tik Tok (Yes = 1; No = 0)	1.639	1.121	2.395	0.011
Twitter (Yes = 1; No = 0)	1.091	0.710	1.676	0.691
Sport activities (Yes = 1; No = 0)	0.953	0.665	1.367	0.794
A constant	0.069			< 0.001

IAT – Internet Addiction Test; CES-DC – Center for Epidemiological Studies Depression Scale for Children;
Nagelkerke's $R^2 = 0.196$

The results of the analysis of distribution of internet addicts and normal internet users in relation to time spent on the internet and the purpose of use are shown in Table 2. A significantly higher percentage of internet addicts compared to normal internet users were spending more than four hours on the internet daily, particularly if the purpose of use was social networks (48.9% *vs.* 20.1%, respectively) and playing computer and video games (10% *vs.* 4.6%, respectively). Among the internet normal users there was a significantly higher percentage of those who did not play computer and video games compared to internet addicts (55% vs 38.5%, respectively). Using the internet for learning was significantly more frequent among internet non-addicts compared to internet addicts (73.5% *vs.* 55.4%, respectively), while aimless "surfing" was significantly more popular among internet problematic users compared to internet normal users (41.6% *vs.* 29%, respectively). Using Tik-Tok was significantly more frequent among internet addicts compared to internet normal users (72.7% *vs.* 49.6%, respectively) and a similar relation was found concerning Twitter use (31.2% *vs.* 23.4%, respectively).

Highly significant differences were observed between the examined groups regarding the need for professional psychological support (Table 3). Among internet addicts, there was a significantly higher percentage of those who sought psychologist/psychotherapist help compared to internet normal users (29.4% *vs.* 12.1%, respectively). There was also a significantly higher percentage of internet addicts who thought of, or used several times the help of a child psychiatrist, compared to internet normal users (11.2% *vs.* 3.9%).

According to the results from Table 3, a CES-DC score ≥ 15, considered indicative of clinically significant depressive symptoms, was found significantly more frequently among internet addicts compared to internet normal users (78.4% *vs.* 46.5%, respectively).

Table 4 shows the regression model with depressive symptoms as the dependent variable and adjusted for variables that were significant or borderline significant in the univariate model. The strongest independent predictor of clinically significant depressive symptoms was Internet Addiction (IAT) and it remained significant even after adjusting for variables on which the IAT categories differ significantly. Practically, the IAT score affects CES-DC total score itself, independently of other parameters that have a relationship with it. The other significant independent predictors of high CES-DC total score were female gender, use of internet for Tik Tok and for aimless "surfing."

The model was tested for multicollinearity using Variance Inflation Factor (VIF), and it was found that no VIF exceeded the value of 1.25 ($1/(1\text{-NagelkerkeR}^2) = 1/$

(1-0.196) = 1/0.804 = 1.244). Thus, we consider that the predictors are not mutually collinear and can be used together in the model.

DISCUSSION

According to our results, more than one-third of investigated students (36.5%) indicated problematic use of the internet and 0.8% showed a high level of internet addiction. An Italian study showed that 28% of high school students were highly dependent on the internet, which is close to our results [17]. According to the results of the latest meta-analysis that aimed to estimate the global prevalence of digital addiction in the general population, an increasing trend of digital addiction in the last two decades and a dramatic worsening during the COVID-19 pandemic were found [18]. In relation to the place of residence, students from urban areas were significantly more prone to internet addiction compared to those from semiurban areas, while the higher percentage of girls compared to boys was borderline significant – these results are similar to those in the research of Kuzmanović et al. [19], where a higher index of excessive internet use was recorded in girls. High school students use the internet for various purposes, learning, education, information, entertainment, playing games, communication, as well as for accessing social networks. Social networks are the most popular among young people and have become an indispensable part of their free time and entertainment [20]. According to our research, high school students mostly use the internet to access social networks (91.8%), which coincides with the results of research conducted in Serbia on a representative national sample of 1500 adolescents, 90% of whom access social networks daily [19].

When it comes to the time spent using the internet, significant differences were observed for searching the internet for social networks and playing games, where almost one-half of the respondents addicted to the internet were spending more than 4 hours daily on the internet. In current circumstances, when a good part of teaching and social life takes place via the internet, it is difficult to determine the criteria for normal or excessive use of the internet. In a study by Hinić [21], it is stated that most respondents who sought help for internet addiction spent more than 30 hours a week online, which would be four and a half hours a day. Although studies have shown that a time interval of two hours of internet use can precede addiction, and 6 hours of use is the main risk factor for internet addiction, recent studies indicate the importance of the time schedule in which the internet is used as a risk factor for internet addiction [22].

In our study, highly significant differences in the need for professional psychological support were observed among the examined groups regarding the extensivity of internet use. Malinauskas and Malinauskiene [23] point out that psychological interventions can help reduce the intensity of internet addiction by focusing on three main goals – reducing the hours of internet use, improving functioning in critical periods of life, and reducing exposure to harmful online content and activities. Also, the quality of parental care is a very important factor in protecting adolescents from mental health disorders and internet addiction [24]. Trumello et al. [24] point out that in the prevention of internet addiction, family interventions aimed at improving the parent–child relationship, improving communication, and understanding are also very important.

Symptoms of depression were significantly more present in the group of internet addicts compared to the comparison group. A regression model with depressive symptoms as a dependent variable adjusted for IAT variables that are significant in the univariate model shows that internet addiction remains a significant predictor. Excessive use of the internet and social networking platforms could weaken the bonds between individuals and their families, friends and loved ones. As a result, individuals may feel lonelier and more depressed [25]. Research conducted in Turkey on a population aged 12–18 years showed a positive relationship between daily internet use and social media addiction and depression [26]. In the same study, symptoms of depression were recorded in 28% of respondents, while in our study the prevalence was significantly higher (58.4%). The results of the study by Obeid et al. [27] show that a higher level of internet addiction is positively correlated with a higher degree of depression in adolescents aged 13–17 years.

The results of a study conducted by Sami et al. [28], on a sample of adolescents from Europe, revealed that pathological internet use is associated with various mental health problems, including depression and suicidal ideation. However, there are also studies showing that depression symptoms predict internet addiction, such that depressed individuals use their phones to cope with unpleasant emotions [29]. Moreover, lonely teenagers find it more difficult to make face-to-face contacts, which may increase their interest in online dating. Some studies indicate a two-way relationship between internet addiction and depression. People who are addicted to the internet tend to develop a depressed mood, while people suffering from depression are prone to excessive use of the internet and internet addiction [30].

Limitations of the study

This research was conducted in 2021 during the COVID-19 pandemic, when classes were mostly conducted online, with students spending more time on the internet, influencing the obtained results on the internet use. There was no insight into the medical documentation about the presence of any other diseases of the students that could be related to depression. We had no insight into the family history and no feedback from the psychologist about the students' visits. We also did not control family relations and parental care, as well as the socio-economic status of the students. We recommend an intervention study aiming at the effects of a positive change in the use of the internet on the students' mental health.

CONCLUSION

Based on the results of our research we can conclude that internet addiction is associated with clinically significant depressive symptoms in high school students. These results may be helpful in planning preventive measures against mental disorders among adolescents.

Conflict of interest: None declared.

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Повезаност коришћења интернета и симптома депресије код средњошколаца

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САЖЕТАК

Увод/Циљ Проблематично коришћење интернета повезано је са различитим проблемима менталног здравља.
Циљ овог истраживања је био да се испита употреба интернета и његова повезаност са симптомима депресије међу средњошколцима.

Методе Ова опсервациона студија пресека обухватила је 620 ученика од првог до четвртог разреда четири пожаревачке средње школе. Подаци истраживања су добијени из *ad hoc* дизајнираног упитника о социодемографским подацима, здравственим навикама и употреби и навикама везаним за интернет, теста зависности од интернета (*IAT*) и скале депресије за децу Центра за епидемиолошке студије (*CES-DC*).

Резултати Од 620 ученика (66,9% девојчица) било је 389 испитаника (62,7%) који су пријавили нормалну ($n = 40$) или просечну употребу интернета ($n = 349$) са благим степеном зависности, док 226 (36,5%) испитаника припада групи проблематичне употребе интернета, а пет ученика (0,8%) показало је висок степен зависности од интернета. *CES-DC* скор ≥ 15, који се сматра индикативним за клинички значајне симптоме депресије, био је значајно чешћи међу зависницима од интернета у поређењу са нормалним корисницима интернета (78,4% према 46,5%, респективно). Међу зависницима од интернета значајно је већи проценат оних који су користили помоћ психолога/психотерапеута у односу на нормалне кориснике интернета (29,4% према 12,1%, респективно). Логистичка регресиона анализа је показала да је најјачи независни предиктор клинички значајних симптома депресије зависност од интернета (*IAT* скор ≥ 50) (*OR* = 3,32; 95% *CI* = 2,24–4,91), после прилагођавања (женски пол, урбани живот, коришћење Тик Тока и Твитера, спортске активности и коришћење интернета за учење или за бесциљно „сурфовање").

Закључак Показали смо да је зависност од интернета позитивно повезана са клинички значајним симптомима депресије код средњошколаца. Здравствено образовање усмерено на правилно коришћење интернета може се сматрати промоцијом менталног здравља.

Кључне речи: интернет; понашање; зависност; симптоми депресије

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cardiac surgery intensive care unit nursing workload assessment using Nursing Activities Score

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SUMMARY

Introduction/Objective Nursing Activities Score (NAS) is one of the most accepted and widely used scores for assessing the workload of the nursing staff in regards of qualitative and quantitative adequacy. The aim of this study was to evaluate and analyze nursing workload in the cardiac surgery intensive care unit (CSICU) using the NAS in a contemporary set of patients undergoing heart surgery.

Methods The study included 809 consecutive patients who had a major cardiac surgery in 2019 admitted to adult CSICU. Demographic data were collected from medical records [sex, age, type of treatment, length of stay (LOS), and discharge], EuroSCORE II, and NAS value.

Results The majority of patients underwent a coronary (43.1%), valvular (32.6%), and combined (24.2%) cardiac surgery procedure. The average patient LOS in CSICU was 2.5 ± 3.4 days. The average NAS value in our sample was 100.8% ± 63.1%. NAS value during the first operative day was a poor marker of the outcome in terms of mortality (C-index 0.520, 95% CI – 0.422–0.617, p = 0.676). Significant difference was observed in terms of average NAS value between the patients submitted to coronary surgery and combined surgery (p = 0.001). NAS has been shown to be useful for assessing activity in a CSICU, confirming the optimal workload of nurses, while higher NAS values in our hospital indicate increased workload compared to similar institutions.

Conclusion NAS provided viable information regarding the care and hospitalization of patients in a CSICU. In accordance with NAS, the optimal level of nursing workload was established in our hospital settings.

Keywords: intensive care unit; nursing workload; cardiac surgery; length of stay

INTRODUCTION

The complexity of modern cardiac surgery procedures is constantly increasing as well as technological influence in the field. Typical patient profile went through a dramatic change over the last decade [1]. Admitted patients showed a substantial increase in the average age and severity of illness. Concurrently, it became clear that, more than ever, intensive postoperative care has a vital role on the outcome of the treatment. A modern cardiac surgery intensive care unit (CSICU) requires personnel with a sophisticated level of education and training in order to comply with ever-increasing demands and increased patient expectations [2]. A significant bourdon of related activities has been put up on nursing personnel, creating challenges.

Nursing workload is significantly affected by nurse staffing ratio, so the number of nursing personnel in the CSICU has to be customized most importantly to satisfy patients' nursing assistance needs and patient outcomes, and the economic aspect of hospital care should also be taken into consideration [3, 4]. Higher nursing workload and lower nurse staffing are associated with higher patient safety risk, particularly with in-hospital mortality [5, 6].

Data recording, collection and analysis are crucial elements in assessing and improving the quality of the provided service and proper surgical ruling in modern cardiac surgery practice [7]. Assessment of the nursing workload is an effective tool for evaluating the time put into patient care, the optimal nurse-to-patient ratio, as well as the required nurses' educational qualifications levels [8, 9].

One of the most accepted and widely used scores is the Nursing Activities Score (NAS), published in 2003 [10]. The NAS increments measure the nursing care activities time required by patients admitted to the ICU. NAS represents a computed percentage of nursing staff's time (over 24-hour period) spent on the execution of activities included in the instrument. NAS score comprises seven categories or domains (basic nursing activities, ventilator support, cardiovascular support, kidney support, neurological support, metabolic support, and specific interventions), which are split into subdomains and further into their items, in a total of 23 [10, 11]. Many intensive care units (ICUs) use NAS daily to determine and monitor the nursing workload [12, 13, 14].

The primary objective of this study was to evaluate and analyze the nursing workload in

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CSICU using NAS in a present-day set of patients who underwent heart surgery.

METHODS

This study was carried out as a prospective study using medical records of the Institute for Cardiovascular Diseases of Vojvodina, Serbia, between January 1, 2019 and October 30, 2019. The included patients exclusively underwent

- isolated coronary surgery (coronary artery bypass grafting and off-pump coronary artery bypass),
- isolated valvular surgery (mitral, aortic, and tricuspid surgery, with prosthetic replacements or repairs, through traditional or minimally invasive techniques),
- combined coronary and valvular surgery,

with the length of stay (LOS) in the CSICU ≥ 8 hours. No matter the priority level, all data were included (elective, urgent, emergency, salvage). The study was approved by the Institutional Review Board of the Institute for Cardiovascular Diseases of Vojvodina.

All data were collected from medical records, i.e., from the hospital information system (BIS), which is updated on a daily basis (sex, age, type of surgery, LOS, EuroSCORE II and discharge, mortality, NAS values, etc.). The data is used for statistical and research purposes. Euroscore II value was calculated a day prior to surgery according to general recommendations [15].

All data were collected only by the nursing staff who had experience with using NAS. During their stay in CSICU, the patients were scored daily with the NAS system. As proposed by Miranda et al. [10], 24-hour NAS was used in the description of nursing workload of a patient in any shift. The NAS was compiled at 6 a.m., reporting the previous 24 hours. The sum of the 23 items ranges 0–177% and according to Miranda et al. [10], an ideal score that a nurse can accomplish per shift in a 24-hour period is the NAS score of 100%. As an example: two patients who have the score of 50% each spent the work of one full-time equivalent per shift around the clock. Analogously, in an ICU, if a total of 350 points has been scored in one day, this unit used the work of 3.5 nursing fulltime equivalents per shift on that day.

The distribution of the quantitative data was estimated using the Kolmogorov–Smirnov test. Categorical variables (expressed as frequencies) were compared between the two groups using the Pearson χ^2 test or the Fisher exact test. Continuous variables (expressed as mean ± standard deviation) were compared between the groups using the Student's t-test if their distribution was normal, or using the Wilcoxon rank-sum test if their distribution was non-normal. Univariate and multivariate logistic regression, including the odds ratio (OR), were utilized in order to estimate the effects of the independent variables on the dependent one. As for the p-value of the performed tests, the value of 0.05 was used as the threshold for statistical significance.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA) and MedCalc for Windows, Version 12.2.1 (MedCalc Software, Mariakerke, Belgium).

The study was approved by the Ethics Committee of the Institute for Cardiovascular Diseases of Vojvodina in Sremska Kamenica (decision no. 3055/1-8).

RESULTS

This study was performed on the total of 809 patients. The patients' mean age was 65.6 ± 8.5 years. Two-thirds of patients were male. Most of the patients underwent coronary (43.1%), valvular (32.6%), and combined (24.2%) cardiac surgery. The average patient LOS in CSICU was 2.5 ± 3.4 days. The distributions of the demographic data and principal operative-related factors of the study population are shown in Tables 1 and 2.

Table 1. Demographic data, preoperative patient profile, and surgery outcomes

Demographic data	Frequency, n	%
Sex		
female	270	33.4%
male	539	66.6%
Type of surgery		
coronary	349	43.1%
valvular	264	32.6%
combined	196	24.2%
PAOD	18	2.2%
Congestive heart failure	148	18.3%
COPD	97	12%
Previous MI < 6 weeks	50	6.2%
Smoking	372	46%
Diabetes mellitus	251	31%
Previous cardiac surgery	21	2.6%
Chronic renal failure	39	4.8%
Postoperative complications	35	4.3%
Hospital mortality	40	4.9%

PAOD – peripheral arterial occlusive disease; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction

Table 2. Patient profile and scoring systems

Parameter	Mean	SD
Age (years)	65.6	8.5
Body mass index (kg/m^2)	28.1	2.7
EF (%)	53.9	7.2
Ventilator time (hours)	14.2	6.8
Time in CSICU (days)	2.5	3.4
EuroSCORE II (%)	2.3	2.6
NAS (%)	100.8	63.1

EF – ejection fraction; CSICU – cardiac surgery intensive care unit; NAS – Nursing Activities Score

The general in-hospital mortality was 4.9%. Refractory cardiovascular failure was determined to be the principal cause of death among our study patients (42.5%). Other fatal causes were multiple systems organ failure (27.5%), sepsis (12.5%), acute cardiac arrest (7.5%), pulmonary

failure (7.5%), and chronic renal insufficiency (2.5%). Additionally, the average CSICU LOS for the patients who expired was 11 days with the average NAS of 160%. The average EuroSCORE II value for the patients with in-hospital mortality was 5.92%. The relation between the LOS in the CSICU and the value of nursing engagement assessed through NAS is shown in Figure 1.

Binary logistic regression analysis was used and only EuroSCORE II value and CSICU LOS emerged as autonomous predictors of in-hospital mortality [OR 1.461, 95% confidence interval (CI) – 1.311–1.627, $p < 0.001$ and OR 1.357, 95% CI – 1.269-1.441, $p < 0.001$, respectively]. NAS was not designated as a predictor of an in-hospital mortality. We also wanted to investigate whether it was possible to predict the outcome of the treatment based on the value of NAS during the first postoperative day. C-index statistics showed that the value of NAS during the first operative day was a poor marker of the outcome in terms of mortality (C-index 0.520, 95% CI – 0.422–0.617, $p = 0.676$).

Substantial difference was observed in terms of average NAS value between the patients submitted to coronary surgery and combined surgery (ANOVA F-ratio 7.038, $p = 0.001$), Figure 2. No such difference was observed between various age groups (ANOVA F-ratio 0.938, $p = 0.455$), Figure 3.

In regard to the structure of the nursing staff of our nine-bed CSICU, the workforce consisted of 19 registered nurses. Every one of them (100%) had a bachelor's degree and three (15.8%) had a master's degree. No significant fluctuations in nursing workload were observed during the period, suggesting effective resource allocation and planning.

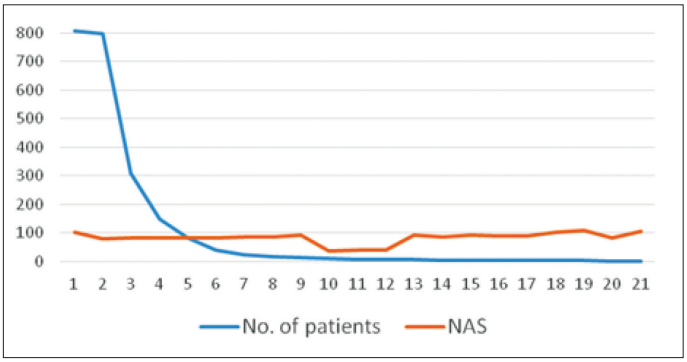

Figure 1. Correlation between the length of stay in a cardiac surgery intensive care unit (CSICU) and the level of nurse engagement assessed through Nursing Activities Score (NAS); there is a slight increase of NAS for the patients with prolonged CSICU stay

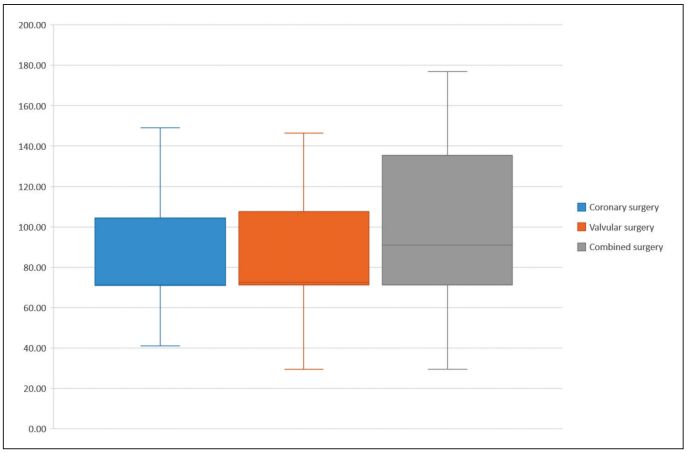

Figure 2. Box plot of Nursing Activities Score values according to the type of surgery; significant difference was found between coronary surgery and combined surgery ($p = 0.001$)

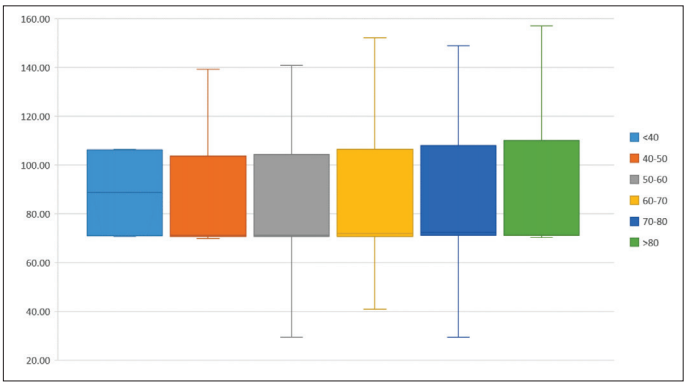

Figure 3. Box plot of Nursing Activities Score values according to different age groups; no significant difference was observed ($p = 0.455$)

DISCUSSION

Planning and organization of the nursing staff and their work processes in order to ensure high quality care has been influenced by constant transformations and improvements in the routine of healthcare practices, especially in hospital settings. Evaluation of the nursing workload is the most essential for ensuring enough staff in the critical care units [9, 16].

A study by Ferreira et al. [17] summarized 18 studies examining the effect of NAS in predicting nursing workload in various ICU conditions. The majority of analyzed hospitals were Brazilian hospitals. The study showed that the average NAS was in range from 50.4% in a Spanish hospital to 104% in a Brazilian hospital. About 60% of the studies examined in the study had an average NAS of 60–70% (the overall average of 65.5%). In only a few studies NAS has been used for measuring nursing workload in CSICUs.

Researchers in Belgium conducted a study to assess nurse workload, in 16 Belgian hospitals, where the mean NAS was 68.6% [18]. In addition, they confirmed the reliability of the NAS application in their hospitals and found that the NAS is a valid instrument that allows reliable assessment of nursing workload. A study done by Velozo et al. [8] showed that the NAS instrument was the best instrument for workload evaluation, estimating the total average working time closer to the recommended for care. Mean NAS values were measured for a total of 4617 observations, which was 56.7 ± 12.5; median 55 (25.3–142.9), also analysed NAS values in 490 patients at admission whose mean value was 62.6 ± 17.3, median 60.1 (33.6–142.9), while the maximum mean value during hospitalization was 67.7 ± 19.7, median 65.6 (33.6–142.9).

A systematic review published by Iranian authors (comprising 23 articles originated from Brazil, Belgium, Greece, Italy, Norway and Spain) reported the following findings:

minimal NAS was 36.1% calculated in the study conducted on 106 patients in Greece, while the highest established NAS was 109.3% in the study involving 285 Iranian patients [13]; in a Norwegian study, the average NAS value was 96.24% ± 22.35. The average NAS value in our sample was 100.8% ± 63.1%, which is higher in comparison with the values in the above-mentioned countries, except those in Iran and Norway [13].

The results of a Brazilian study exploring the workload in the postoperative period of heart surgery in a CSICU of a university hospital showed a higher mean daily NAS (74.62%) and 96.79% in the first postoperative day [19]. In a Portuguese retrospective observational study, the average workload of nurses per patient admitted to intensive care was 67.52 ± 10.91 NAS points, while on the first day of stay it was on average higher by 19.36 ± 2.61, i.e., 80.52 ± 10.89 [20]. In an integrating review conducted by Nobre et al. [12], it was reported that in three CSICUs the minimum NAS score was 58.1 and maximum is 66.36.

Comparing different ICU units, the results of the study by Ko and Park [9] revealed that the nursing workload was the highest in the surgical unit, followed by internal medicine and comprehensive nursing units. Riklikiene et al. [16] in their research came to the conclusion that when planning the operative program and the optimal number of nurses in the postoperative period in intensive care after cardiothoracic surgery, it is necessary to take into account the type of surgery as a factor that affects the workload of nurses. An important finding coming from our study is that the average NAS value for the patients submitted to combined surgery (coronary + valvular) is compellingly higher compared to the value of the patients submitted to coronary surgery (105% *vs*. 88%, p = 0.001). This finding can be explained by the fact that combined surgery patients are usually associated with more comorbid conditions demanding increased postoperative care.

An extensive retrospective Italian study analyzed the application of the NAS in three different ICUs (CICU: Cardiothoracic Intensive Care Unit; GICU: General Intensive Care Unit; and Neuro ICU: Neurosurgical Intensive Care Unit) during a six-year period [11]. The study results were as follows: the mean NAS for all the patients was 65.97% ± 2.53, GICU 72.55% ± 16.28, Neuro ICU 59.33% ± 6.54, CICU 63.51% ± 14.69. The average LOS was 4.82 ± 8.68 days.

Our mean NAS is also close to Norwegian NAS score published in a multicentric study conducted in seven countries in which variations in NAS mean values in range from 44.5 in Spain to 101.8 % in Norway were identified. In the total sample of the studies analyzed by Padilha et al. [14], the mean NAS was 72.8%, the mean age was 63.5 years, the mean LOS was 4.4 days, and the mortality rate was 8.2%.

In a Brazilian study conducted in three organizational units in an ICU over a period of four months, the average NAS was 71.7% ± 10.4 (min 48.2%; max 109.1%), LOS 9.2 ± 13.3 days, and average age 56.8 ± 18.5 years [21]. NAS presented a negative correlation with LOS (-0.23). There was no significant correlation between age and nurse workload p = 0.070.

In our study, the average patient LOS in CSICU was 2.5 ± 3.4 days. There is a slight increase of NAS for the patients with prolonged stay in CSICU. The patients' mean age was 65.6 ± 8.5 years with two-thirds of patients being of male sex. There is no significant difference in NAS values (p = 0.455) related to age groups. Similarly, in the study done by Ferretti et al. [22], it was reported that even though the care of older patients was associated with an increase in nursing workload, the ageing itself was not a sufficient predictor of NAS (p = 0.005).

Ricci de Araújo et al. [23] wanted to estimate the intensive care costs of a Brazilian hospital and one of the parameters used for this purpose was the actual hours of nursing care estimated based on the results of the nursing activities of the NAS, median 88 (54–107). They came to the conclusion that costs were underestimated in patients who needed a higher intensity of care (NAS > 100). In his study Bruyneel et al. [24] showed a strong correlation between the NAS and costs in the ICU. Another study by the same author conducted in Belgium showed that the optimal number of nurses should be twice the number provided for in the legislation [18]. The results of a number of studies also show that the number of nurses per patient calculated by the NAS system is (often) higher than foreseen in the relevant legislation [9]. Our results showed that the nurse-to-patient ratio was slightly above 1 (mean NAS 100.8), indicating an almost ideal engagement of the nursing staff and/or proper competency in nursing activities, showing sufficient and adequate nursing workforce.

Greek authors in their study carried out on 313 consecutive CSICU patients identified the risks affecting elevated in-hospital mortality in patients who underwent cardiac surgery [25]. The study showed that the risk of in-hospital mortality was nearly 3.3 times higher (OR 3.3, 95% CI 1.4–8) in patients who had high value of NAS on the first postoperative day. Similarly, research carried out by Padilha et al. [26] showed that patients who died while hospitalized in an ICU had 2.65 times higher NAS then other ICU patients. In a systematic review that included six studies with a total of 175,755 intensive care and/or cardiac/cardiothoracic units' patients it was found that every increase in one nurse decreases the probability of dying in hospital by 14% [27].

In our study, the general in-hospital mortality was 4.9%. NAS was not designated as a predictor of in-hospital mortality and only EuroSCORE II value and CSICU LOS emerged as autonomous in-hospital mortality predictors. We also wanted to investigate if it were possible to predict the outcome of the treatment based on the value of NAS during the first postoperative day. Our results did not show an association between the first day NAS value and the outcome of the treatment in terms of mortality.

Our study contributes to the science of assessment of nursing workload in ICUs. The unique contribution is the comprehensive approach to understanding of the NAS as a tool that can supply information regarding the process of caring for patients that are hospitalized in a CSICU as well as the nursing workload in the same settings. Nevertheless, we agree with most of the authors who

concluded that large differences between nursing workload among countries could be a consequence of various nurse-to-patient ratio on a shift-by-shift basis, patients' characteristics, and type and regulations of care and treatment services in the countries. What is clear from most of the studies is that nurse workload in the ICU is high and that average number of nursing staff calculated by NAS is higher than the average number of nursing staff stipulated by country legislation. The average NAS value varies significantly not only between different countries and populations for the same type of ICU but also within the same country. NAS value summarizes the overall settings in which the patient is treated, including the following: 1 – patient profile (the presence of comorbidities requiring increased postoperative nursing care); 2 – institution profile and its unit's structure and organization; and 3 – available nursing workforce, and its effective management as a component of the effectiveness of the health care [5, 12, 13, 21].

Study limitations

We acknowledge that our study has potential limitations: it was performed in a single-center and in a single ICU, hence our data can be associated with site-inherent limitations and site-specific biases. Caution must be used in extrapolating the results of our study to other centers with similar settings.

CONCLUSION

In conclusion, the NAS tool provided useful information regarding the process of caring for patients hospitalized in a CSICU; by applying it in our study, it was confirmed that there was the optimal level of nursing workload in our CSICU. Patients treated in our CSICU had a higher average NAS value compared to other similar hospitals, indicating greater nursing workload in our settings. No significant fluctuations in nursing workload were observed during the period, suggesting effective resource allocation and planning. The application of the NAS instrument for measuring the nursing workload can assist us in planning the size of the required nursing staff in our CSICU to ensure high quality patient care and to improve patient outcomes.

However, given that the NAS system is a new instrument for assessing workload and was used for the first time in our institution, research should be extended to more cardiac surgery centers in the country and the surrounding area for a better assessment of its performance.

Conflict of interests: None declared.

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Процена радног оптерећења медицинских сестара у кардиохируршкој јединици интензивне неге помоћу Бодовног система активности медицинских сестара (*NAS*)

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САЖЕТАК

Увод/Циљ Бодовни систем активности медицинских сестара (*Nursing Activities Score – NAS*) један је од најприхваћенијих и најшире коришћених система који се користе за процену радног оптерећења медицинског особља у погледу квалитативне и квантитативне адекватности.

Циљ рада је био да се применом система *NAS* процени и анализира оптерећење медицинских сестара у кардиохируршкој јединици интензивне неге у групи болесника после кардиохируршке операције.

Методе Студија је обухватила 809 болесника који су смештени у јединицу интензивне неге после кардиохируршке операције у току 2019. године. Демографски подаци су прикупљени из медицинске документације (пол, старост, врста лечења, дужина боравка и отпуста) и *NAS*.

Резиултати Највећи број болесника био је подвргнут коронарној (43,1%), затим валвуларној (32,6%) и комбинованој хирургији (24,2%). Просечна дужина боравка у јединици интензивне неге била је 2,5 ± 3,4 дана. Средња вредност *NAS* у узорку износила је 100,8 ± 63,1. Вредност *NAS* током првог постоперативног дана била је лош маркер исхода у погледу морталитета (*C*-индекс 0,520, 95% *CI* – 0,422–0,617, $p = 0,676$). Уочена је значајна разлика у погледу просечне вредности *NAS* између болесника подвргнутих коронарној хирургији и комбинованој хирургији ($p = 0,001$). *NAS* се показао корисним за процену активности после кардиохируршке операције у јединици интензивне неге, потврђујући оптимално оптерећење медицинских сестара, док веће вредности *NAS* у нашој болници указују на повећано оптерећење у поређењу са сличним установама.

Закључак *NAS* је пружио одрживе информације о нези и хоспитализацији болесника у кардиохируршкој јединици интензивног лечења. У нашим болничким условима успостављено је оптимално оптерећење медицинских сестара.

Кључне речи: јединица интензивног лечења; радно оптерећење; кардиохирургија; дужина боравка

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The first human case of multilocular echinococcosis recognized in Serbia

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SUMMARY

Introduction *Echinococcus multilocularis* causes multilocular or alveolar echinococcosis, which differs from infection caused by *Echinococcus granulosus* in clinical presentation in humans. The most common definitive hosts for *E. multilocularis* are foxes and jackals, while domestic mammals like dogs and cats are rare. Humans are rare and accidental intermediate hosts. Cystic echinococcosis in humans is endemic in Serbia, while more severe alveolar echinococcosis has not yet been recorded.

Case outline We present a case of a 67-year-old female from a small village in the Sremska Mitrovica municipality. The onset of symptoms was several years ago, with liver pain which progressed over time. Differential diagnoses included benign liver tumors like haemangioma, cystic echinococcosis and abscess formed in the cystic echinococcal lesion. Left lateral hepatectomy was performed, and S II/III liver segments were removed. Pathological examination showed numerous small empty vesicle spaces with chitin membrane without protoscolices, surrounded by massive fibrosis and infiltrative growth into the liver parenchyma, all indicative marks of multilocular echinococcosis. Surgical margins were found positive for echinococcal vesicles showing that echinococcal tissue was not completely removed. Thus albendazole therapy was introduced. Epidemiological interview revealed that the patient lived in an endemic region of multilocular echinococcosis, in a house with two hunting dogs and backyard where contamination of soil with fox feces could occur.

Conclusion This is the first case of human multilocular echinococcosis recorded in Serbia, which should alert the medical community to improve prophylactic and diagnostic procedures and surgical techniques to better manage this zoonotic disease.

Keywords: *Echinococcus multilocularis*; human case; Serbia; Srem region; Mačva region; Vojvodina Province

INTRODUCTION

Echinococcosis is a well-known, often devastating parasitic disease in humans, which also has a great economic impact for livestock production all over the world. More than a milion people are actually infected each year, as reported by the WHO in 2021.

The *Echinococcus* genus involves small taeniid cestodes, with *E. granulosus* and *E. multilocularis* as the two main species. Currently, only *E. granulosus (sensu lato)* is endemic in Serbia, with two variants, *E. granulosus sensu stricto* and *E. canadensis*, causing well-known cystic echinococcosis in humans [1, 2]. Human infection occurs through direct or indirect contact with dogs that carry adult cestodes in their small intestine. Echinococcal cysts in humans, larval stage or metacestode, are primarily localized in the liver but can also be found in other organs, including the brain and bones. Their growing pattern is expansive, but surgical enucleation is possible.

The adult form of *E. multilocularis* lives in the small intestine of carnivores, primarily foxes and jackals. In intermediate hosts (wild rodents such as voles or field mice), this cestode produces numerous small cystic formations, primarily in the liver, representing larval forms filled with protoscolices. In humans, who are not natural hosts, cysts are also primarily localized in the liver but usually remain sterile, not containing protoscolices. Multilocular echinococcosis in humans is dangerous because parasitic cysts grow infiltratively into the liver, resembling malignant tumors, and can metastasize into surrounding tissues and other organs including the brain.

The first report of multilocular echinococcosis in Serbia was in an animal, a beaver from Zasavica, the Special Nature Reserve near the Srem region of the Province of Vojvodina, which is its northern part between the Sava and the Danube rivers [3]. The beaver, being an intermediate host, had a liver lesion, and the dilemma was whether it was a natural local infection or it was imported from Germany, from where the beaver was brought into the Zasavica Reserve. Recently, the Srem region in Serbia was identified as endemic for wild animal multilocular echinococcosis. In this region, 17.9% of foxes and 14.3% of jackals were

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registered as infected with the intestinal adult form of *E. multilocularis* [4]. Interestingly, a recent paper from Serbia reported a larval form of *E. multilocularis* in the liver of a golden jackal, showing the jackal can be both a definitive and intermediate host [5].

Since no cases of human multilocular echinococcosis have previously been reported in Serbia, clinical recognition of this disease is a most important issue. We here report the first case of human multilocular echinococcosis in Serbia.

CASE REPORT

We present a case of a 67-year-old female patient with upper abdominal symptoms that started a few years earlier, with weakness and gastritis, and a hiatal hernia. Three years prior to operation, the patient had an episode of collapse, and a subsequent medical examination revealed a liver lesion, which progressively worsened with liver pain. Benign liver tumors such as hemangioma, cystic echinococcosis, and abscess in a cystic echinococcal lesion were included in the differential diagnosis. Blood tests showed mild anemia, erythrocyte sedimentation of 16–20 mm, and no eosinophilia. Immunological markers characteristic of liver tumours such as carcinoembryonic antigen, alpha-fetoprotein and carbohydrate antigen 19-9 were whitin normal limits, as was serology for echinococcosis. Before the operation, pulmonary and cardiac functions were normal. Liver segments S II /III were removed by left lateral hepatectomy.

The specimen received for pathological analysis was a resected liver fragment, 11 × 6.5 × 5.2 cm in size (Figure 1). Capsular surface was thin, slightly uneven and glistening. The surgical margin was coloured green. On a cross-section, one larger (5.3 × 5 × 3.3 cm) and a few smaller cystic cavities were present in the centre of the liver fragment. Cavities contained yellowish, thick and pasty material, and their inner surface was thickened and rugged. The remainder of the liver parenchyma was brown and homogeneous. Pathological examination clearly showed multilocular echinococcosis with numerous small empty vesicle spaces with chitin membrane without protoscolices, surrounded by massive fibrosis and infiltrative growth into the liver parenchyma. Surgical margins were found positive for echinococcal vesicles (Figure 2) showing that echinococcal tissue was not completely removed. Thus albendazole therapy was introduced.

Epidemiological interview revealed that the patient lived in the endemic region for multilocular echinococcosis, in the village Radenković (coordinate: 44° 55′ 16.8″ N, 19° 29′ 21.6″ E) in the municipality of Sremska Mitrovica, Vojvodina Province (Figure 3), in a house with two hunting dogs, and backyard where contamination of soil with fox feces is possible.

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.

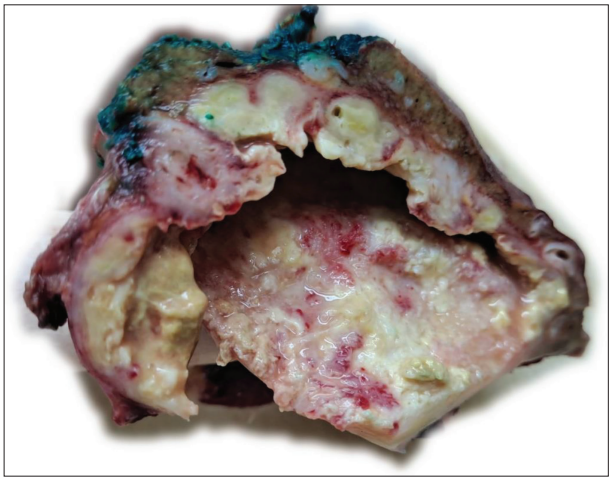

Figure 1. Liver resection with uneven central cavitation, macroscopic view

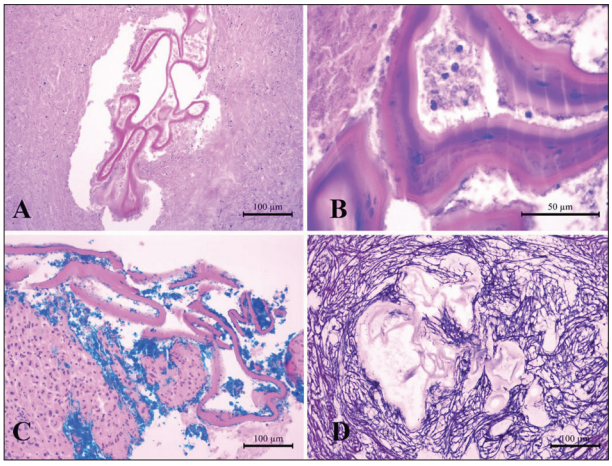

Figure 2. Pathohistology of the liver lesion: A – uneven shapes of echinococcal membranes; B – layered membrane structure; C – membrane on the resection margin, stained with green ink; D – extensive fibrosis around alveolar membranes, reticulin stain (A, B, C – hematoxylin-eosin; D – Gordon and Sweet's silver staining)

Figure 3. Village Radenković in Sremska Mitrovica municipality near Zasavica Reserve, where a beaver infected with *E. multilocularis* was found ten years earlier [from Wikipedia, modified (https://upload.wikimedia.org/wikipedia/commons/archive/8/85/20110531171606%21Northern_macva03_map.png, 07.01.2023]

DISCUSSION

Rudolf Virchow first recognized multilocular echinococcosis in 1855 ("Die multiloculäre, ulcerirende Echinokokkengeschwulst der Leber") as a distinct form

of the disease characterized by many small alveolar spaces surrounded by echinococcal membranes, with rare or no protoscolices at all [6]. Virchow described an infiltrative lesion growth in a liver, with central cavitation filled with necrotic fluid, similar to what we found in our patient.

Pathohistological diagnosis of multilocular echinococcosis based on surgical material is completely sufficient, as described in classical textbooks (Binford, Conor. AFIP, 1976; Saltykow, 1951). In liver needle biopsy of a suspected lesion, the histomorphological diagnosis of echinococcosis is easy if chitin membranes are found. The presence of protoscolices or at least chitin hooklets suggests hydatid or cystic echinococcosis because alveolar or multilocular echinococcus does not produce protoscolices in humans. Hence the absence of protoscolices or hooklets in a material is considered an important morphological diagnostic criterion of multilocular or alveolar echinococcosis. The distinction between multilocular echinococcosis and multiple cystic echinococcosis, following the rupture of a primary liver cyst and dissemination of protoscolices with their cystic metamorphosis, may represent a diagnostic challenge. We described a case in a 12-year-old girl with disseminated peritoneal cystic echinococcosis localized in the small pelvis and ovary [1]. When only biopsy material is taken from a patient, the monoclonal antibody Em2G11, highly specific for *E. multilocularis*, may be helpful [7].

The increase in the fox and jackal populations as a result of the eradication of rabies in Serbia [8] caused the spread of their parasites, not only *E. multilocularis* [9] but *Capillaria aerophila*, agent of pulmonary capillariasis, too [10]. Multilocular echinococcosis has recently been reported in the neighbouring countries of Serbia, including Croatia [11] and Bosnia and Hercegovina [12]. The first human case in Croatia had mushroom-picking in the forest as a risk factor, and interestingly, the patient in question also came from the Srem region. The part of Sremska Mitrovica municipality, where the village Radenković is located, is south of the river Sava, which is near the place where the first case of *E. multilocularis* was found in a beaver 10 years ago [3]. This part geographically belongs to the Mačva region, but administratively to the Vojvodina Province. Taken together, these findings show an expansion of the area of multilocular echinococcosis to the south.

In Serbia, where cystic echinococcosis is endemic, multilocular echinococcosis is becoming a new diagnostic and therapeutic challenge. To start with, careful use of terminology is important, because multiple cystic echinococcosis is not multilocular echinococcosis [13, 14]. The range of diagnostic tools for multilocular echinococcosis has increased lately, especially with the introduction of molecular methods [15, 16, 17], and those need to be introduced in routine medical practice in Serbia.

E. multilocularis, a zoonotic agent whose eggs are very resistant to low temperatures and disinfectants, is in expansion in Europe, including in countries neighboring Serbia such as Hungary [18] and Croatia [11], as well as across the world, notably in some Asian countries [19, 20]. The treatment of choice is obviously surgery, but therapeutic options in complicated inoperable cystic and multilocular echinococcosis are quite limited, and long-term (up to lifelong) albendazole is the first line treatment [21].

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Conflict of interest: None declared.

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Први препознати случај мултилокуларне ехинококозе код људи у Србији

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САЖЕТАК

Увод Инфективни агенс мултилокуларне или алвеоларне ехинококозе, *Echinococcus multilocularis*, врста је различита од *E. Granulosus*, који изазива цистичну ехинококозу, не само по биолошким својствима него и по клиничком значају код људи, који могу бити ретки и случајни прелазни домаћини. Дефинитивни домаћини за *E. multilocularis* обично су лисице и шакали, а ретки су домаћи сисари попут паса и мачака. Цистична ехинококоза код људи у Србији је ендемска, док по клиничком току и исходу много опаснија мултилокуларна ехинококоза није још препозната.

Приказ болесника Наш случај је била жена, 67 година, из малог села у општини Сремска Митровица. Њени симптоми су почели неколико година раније и прогресивно су се погоршавали са болом у јетри. У диференцијалну дијагнозу укључени су бенигни тумори јетре, попут хемангиома, цистичне ехинококозе и апсцеса у цистичној ехинококној лезији. Сегменти јетре С II/III су уклоњени левом латералном хепатектомијом. Патохистолошким прегледом јасно је утврђена мултилокуларна ехинококоза са бројним малим празним везикулама од хитинских мембранозних простора без протосколекса, окружених масивном фиброзом и са инфилтративним типом раста у паренхиму јетре. Ехинококне везикуле су нађене и на хируршким маргинама и закључујемо да није потпуно уклоњено цело ехинококно ткиво, те је препоручена терапија албендазолом. Епидемиолошком анкетом утврђено је да болесница живи у ендемском региону мултилокуларне ехинококозе, у кући са два ловачка пса и двориштем где је могућа контаминација земљишта лисичјим изметом.

Закључак Овај случај је први препознати случај мултилокуларне ехинококозе код људи у Србији. Морамо побољшати профилактичке и дијагностичке процедуре и хируршку технику за ову зоонотску болест.

Кључне речи: *Echinococcus multilocularis*; хумани случај; Србија; Сремски регион; Мачвански регион; Војводина

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Focal myocarditis, an unusual imitator – case report and short review

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SUMMARY

Introduction Acute myocarditis is a serious inflammatory condition of the myocardium. Clinically, symptoms may differ from case to case, and as such can pose a significant diagnostic dilemma. Here we present a case of acute focal myocarditis with markedly elevated troponins, in which diagnosis was finally made using cardiac magnetic resonance (CMR).

Case outline A male patient, 26-year-old, without cardiovascular risk factors presented with severe chest pain, diaphoresis, pallor, and dyspnea. Blood pressure was 160/110 mmHg, and electrocardiogram (ECG) showed ST-segment elevation in inferior leads. In laboratory there was an extreme elevation of Troponin. Inferior-posterior-lateral STEMI was suspected, and initial treatment was given according to that suspicion. The patient was then sent to catheterization laboratory for further evaluation, which showed absence of coronary artery disease. A working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) was established. To distinguish MINOCA from other causes of myocardial injury with elevated troponins, a CMR was done, and its finding was consistent with focal myocarditis of inferolateral localization. Further treatment consisted of beta blockers, angiotensin-converting-enzyme inhibitors and avoidance of strenuous activity for the next six months. The patient fully recovered and had no further complications with ECG only showing flat T-wave in D3 lead.

Conclusion Focal myocarditis is an unusual manifestation of myocardial disease and can confuse physicians, especially if it occurs along with elevated cardiac markers and ST-elevation, but in a young patient, without any known comorbidity, this diagnosis must be considered. Here, a CMR may be a useful tool.

Keywords: myocardial infarction with non-obstructive coronary arteries; cardiac magnetic resonance; troponin

INTRODUCTION

Acute myocarditis is a serious inflammatory condition of the myocardium, the middle layer of the heart that contains cardiac muscle cells. It affects people of all ages and has a broad etiology (Table 1). Clinically, symptoms may differ from case to case, and as such can pose a significant diagnostic dilemma [1, 2]. Dramatic and acute electrocardiogram (ECG) ST-elevation can be wrongly interpreted as acute coronary syndrome, thus misleading physicians. Invasive coronary angiography is necessary for evaluation of myocardial injury. Absence of coronary artery stenosis (50% or greater) leads to the working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA). There are different algorithms in evaluating this diagnosis of myocardial injury. For Figure 1 illustration, we used modified algorithm mentioned by Occhipinti et al. [3]. In this case, careful history, clinical exam, and eventual cardiac magnetic resonance (CMR), could provide a solution for the dilemma [4]. Here we present a case of acute focal myocarditis with markedly elevated troponins, in which diagnosis was finally made using CMR.

CASE REPORT

A male patient, 26-year-old, without cardiovascular risk factors presented with severe chest pain, diaphoresis, pallor, and dyspnea. He had no fever. Blood pressure was 160/110 mmHg. ECG is shown in Figure 2. In laboratory findings, there was an extreme elevation of Troponin (I day – 6.374 ng/ml, II day – 16.947 ng/ml, III day – 10.302 ng/ml, V day – 0.207 ng/ml). Other laboratory parameters were normal. As there was an increase in troponin levels along with inferior leads ischemic ST elevation, initial diagnosis of acute coronary syndrome-Inferior-posterior-lateral STEMI was suspected. Initial treatment was given according to that suspicion and consisted of acetylsalicylic acid, clopidogrel, pantoprazole, tramadol, ramipril, bisoprolol, diazepam. Echocardiography showed normal ejection fraction (52%), heart size and ventricle wall thickness, with hypokinesia of medial basal segment of inferior wall of left ventricle. The patient was then sent to catheterization laboratory for further evaluation, which showed absence of coronary artery disease (Figure 3). A working diagnosis of MINOCA was established. Viral serology was negative for acute infection with cytomegalovirus, Epstein–Barr virus, parvovirus B19, adenovirus and coxsackievirus, with only

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Table 1. Causes of myocarditis-illustrative

Viruses	Bacteria and rickettsia	Fungi and protozoa	Parasites	Immune and systemic	Drug reactions and toxins
Coxsackie B Echovirus Epstein–Barr virus Cytomegalovirus Adenovirus Influenza virus Mumps Measles Rubella HIV Hepatitis B and C Varicella-zoster virus Respiratory-Syncytial virus Sars-CoV-2 Parvovirus B19 Herpesvirus Arbovirus Polio virus	*Corynebacterium Diphtheriae* *Staphylococcus* *Streptococcus* *Tuberculosis* *Clostridium tetani* *Mycoplasma pneumoniae* *Brucella* *Neisseria gonorrhoeae* *Hemophilus influenzae A* *Actinomyces* *Salmonella* *Rickettsia* *Borrelia burgdorferi* *Leptospira* *Tropheryma whipplei* *Francisella tularensis* *Vibrio cholerae*	*Aspergillus* *Candida* *Cryptococcus* *Coccidioides* *Histoplasma* *Trypanosoma cruzi* *Malaria spp.* *Leishmania spp.* *Toxoplasma gondii*	*Ascaris lumbricoides* *Trichinella spiralis* *Echinococcus granulosus* *Taenia solium* *Paragonimus westermani* *Schistosoma* *Visceral larva migrans* *Toxocara canis*	Kawasaki disease Scleroderma Multisystem inflammatory syndrome in children and adults Systemic lupus erythematosus Vasculitis Toxic shock syndrome Hypereosinophilia Wegener granulomatosis Sarcoidosis Inflammatory bowel disease Phaeochromocytoma	Chemotherapy agents Antipsychotics Antibiotics [Penicillin Cephalosporins Tetracyclines Sulfonamides] Tricyclic antidepressants Lithium Diuretics Alcohol Arsenic Snake venom Tetanus toxoid Carbon monoxide Heavy metals [Iron, Copper] Insect bites Cocaine Methyldopa

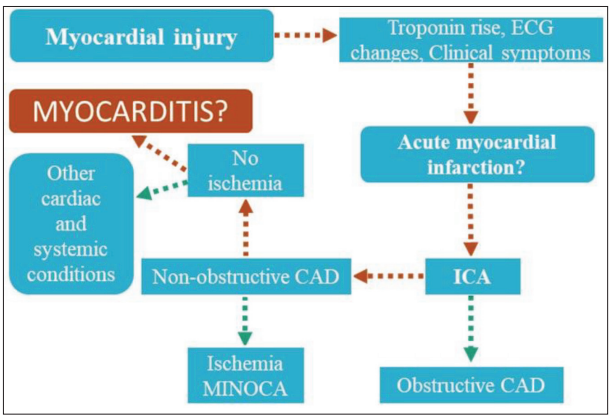

Figure 1. Example of focal myocarditis diagnostic pathway

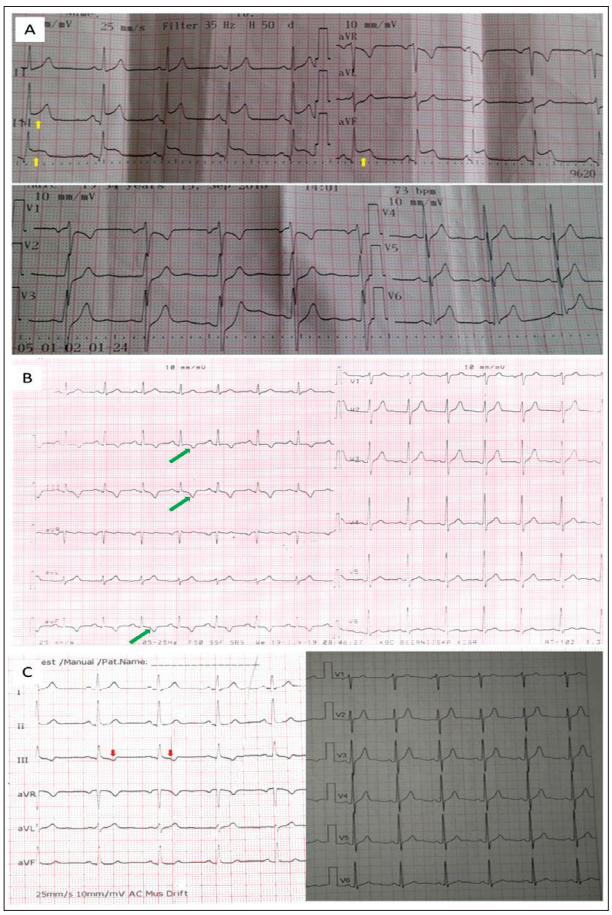

Figure 2. A – Echocardiogram (ECG) on admission: sinus rhythm, heart rate = 110/min, ST- elevation (yellow arrows) in D2, D3, aVF up to 4 mm; B – ECG one month later: negative T-wave (green arrows) in D2, D3, aVF up to 4 mm; C – last ECG, year after the event: sinus rhythm, heart rate = 75/min, negative T-wave in D3 (red arrows)

IgG antibodies present for cytomegalovirus, Epstein–Barr virus, and parvovirus B19. During next days of hospital stay, patient complained of chest discomfort, but there were no further ECG changes, and troponin levels normalized. To distinguish MINOCA from other causes of myocardial injury with elevated troponins, a CMR was done (example of CMR myocarditis is shown in Figure 3). CMR finding showed inferolateral subepicardial edema on T2 and STIR sequences with late gadolinium enhancement (LGE) in the same region. The finding was consistent with focal myocarditis of inferolateral localization. Further treatment consisted of beta blockers, angiotensin-converting-enzyme inhibitors and avoidance of strenuous activity for the next six months. The patient fully recovered and had no further complications with ECG only showing flat T-wave in D3 lead. 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

Myocarditis is an inflammatory disease of myocardium that is likely underdiagnosed. The prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide and is more common in men with about 1:2–4 female–male ratio, with women reported to have better survival of dilated cardiomyopathy [5]. It is a significant public health issue, especially for young adults.

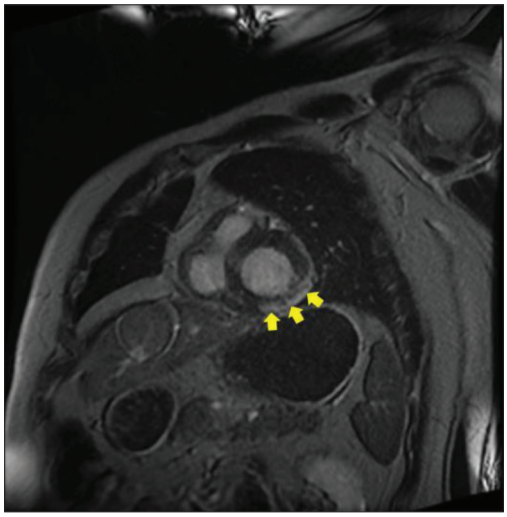

Figure 3. Short axis late gadolinium enhancement pathologic intramyocardial and pericardial late gadolinium enhancement (10–20 min) in lateral and inferior wall of the left ventricle; case courtesy of Dr. Igor Yamola (radiopaedia.org, rID: 98955)

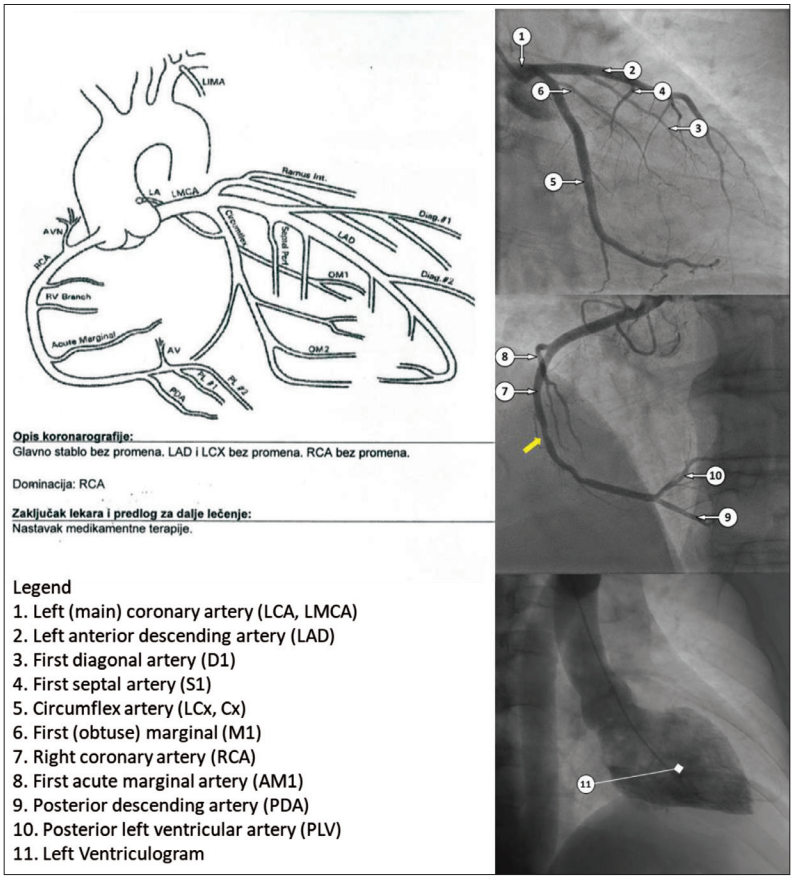

Figure 4. Coronary angiography report of our patient along with near normal coronary angiography (only minor mid right coronary artery stenosis-yellow arrow, in a 45-year-old male); case courtesy of Dr. Craig Hacking (radiopaedia.org, rID: 63081)

Myocarditis has a generally good prognosis, but in up to 20% of cases, it may progress to a dilated cardiomyopathy [6, 7]. Acute myocarditis can be defined as a period of < 1 month between symptom onset and diagnosis. Most common symptoms noted are chest pain (in 85–95% of cases), fever (in about 65%) and dyspnea (19–49% of cases) [8]. Another entity to be aware of in differential diagnosis besides acute coronary syndrome is left dominant arrhythmogenic cardiomyopathy, which is underrecognized, but can also present with chest pain and elevated cardiac enzymes [9]. Here we presented a case of a young patient with acute focal myocarditis and extremely elevated troponins, that was initially considered acute myocardial infarction, then evaluated as MINOCA, and finally diagnosed using a CMR. The absence of fever in our patient was an aggravating feature for making the diagnosis of focal myocarditis.

Focal myocarditis has already been described as a myocardial infarction simulator. In cases, were endomyocardial biopsy was ordered, etiology was mostly viral (ADV, cytomegalovirus, Epstein–Barr virus, PVB19) [10, 11]. Young patients that present as STEMI must be evaluated in direction of focal myocarditis, especially if there is a positive history of recent viral illness.

Endomyocardial biopsy is the gold standard for diagnosis of myocarditis. After using a transfemoral, or radial approach, a specimen is histologically and immunologically evaluated for presence of infectious agents, and tissue architectonic is considered for other (e.g., autoimmune) forms of inflammation [12]. In our case, due to focal nature of inflammation, endomyocardial biopsy could not be done. Patchy and focal inflammation of myocardium can sometimes work against this diagnostic approach.

ECG with ST-segment elevation may occur in pericarditis, myocarditis, myocardial infarction (STEMI), LV aneurism, and in some rare or uncommon conditions (e.g., Brugada syndrome, Takotsubo cardiomyopathy), and benign conditions (e.g., benign early repolarization) [13].

Elevated cardiac markers must be inclusively considered along with clinical and other diagnostic findings, as they do not define type of myocardial injury. The treatment should therefore be aimed at the cause of myocardial injury. Troponins may be an indicator of a disease severity and may rise in myocarditis, but they do not carry an adverse prognosis as in acute coronary syndrome [14, 15].

CMR may be crucial in diagnosis of acute focal myocarditis and is best to be done early after symptoms onset and can also be used to track disease progression/resolution. Time window for optimal sensitivity for diagnostic imaging is few weeks from its presentation. In our case, CMR has been proven diagnostically two weeks after disease onset. As edema is a universal marker of inflammation that also occurs in focal myocarditis, a T2-weighted imaging and high STIR signal may be indicative of myocardial edema [16, 17]. Lake Louise criteria for CMR in myocardial inflammation were established in 2009. For diagnosis of acute myocarditis, two out of three of the following features are needed: edema (with T2-weighted sequences), hyperemia (with early Gadolinium Enhancement) and necrosis or fibrosis (with LGE) [18]. Updated Lake Louise criteria were established in 2018 and include main criteria ("2 out of 2"): T2 based imaging – Regional high (10 pixels) T2 signal intensity or

global T2 signal intensity ratio ≥ 2.0 in T2-weighted images or regional or global increase of myocardial T2 relaxation times; T1 based imaging – Regional or global increase of native myocardial T1 relaxation times or extracellular volume (highly sensitive to detecting both acute and chronic forms of increased free water content within the myocardium). Supportive criteria are pericardial inflammation and left ventricular disfunction. All of mentioned criteria may as well be an indicator of focal myocarditis [19, 20].

Focal myocarditis is an unusual manifestation of myocardial disease and can confuse physicians, especially if it occurs along with elevated cardiac markers and ST-elevation, but in a young patient, without any known comorbidity, this diagnosis must be considered. Here, a CMR may be a useful tool.

Conflict of interest: None declared

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Фокални миокардитис, необични имитатор – приказ болесника и кратак преглед литературе

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САЖЕТАК

Увод Акутни миокардитис је озбиљно инфламаторно стање које погађа миокард. Клинички, симптоми се разликују од случаја до случаја, представљајући дијагностичку дилему. Приказаћемо случај акутног фокалног миокардитиса са изразито високим тропонинима, код којег се до дијагнозе дошло употребом магнетне резонанце срца.

Приказ болесника Мушкарац старости 26 година, кардиваскуларних фактора ризика, јавља се због изразитог бола у грудима, дијафорезе, бледила и диспнеје. Притисак на пријему био је 160/110 *mmHg*, а ЕКГ је показивао елевацију *ST*-сегмента у доњим одводима. Лабораторијски је евидентирана висока вредност тропонина и постављена је сумња на инферо-постеро-латерални *STEMI*. Иницирана је терапија под том сумњом. Пацијент је потом послат на коронарографију, која је показала одсуство коронарне болести срца. Постављена је радна дијагноза инфаркта миокарда без опструкције коронарних артерија. Како би се утврдило да ли је заиста у питању ова дијагноза, затражена је магнетна резонанца срца, чији је налаз био конзистентан са фокалним миокардитисом инферолатералне локализације. Даља терапија садржала је бета-блокаторе, *ACE* инхибиторе и избегавање захтевне физичке активности наредних шест месеци. Пацијент се потпуно опоравио и није имао даље компликације, осим што је на ЕКГ-у перзистирао налаз аплатираних Т-таласа у Д3 одводу.

Закључак Фокални миокардитис је необична манифестација болести миокарда и може збунити лекаре, нарочито ако се дешава у склопу повишених срчаних ензима и *ST*-елевације на ЕКГ-у, али код младих особа, без познатих коморбидитета, ова дијагноза се мора узети у обзир. У овом случају, кардиоваскуларна магнетна резонанца може бити користан алат.

Кључне речи: инфаркт миокарда без опструкције коронарних артерија; магнетна резонанца срца; тропонин

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cardiac arrest and repeated ST-segment elevation caused by initially unrecognized coronary vasospasm

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SUMMARY

Introduction Coronary artery spasm (CAS) is defined as a transient vasoconstriction of an epicardial coronary artery with a total or subtotal vessel occlusion, causing myocardial ischemia. Although the overall incidence of CAS during coronary angiography is estimated to be between 0.3% and 1%, CAS remains an underdiagnosed and undertreated cause of acute cardiac events.

Case outline We report a case of a 62-year-old male presenting with cardiac arrest and repeated ST-segment elevations during chest pain episodes, caused by initially unrecognized CAS. Although percutaneous coronary intervention (PCI) is generally not recommended for the treatment of CAS, due to clinical manifestations and the presence of underlying flow-limiting stenosis, we decided to perform PCI of the left anterior descending coronary artery. During the two-year-follow up period, the patient reported no chest pains nor exercise limitations at regular outpatient controls.

Conclusion CASs should be considered an unrecognized cause of refractory angina, acute coronary syndrome, malignant arrhythmia, and even cardiac arrest. Although medical therapy is the first option for CAS treatment, PCI could be a safe and effective approach in selected patients.

Keywords: coronary vasospasm; fractional flow reserve; myocardial infarction; optical coherence tomography; percutaneous coronary intervention

INTRODUCTION

Coronary artery spasm (CAS) is defined as a transient vasoconstriction of an epicardial coronary artery with a total or subtotal vessel occlusion, causing myocardial ischemia [1, 2, 3]. Depending on the site, duration, and severity of the spasm, the clinical presentation of CAS ranges from "silent ischemia" to transmural myocardial infarction, malignant arrhythmias, and even sudden cardiac death [2]. Although the exact prevalence of CAS remains unknown, it is believed that prevalence is decreasing, probably due to the wide usage of angiotensin-converting enzyme inhibitors, calcium channel blockers, and statins in cardiovascular medicine, as well as the decrease in smoking habits in developed countries [4, 5]. However, CAS remains an underdiagnosed and undertreated cause of acute cardiac events [2, 6]. In this article, we report a case of a 62-year-old male presenting with cardiac arrest and repeated ST-segment elevations during chest pain episodes, caused by initially unrecognized CAS.

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CASE REPORT

A 62-year-old male was admitted to the Emergency Department due to sharp chest pain that lasted for 15 minutes. Except for smoking and dyslipidemia, no other cardiovascular risk factors were identified. He was asymptomatic on admission, the electrocardiogram (ECG) showed no significant findings, troponin I was in the reference range, and the transthoracic echocardiography (TTE) was orderly. After 12 hours of observation, the patient was discharged for further home treatment, with a prescription for 100 mg of acetylsalicylic acid per day. Three days after, he performed an exercise stress test (Bruce protocol), which was interrupted before reaching a submaximal heart rate, due to extreme fatigue. ECG before and during the test was without ischemia-related changes. However, after four minutes of rest, the patient experienced cardiac arrest with a rhythm of ventricular fibrillation. Regular heart rhythm was restored after cardioversion, and ECG showed ST elevation in leads V1–V5. The patient was immediately transferred to the Emergency Department, where ECG showed 0.5 mm elevations of ST-segment in inferior leads, without any ST-segment denivelations in anterior leads. A coronary angiogram, performed after 30 minutes, visualized stenosis up to 80% in the proximal part and borderline stenosis above the ectatic segment in the medial right coronary artery (RCA). The finding on the left coronary artery (LCA) was orderly, except for borderline stenosis in the medial left anterior descending (LAD) artery (Figures 1A and 1B). We note that the patient reported no chest pain at the Catheterization laboratory, and ECG monitoring was without ST-segment denivelations. We decided to perform the percutaneous coronary intervention (PCI) of the RCA. After administering 180 mg of ticagrelor

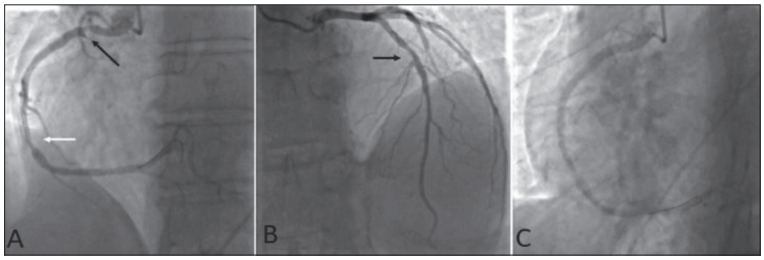

Figure 1. Coronary angiogram at admission;

A – coronary angiogram of the right coronary artery, showing stenosis up to 80% in the proximal part (black arrow) and borderline stenosis at the medial segment (white arrow); B – coronary angiogram showing borderline stenosis in the medial segment of the left anterior descending artery; C – coronary angiogram after performing percutaneous coronary intervention of the right coronary artery

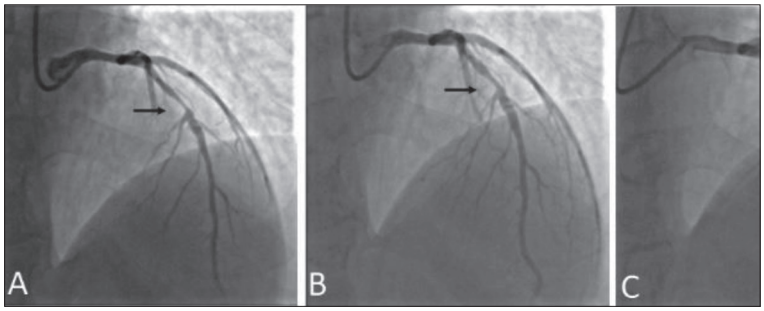

Figure 2. Repeated coronary angiogram and percutaneous coronary intervention of the left anterior descending coronary artery;

A – coronary angiogram showing stenosis up to 85% in the medial part of the left anterior descending coronary artery (black arrow); B – spasm reduction after nitroglycerin was administered intracoronary, with a persistence of a significant lumen reduction (black arrow); C – coronary angiogram after performing percutaneous coronary intervention of the left anterior descending artery

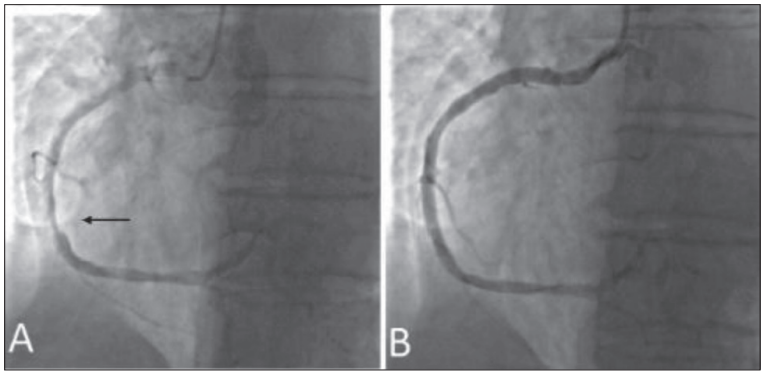

Figure 3. Repeated coronary angiogram and percutaneous coronary intervention of the right coronary artery;

A – coronary angiogram showing 70% lumen reduction in a distal segment of the right coronary artery (black arrow); B – coronary angiogram after performing percutaneous coronary intervention of the right coronary artery

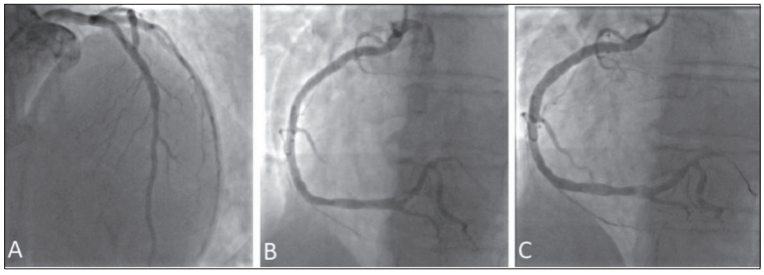

Figure 4. Repeated coronary angiogram, three months after the index hospitalization;

A – orderly coronary angiogram of the left coronary artery; B – angiogram of the right coronary artery, before optical coherence tomography and stent optimization; C – angiogram of the right coronary artery after the stent optimization

and lesion preparation, the 4.0 × 18 mm drug-eluting stent (DES) was implanted in the proximal RCA (Figure 1C). The patient continued the inpatient treatment at the Cardiology clinic for further observation. Control TTE findings after the procedure showed reduced global systolic function, with the left ventricle ejection fraction estimated at 45–50%, hypokinesia of the basal and medial segment of the inferior wall, as well as the basal segment of the septum.

The patient developed intense chest pains in the early morning of the fourth hospital day, accompanied by nausea and vomiting. The ECG recorded significant ST-segment elevations in precordial leads, with minimal ST-segment depression in the inferior leads. The patient was immediately transferred to the Catheterization Laboratory, where a coronary angiogram showed stenosis up to 85% in the medial part of the LAD (Figure 2A). The stenosis in the distal RCA was estimated at 70% (Figure 3A). After the intracoronary administration of nitroglycerin, the spasm in the LAD was reduced (Figure 2B). The fractional flow reserve (FFR) value distal to stenosis was 0.78. Due to the underlying flow-limiting stenosis, we decided to perform PCI of the LAD. After predilatation with a 3 × 15 mm semi-compliant balloon, the 4 × 15 mm DES was implanted. The stent was optimized using the 4.5 × 12 mm non-compliant (NC) balloon at 16 atmospheres. The final angiographic result was optimal with the "Thrombolysis In Myocardial Infarction" (TIMI) 3 flow along the LAD (Figure 2C). After that, we decided to perform PCI of the distal RCA. The 4 × 24 mm DES was implanted, with the optimal final angiographic result and the TIMI 3 flow after the NC balloon postdilatation (Figure 3B).

After nine days of hospital treatment, the patient was discharged from the Cardiology Clinic. In addition to acetylsalicylic acid 100 mg daily and ticagrelor 90 mg twice a day, we opted for a statin, selective beta blocker, and dihydropyridine calcium channel blocker.

Repeated coronary angiography with optical coherence tomography (OCT) of the RCA and LAD was performed three months after the index procedure. The angiogram of the LCA was orderly, and OCT showed adequate stent expansion and apposition, without any stent-related complications (Figures 4A and 5A). Although the angiogram of the RCA was orderly (Figure 4B), OCT revealed malposition of the proximally

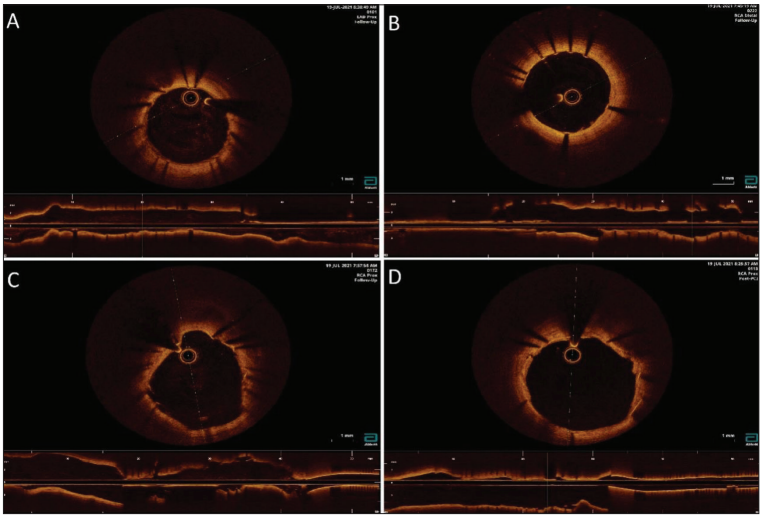

Figure 5. Optical coherence tomography (OCT) imaging after three months follow-up; A – OCT imaging of the proximal left anterior descending artery showed adequate stent expansion and apposition, without any stent-related complications; no signs of atherosclerotic disease were visualized outside the stented segment; B – OCT imaging of the distal right coronary artery showed adequate stent expansion and apposition, without any stent-related complications; C – OCT imaging of the proximal right coronary artery showed malposition of the implanted stent; D – control OCT imaging of the proximal right coronary artery showed adequate stent expansion and apposition

implanted stent, with adequate apposition and expansion of the second stent (Figures 5B and 5C). Therefore, stent optimization was conducted using the 5 mm NC balloon, with satisfactory control OCT run (Figures 4C and 5D).

During the two-year-follow up period, the patient reported no chest pains nor exercise limitations at regular outpatient controls.

We obtained verbal and signed consent of the patients to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki.

DISCUSSION

CAS is a phenomenon caused by smooth muscle cell hyperactivity and vascular wall hypertonicity, which results in a transient complete or partial closure of a coronary artery with subsequent myocardial ischemia [2]. The exact pathogenesis has not been fully elucidated; however, the current findings suggest a complex interaction of several important mechanisms such as primary hyperactivity of vascular smooth muscle cells, endothelial dysfunction, chronic low-grade inflammation, altered autonomic nervous system response, and others [1, 2, 3]. The common clinical presentation of CAS-induced myocardial ischemia are ST-segment changes and chest pain, similar to that in a stable angina and myocardial infarction [4, 5]. However, there are several distinctions that should be considered. First of all, "silent" ischemia is twice more prevalent in patients with CAS compared to symptomatic presentation. In those with symptomatic ischemia, chest pains are usually more severe, prolonged, and accompanied by cold sweating, nausea, and even syncope. ECG changes commonly consist of transient ST-segment elevation, but can also include ST-segment depression, T wave alterations, negative U wave, and even malignant arrhythmias, more often seen in multi-vessel CAS [2, 3, 5]. Importantly, due to its association with the circadian rhythm, coronary vasospasm occurs at rest, often between midnight and early morning. In contrast to effort angina, CAS is usually not associated with physical activity, however, it is shown that even mild activity in the morning can potentiate the spasm. Additionally, coronary vasoconstriction could be potentiated by several factors, including cigarette smoking, prolonged emotional stress, Valsalva maneuver, exposure to cold, and use of some medications, such as sympathomimetic agents, nonselective beta-blocker, and others [1, 5]. The sex differences also exist and latest meta-analysis in that regard demonstrate it [6], beyond case reports [7], while women with confirmed CAS tend to have more autoimmune rheumatic diseases in the Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction cohort [8] and long-term follow-up solutions for this growing patient group remains in the normalization of the concept of heart centers for women – both internationally and locally, in Serbia [9, 10].

An important obstacle in diagnosing is the difficult recognition of CAS in a coronary angiogram, since vasospasm, if even present, cannot be easily distinguished from atherosclerotic narrowing [11]. Definitive diagnosis is made after angiographic evidence of coronary vasoconstriction that reverses with the administration of intravenous or intra-arterial nitroglycerin [1, 12]. Findings from OCT studies suggest that a significant portion of CAS occurs at the site of the atherosclerotic segment, and unrecognized CAS increases the risk of overestimating the stenosis severity [13]. This is particularly important since PCI is generally not recommended for the treatment of CAS in the absence of severe atherosclerotic disease [6]. Recommended medical treatment options consist of pharmacological agents that prevent vasoconstriction and promote vasodilation in the coronary vasculature, such as calcium channel blockers and nitrates. Additionally, lifestyle changes such as smoking cessation, improving diet and exercise habits, and managing stress can also help prevent vasospasm from occurring [1]. However, despite medical therapy, some patients experience refractory angina and other CAS-related complications. The potential reason could be the residual, flow-limiting atherosclerotic stenosis, even after complete spasm resolution [14]. Findings suggest that CAS induces local thrombus formation as well as the production of inflammatory mediators, therefore increasing the risk of atherosclerotic plaque progression and ischemic events in patients with CAS [14]. In addition, studies have shown that patients

with coexisting CAS and obstructive flow-limiting stenosis have a greater risk of major adverse cardiac events and worse outcomes [15, 16]. Therefore, PCI management of CAS associated with significant atherosclerotic stenosis could be considered in selected patients [2, 6, 11]. In adequate decision-making, adjuvant methods such as functional coronary assessment and intracoronary imaging can be helpful. OCT imaging can be useful in both diagnosing and understanding the pathophysiology of CAS [17]. In addition, OCT is recognized as a helpful tool for accessing procedural complications and improving stent apposition and expansion, therefore decreasing the risk of stent thrombosis and the incidence of stent-related complications [17]. In our case, OCT was not used in the index procedure by the operator's choice, due to already confirmed CAS in the setting of flow-limiting atherosclerotic plaque. OCT was used in the follow-up, to access the quality and the potential complications of the stent implanted in the segment affected by CAS. In our case, the OCT run showed adequate apposition and expansion, without any complications.

In conclusion, CAS should be considered an unrecognized cause of refractory angina, acute coronary syndrome, malignant arrhythmia, and even cardiac arrest. Although medical therapy is the first option for CAS treatment, PCI could be a safe and effective approach in selected patients. In adequate decision-making, adjuvant methods such as functional coronary assessment and intracoronary imaging should be considered.

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Conflict of interests: None declared.

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Срчани застој и понављане елевације *ST*-сегмента узроковане иницијално непрепознатим коронарним вазоспазмом

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САЖЕТАК

Увод Коронарни артеријски спазам се дефинише као транзиторна вазоконстрикција епикардне коронарне артерије са тоталном или суптоталном оклузијом крвног суда и последичном исхемијом миокарда. Иако је описан у 0,3–1% коронарних ангиографија, сматра се да коронарни вазоспазам у значајној мери остаје недијагностикован узрок акутних коронарних догађаја.

Приказ болесника У овом раду приказујемо 62-годишњег пацијената са срчаним застојем и понављаним елевацијама *ST*-сегмента током епизода бола у грудима, који су узроковани иницијално непрепознатим коронарним вазоспазмом. Иако перкутане коронарне интервенције генерално нису препоручен избор лечења коронарног вазоспазма, услед клиничких манифестација и присуства удружене значајне атеросклеротске болести, одлучили смо се за имплантацију стента на левој предњој десцедентној коронарној артерији. Током двогодишњег праћења на редовним амбулантним контролама, пацијент негира ангинозне болове и ограничења у физичкој активности.

Закључак Коронарни артеријски спазам би требало размотрити као непрепознат узрок рефракторне ангине, акутног коронарног синдрома, малигних аритмија и срчаног застоја. Иако је медикаментна терапија прва опција у лечењу коронарног вазоспазма, перкутана коронарна интервенција би могла бити безбедна и ефикасна метода лечења код одређених пацијената.

Кључне речи: инфаркт миокарда; коронарни вазоспазам; оптичка кохерентна томографија; перкутане коронарне интервенције; фракциона резерва протока

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Anesthesia for thyroid surgery in heart transplant patients – the first case study in Serbia

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SUMMARY

Introduction The number of patients in the world who have undergone heart transplantation is increasing, with better and longer survival rates, and therefore the number of patients who undergo various surgical interventions after transplantation is also increasing. This presents a challenge for anaesthesiologists.

Case outline A 45-year-old female patient underwent a total thyroidectomy due to suspected thyroid cancer. She had a heart transplant three years earlier. Preoperative preparation included evaluation of cardiac function, consultative examinations by a transplant cardiologist, laboratory and other diagnostic procedures, as well as a detailed analysis of all 20 medications that the patient uses in daily therapy. Common drugs were used for premedication and general endotracheal anaesthesia, with careful dose titration. Medicines were also prepared for the occurrence of heart rhythm disorders, bearing in mind that the heart is denervated, but there was no need for their use. The operation and postoperative course went smoothly and on the third postoperative day the patient was discharged from the hospital in good general condition.

Conclusion Preoperative preparation, anaesthesia, and postoperative treatment of this patient represented a challenge for our team, which was successfully overcome, considering that this is the first case of operative treatment of a patient with a transplanted heart in Serbia.

Keywords: thyroidectomy; transplanted heart; preoperative preparation

INTRODUCTION

Heart transplantation is the treatment of choice for decompensated heart failure that does not respond to conventional therapy, idiopathic dilated cardiomyopathy, and terminal ischemic heart disease. [1, 2] Since 1967, when Christian Bernard performed the first heart transplantation, a large number of those operations have been performed and it is constantly increasing. Only in the USA, over 3000 heart transplant operations are performed each year, while, according to the data of the International Society for Heart and Lung Transplantation in Europe, that number is around 1500–3000 annually [3]. Five-year survival rate after heart transplantation is over 72.5%, and 20-year survival is 21% [4]. Considering the increasing number of transplantations and life expectancy of those patients, the number of non-cardiac interventions performed on patients with previous heart transplantation is rising. In Serbia, the first heart transplant procedure was performed in 1995, when five patients were successfully operated on. The Heart Transplant Program was revived in 2013, and so far, 49 patients have been successfully surgically treated at the University Clinical Centre of Serbia (UCCS). To the best of our knowledge, apart from our patient, none of the others, previously mentioned patients, have yet undergone any other post-transplantation surgery, which certainly represents a great challenge for us. Naturally, post-transplantation surgery requires the participation of the cardiologist involved in the post-transplantation monitoring program and an experienced team of anesthesiologists.

CASE REPORT

A female patient, 45 years old, was admitted to the UCCS Clinic for Endocrine Surgery for surgical treatment of the thyroid gland. In 2018, she underwent the heart transplantation procedure. Her heart problems began in 2005, when she received the seasonal flu vaccine, after which she developed a fever, malaise lasting four weeks, along with fatigue, angina pectoris, and dyspnea. Multiple chest X-rays were performed, as well as other examinations, but there were no signs of pneumonia nor cardiac decompensation. Her medical problems lasted two and a half years, while she was being treated with antibiotics under suspicion of chronic bronchitis. After the mentioned period, episodes of angina pectoris and dyspnea reappeared. Coronary disease was excluded by coronary angiogram examination. None of the branches of the coronary arteries showed significant stenosis in their proximal and distal parts. An echocardiogram revealed a pericardium filled with fluid, enlarged heart cavities, with severe reduction of the left ventricular

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systolic function with ejection fraction of the left ventricle (EF LV) of 17%, which led to a diagnosis of dilated cardiomyopathy. The next cardiac deterioration occurred in 2014 after a common cold, when she was treated conservatively, but due to her weakened heart and compromised hemodynamic stability, a pacemaker and defibrillator were implanted (single-chamber implantable cardioverter-defibrillator – ICD-VR). The heart transplantation was performed in 2018. The graft that was used was a healthy heart with normal anatomic characteristics and EF LV of 65%. During operation, the pacemaker and defibrillator were removed, but their wires couldn't be removed because one of them had fused with the vagal nerve, and the other one had been dislocated towards the right heart cavities where it is still located (Figure 1). Short- and long-term postoperative outcomes were uneventful (no form graft rejection, infections, allograft vasculopathy, nor malignancy).

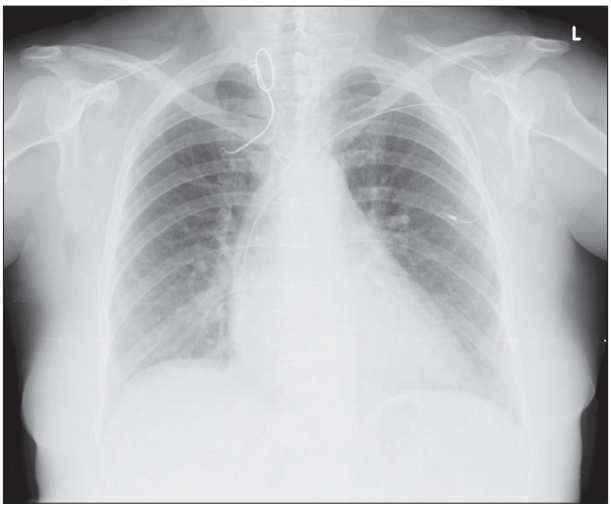

Figure 1. The patient's chest X-ray

Regarding her comorbidities, our patient is obese (body weight = 99 kg, body height = 176 cm, body mass index = 32 kg/m^2), has confirmed hyperlipidemia, arterial hypertension, and mild pulmonary hypertension. Since 2021, she has been treated for diabetes with intensive insulin therapy (short acting human insulin 6 + 8 + 8 IU before meals and intermediate acting human insulin 14 IU at 10 p.m.). She had COVID-19 on two occasions, once treated at home (in 2021) and the other time in the hospital (in 2022), both times with mild symptoms. She has not been vaccinated against the corona virus.

On June 22, 2022, she was admitted to the Clinic for Endocrine Surgery of the UCCS for operative treatment of the thyroid gland. A neck echotomographic examination verified a node in the left lobe of the thyroid gland about 4.5 cm in size of iso- to heteroechoic characteristics with the presence of intranodal vascularization. Fine-needle aspiration biopsy was performed and the obtained sample was analyzed. The result indicated an atypia of undetermined significance – Bethesda category III, which established the probability of thyroid cancer. Laboratory analyses (blood count, biochemistry, coagulation status) performed on the hospital admission day showed no significant deviations from the reference values. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) was 68 pg/mL before operation. Electrocardiogram (ECG) showed the presence of a biphasic p-wave with rhythm of 82 beats per minute. Chest radiography did not show any presence of consolidations and X-ray of cervical spine indicated degenerative changes in the form of uncarthrosis and reduction of the C5–C6 intervertebral space. Echocardiogram revealed an accelerated flow through the aortic valve, paradoxical movement of interventricular septum, EF LV of 70%, weaker longitudinal function of the right ventricle, severe tricuspid regurgitation, an indirectly assessed elevated systolic pressure in the right ventricle, and a wire visible in the right heart cavity.

Together with the transplant cardiologist who followed-up the patient after the transplantation, all 20 drugs that the patient uses on a daily basis were analyzed, in order to determine the optimal regimen, doses and timing for their application in the perioperative period, as well as possible interactions with medications that could be used during anesthesia (Table 1). She regularly took her therapy the day before surgery, and morning on the surgery day. Also, she received an antibiotic one hour before surgery (vancomycin 2 g intravenously), low molecular weight heparin (enoxaparin sodium 0.4 mL subcutaneously) two hours before surgery, gastro protective therapy (pantoprazole 20 mg orally), as well as her personal cardiology therapy (ivabradine 7.5 mg orally) and therapy for the regulation of pulmonary hypertension (sildenafil 20 mg).

For premedication, the patient received 5 mg of midazolam intramuscularly half an hour before surgery. During that period, she was under constant observation. In the meantime, in the operating room we prepared medications for possible intraoperative bradycardia (adrenaline in a dilution of 1:200,000) and tachycardia (amiodarone in a dilution of 1:4), as well as a defibrillator.

Non-invasive monitoring (ECG, pulse oximetry, noninvasive blood pressure, end-tidal CO_2, respiratory rate) was used intraoperatively. Before general endotracheal anesthesia (GEA) induction, the patient was preoxygenated with 100% oxygen (flow of 6 L/minute) for five minutes. During preoxygenation, she received 25 mg of hydrocortisone intravenously, in order to prevent acute adrenal insufficiency, bearing in mind that she regularly used glucocorticoids (prednisone) after transplantation.

Propofol (160 mg) was used for GEA induction, rocuronium bromide at a dose of 0.8 mg/kg was used for intubation and muscle relaxation. The patient was intubated using a video laryngoscope (GlideScope; Verathon, Bothell, WA, USA). To maintain anesthesia, a gas mixture of sevoflurane (2 vol%), oxygen (50%) and air (50%) was used. For analgesia, diluted fentanyl (1:4) was used in intravenous bolus doses, starting before induction, up to a total dose of 150 μg. Sugammadex was used to reverse the neuromuscular block in a dose of 4 mg/kg.

During the procedure, hemodynamic parameters remained stable. Initial arterial tension was 123/74 mmHg, and heart rate was 80 beats per minute. The highest measured value of arterial tension was 130/75 mmHg, and

Table 1. Drugs, doses, and timing of their use

Drug name	Drug group	Drug dose	Timing
Furosemide	Diuretic	40 mg	8 a.m.; 6 p.m.
Amlodipine	Antihypertensive	2.5–5 mg	12 p.m.
Sildenafil	Antihypertensive	20 mg	8 a.m.; 4 p.m.; 12 a.m.
Ivabradine	Antiarrhythmic	5 mg	8:15 a.m.
Human insulin*	Antidiabetic	6 + 8 + 8 IU	before meals
Human insulin**	Antidiabetic	14 IU	10 p.m.
Prednisone	Corticosteroid	5 mg	8:15 a.m.
Mycophenolic acid	Immunosuppressant	1000 mg	10 a.m.; 10 p.m.
Tacrolimus	Immunosuppressant	3 mg	10 a.m.; 10 p.m.
Rosuvastatin	Statin	10 mg	10 pm
Trimethoprim-sulfamethoxazole	Antibiotic	800/160 mg	Tuesdays, Thursdays, and Sundays at 10 a.m.
Pantoprazole	Gastro Protection	40 mg	7:30 a.m.; 7:30 p.m.
Bromazepam	Anxiolytic	1.5–3 mg	optionally
Potassium chloride	Supplement	1 bag, each 3rd day 2 bags	9 a.m.
Calcium carbonate	Supplement	1000 mg	8:30 a.m.
Vitamin C	Supplement	1000 mg	9 a.m.
Vitamin D_3	Supplement	2000 IU	8 p.m.
Folic acid	Supplement	5 mg	10 a.m.
Iron	Supplement	1000 mg	7:30 a.m.
Magnesium	Supplement	375 mg	8:15 a.m.; 8:15 p.m.

*short-acting;
**intermediate acting

heart rate 80 beats per minute. The operation (total thyroidectomy) lasted 50 minutes and was uneventful. The patient was extubated on the operating table, after all conditions were met (consciousness presence, performing all instructions, adequate motor response, spontaneous respiration with a frequency of 12 breaths per minute, oxygenation > 95%, hemodynamically stable). She was transferred to the Coronary Care Unit (CCU) for 24-hour monitoring by a cardiologist. In the CCU she received her own cardiac, immunosuppressive, and other chronic therapy. The concentration of tacrolimus in the blood was in the therapeutic range postoperatively. Postoperative value of NT pro-BNP was 75 pg/mL. The patient was transferred to the surgical ward 24 hours after the operation, and on the third postoperative day she was discharged from the hospital with therapy recommendations. The postoperative period was uneventful. No arrhythmias were detected during the perioperative period.

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

DISCUSSION

The number of heart transplantations worldwide is constantly rising; the success of this surgical procedure is greater with higher post-transplant survival rate, and experiences with non-cardiac surgeries of those patients are increasing [5]. However, here in Serbia we cannot claim that we have excessive numbers and experience with such patients. To the best of our knowledge, this was the first case of a patient with previous heart transplant undergoing non-cardiac surgery, so the challenge for our anesthesia team was even greater.

Numerous physiological factors within previous heart transplant patients must be taken into account during the preoperative preparation and GEA, such as the denervation of the transplanted heart, the number and influence of other medications those patients use on a daily basis (e.g., the interaction between immunosuppressants and anesthetics), the possibility of the graft rejection, proper perioperative pain therapy, and the possibility of infection [6].

After heart transplantation, the graft tissue has its own sinoatrial node, which is completely denervated and independent of the host's autonomic nervous system, so in those patients we can expect the following: a lack of baroreceptor reflex, no response to carotid sinus massage, a change in the heart frequency as a postural change, and the lack of reaction to Valsalva maneuvers [7, 8]. It is also known that after heart transplantation, due to vagal denervation and increased sensitivity of the graft myocardium to circulating catecholamines, episodes of arrhythmias and blockages (such as the first-degree atrioventricular block) can occur, which are usually detected after the transplant surgery [9]. Having that in mind, the use of atropine in case of intraoperative bradycardia would not be effective, and the use of beta-blockers in case of intraoperative tachycardia is not advised because of their wide range of cardiopulmonary effects and it can also cause potential total blockade of the heart muscle [10]. Considering these facts, our team was prepared to respond to potential rhythm changes with solutions of amiodarone and adrenaline. Some authors recommend verapamil for tachycardia and vasopressors (noradrenaline, dobutamine) for bradycardia treatment [11, 12].

Unlike in the non-heart transplant patients, reversing neuromuscular blockade with neostigmine and atropine in heart transplant patients remains a topic for further scientific research. It is also known, from the available scientific literature, that meta-analysis had been performed and proved that a smaller number of adverse reactions occur when using sugammadex compared to anticholinesterase drugs; therefore, we decided to reverse the neuromuscular block using sugammadex [3].

Signs of graft rejection must always be ruled out preoperatively, because scientific evidence showed that patients who undergo a surgical procedure and have proven indicators of graft rejection have a higher morbidity compared to those in whom rejection is excluded [13]. For these reasons, a heart muscle biopsy was performed preoperatively in our patient to rule out signs of rejection reaction.

It is better to avoid invasive procedures whenever possible because the risks of various complications (including infection) outweigh the benefits that invasive monitoring can provide, so we decided to use non-invasive monitoring because we assessed that it was an operation with low intraoperative risk and that the patient was stable in terms of comorbidities, thus reducing the risk of infection [14]. This proved to be a good strategy because the patient was hemodynamically stable throughout the operation.

In conclusion, the patient who had a heart transplant four years earlier underwent total thyroidectomy under suspicion of thyroid cancer under general endotracheal anesthesia. In cooperation with the transplant cardiologist, she was well pre-operatively prepared for the operation. She tolerated the operation and GEA well and was discharged from the hospital on the third postoperative day in good condition. This is the first case of operative treatment of a patient with a transplanted heart in Serbia.

Conflict of interest: None declared.

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Анестезија за операцију штитасте жлезде код болесника са трансплантираним срцем – приказ првог случаја у Србији

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САЖЕТАК

Увод Све је већи број пацијената у свету којима је трансплантирано срце, са све бољим и дужим преживљавањем, па самим тим расте и број пацијената који се после трансплантације подвргавају различитим хируршким интервенцијама. То представља изазов за анестезиологе.

Приказ болесника Болесница старости 45 година подвргнута је тоталној тиреоидектомији због сумње на карцином штитасте жлезде. Код болеснице је три године раније учињена трансплантација срца. Преоперативна припрема укључивала је евалуацију срчане функције, консултативне прегледе трансплантационог кардиолога, лабораторијске и друге дијагностичке процедуре, као и детаљну анализу свих 20 медикамената које болесница користи у свакодневној терапији. За премедикацију и општу ендотрахеалну анестезију коришћени су уобичајени лекови, уз пажљиво титрирање доза. Припремљени су и медикаменти за случај појаве поремећаја срчаног ритма имајући у виду да је срце денервисано, али није било потребе за њиховом примену. Операција и постоперативни ток су протекли уредно и трећег постоперативног дана болесница је отпуштена из болнице у добром општем стању.

Закључак Преоперативна припрема, анестезија и постоперативно лечење ове болеснице представљали су изазов за наш тим, који је успешно савладан, с обзиром на то да је ово први случај оперативног лечења пацијента са трансплантираним срцем у Србији.

Кључне речи: тироидектомија; трансплантирано срце; преоперативна припрема

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Large bowel's tumor of unclear histogenetic origin from the group of neuroendocrine tumors with life-threatening hemorrhage and hemorrhagic shock

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SUMMARY
Introduction Neuroendocrine neoplasms (NENs) of the gastrointestinal tract (GIT) are slow-growing and rare tumors with different clinical, histological, and biological characteristics with an increased incidence in recent years. Most of them are indolent and colonic NENs are rare among all GIT-NENs. Compared to colorectal adenocarcinoma neuroendocrine tumors of the colon and sigmoid colon are uncommon.
Case outline We present a 25-year-old female patient, who was admitted to our department in hemorrhagic shock due to life-threatening bleeding from a tumor on the sigmoid colon, and after unsuccessful endoscopic hemostasis during colonoscopy. The complaints started the day before admission to the ward with hematochezia. The patient had no complaints before that. Emergency operation and colon resection with terminal colostomy were performed. Pathohistological and immunohistochemical analysis of the tumor showed unclear histogenetic origin from the group of neuroendocrine tumors.
Conclusion Regardless of the asymptomatic period of the disease, these tumors can cause severe bleeding as the first symptom, which can be life-threatening.
Keywords: neuroendocrine neoplasms; hemorrhagic shock; colon tumors; surgery

INTRODUCTION

Colorectal tumors are one of the most common malignant tumors with around 1.9 million new cases diagnosed in 2020, and the second most common cause of cancer death with the highest incidence in developed countries representing significant medical problems [1]. Although there is a decrease in the frequency of colon neoplasms in the elderly in recent time, in younger adults the frequency is increasing. About 10% of newly diagnosed cases are identified in people younger than 50 years old [2]. Men are at higher risk of developing these neoplasms, in comparison to women with worse prognosis and higher mortality [1].

Neuroendocrine neoplasms (NENs) are rare and among them, large bowel neuroendocrine carcinoma (NEC) appears in less than 1% of all cases. NENs can be benign or cancerous; if they are malignant, these tumors have the property of metastasizing, even though the tumor itself grows very slowly [3].

We are presenting a rare emergency case report of a previously healthy young woman with a life-threatening hematochezia and hemorrhagic shock as a first manifestation of a previously asymptomatic sigmoid tumor from the group of neuroendocrine tumors (NET).

CASE REPORT

A 25-year-old female patient was transferred from the Department of Gastroenterology to the Department of Surgery at the Novi Pazar General Hospital, as an emergency, after a colonoscopy, due to bleeding from the colon. The complaints started the day before admission with bloody stools, followed by weakness, dizziness, and malaise. The patient states that before the onset of bleeding from the colon, she had no complaints. She had a vaginal delivery four months ago; pregnancy course and labor were normal. Abdominal ultrasound and lung X-ray were normal. The patient had no significant comorbidities. In the family medical history, she mentioned the death of the mother and aunt at a young age due to an obscure tumor in the abdomen. During the colonoscopy, a tumor formation in the sigmoid colon with bleeding from an arterial blood vessel at the base of the tumor is observed. Endoscopic hemostasis was attempted, but without success, and as an emergency case, surgery was performed. On admission, the patient was pale, hypotensive, and malaise with red blood cell count 2.14×10^{12}/L, hemoglobin count 68 g/L, platelet count 132×10^{9}/L. The indication for urgent laparotomy was established. The abdomen was opened by medial laparotomy. The abdomen was without the presence of free fluid. A tumor formation was present on the sigmoid colon (Figure 1 A and B), which is why a 130-mm-long resection of the rectosigmoid part of the colon was performed, with a terminal colostomy (Hartman operation). The patient's postoperative course was normal. Treated with conservative therapy with blood transfusion and other supportive therapy. She

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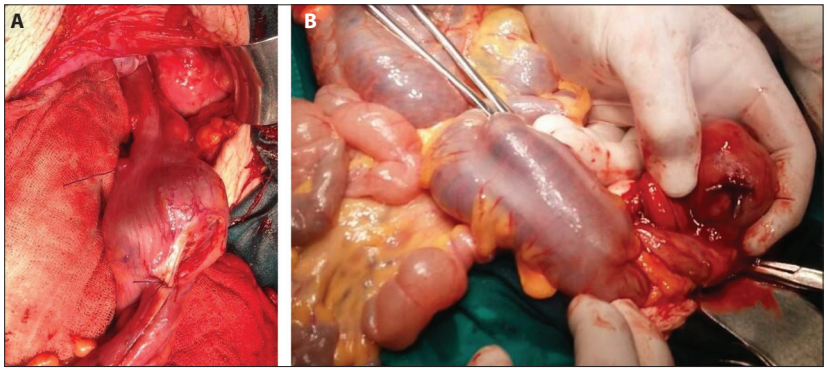

Figure 1. A – sigmoid colon before opening the intestine; B – sigmoid colon after opening and surgical hemostasis – clips from endoscopic hemostasis are observed

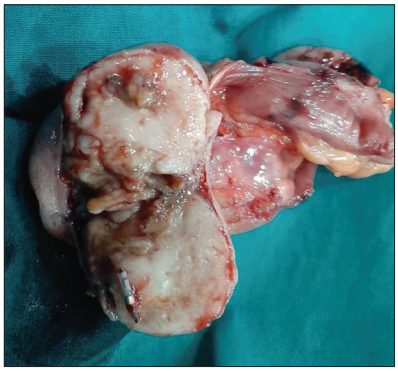

Figure 2. Macroscopic view of the tumor

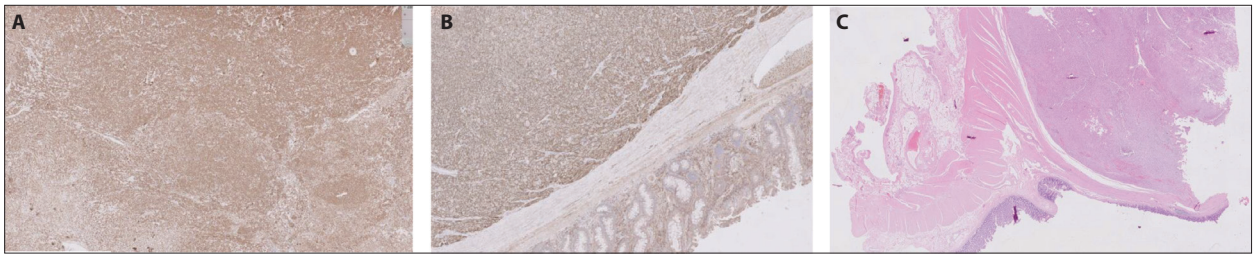

Figure 3. A – NB84 (magnification × 10); B – CD-56 (magnification × 5); C – H&E staining (magnification × 1.25)

was discharged seven days after the operation. After two months, the reconstruction of the colon with colorectal terminal-lateral anastomosis was performed and the continuity of the digestive tract was established. Control computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis, six and 12 months after the operation, were normal.

The pathohistological findings of the tumor indicate that it is an intramural, predominantly submucosal tumor of size 40 × 35 × 35 mm, with a clear limitation towards the muscular layer of the intestinal wall and minor ulcerative changes in the mucosa (Figure 2). Found and analyzed lymph nodes were tumor-free (0/6). There were no tumor cells at the line of bowel resection – R0 resection. Tumor tissue preparation stained with a hematoxylin-eosin method and immunohistochemical staining NB84. The largest number of tumor cells shows strong immunoreactivity to NB84 and synaptophysin, and focally observed immunoreactivity to myogen and actin (SMA-alpha). No immunoreactivity for desmin, Myo-D1, CD117, DOG-1, PDGFRA, CD34, ALK, S-100 protein, GFAP, SOX-10, AE1-AE3, EMA. Positivity on NB84 points to a ganglioneuroblastoma, but the presence of a ganglioneuroma component rich in Schwannoma stroma is not observed in the sample, which is also confirmed by S-100 negative staining. Considering the obtained focal positivity for muscle markers, additional immunohistochemical staining were performed to rule out the presence of a rhabdoid tumor (INI-1+), a tumor from the Ewing/PNET group (CD99-). Only the focally obtained positivity for Melan A. Additional immunohistochemical staining revealed clear membrane positivity for CD56 (Figure 3), and in part of the sample cytoplasmic positivity for chromogranin A. The mitotic index is < 2, and Ki 67 < 3%.

We obtained verbal and written consent from the patient to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the ethical principles of the Declaration of Helsinki.

DISCUSSION

NENs represent an expansive group of neoplasms that differ from each other by a clinical spectrum of manifestations, localization, applied treatment response, geographical distribution, morphology and survival rate. They are primary epithelial neoplasms, with signs of neuroendocrine differentiation diffusely distributed across the mucosa of the gastrointestinal and respiratory tract, but they are also described in the other organs [4]. According to WHO 2019 scheme, NENs are classified into NEC, NET, and mixed neuroendocrine-non NEN (MiNEN) [5]. While NETs can behave indolently (appendix) or more aggressively (in the colon), NEC and MiNEN are aggressive neoplasms that are usually diagnosed at an advanced stage [5]. Based on the degree of differentiation and proliferation activity based on mitotic rate and/or Ki-67 proliferation index. gastrointestinal NETs are categorized into: grade 1 (low grade), grade 2 (intermediate), and grade 3 (high grade). NECs are always high-grade neoplasms, and they are not assigned any grade [6, 7].

About two-thirds of NEN locations are located in the digestive tube and pancreas with the biggest incidence in the

small bowel and rectum [4, 5]. NENs of the colon represent up to 7% of all well-differentiated gastroenteropancreatic NETs and 25% of all gastroenteropancreatic NEC [5]. The frequency of NEN has increased in recent years, probably due to earlier diagnoses, new genetic-molecular and immunohistochemical methods development as well as more available sophisticated diagnostic procedures such as endoscopy and radiology imaging (CT, MRI, and ultrasound), but they are still rare. The incidence of rectal and colonic NENs is 0.2 and 1.2 new cases per 100,000 persons/year [6], and colon NEC accounts for 1% of all colorectal cancers [3].

Genetic studies of NET and NEC are still ongoing. It has been found that in gastrointestinal NEC there are mutations in the TP53 and RB1 genes similar to those in pancreatic lesions. On the other hand, NETs often do not have recurrent mutations, so genetic analysis for diagnostic purposes in NETs has not proven to be relevant [6]. Riechelmann et al. [8] indicate that in NENs carcinogenesis in young adults there is a significant role of inherited genetic alterations, particularly in DNA repair genes, which can lead to the possibility of a higher frequency of cancer and NEN in the family. In our case, a positive family history of the death of the mother and aunt at a younger age from an obscure tumor in the abdomen may raise the suspicion that it is a hereditary disorder, but the cause of the death of the mother and aunt was not identified through the medical documentation.

These tumors most often appear in the seventh decade of life. The most common site of occurrence of colon NENs is the right colon and cecum [3]. In our case, the patient was a young 25-year-old woman and a tumor was located on the sigmoid colon.

A large percentage of these tumors are asymptomatic and are discovered as an incidental finding during the surgery or colonoscopy, but there are patients who also have symptoms. Clinical symptoms also depend on whether they occur in the right or left colon and may manifest as anemia, weight loss, abdominal discomfort, dyspeptic symptoms, bleeding, obstructive symptoms and constipation. The diagnosis is usually made after a biopsy during a colonoscopy or after surgery. About 10% of patients with NETs will experience carcinoid syndrome, caused by the overproduction of serotonin or other hormones secreted by some NETs [9]. Our patient was asymptomatic until the lower gastrointestinal bleeding occurred.

Acute lower gastrointestinal bleeding accounts for up to 20% of all cases of gastrointestinal bleeding and is defined as bleeding distal to the Treitz ligament. It can manifest as melena or hematochezia. Endoscopic diagnostic methods (colonoscopy and gastroscopy) with endoscopic hemostasis are indicated in patients with these symptoms [10, 11, 12]. Sometimes these bleedings can lead to massive blood loss and emergency conditions in some patients. In our case, due to failed endoscopic hemostasis during colonoscopy, and due to the poor general condition caused by sudden bleeding and huge blood loss, an urgent surgical intervention was performed. We did not wait for the findings of the tumor biopsy to operate, because it was an emergency case, and therefore the operation was not performed according to all oncological principles.

Diagnosis of NEN, apart from clinical examination and history, involves determining the level of tumor markers (5- HIAA and chromogranin A (CgA), radiological methods (CT, MRI), positron emission tomography (PET); PET combined with CT, has become imaging gold standard and simultaneous high-contrast PET-MRI can be important clinical tool for the whole-body imaging in one place [13]), upper and lower endoscopy, pathohistological verification and immunohistochemical methods. Pathohistological verification represents the gold standard for the diagnosis of NENs (recommended by the European Neuroendocrine Tumor Society) [14] and includes standard hematoxylin-eosin staining and supplementary immunohistochemical tests [including cytosolic markers (neuron-specific enolase), synaptophysin, cell membrane-specific markers (CD 56) and CgA] [4]. Histologic features of colorectal NETs and NECs are similar to those in other organs. Ki-67 index and mitotic index correlate with cellular proliferation. Ki-67 proliferation index alone cannot be used to distinguish NETs from NEC [6].

From the above, it can be said that in our case report it is a tumor of unclear histogenetic origin and that the immunohistochemical activity of tumor cells with neuroendocrine markers is most indicative of belonging to the group of NETs.

In conclusion, due to all the characteristics of NEN, it is difficult to manage; and that is why early diagnosis, knowledge of this disease, and adequate treatment are very important. Also, regardless of the asymptomatic period of the disease, these tumors can cause severe bleeding as the first symptom, which can be life-threatening.

Conflict of interests: None declared.

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Тумор дебелог црева нејасног хистогенетског порекла из групе неуроендокриних тумора са крварењем опасним по живот и хеморагичним шоком

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Општа болница Нови Пазар, Нови Пазар, Србија

САЖЕТАК

Увод Неуроендокрине неоплазме гастроинтестиналног тракта су споро растући и ретки тумори различитих клиничких, хистолошких и биолошких карактеристика са повећаном инциденцом последњих година. Већина њих је индолентна и неуроендокрине неоплазме дебелог црева су ретке међу свим неуроендокриним неоплазмама гастроинтестиналног тракта. У поређењу са колоректалним аденокарциномом, неуроендокрини тумори дебелог и сигмоидног колона су ретки.

Приказ болесника Представљамо болесницу стару 25 година, која је примљена на наше одељење у хеморагичном шоку због животно опасног крварења из тумора на сигмоидном колону, а после неуспешне ендоскопске хемостазе током колоноскопије. Тегобе су почеле са хематохезијом дан пре пријема на одељење. Болесница је навела да пре тога није имала никаквих тегоба. Урађена је хитна операција и ресекција дебелог црева са терминалном колостомом. Патохистолошка и имунохистохемијска анализа тумора показале су нејасно хистогенетско порекло из групе неуроендокриних тумора.

Закључак Без обзира на асимптоматски период болести, ови тумори као први симптом могу изазвати јака крварења, која могу бити опасна по живот.

Кључне речи: неуроендокрине неоплазме; хеморагични шок; тумори дебелог црева; хирургија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Migration of biliary endoprosthesis – case report and literature review

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SUMMARY

Introduction The most common indications for placing a biliary stent are benign and malignant diseases that interfere with the normal flow of bile through the extrahepatic bile ducts. This procedure carries the risk of developing early and late complications.

Case outline We present a case of a 63-year-old female patient admitted to our hospital for additional diagnostics and treatment. At admission the patient reported the onset of the following symptoms several days prior to hospitalization: severe abdominal pain, predominantly in the upper quadrants, nausea, vomiting, and icterus. With the initial idea of carrying out non-surgical treatment of this condition, the patient was referred for endoscopic retrograde cholangiopancreatography for the purpose of endoscopic calculi extraction. However, due to technical difficulties, the aforementioned procedure was not carried out. Instead, upon endoscopic papillotomy, a plastic biliary stent was placed. The second day after the procedure, the patient reported passing dark stools. After that, an esophagogastroduodenoscopy was performed, which revealed a biliary stent in the duodenum, but without active bleeding. As part of the same procedure, the biliary stent was removed, and the next day the patient underwent surgical treatment.

Conclusion In order to prevent and reduce the incidence of adverse effects and complications, special caution should be applied when performing the procedure. It is even more important to timely recognize the occurrence of complications and to treat them promptly, in order to achieve the best treatment outcomes possible.

Keywords: biliary stent; duodenum; procedure; complications

INTRODUCTION

One of the significant complications that may occur after endoscopic retrograde cholangiopancreatography (ERCP) and biliary stent (BS) placement, is stent migration. In current literature, this complication has been described in 5–10% of the cases [1]. The most common indications for the placement of the BS are benign and malignant diseases which obstruct the normal flow of bile through extrahepatic bile ducts. This procedure carries the risk of the development of early complications, such as bleeding, pancreatitis, cholangitis, and perforation, as well as the risk of the occurrence of delayed (late) complications, such as stent migration and late perforation [2, 3].

The aim of our study is to present a rare case of early BS migration. We also present the endoscopic resolution of the said complication, as well as the definitive treatment and the treatment outcome.

CASE REPORT

We present the case of a 63-year-old female patient admitted to our hospital for additional diagnostics and treatment. Her medical records showed that she had been surgically treated 15 years earlier, when cholecystectomy had been performed, as well as that she was being treated for hypertension. At admission, the patient reported the onset of the following symptoms several days prior to hospitalization: severe abdominal pain, predominantly in the upper quadrants, nausea, vomiting, and jaundice – icterus. Upon clinical examination and laboratory test analyses, which showed elevated inflammation markers (leukocytes: 14×10^9/L, C-reactive protein: 87 mg/L, as well as a total bilirubin level of 245), magnetic resonance imaging (MRI) of the abdomen with magnetic retrograde cholangiopancreatography (MRCP) was performed, which verified diffuse dilatation of the bile ducts, as well as calculi in the common bile duct (Figure 1).

With the initial idea of carrying out non-surgical treatment of this condition, the patient was referred for ERCP for the purpose of endoscopic calculi extraction. However, due to multiple large stones, the aforementioned procedure was attempted but not carried out. Instead, upon endoscopic papillotomy, a 10-French plastic BS was placed. A second ERCP attempt was planned within three months. After the procedure, the

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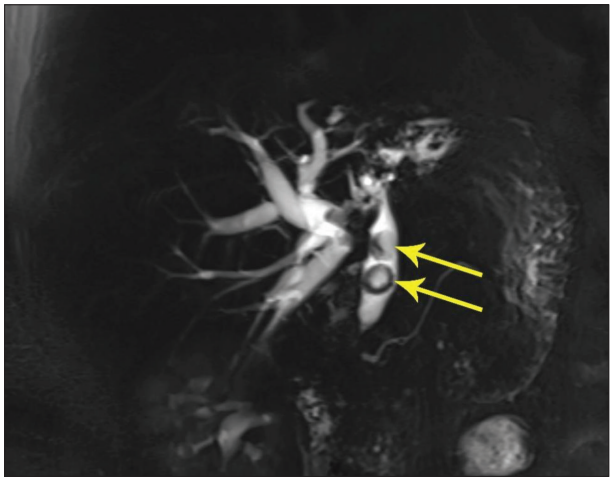

Figure 1. Preoperative magnetic resonance imaging of the abdomen; stones in the main bile duct are marked with yellow arrows

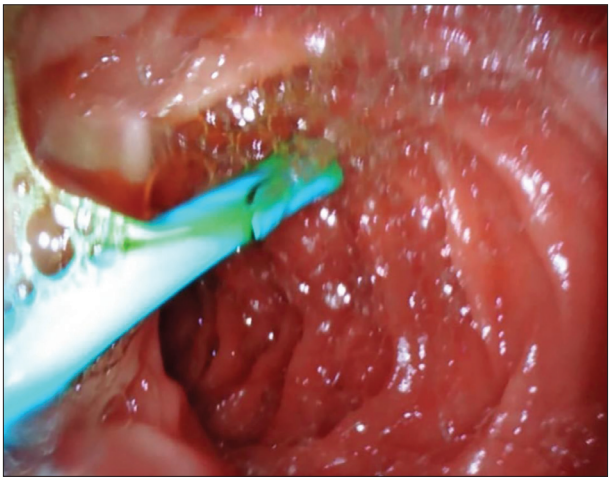

Figure 2. Esophagogastroduodenoscopy finding with a migrated biliary stent in the duodenum

patient was feeling well. However, on the second day after ERCP, the patient reported passing a dark stool, which had the hue of coffee dregs. Examination verified a dark stool, upon which esophagogastroduodenoscopy (EGD) was performed, which revealed the BS in the duodenum, however, without active bleeding (Figure 2). Within the same procedure, the BS was removed, while the patient was surgically treated on the following day, whereby a biliary bypass was performed, i.e., Roux-en-Y hepaticojejunostomy.

The patient was discharged from hospital to recover at home on the fifth postoperative day, while the follow-up MRI and MRCP, upon six months, showed a normal finding. The patient currently still comes in for regular follow-up.

All the procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DISCUSSION

It has been 40 years since Soehendra and Reynders-Frederix first described the placement of a BS into the common bile duct, which has become an alternative procedure for patients who are not eligible for surgical treatment, in many benign and malignant diseases. In most cases, the placement of the BS is free from complications; however, a certain percentage of complications is unavoidable. The most frequent complications range from stent migration, intestinal lesions, to complications with a lethal outcome [4, 5].

Distal migration of the BS represents the most frequent complication, as well as the most frequent cause of the development of further complications. According to the data from current literature, its incidence is around 6%. The duodenum is the localization with the highest incidence of lesions, although perforation occurs in only 1% of the cases [6, 7]. Extrahepatic stent migration is very rare, but pleural effusion, bronchobiliary fistula, biliary pneumonitis, hepaticogastric fistula, and abdominal wall abscess have been reported after stent migration through the liver capsule [8, 9, 10].

In most documented cases, late BS migration was reported, and it usually occurred weeks or even months after the procedure. Early migration, such as the one we have presented in our case, is a rare occurrence [11].

In our patient, common bile duct was dilated, with a maximum diameter of 17 mm. In the current literature, possible risk factors for BS migration have been described, such as common bile duct diameter > 10 mm; time elapsed since stent placement > one month; stent of a greater diameter; performing endoscopic sphincterectomy prior to stent placement, etc. [12]. In our case, the patient had undergone endoscopic papillary sphincterotomy before the occurrence of bile duct stent migration. Endoscopic sphincterotomy before stent placement and a long BS are considered risk factors for migration of the distal part of the stent rather than its proximal part [13].

The most frequent signs and symptoms following BS migration and the possible development of further complications (such as intestine perforation and the like) include abdominal pain, the elevation of inflammation markers in laboratory test results, and the elevation of amylase levels. However, the elevation of inflammation markers in laboratory test results and the elevation of amylase levels may be evidence of acute pancreatitis, which is yet another possible complication [12, 14].

In the case report that we present, migration of the BS into the duodenum occurred within the first 48 hours of placement, with non-specific symptomatology. After the occurrence of a dark stool, EGD and stent removal was indicated.

The diagnostics, in such cases, comprises the analysis of laboratory parameters, the clinical presentation, the present symptomatology, the findings of abdominal computerized tomography, as well as repeated EGD [14].

In our case, the BS was not the option of first choice, i.e., it was placed as a temporary solution, upon unsuccessful

endoscopic treatment, whereby surgical treatment was the only remaining option for further treatment and resolution of the complications that had developed.

The treatment of complications can be surgical or non-surgical, depending on the previous indication for the placement of a BS, as well as on the degree of the complications that occur. Surgical treatment is performed when, even after the removal of the migrating stent, the status is such that it cannot be resolved endoscopically, or when the BS has previously been placed as a temporary solution. Non-surgical treatment involves endoscopic BS removal and further conservative treatment [14, 15].

The placement of a BS is a definitive or temporary treatment option for most benign and malignant diseases of the biliary tree. Although this is mostly an efficient and safe method, it still carries with it certain risk factors for the development of complications. In order to prevent and reduce the incidence of adverse effects and complications, special caution should be applied when performing the procedure. It is even more important to timely recognize the occurrence of complications and to treat them promptly, in order to achieve the best treatment outcomes possible.

Conflict of interest: None declared.

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Мигрирајућа билијарна ендопротеза – приказ болесника и преглед литературе

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САЖЕТАК

Увод Најчешће индикације за постављање билијарног стента су бенигне и малигне болести које ометају нормалан проток жучи кроз екстрахепатичне жучне канале. Ова процедура носи ризик од развоја раних и касних компликација.

Приказ болесника Представљамо случај 63-годишње болеснице која је примљена у нашу болницу због додатне дијагностике и лечења. На пријему је болесница навела тегобе које су почеле неколико дана пре хоспитализације: јак бол у стомаку, претежно у горњим партијама, мучнина, повраћање и иктерус. Првобитна идеја је била спровођење нехируршког лечења. Болесница је упућена на ендоскопску ретроградну холангиопанкреатографију ради ендоскопске екстракције камења из главног жучног вода. Међутим, због техничких потешкоћа, наведени поступак није спроведен. Уместо тога, након ендоскопске папилотомије, постављен је пластични билијарни стент. Другог дана после процедуре, болесница је пријавила да има тамну столицу. Након тога је урађена езофагогастродуоденоскопија, која је открила билијарни стент у дуоденуму, али без активног крварења. У оквиру истог поступка уклоњен је билијарни стент, а сутрадан је болесница подвргнута хируршком лечењу.

Закључак Да би се спречила и смањила инциденца нежељених ефеката и компликација, при извођењу процедуре пласирања билијарног стента потребан је посебан опрез. Још важније је благовремено препознати појаву компликација и благовремено их лечити, како би се постигао што бољи исход лечења.

Кључне речи: билијарни стент; дуоденум; процедура; компликације

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Fascial turnover flap – an effective method to resolve cartilage exposure after autologous microtia reconstruction

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SUMMARY

Introduction Microtia presents a congenital ear deformity ranging from a minor and barely visible defect to a complete absence of the ear. Currently, there are three options for ear reconstruction: autologous costal cartilage, silicon prothesis, and prosthetic ear. Ear reconstruction with autologous costal cartilage is usually performed in two stages. During the first stage, the cartilaginous framework is fabricated and placed under the skin, in the anatomical position of the ear. In the second stage, the elevation of the frame is performed. During these procedures, complications such as vascular compromise of the skin envelope can occur. Cartilage exposure can lead to its resorption and distortion, leading to an unsatisfactory anatomical result, and this should be resolved as soon as possible. Cartilage exposure at the convex part of the frame is especially problematic. The goal of this paper is to show that fascial turnover flap is a safe method to deal with cartilage exposure as a complication.

Outlines of cases We present two patients with anotia and hemifacial microsomia. Both underwent autologous cartilage microtia repair. In both patients, the cartilage exposure at the convex part of the ear was revealed as a complication. Fascial turnover flap has been used to resolve this complication in both patients.

Conclusion Fascial turnover flap is a safe method to deal with cartilage exposure after microtia reconstruction with autologous cartilage.

Keywords: microtia; complications; necrosis; flap; fascial

INTRODUCTION

Microtia is a congenital malformation of the ear with multifactorial etiology that can be expressed as a minimal structural abnormality or a complete absence of the ear [1–6]. Microtia is dominantly unilateral, on the right side, and occurs more frequently in males [1, 2, 3]. Some ethnic groups (Hispanics, Native Americans, Andeans, and Asians) have a significantly higher incidence than others [2, 5]. There are different classification systems adopted for microtia [1, 2, 4, 5].

Management of the microtia includes: no treatment, autologous costal cartilage reconstruction, surgical reconstruction with a synthetic biocompatible porous polyethylene implant, and prosthetic ear placement [2–9].

Reconstruction with autologous costal cartilage graft is usually performed when a patient reaches 8–10 years of age [2–5, 8, 9]. At this age, adequate costal cartilage stock for reconstruction is achieved [8, 9]. The number of required stages (three to four stages) is reduced and now this procedure is mostly performed in two stages [3, 4, 5, 8].

A surgical classification scheme that is applicable to all types of microtia was introduced by Dr Françoise Firmin, who established her own two-stage autologous technique for microtia reconstruction [8, 9]. At the first stage, costal cartilage is harvested from the ipsilateral side through obliquely oriented skin incision with access to the fifth to ninth ribs [3, 5, 8, 9]. The constructed cartilaginous framework is placed in the previously prepared skin pocket [2, 3, 6, 8, 9]. The second stage is usually performed six months after the first operation, and during this stage the elevation of the ear is performed, followed by skin lining of the sulcus [2, 3, 4, 8, 9]. There are three types of skin incisions, three types of frameworks, and three different projection pieces according to Dr. Firmin's classification.

Skin incisions (in correlation with the location of the lobule and the types of framework required) are divided into type 1, type 2, and type 3 (a, b); frameworks are divided into the following: type I – includes base, helix, antihelix, antitragus, and tragus; type II – includes base, helix, antihelix, and antitragus; and type III – includes base, helix, and antihelix; and projection pieces (that can be added to provide stability and projection of the framework) are divide into PI, PII, and PIII [8, 9].

There are four types of second stage according to Dr. Firmin (type A, B, C, and D). Types A and B are modifications of Nagata's and Brent's technique, type C is rarely used, and type D is

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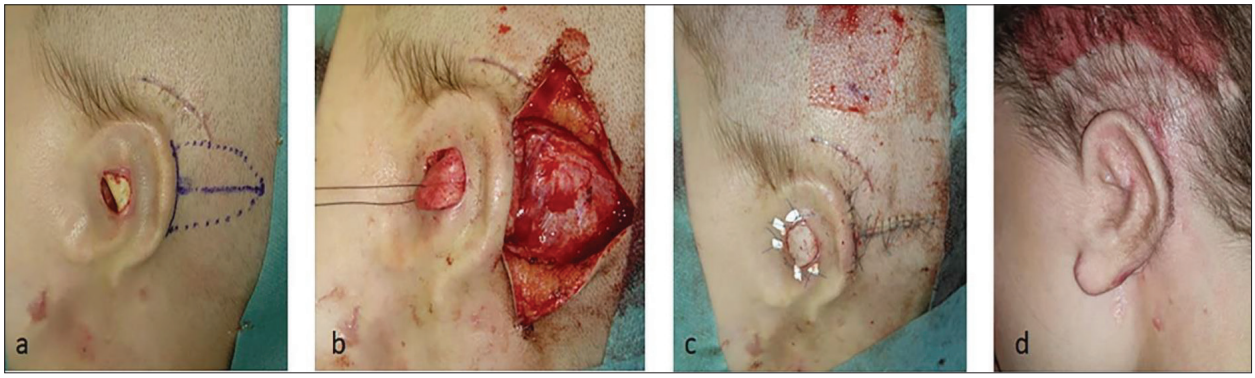

Figure 1. a: Skin necrosis at the central part of the antihelix projection after left side anotia; reconstruction with autologous cartilage; **b:** retroauricular fascial turnover flap, raised and rotated upward, placed over the cartilage; **c:** retroauricular fascial turnover flap fixed and covered with split-thickness graft; **d:** the definitive result after the second stage, with deformation of the middle antihelix

Dr. Firmin's own method, most commonly used in her practice (also known as the "tunnel" technique) [8, 9, 10].

Children who undergo high-density porous polyethylene implantation are candidates at a younger age, typically when three to five years old [2–6, 10]. The temporoparietal fascial flap (TPF) is used to cover the implant [2, 4, 10]. This procedure is used as an alternative to autologous costal cartilage graft for ear reconstruction [there is a higher rate of infection and extrusion (if TPF is not used) compared to autologous costal cartilage reconstruction] [5, 6]. The ear prosthesis is an alternative to surgical reconstruction and this procedure should be considered for some specific cases [4–7, 10]. The future of ear reconstruction is strongly influenced by bioengineering, and there are already papers confirming safety and stability of framework by using autologous cell-engineered chondrocytes [6, 11].

There is a high association between microtia and aural atresia [3, 4, 10]. Hearing should be closely monitoring through development [3, 10]. Ear reconstruction does not affect hearing, and atresiaplasty is usually performed after auricle reconstruction with autologous costal cartilage [4, 5, 10, 12]. Auricular reconstruction can be associated with minor or severe surgical complications [8, 13–18]. Only a few studies related to complications following ear reconstruction with autologous costal cartilage graft have been published [13–18]. These acute complications include donor site complications (pneumothorax from costal cartilage harvest), and recipient site complications such as infection (skin or cartilage), extrusion of cartilage framework, changes in framework size and migration of the frame [13–16]. In this paper we present our experience in treatment of skin necrosis and cartilage exposure following microtia reconstruction with autologous costal cartilage graft.

REPORTS OF CASES

Case 1

A 14-year-old female was admitted for ear reconstruction for left side anotia as a part of ipsilateral hemifacial microsomia. Excision of the preauricular sinus and preauricular appendices was performed prior the auricular reconstruction. According to Firmin surgical classification scheme, framework Type I was constructed, and placed subcutaneously using the 3b skin approach [6, 10]. Two drains close to the ear under continuous suction were used. Skin discoloration at the antihelix projection was spotted on the third postoperative day, followed by complete skin necrosis evident on the 13th postoperative day despite constant conservative treatment (gentle debridement and continuous application of antibiotic ointment or Vaseline gauze dressing) (Figure 1a). The decision to perform surgical treatment of the necrosis was made. Retro auricular fascial turnover flap was planned, raised, and rotated upward (Figure 1b). After performing the dissection between the frame base and antihelix, the flap was placed through and over the cartilage, and fixed (with care to prevent skin necrosis). Split thickness skin graft was placed over the flap (Figure 1c). The postoperative period was uneventful. The long-term result showed a slight deformation of the medial part of the antihelix (Figure 1d).

Case 2

A 13-year-old female was admitted for ear reconstruction for left side microtia. Clinically, only a small part of the lobule was present. According to the Firmin's surgical classification scheme, framework type I was constructed, and placed subcutaneously using type 3 skin approach, followed by two drains placed under continuous suction (Figure 2a) [10]. Skin necrosis was spotted on the seventh postoperative day at the central part of the antihelix projection (Figure 2b). Conservative wound treatment was immediately started but without success (debridement, antibiotic ointment treatment, and full-thickness graft placement). Cartilage exposure was definitive. Fascial turnover flap was raised and placed on the16th postoperative day by the same technique used for the first case (Figure 2c). Postoperative period was uneventful. Stitches were removed on the 14th postoperative day (Figure 2d).

The subjects' written consent was obtained, and the study has been approved by the competent ethics committee, and it conforms to the legal standards.

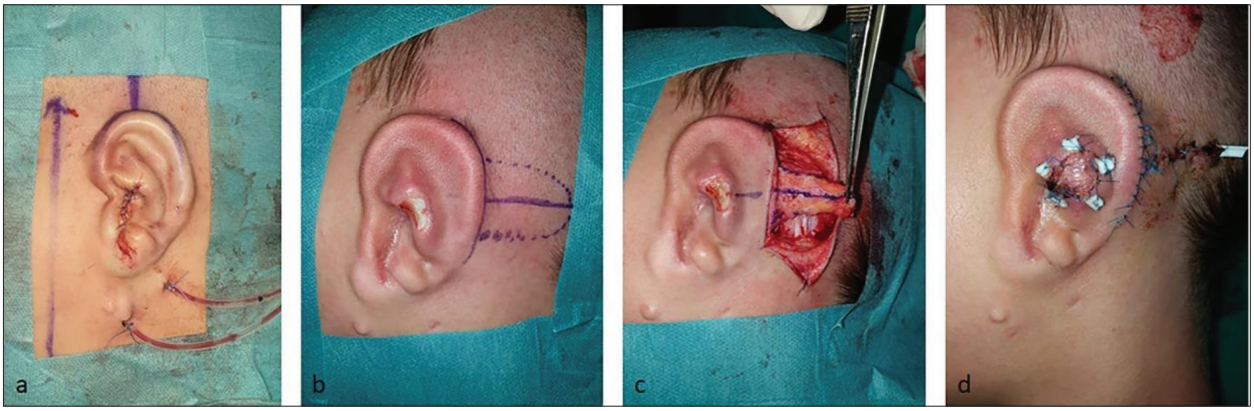

Figure 2. a: Intraoperative result after left-side anotia reconstruction with autologous cartilage; **b:** complete skin necrosis and cartilage exposure; **c:** retroauricular fascial turnover flap, raised; **d:** postoperative result with split-thickness graft placed over the flap

DISCUSSION

Microtia reconstruction presents an extremely demanding procedure [2, 3, 5, 8]. Surgeons involved in this subject need to have experience especially in reconstructive and ear surgery. It is very important that the surgeon undergoes training in harvesting of the framework before starting surgical treatment of ear deformities [8, 9]. During ear reconstruction surgery, even the smallest details can affect the final result, such as carefully harvesting the rib cartilage, choosing the adequate framework type, optimal skin approach, constant postoperative follow-up, and constant monitoring of drainage treatment, including autologous costal cartilage reconstruction, surgical reconstruction with a high-density porous polyethylene implant, and prosthetic ear placement [2–10, 12].

Auricular reconstruction with autologous cartilage should be performed at the age of 8–10 years [2, 5, 6, 8, 9]. During the past several decades, surgical technique for ear reconstruction has been significantly improved and the number of procedures has been reduced [2, 5, 8, 10]. Françoise Firmin created a surgical classification scheme applicable to all types of microtia, and she established her own two-stage autologous technique for microtia reconstruction [6, 8, 9, 10]. There are only a few published studies about complications after autologous microtia reconstruction [2, 6, 13–18]. The range of complications vary 0–33% (by some authors these rates range 0–72%, probably due to differences in experience with the procedure [14, 18]. Wound infection is the most common complication reported [18]. Complications can occur both at the donor (atelectasis, pleural tear, chest wall deformities) or the recipient site (infection, hematoma, skin necrosis, frame exposure, cartilage absorption, wire or suture extrusion, helix broken, keloids, etc.) [13–18]. Hair growth on the on the reconstructed auricle can be considered a minor complication, successfully solved by permanent hair removal. Fu et al. [13] stated that at the recipient site complications occur in 10% of patients after using Brent and Nagata technique for ear reconstruction, with or without meatoplasty. There are different techniques for treating complications, such as local flaps, TPF coverage with skin grafts, turnover fascial flap, etc., and the technique selection is based on the location involved [14, 15]. According to Dr. Firmin, cartilage exposure less than 3 mm can be treated conservatively (by some authors, the cartilage exposure less than 10 mm) [15]. In both of our cases, skin loss was less than 10 mm but we could not achieve wound healing with conservative approach. In both our cases, surgical treatment was necessary.

In our group of 33 patients with microtia (two bilateral) and three patients with traumatic ear amputations (38 reconstructions in total) that were operated on using the Firmin's technique, there were four cartilage exposures (10.52%). Two of them (5.26%) had the exposure of cartilage at the posterior part of the helix after skin graft necrosis (less than 3 mm), and we manage to resolve this by conservative treatment. Two patients (5.26%) had cartilage exposure at the antihelical region (near 10 mm), and both of them were resistant to conservative treatment. We used a fascial turnover flap and a skin graft to cover the cartilage, according to instructions of Dr. Firmin [8].

A "T" incision was made on the skin with short limbs along the helical rim of the framework and long limb posteriorly over the mastoid region. The fascial flap was harvested and elevated from the deep mastoid fascia. The fascial flap was turned over and placed through the tunnel of cartilaginous framework and then over the cartilage. The fascial flap was covered by a skin graft. In both cases the same surgical procedure was applied. The postoperative period was uneventful. In our opinion, the optimal period for the reconstruction of skin necrosis is between the 10th and the 15th postoperative day, when the necrosis demarcation is complete. A prolonged period of conservative treatment can lead to the loss of the anatomical appearance of the cartilage. Complications of the turnover fascial flap procedure include flap necrosis, skin graft necrosis, and frame distortion. The turnover fascial flap surgery followed by skin graft placement was performed successfully in both patients and the result of this approach was complete healing of the wound, with acceptable aesthetic result.

CONCLUSION

Turnover fascial flap is an effective method to resolve cartilage exposure after microtia reconstruction. The advantages of this technique are that skin incisions are placed along the lines for the incisions that will be performed during the second stage, there is no need for distant flaps, and the chondral frame stays anatomically preserved. Flap vascularization is reliable and it can be used for defects of high variety in size. This method is in our experience shown to be applicable for cartilage exposure at the convex parts of the ear. We strongly advocate turnover fascial flap for cartilage exposure after ear reconstruction.

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Фасцијални режањ – ефикасан метод за решавање изложености хрскавице после реконструкције микротије аутологном хрскавицом

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САЖЕТАК

Увод Микротија представља урођени деформитет уха који се може манифестовати као мали и једва видљиви деформитет па чак и као потпуно одсуство уха. Тренутно постоје три опције за реконструкцију уха и то коришћењем аутологне ребарне хрскавице, силиконске протезе и протезе. Реконструкција уха аутологном ребарном хрскавицом се обично изводи у две фазе. У првој фази се израђује хрскавични оквир који се поставља испод коже, у анатомску позицију уха. У другој фази се врши подизање оквира. Током ових процедура може доћи до компликација, као што је ослабљена васкуларизација кожног омотача. Излагање хрскавице може довести до њене ресорпције и изобличења, што доводи до незадовољавајућег анатомског резултата и то треба што пре решити. Посебно је проблематично излагање хрскавице на конвексном делу рама. Циљ овог рада је да покаже да је фасцијални обрнути режањ сигуран метод за решавање експозиције хрскавице као компликације.

Приказ болесникâ Представљамо два болесника са анотијом и хемифацијалном микрозомијом. Оба болесника су подвргнута реконструкцији микротије аутологном хрскавицом и код оба болесника је као компликација откривена експозиција хрскавице на конвексном делу уха. За решавање ове компликације коришћен је фасцијални обрнути режањ.

Закључак Фасцијални обрнути режањ је безбедан метод за решавање изложености хрскавице после реконструкције микротије аутологном хрскавицом.

Кључне речи: микротија; компликације; некроза; режањ; фасција

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Preoperative embolization of juvenile nasopharyngeal angiofibroma using medium to large size particles

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SUMMARY

Introduction Juvenile nasopharyngeal angiofibroma are benign tumors, with locally aggressive behavior. Preoperative tumor embolization with polyvinyl alcohol particles can reduce intraoperative blood loss and facilitate surgical resection.

Case outline A 16-year-old male was admitted to hospital due to profuse epistaxis and sense of nose fullness. Multidetector computed tomographic angiography examination showed a tumor mass in the right nasal cavity with extension to the right maxillary sinus and ethmoidal cells on the right, and in the left nasal cavity. It rested on the nasal septum, but without bone destruction. After application of contrast agent, described mass became intensely opacified. Preprocedural digital subtraction angiography of external and internal carotid arteries of both sides showed extensive pathological vascularization, which received main contribution from branches of maxillary artery on right and, to a lesser extent, on left side. Due to danger of penetration of a particle embolization agent of smaller diameter into orbital branches and possible retrograde migration into carotid artery, we decided to apply particle embolization agent of larger diameter (500–700 μm) than prescribed by modern standards. Tumor was completely surgically removed third day after embolization, and patient was discharged without any neurological deficit. Control contrast enhanced multidetector computed tomographic angiographies were performed at third and seventh month after surgery and showed no tumor residue or recurrence.

Conclusion The use of particles of larger diameter gave satisfactory results during operation – surgical excision of tumor, when dangerous anastomoses do not allow use of particles of smaller diameter and can be safely performed without significant neurological nor systemic complications.

Keywords: juvenile nasopharyngeal angiofibroma; embolization; large size particles

INTRODUCTION

Juvenile nasopharyngeal angiofibromas (JNA) are benign tumors, that grow from the posterior nasopharynx, typically along the sphenopalatine opening and are locally aggressive with extension into the pterygopalatine fossa, maxillary sinus, anterior nasal cavity, orbit, sphenoid sinus, base of the skull, and possibly, the intracranial compartment and cavernous sinus [1–5].

Preoperative tumor embolization with polyvinyl alcohol (PVA) particles has been adopted as routine protocol, and can significantly reduce intraoperative blood loss and thus, facilitate surgical resection in tumors vascularized predominantly from external carotid artery branches [2, 6, 7].

CASE REPORT

A 16-year-old male, was admitted to the hospital due to profuse epistaxis and sense of fullness in the nose. Multidetector computed tomographic angiography (MDCT) examination showed a tumor mass in the right nasal cavity, measuring 54 × 42 × 21 mm (antero-posterior × caudo-cranial × latero-lateral diameter; AP × CC × LL) with extension to the right maxillary sinus and ethmoidal cells on the right, and posterior parts of the left nasal cavity. The described mass rested on the nasal septum, but without bone destruction. After application of the contrast agent, tumor became intensely opacified (Radkowski IIb) [8] (Figure 1A and 1B).

In the angio-suite, under conditions of analgosedation and subcutaneous anesthesia in the region of the right groin, the 6F sheath was positioned in the femoral artery, through which the guiding catheter Envoy 6F (Cerenovus, Irvine, CA, USA) was introduced. Preprocedural digital subtraction angiography of the external carotid arteries (ECA) and internal carotid arteries (ICA) of both sides showed extensive pathological vascularization, which received the main contribution from the branches of the maxillary artery on the right, and, to a lesser extent, on the left side. We positioned the guide catheter in the right maxillary artery, through which, microcatheter Prowler 21 (Codman Neurovascular, Raynham, MA, USA) was advanced in the distal third of the

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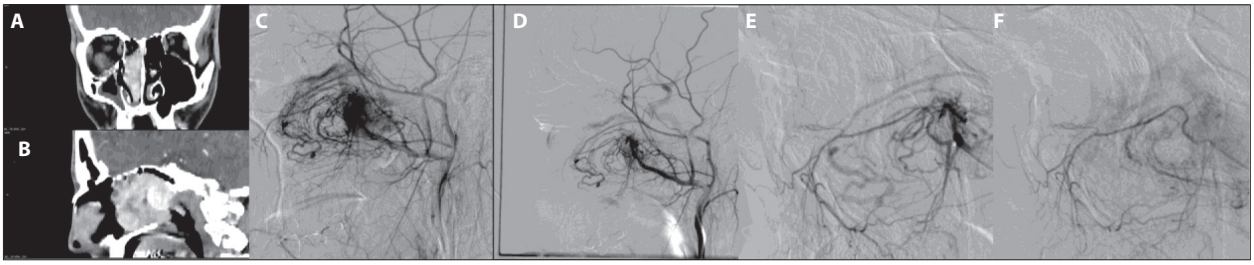

Figure 1. A – coronal and B – sagittal contrast-enhanced computed tomography showed tumor mass in the right nasal cavity; C – right and D – left external carotid artery digital subtraction angiography demonstrated pathological vascular network; E and F represent superselective angiograms

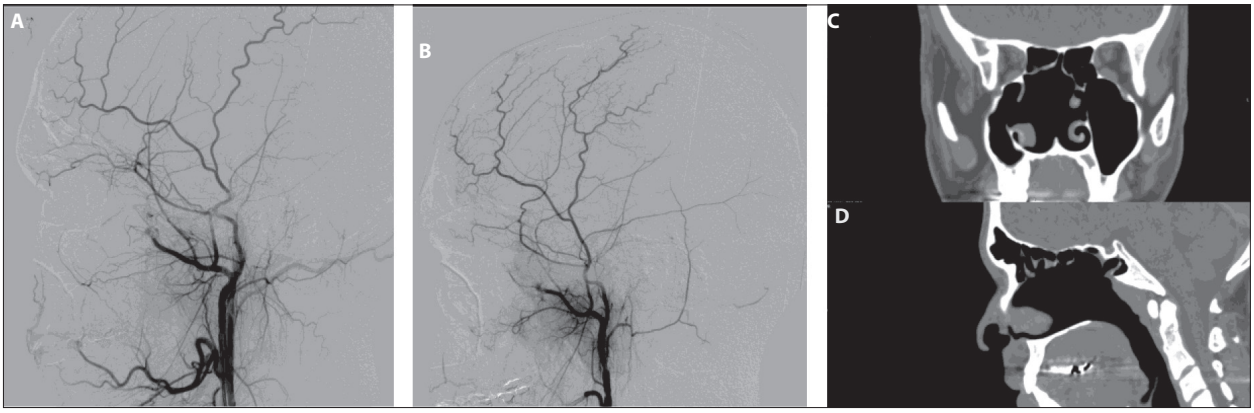

Figure 2. A – right and B – left external carotid artery post-procedural digital subtraction angiography showed maximal reduction of tumor vascularization; C – coronal and D – sagittal contrast-enhanced computed tomography after seven months showed no tumor residue nor recurrence

maxillary artery. Superselective angiograms showed the communication between the right sphenopalatine artery and the right orbital arteries. Due to danger of penetration of a particle embolization agent of smaller diameter into the orbital branches and possible retrograde migration into the ICA, we decided to apply a particle embolization agent of larger diameter than prescribed by modern standards, 500–700 μм Embosphere® (Microspheres, Merit Medical, South Jordan, UT, USA). When an angiographically satisfactory degree of occlusion of the tumor from the right maxillary artery was achieved, same procedure was performed at the contralateral side (Figure 1C–F).

Tumor was surgically removed third day after embolization. Complete resection was achieved with a total of two units of blood used intraoperatively (550 ml). He left the clinic in good general condition, without neurological deficit (modified Rankin scale 0).

Control MDCT examinations, with and without contrast agent application, were performed at third and seventh month after surgery and showed no tumor residue or recurrence (Figure 2).

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

Management of JNA is challenging because of its rich vasculature, complex anatomy of the affected region, and the young age of the population [9, 10].

The modern approach of a combination of preoperative angiography, embolization, and endoscopic surgery has facilitated and made the surgical treatment of JNA much safer [8, 9, 11–18]. Recommended mean particle size for this type of tumor should be 200 μм [19]. In a series of 19 patients, Ballah et al. [20] reported a mean intraoperative blood loss of an average of 655 mL (range 50–2000 mL). Chan et al. [11] in a series of 37 patients described an average blood loss of 2660 mL in the group where open surgery or endoscopic surgery was performed, while an average of 2029 mL was lost in the group where patients underwent a combination of open and endoscopic surgery. Overdevest et al. [1] in a series of 26 patients reported that the mean value of intraoperative JNA blood loss vascularized exclusively from ECA branches was 762 mL. The mean value in 14 cases with bilateral vascularization was as much as 2146 mL compared to unilateral in which this value was 617 mL of blood. It also states that post-embolizing tumor blush was not associated with expected blood loss [1]. Meher et al. [14] in his series had 1163 ml mean blood loss (range 500–1900 ml) during surgery and in 7/22 (31.81%) subjects required intraoperative blood transfusion. In his analysis of the group of patients who were preoperatively embolized and those who were not, Diaz et al. [15] found that in those who were embolized, the average blood loss was reduced by 798 ml. Pamuk et al. [2] in his 11 experiences with 48 patients indicate that pre-operative embolization particles PVA reduces intraoperative hemorrhage in patients with JNA lower grade (vascularization exclusively from the ECA). Lv et al. [21] state that the preoperative embolization JNA liquid embolizing agent in a series of 22 patients with Radkowski IIc,

IIIa and IIIb classified tumors enabled surgical dissection of the tumor without blood loss.

Regardless of the type of procedure, it is evident that the frequency and severity of postoperative complications are directly related to the volume of intraoperative blood loss during resection [8, 9, 11].

The use of particles of larger diameter gave satisfactory results during the operation – surgical excision of the tumor, when dangerous anastomoses do not allow application of smaller diameter particles and can be safely performed without significant neurological nor systemic complications.

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Преоперативна емболизација јувенилног назофарингеалног ангиофиброма коришћењем партикула средњег и великог промера

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САЖЕТАК

Увод Јувенилни назофарингеални ангиофиброми су бенигни тумори са локално агресивним понашањем. Преоперативна емболизација тумора честицама поливинил-алкохола може смањити интраоперативни губитак крви и олакшати хируршку ресекцију.

Приказ болесника Шеснаестогодишњи мушкарац примљен је у болницу због обилне епистаксе и осећаја пуноће у носу. Преглед мултидетекторском компјутеризованом томографском ангиографијом показао је туморску масу у десном носном ходнику са инвазијом десног максиларног синуса и етмоидних ћелија у десни и у леви носни ходник. У контакту је са носним септумом, али без разарања кости. После примене контрастног средства описана маса се интензивно опацификовала. Препроцедурална дигитална суптракциона ангиографија спољашњих и унутрашњих каротидних артерија обострано показала је екстензивну патолошку васкуларизацију, у већој мери прокрвљену гранама максиларне артерије на десној и, у мањој мери, на левој страни. Због опасности од продора честичног емболизационог средства мањег дијаметра у орбиталне гране и могуће ретроградне миграције у каротидну артерију, одлучили смо се за примену честица већег пречника (500–700 *μм*) него што је прописано савременим стандардима. Тумор је комплетно хируршки уклоњен трећег дана после емболизације и пацијент је отпуштен без неуролошког дефицита. Контролни прегледи мултидетекторском компјутеризованом томографском ангиографијом са апликацијом контраста урађени су у трећем и седмом месецу после операције и нису показали остатке тумора или рецидив.

Закључак Употреба честица већег пречника дала је задовољавајуће резултате током операције – хируршке ексцизије тумора, када опасне анастомозе не дозвољавају примену честица мањег пречника и могу се безбедно извести без значајних неуролошких и системских компликација.

Кључне речи: јувенилни назофарингеални ангиофибром; емболизација; партикуле великог промера

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Teduglutide therapy in a child with short bowel syndrome

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SUMMARY

Introduction Short bowel syndrome (SBS) in children is a rare disease. One of the most common etiological factors for the development of SBS in children is atresia of the small intestine. After surgical correction of the congenital anomaly, the remaining intestine attempts to increase absorption to restore homeostasis, and the process of intestinal adaptation begins. This process of adaptation can be assisted with analogues of endogenous growth factors of the intestine, such as teduglutide.

Case outline This report presents a girl, aged two years and eight months, who had an estimated 20 cm of small intestine after surgical correction of congenital small bowel atresia and clinical signs of SBS. She was repeatedly hospitalized due to frequent need for parenteral correction of fluid, electrolyte, and nutrient imbalances. Stagnation in body weight and slow growth in body height were accompanied by weakened gross motor strength and slowed psychophysical development. After exploit conservative treatment measures, stimulation of intestinal adaptation was initiated with the drug teduglutide. After six months of drug therapy, progress was observed in body parameters, as well as an increase in intelligence quotient and motor abilities.

Conclusion SBS is a challenging entity for every clinician, and its previous therapy has mainly consisted of parenteral substitution of nutrients, fluids, and electrolytes. Surgical treatment carries the risk of loss of the remaining bowel and lifelong immunosuppression. The pharmacological possibilities of promoting intestinal adaptation using drugs such as teduglutide represent a light at the end of the tunnel for patients with SBS.

Keywords: short bowel syndrome; child; teduglutide; glucagon-like peptide-2

INTRODUCTION

Short bowel syndrome (SBS) is defined as a total functional small bowel length less than 200 cm in adult patients who require substitution of food and/or fluids [1]. In pediatric population, SBS does not have such a pragmatic definition in terms of functional bowel length expressed in centimeters, as the length of the bowel increases with growth in children [2]. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition defines SBS in children as the need for parenteral nutrition (PN) for more than 60 days after bowel resection or a bowel length less than 25% of the expected length [3].

The incidence of SBS in infants is 24.5 per 100,000 live births [4]. There are two types of SBS: primary (as a result of prenatal pathological conditions such as atresia of the small intestine) and secondary (as a result of postnatal pathological conditions) [5].

Small bowel atresia is a rare congenital defect of the small intestine characterized by a disruption in the normal continuity of the small intestine, leading to obstruction of the bowel [6].

The first phase of treatment involves decompression of the intestine through a nasogastric tube, fluid replacement, and antibiotic therapy as a bridge to surgical correction. The second phase of treatment aims to provide adequate function of the remaining part of the digestive tract, often requiring prolonged PN. To reduce the need for PN, surgical procedures for lengthening the intestine and small bowel transplantation can be performed. Surgical treatment options carry the risk of loss of the remaining bowel and lifelong immunosuppression. An alternative to high-risk surgical treatment of SBS is the use of drugs that stimulate intestinal adaptation, such as teduglutide [7].

After an event, such as small bowel atresia, leading to SBS, the rest of the gut attempts to increase absorption to restore homeostasis and the process of intestinal adaptation begins. Numerous growth factors are involved in this process. Glucagon-like peptide-2 (GLP-2) is an endogenous growth factor strongly associated with intestinal growth and post-resection intestinal adaptation. GLP-2 therapy improves intestinal function in children with SBS by increasing intestinal absorption through increased blood flow to and from the intestine, slowing the rate at which food passes through, and reducing stomach acid secretion that can interfere with absorption in the intestine. Teduglutide is a GLP-2 analog and can be an effective and safe therapeutic option for treating SBS in adults and children over one year of age [7].

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The drug is administered as a subcutaneous injection into the abdominal skin at the recommended daily dose of 0.05 mg per kilogram of body weight [7]. The treatment effect should be evaluated after six months of treatment, and in children under the age of two, this can be done after 12 weeks [8, 9].

CASE REPORT

A girl aged two years and eight months was hospitalized, due to frequent, unformed stools, and dehydration. On admission, parameters indicating malnutrition were recorded: body weight of 11.5 kg (eighth percentile), body length of 90 cm (48th percentile) and body mass index of 13.9 kg/m² (third percentile). During the examination, reduced adipose tissue was observed in all predilection sites and inability to walk independently. Laboratory tests showed negative acute-phase reactants, normal blood counts, and biochemical parameters of the liver, pancreas, and kidney function, negative microbiological stool test, and normal urine test.

She is the first child conceived by in vitro fertilization. At 32 weeks of gestation, the mother notices weaker fetal movements. During a gynecological examination fetal tachycardia and deceleration were recorded, and ultrasonographically, ascites and hydroaeric levels were described in the fetal abdomen with a dilated stomach and lower bowel. The emergency caesarean section was indicated.

The child was born in perinatal asphyxia (Apgar score 3/7) with hypotonia, but with eutrophic body parameters: birth weight of 1890 g (50th percentile), birth length of 45 cm (75th percentile), and head circumference of 31 cm (50th percentile). Dilated bowel loops and free fluid in the abdomen were observed on ultrasound. The newborn with a picture of ileus and signs of pneumoperitoneum was operated, when a part of the small intestine was resected. After the resection of the twisted part of the intestine, a distal atretic segment of the ileum was observed; the total remaining length of the small intestine is approximately 26 cm. PN was initiated on the second postoperative day. After one week, due to re-development of the clinical picture of acute abdomen, a resection of a portion of gangrenous distal jejunum in the area of the stoma was performed, along with a T-T jejunoileal anastomosis (the remaining small intestine segment estimated to be 20 cm). Postoperative PN continued until the 19th day of life. From the 15th day of life, intestinal passage was established, and the intake of breast milk and amino acid formula was gradually increased. The child was first fed through a nasogastric tube, and from the 40th day of life, was fed from a bottle.

In laboratory tests, from birth, unconjugated hyperbilirubinemia with elevated gamma glutamyl transferase (GGT) predominated in liver function, until the 10th day of life when a normal GGT was recorded. After that, there was a deterioration in liver function and conversion to conjugated hyperbilirubinemia from the 13th day of life during PN. Conjugated hyperbilirubinemia continued to increase over the next few days, reaching 60% of the total bilirubin value. Signs of cholestasis were maintained with normal values of transaminases and GGT. Ursodeoxycholic acid was introduced on the 18th day of treatment. Stools were spontaneously golden yellow in color with negative bilirubin in stool. It was most likely a case of intestinal failure associated with cholestatic liver disease (IFALD).

On the 54th day of life, the patient was discharged with the following physical parameters: body weight 2140 g (below the third percentile), body length 46.5 cm (10th percentile), head circumference 32 cm (10th percentile).

At the age of three months, she was hospitalized at the University Children's Hospital in Belgrade due to subicterus and malnutrition, where an intraoperative cholangiography with liver biopsy was performed, which showed regular arborization of the bile ducts, and the pathohistology report of the liver biopsy showed preserved structure with moderately expressed cellular and canalicular cholestasis with rare focal necroses in the parenchyma. In the laboratory findings, the following values were elevated: inflammation marker C-reactive protein, ammonia, conjugated hyperbilirubinemia, transaminase and GGT. Lactulose and oral vancomycin were introduced due to hyperammonemia. The patient was fed with an adapted milk formula based on milk proteins, but due to formula intolerance, it was first replaced with an extensively hydrolyzed milk and then with an amino acid-based formula.

The child was regularly monitored at our Institute. The use of vancomycin and lactulose was discontinued from the fourth month with normalization of ammonia levels. Oral therapy with ursodeoxycholic acid was continued until GGT normalized at the age of one year. Supplementation with fat-soluble vitamins continued as regular therapy until the writing of this paper. Over time, there was an improvement in digestive function, the child tolerated a larger amount of food per meal, began to gain weight, and had less frequent stools that were not formed. Mixed non-milk diet was introduced, but inadequate weight gain persisted. The child was hospitalized multiple times due to the need for intravenous fluid replacement and correction of the internal environment.

Given that the patient with SBS and intestinal insufficiency experienced a halt in growth and significant delay in development, failing to achieve three out of six major motor milestones for the age despite all exploit treatment measures, intestinal adaptation was stimulated by starting the use of the drug teduglutide. Teduglutide was administered once a day by subcutaneous injections at a dose of 0.05 mg/kg/day.

After six months of teduglutide treatment, a clinical evaluation and assessment of psychophysical abilities were performed. Although the physical parameters expressed in percentiles for age and gender remained the same, progress was observed in physical parameters: body weight 12.2 kg (+ 700 g in six months, after 18 months of stagnation in body weight, i.e., eighth percentile), and body height 95 cm (+ 5 cm in six months, i.e., 46th percentile) and body mass index 13.51 kg/m² (third percentile).

During teduglutide therapy, the girl began to walk independently. As part of monitoring gross motor development,

a functional motor assessment [gross motor function measure (GMFM)] was performed, and an increase in GMFM score was observed, which was 69.08% before the therapy and 72.79% after six months of treatment with the GLP-2 analogue.

After six months of teduglutide therapy, an assessment of intelligence was performed using the Binet–Simon scale, which showed an increase in the intelligence quotient, indicating normal intellectual ability in the average category.

We confirm that we have read the journal's statement on issues involving ethical publishing and confirm that this work is in accordance with those guidelines, as well as with the ethical standards of the Institute and the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. Written consent to publish all presented material was obtained from the patient's parents.

DISCUSSION

Modern pharmacotherapy, surgical techniques, and improved hygiene have led to the SBS becoming a clinical entity with an increasing incidence and a reduction in mortality [10]. These epidemiological data have contributed to the stimulation of intestinal adaptation using analogs of intestinal growth factors, such as teduglutide.

Tompson believes that patients with SBS require preventive cholecystectomy due to an increased risk of developing cholelithiasis, especially in cases of need for long-term PN [11]. In our patient, preventive cholecystectomy was not performed, and she had signs of cholestatic syndrome in the first year of life, which we attributed to the first phase of IFALD development. Previous studies and meta-analyses suggest that the main reason for IFALD development is the type of intravenous lipid emulsion for PN. Avoidance of soy-based emulsions is recommended, while fish oil-based emulsions are emphasized as desirable [12].

According to the proposed algorithm for patients with SBS, which is based on the length of residual intestine and the presence of the ileocecal valve and colon, published by Spanish authors, our patient (with residual intestine less than 40 cm and the presence of the ileocecal valve and colon) is a candidate for surgical procedures to lengthen the intestine [12]. According to these authors, with the help of this surgical procedure, sufficient intestinal adaptation will be achieved so that most patients will not have further need for PN or intestinal transplantation [13]. However, new drugs such as teduglutide require a revision of these algorithms. Intestinal hormone analogs may not be a solution for everyone in terms of eliminating the need for PN, but they will allow such patients to achieve better preoperative conditioning and maximum intestinal adaptation.

After six months of treatment, our patient did not require PN anymore, but had one upper respiratory tract infection. The adverse effects of teduglutide have been described in several studies. Ramos Boluda et al. [14] and Kocoshis et al. [15] did not report any adverse effects that required discontinuation of teduglutide. The most commonly reported adverse effects are gastrointestinal in nature, up to 77%: vomiting, abdominal pain, stoma hypertrophy, and cholecystitis, while severe adverse events occur in up to 30% of patients: catheter-related sepsis, heart failure and respiratory diseases [14–17].

This is the first study that used an assessment of gross motor strength and psychological assessment of development to monitor the effect of therapy. The efficacy of teduglutide has mainly been evaluated through the parameter of reducing the amount of fluid needed for parenteral replacement [14–17].

This is the first use of teduglutide in pediatric patients in Serbia. We believe that a treatment guideline for SBS and the use of teduglutide is needed, as it exists in other countries [9].

Conflict of interest: None declared.

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Терапија тедуглутидом код детета са синдромом кратког црева

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САЖЕТАК

Увод Синдром кратког црева код деце је ретка болест. Један од најчешћих етиолошких фактора за развој синдрома кратког црева код деце је атрезија танког црева. После хируршке корекције урођене аномалије остатак црева покушава да повећа апсорпцију како би се повратила хомеостаза и почиње процес интестиналне адаптације. Процес адаптације се може помоћи аналозима ендогених фактора раста црева, као што је тедуглутид.

Приказ болесника У овом раду приказано је женско дете узраста две године и осам месеци које је после хируршке корекције урођене атрезије танког црева имало процењених 20 *cm* танког црева и клиничке знакове синдрома кратког црева. Вишеструко је хоспитализована због честе потребе за парентералном корекцијом баланса течности, електролита и хранљивих материја. Стагнација у телесној тежини и успорено напредовање у телесној висини праћени су ослабљеном грубом моторичком снагом и успореним психофизичким развојем. Након што су исцрпљене конзервативне мере лечења, започето је подстицање интестиналне адаптације применом лека тедуглутид. После шест месеци примене лека уочен је напредак у телесним параметрима, а забележен је и пораст коефицијента интелигенције и моторичких способности.

Закључак Синдром кратког црева је за сваког клиничара изазован ентитет, а његова досадашња терапија углавном се састојала у парентералној супституцији хранљивих материја, течности и електролита. Хируршко лечење носи ризик од губитка преосталог црева и доживотне имуносупресије. Фармаколошке могућности подстицања интестиналне адаптације применом лекова као што је тедуглутид представљају светло на крају тунела за пацијенте са синдромом кратког црева.

Кључне речи: синдром кратког црева; дете; тедуглутид; глукагону сличан пептид 2

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REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Sex-specific differences in the epidemiology, progression, and outcomes of chronic kidney disease

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SUMMARY

Higher prevalence of chronic kidney disease (CKD) in women than in men was reported all over the world. This difference could be partly explained by longer life expectancy and slower CKD progression rate in women. Potential factors associated with sex differences in CKD progression are as follows: difference in glomerular hemodynamic and the response to angiotensin II; sex hormones – estrogen has protective and testosterone deleterious effects on CKD progression; lifestyle. In most countries, the percentage of men is higher than that of women among incident and prevalent patients on hemodialysis (HD). In HD patients, the Kt/V index overestimates HD adequacy, secondary hyperparathyroidism is more common in women, and women require higher doses of erythropoiesis-stimulating agents for achieving and maintaining the hemoglobin target level. The survival of HD patients is equal for both sexes. In earlier years, an equal percentage of women and men started peritoneal dialysis, but in recent years, a higher percentage of women, especially at younger ages, start peritoneal dialysis. Initial peritoneal transport properties differ between men and women. A smaller percentage of women than men receive deceased donor kidneys, but women are more likely to be living kidney donors. Kidney allograft outcome depends on the sex and age of both the recipient and the donor. Cardiovascular diseases are the most common cause of death for renal replacement therapy patients of both sexes.

Although sex-specific differences have been described in CKD patients, the inequality of patients in access to medical care has not been found in most regions of the world.

Keywords: sex-specific differences; chronic kidney disease; prevalence; progression; renal replacement therapy

INTRODUCTION

Although many studies in humans and animals showed sex differences in kidney size, structure and function [1, 2], recommendations for the treatment of kidney diseases generally do not take into account the differences between the sexes. The National Institutes of Health has repeatedly mandated that women should be included in clinical trials, as well as in analysis and reporting of trial results [3].

World Kidney Day in 2018, titled "Kidneys and Women's Health," pointed out the significance of sex-specific differences in kidney diseases. Although this action was mostly aimed at the impact of kidney disease on women's health, it also highlighted the importance of sex-sensitive prevention, detection and treatment of kidney disease. In recent years, the number of papers on the sex differences in kidney diseases, especially chronic kidney disease (CKD), has been increasing [4, 5, 6]. The significance of these studies is not only in discovering sex differences but in their impact on the development of guidelines in which the sex difference will be taken into account. It will enable more correct and effective treatment of kidney diseases.

This review presents the results of studies that dealt with the difference in the prevalence and progression of CKD between the sexes as well as sex-specific differences in the epidemiology, response to the treatment, and outcome of patients on renal replacement therapy (RRT).

SEX-SPECIFIC DIFFERENCES IN THE EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

During the most recent decades, an increase in the prevalence of CKD has been registered throughout the world. The Global Burden of Disease (GBD) study reports that the global all-age prevalence of CKD increased by 29.3%, while the global all-age mortality rate from CKD increased by 41.5% between 1990 and 2017 [7]. According to the data of the Institute for Public Health of Serbia, during the 2009–2018 period, the mortality rate from diseases of the genitourinary system increased from 28.23 to 33.81/100,000 inhabitants [8]. A secondary analysis of data collected in the 2013 National Health Survey showed that out of 14,587 respondents aged 15 years or older, 5.6% reported the presence of kidney disease. Among them, there was a higher proportion of females (61.2%), and female sex was selected as an independent predictor for the presence of kidney diseases [9]. A higher CKD prevalence in women than in men is reported in most

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countries, although there are differences in prevalence between individual countries. These differences could be explained by the existence of real differences in CKD prevalence, but also by differences in data collection, the use of different equation for estimating glomerular filtration rate (eGFR), but also due to the longer life expectancy and slower CKD progression rate in women [4, 10]. Although in most countries the prevalence of CKD is higher in women than in men, more men than women commence RRT for end-stage renal disease (ESRD) [4, 11]. GBD also reported higher prevalence of early stages of CKD in females but higher mortality in males, which could be a consequence of faster progression of CKD in males [7]. This prompted additional studies on sex-related differences of CKD progression and outcome.

SEX DIFFERENCES IN CHRONIC KIDNEY DISEASE PROGRESSION

Although two large meta-analyses have reported conflicting data on the sex difference in the progression of CKD [12, 13], the most subsequent studies reported slower decline of GFR with age, as well as slower CKD progression in women than in men [4, 14]. Thus, the study PREVEND, involving 5488 subjects, showed not only significant sex difference in the mean eGFR slope over time but also sex differences in the predictors of eGFR decline [15]. Similarly, a recent observational cohort study that analyzed data from the Swedish Renal Registry, including 26,279 incident CKD patients, found that women had slower CKD progression and mortality in comparison to men [10]. Although the factors and mechanisms underlying sex difference in CKD progression have not yet been fully elucidated, several factors have been pointed out (Table 1).

Table 1. Factors associated with sex-related differences in chronic kidney disease (CKD) progression

Sex-related difference in renal hemodynamics
Difference in renal vascular resistance
Difference in renal hemodynamic responses to angiotensin II
Effects of sex hormones on the following processes of importance for CKD progression
Collagen synthesis and matrix degradation
Transforming growth factor beta expression
Apoptosis of podocytes and proximal tubular cells
Nitric oxide syntheses
Oxidative stress
Sex-related differences in lifestyle
Tobacco use
Adherence to the prescribed diet
Hypertension control
Obesity

Factors associated with sex difference in the progression of chronic kidney disease

Difference in glomerular hemodynamics

Experimental studies showed lower whole-kidney GFR and renal plasma flow but higher renal vascular resistance in females than in male rats [16]. In humans, a difference in the hemodynamic response to angiotensin II has been reported. Infusion of angiotensin II caused an increase in GFR and filtration fraction in men, while in women, GFR decreased and filtration fraction increased less than in men [17]. Neugarten et al. [12] considered that this angiotensin II response protects women from the increase in glomerular capillary pressure that occurs in the progression of CKD.

Sex hormones and CKD progression

Several experimental and clinical studies have shown that estrogen has protective and testosterone deleterious effects on CKD progression. Thus, testosterone increases and estrogen decreases the expression of TGF-beta, which consequently has an opposite effect on apoptosis of podocytes and proximal tubular cells, as well as on collagen synthesis [12]. The impact of sex hormones on oxidative stress is also significant. While testosterone inhibits antioxidant enzymes, estrogen has the opposite effect and reduces generation of superoxide anion [12]. Oxidative stress has a significant role in the progression of non-diabetic and diabetic kidney disease [18, 19]. Despite these favorable estrogen effects, it has been rarely used for slowing down the CKD progression and conflicting results have been obtained [12, 20].

Lifestyle and social factors

Differences in lifestyle between men and women could have an impact on CKD progression. Men are more likely to smoke, to keep their hypertension under control, they are less likely to adhere to the suggested dietary regimen, but women are more often obese [4, 12]. In our study conducted in collaboration with family doctors, we found that men come to the doctor's check-ups less often than women. However, among those with reduced kidney function, there was no difference in the frequency of the doctor's check-ups between men and women [21]. García et al. [6] described significant differences in risk factors for CKD between men and women, as well as sex-related social inequalities and access to medical care. However, these differences exist only in certain parts of the world, and our previous studies did not confirm that they exist in our region [21, 22].

SEX-RELATED DIFFERENCES AND RENAL REPLACEMENT THERAPY

The percentage of women who start RRT worldwide is lower than that of men. This is explained by the difference in the rate of CKD progression between women and men, as well as by the greater burden of men with risk factors for ESRD. The analysis of sex-specific differences in RRT incidence and prevalence in nine countries included in the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry showed that in all analyzed countries the percentage of men was higher than that of women, both among incident and prevalent patients during the entire observed period from 1965 to 2015 [23].

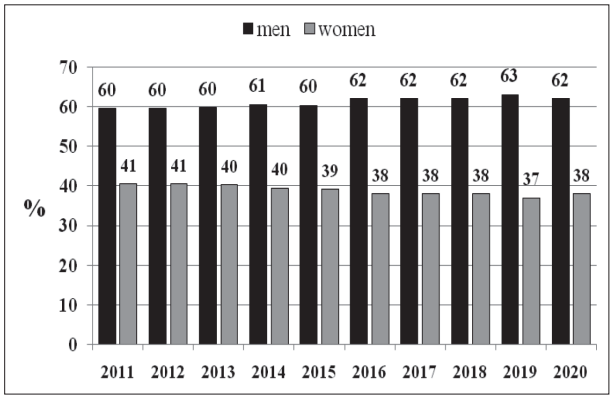

Figure 1. Percentage of men and women among prevalent patients on renal replacement therapy in Serbia in the period 2011–2020

Data from Serbia also showed a higher percentage of men among both incident and prevalent patients (Figure 1) [24]. The last annual report of the ERA-EDTA Registry shows that the percentage of men among incident RRT patients varies 52–74% and is similar among the prevalent patients. This registry also shows that hemodialysis (HD) is the most common method of RRT for ESRD patients [24].

Sex-specific differences in hemodialysis patients

Kt/V – index adequacy

HD adequacy is most often assessed using the Kt/V index, where V is the urea distribution volume, which is approximately equal to total body water. Using V as denominator in the formula results in an overestimation of HD adequacy in woman, as well as in all small patients. We and others have confirmed that Kt/V was significantly higher in women than in men, which can only be a consequence of overestimating the adequacy by the formula [11, 25]. Therefore, women and generally small patients on HD with the minimal recommended value of Kt/V may be underdialyzed. This encouraged many authors to search for a more adequate parameters for evaluating HD adequacy (body surface area, resting energy expenditure, bioelectrical resistance, etc.) [26].

Hemodialysis vascular access

Although arteriovenous fistula (AVF) is recommended as the optimal vascular access for HD, there are large regional differences in the percentage of patients who are dialyzed via AVF among incident (32–85%) as well as prevalent HD patients (49–92%) [27]. HD centers in Serbia can boast of a high percentage of patients who are dialyzed via AVF, although this percentage has decreased in several previous years from 92% to 77% [28]. However, sex difference in the vascular access has only recently been examined. Three large longitudinal studies from different parts of the world have reported that fewer women than men start HD with AVF [29, 30, 31]. This difference was tried to be explained by differences in the size and structure of blood vessels, underlying kidney disease, comorbidities, and social differences between men and women [32]. In our retrospective longitudinal closed cohort study involving 441 incident HD patients from 28 HD centers in Serbia, no significant difference in vascular access between men and women was found [11].

Secondary hyperparathyroidism

Several studies have shown that in HD patients secondary hyperparathyroidism is more common and more aggressive in women than in men, although this difference varied depending on the region and patient age [11, 33, 34]. Although the cause of this difference is not yet fully explained, it is considered that estrogen increases the *PTH* gene expression and consecutively PTH secretion. In addition, a higher serum phosphate level was found in women than in men, so women require higher doses of phosphate binders [11, 33].

Anemia and erythropoiesis stimulating agent response

It is known that in the general population, women have lower hemoglobin level than men, and such a difference also exists in patients in all stages of CKD. The use of erythropoiesis-stimulating agents (ESA) enabled the effective treatment of anemia in CKD patients, but it was reported that women on maintenance HD require higher doses of ESA agents for achieving and maintaining the hemoglobin target level [12, 34, 35, 36]. As lower hemoglobin levels are associated with higher mortality [37, 38], the investigation of the causes of more severe anemia and weaker response to ESA in women requires further investigation.

Hemodialysis patient outcome

While in the general population women have a longer life expectancy than men, several studies have shown that survival of HD-dependent ESRD patients is equal for both sexes [29, 34]. Nevertheless, there are regional differences in male-to-female mortality rate among HD patients [34, 39]. Our study showed equal survival time between men and women and no difference in causes of death between the sexes [11]. Cardiovascular diseases are the most common cause of death in HD patients of both sexes, which is another difference as compared to the general population. Data on the change in the male-to-female mortality rate in HD patients over time are contradictory. We did not find that this ratio changed over five years [11], while analysis of the ERA-EDTA registry showed equal mortality of women and men only in the first months, and thereafter survival of women increased [23]. In contrast, a recent large retrospective study of HD patients from Australia and New Zealand for the period 1998–2018 showed that women have a higher risk of all-cause mortality in the first five years from the onset of HD, but not later [40].

Although we have shown certain differences between men and women on HD, it should be emphasized that the existence of inequality between the sexes has not been established [11]. Nevertheless, there are parts of the world where sex-related social inequalities as well as access to

medical care are described, which requires further efforts to overcome such differences [6].

Sex-specific difference in peritoneal dialysis

Peritoneal dialysis is insufficiently used globally, especially in low-income and lower-middle-income countries [41]. Also, there is not much data on the sex difference in peritoneal dialysis (PD). The United States Renal Data System reported that among incident patients on RRT, 86.1% were on HD and 11% were on PD [42]. Similarly, according to the ERA registry, among the incident patients, there were 82% on HD and 14% on PD [24]. Both of these registries show large regional variations in these percentages. A longitudinal study showed that both PD incidence and prevalence increased more in men than in women during the previous years [43].

The male-to-female ratio among incident PD patients changed over the time. While in earlier years there was no difference in the percentage of men and women starting PD [4], in recent years a higher percentage of women start PD [24, 44]. The male-to-female ratio also depends on age and younger women more often choose PD as the initial RRT [43].

The risk of all-cause death, noncardiovascular and noninfections death was found to be lower in women than in men on PD [39]. However, due to the negative effect of diabetes on death, which is greater in women than in men, women with diabetes have higher all-cause, noncardiovascular and noninfections mortality than males [39]. Cardiovascular diseases are the main and equally frequent cause of death in both sexes, but women had higher infection-specific mortality than men [39, 41].

Although many studies have addressed peritoneal transport, only recently has the sex impact on peritoneal transport been examined. It has been shown that at the beginning of PD treatment, women had lower dialysate-to-plasma ratio of creatinine at four-hour peritoneal equilibration test, better ultrafiltration ability and higher Kt/V [45]. The mechanism of these sex differences in peritoneal transport requires further elucidation.

Sex-specific differences in kidney transplantation

As there is a higher percentage of men on maintenance HD, a higher percentage of men receive deceased donor kidneys [5, 6]. This was confirmed by data from various regions of the world, but in recent studies a more detailed analysis of sex differences in kidney transplantation was examined.

Organ donation and sex-specific differences

Many studies have shown that women are more likely to be living kidney donors than men and women are also more often donors to their spouses [4, 46]. This was explained both by the higher proportion of women in the general population, traditional relationships in the family, and perhaps by the longer life of women. On the other hand, men more often suffer from diseases that make them unsuitable for donation [46, 47]. However, there are studies, including ours, in which either no sex difference was found among donors or those differences changed over time [46, 48].

Sex-specific differences and kidney transplantation outcome

Kidney allograft outcome depends on the sex of the recipient, but even more so on the sex of the donor. Data on renal allograft outcome in recipients of a different sex are inconsistent. On the other hand, the survival of female donor kidney allografts is worse than that of male donor kidney allografts. In addition, a worse outcome has been described in male recipients of kidneys from female donors than in the reverse case [49]. However, it was recently described that this is not found in all age groups, because graft survival also depends on the recipient's age [5, 46, 47]. These differences in allograft outcome have been described as a consequence of the sex-specific differences in immune reactivity, the number of nephrons in the donor allograft, metabolic demands, hormonal differences, sensitization during pregnancy, differences in the post-transplant incidence of various diseases, psychosocial factors including compliance in the use of therapy, and controls [4, 5, 47]. All these factors should be taken into account when treating patients after transplantation in order to achieve the best possible outcome for both the recipient and the allograft.

CONCLUSION

A higher prevalence of CKD in women than in men was reported in most countries. This difference could be explained by longer life expectancy and slower CKD progression rate in women than in men. Differences in glomerular hemodynamics, sex hormones, and lifestyle are reported as factors associated with sex difference in the progression of CKD. Although the prevalence of CKD is higher in women than in men, more men than women have to start RRT in most countries. In HD patients, the Kt/V index overestimates HD adequacy, secondary hyperparathyroidism is more common in women than in men, and women require a higher dose of ESA to maintain the hemoglobin target level. Earlier, an equal percentage of women and men started PD, but in recent years, a higher percentage of women, especially at younger ages, start PD. Sex inequalities in kidney transplantation rates were reported: a smaller percentage of women than men receive deceased donor kidneys, but women are more likely to be living kidney donors than men. Kidney allograft outcome depends on the sex and age of the recipient, but also on the sex of the donor. Survival of men and women on RRT is similar and cardiovascular diseases are the most common cause of death. Although sex-specific differences in CKD patients were described in most regions of the world, the inequality of patients in access to medical care requires additional research.

Ethics: This article was written in accordance with the ethical standards of the institutions and the journal.

Conflicts of interest: None declared.

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Разлике међу половима у епидемиологији, прогресији и исходу хроничне болести бубрега

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САЖЕТАК

Широм света забележена је већа преваленца хроничне болести бубрега (ХББ) код жена него код мушкараца. Ова разлика се објашњава дужим животним веком и споријом прогресијом ХББ код жена него код мушкараца. Сматра се да разлику у прогресији ХББ међу половима узрокују разлика у гломерулској хемодинамици и одговору на ангиотензин II; сексуални хормони – естроген има протективан, а тестостерон негативан утицај на прогресију ХББ; начин живота и навике. У већини земаља света више мушкараца него жена је међу инцидентним и превалентним болесницима који се лече редовним хемодијализама. Код болесника на хемодијализи индекс *Kt/V* прецењује адекватност хемодијализе, секундарни хиперпаратироидизам је чешћи код жена него код мушкараца, а жене захтевају примену већих доза стимулатора еритропоезе за постизање и одржавање циљних вредности хемоглобина. Раније је подједнак број жена и мушкараца започињао лечење перитонеумском дијализом, али последњих година већи проценат жена, посебно у млађим узрастима, бира перитонеумску дијализу као почетни метод лечења. Постоје разлике међу половима и у карактеристикама перитонеалног транспорта. Испитивање разлике међу половима у трансплантацији бубрега је показало да мањи проценат жена добија бубрег од можданo мртве особе, али су жене чешће даваоци бубрега. Исход калема бубрега зависи од старости и пола и примаоца и даваоца. Кардиоваскуларне болести су најчешћи узрок смрти за болеснике који се лече методама за замену функције бубрега оба пола. Иако су откривене разлике међу половима у карактеристикама ХББ, у већини региона света није откривена неједнакост међу половима у приступу здравственој нези и лечењу.

Кључне речи: разлике међу половима; хронична болест бубрега; преваленца; прогресија; методе за замену функције бубрега

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HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНА

The history of pediatric anesthesia

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SUMMARY

The beginnings of pediatric anesthesiology go back to the middle of the 19th century and it is associated with a rural physician Crawford W. Long, MD, who in the 1842 recorded the first case of giving diethyl ether anesthesia to an eight-year-old boy.

The start of development of contemporary pediatric anesthesia is considered to be in 1930, which marked two periods of progress. In the first period, anesthesia techniques and accessories adjusted to different children's ages were developed. In the second period, modern anesthetic medications and supervision were introduced into everyday clinical practice in order to better protect vital organs and their functions in the child's body. The first multidisciplinary pediatric intensive care unit at the Children's Hospital of Gothenburg in Sweden was established in 1955. Dr. Branka Mitrović is considered to be the founder of pediatric anesthesiology in Serbia, as she founded the Department of Anesthesiology and Reanimation at the University Children's hospital in 1955. The history of pediatric regional anesthesia began after its introduction in adults, which occurred after the invention of cocaine in 1884. The Ministry of Health of the Republic of Serbia approved a specialization in pediatric anesthesiology in 2018.

The development of pediatric anesthesia is fascinating because it completely followed the development of pediatric surgery. Modern pediatric anesthesiology is entirely prepared to meet the needs of the most complex surgical interventions, as well as the treatment of critically ill children, and significantly contributes to better treatment outcomes of pediatric surgical patients.

Keywords: children; pediatric anesthesia; history; development

INTRODUCTION

Today it is impossible to understand how even the simplest surgical procedures could be performed without all the benefits provided by anesthesia. The beginnings of anesthesia go back to the 19th century, which enabled many of the advances that occurred in the 20th century that compose everything what we currently take for granted.

Children received anesthesia from the start of the earliest clinical applications [1]. During the first decades of the 20th century, most doctors treated children as "little adults," which we all know today is an incorrect view. At the onset of developing pediatric anesthesia, all equipment, techniques, and medications were founded in the literature concerning adults. Most medications utilized in children were not tested or researched, or recommended to be used in children, so their use was based on adult studies and expert consensus. Morbidity and mortality were high [2].

During the history of the development of pediatric anesthesiology in our country, many pediatric anesthesiologists have contributed to the fact that we follow world trends in the development of pediatric anesthesiology. We hope we have not omitted any of the early contributors to the development of our specialty.

FROM THE BEGINNING OF THE 19TH CENTURY

On March 30, 1842, Crawford W. Long, MD provided diethyl ether to a patient named James Venable to incise a cyst on the patient's neck [3]. His third patient was an eight-year-old boy, about whom he said the following: "My third experiment in etherization was made on the 3rd July 1842, and was on a Negro boy, the property of Mrs. S. Hemphill, who resides nine miles from Jefferson. The boy had a disease of the toe, which rendered its amputation necessary, and the operation was performed without the boy evincing the least sign of pain" [3, 4]. He did not publish his experiments until 1849. It is obvious that anesthesia care of children had primacy from the start, within the surgical records of the Massachusetts General Hospital from 1846 to 1947, when 80% of all pediatric patients received anesthesia [1]. It absolutely was noticed, from the earliest beginning, that children were at higher risk than adults for complications associated with anesthesia [1]. In 1846, Bigelow published a paper about the use of ether in the Boston Society for Medical Achievements, when he warned of the use of ether in young children [5].

The first anesthetic death (1846) comes from the report in an issue of the London Gazzete about the use of ether in an 11-year-old boy, in which it was reported that the anesthesia "was not totally effective and, in addition, death

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occurred shortly following the surgery" [1]. The cause of death was considered to be associated to the injuries the boy had. Two years later (1848), the Edinburgh Medical and Surgical Journal published a case report of a 15-year-old girl, named Hannah Greener, who had a heart attack after chloroform anesthesia was applied [6]. The autopsy of the girl was negative except for pulmonary edema and the stomach full of food [7]. The conclusion of this case report was that the death was secondary to the anesthetic.

John Snow, from London, was the first physician who specialized in anesthesia and who is considered the father of anesthesia practice [8]. He began providing anesthesia with diethyl ether for adults and children in 1847 [9]. Soon he switched to chloroform, more potent and rapidly acting halogenated ether, but dangerously toxic [9]. After one decade into practice, Snow reported his experience with chloroform anesthesia on several hundred children, including 186 under the age of one year [8]. His observation was that in children "the effects of chloroform are more quickly produced and also subside more quickly than in adults, owing no doubt to quicker breathing and circulation" [8]. Throughout the time of John Snow, thousands of newborns, infants, and children survived surgery and anesthesia in North America and Europe. However, in the hands of those less experienced, the use of chloroform brought on an unacceptably high incidence of complications. However, though widespread application diethyl ether showed to be the most effective, even anesthesia with diethyl ether posed significant hazards and side effect – but there was no better alternative [1].

A few decades later (1897), due to great concern over deaths associated with the use of chloroform, the Boston Society for Medical Achievement Committee made a decision that the use of ether was safe, while the use of chloroform was not [10]. At that time, chloroform made up 50% of all anesthetics in the USA. In 1888, Buxton described the use of a mixture of N_2O and ether [11]. However, Buxton is also remembered for making a misconception that lasted for the next 50 years and served as an excuse for anesthesiologists whose pediatric patients died under anesthesia, and the claim was that the condition of the thymus lymph tissue changed during anesthesia [11]. Despite the fact that chloroform was declared unsuitable for use in the human population, its use was continued until incidental cardiac arrest and fatal hepatotoxicity occurred in children, first described in 1894 [8].

THE FIRST HALF OF THE 20TH CENTURY

The greatest advance of anesthesia in the early 20th century was primarily due to progress of surgery in treating congenital and acquired diseases and the need for anesthesia to follow it. Any development before the 1940s was exclusively the result of individual efforts. Between 1846 and the 1940s, anesthesia was a dangerous procedure for children due to poor anesthesia equipment not adapted to children, insufficient training in the placement of vascular lines, poor understanding of resuscitation, surgical techniques were primitive and antibiotics did not exist [12]. William Ladd as one of the pioneers of modern pediatric surgery, initiated the inevitable evolution of pediatric anesthesia [1]. From 1917 to 1945, he introduced surgical procedures for many congenital anomalies and a number of diseases primarily related to young children, thus imposing the need to develop clinical and academic specialties in pediatric anesthesia [1]. For this work he is considered the father of pediatric surgery. Another anesthesiologist, Dr. Charles Robson, is one of the pioneers of this early period who deserves to be mentioned, and he is the first person who could be marked as a pediatric anesthesiologist [13].

In those years, ether and ethyl chloride became the main anesthetics in pediatric anesthesia and were applied by "dropwise" until the 1920s, when reliable evaporators and precise gas flow meters for the simultaneous use of N_2O and oxygen were invented and produced [14, 15]. James Gwathmey in his book "Anesthesia" (1914) describes the techniques of pediatric anesthesia, emphasizing the importance and tenderness of gentle treatment of children during the introduction of anesthesia, all in order to keep the course of anesthesia calm [16]. Arthur Guedel recommends holding the mask a few inches from the face of a small child, and sticking to the face only when the child falls asleep. This method of induction, better known as "stolen induction," is used today, primarily because it allows a peaceful anesthesia induction [16]. Charles Robson in 1920 and Langton Hewer three years later advocated mandatory intubation of children during all surgical procedures. However, in that period, there was no adequate equipment for the pediatric population, so intubation with the help of a laryngoscope was performed very rarely [14]. The beginning of the development of modern pediatric anesthesia is considered to be in 1930. For the next two decades, anesthesia techniques and equipment adapted to children were developed, and then new and safer intravenous and inhalation anesthetics were introduced [11]. The first tubes for children, made of red rubber, were constructed by Ivan Magill in 1930. Soon after, Philip Woodbridge developed the idea of latex tubes with a metal spiral that could not be bend (reinforced tubes) [11].

Dr. Philip Ayre is one of the prominent figures in the history of pediatric anesthesia. In 1938 he was a visiting anesthetist at the Babies' Hospital, Newcastle-Upon-Tyne, England, when he developed an especially suitable pediatric anesthesia breathing system in the shape of the letter T, which is called "T system without back breathing" [17]. It was used with tracheal intubation during the operation of cleft lip and palate malformations in infants. This year is also significant because the American Board of Anesthesiology was formed, giving anesthesiology a professional status. In 1941, Robert Miller described his own modification of a flat spatula, which was slightly longer and narrower than the others, it had a thinned and gently rounded tip [18]. Slightly later, in 1943, Robert Macintosh constructed the first laryngoscope spatula, which was curved along its entire length [18]. Due to its anatomical characteristics, Miller's spatula is used in infants, while Macintosh's spatula is used for older children.

AFTER WORLD WAR II

The first book "Pediatric Anesthesia" was published in 1948 by Digby M. Leigh and Kettlin M. Belston [19, 20]. The use of halothane began in 1956, and soon became the most popular anesthetic in pediatric anesthesia [21]. Three years later, the era of neuroleptic anesthesia begins, first in the adult population, and then in children. In the same year (1956), ketamine was introduced into clinical practice, and still is most commonly used in children. After World War II and into the 1960s, a group of dedicated anesthesiologists made efforts in developing pediatric anesthesia into a subspecialty. Members of this group were the following: Dr. Leigh, Dr. Jackson-Rees, Dr. Smith, Dr. C. Ronald Stephen, Dr. Digby Leigh's successor in Montreal; Dr. Margot van Deming, the first director of anesthesia at the Children's Hospital of Philadelphia, who worked with the pediatric surgeon C. Everett Koop, who demonstrated the relationship between anesthetic blood levels and the anesthetic state in infants [22]; and Dr. Robert Cope, who set new standards for British pediatric anesthesia practice during his long residence at London's Great Ormond Street Hospital for Sick Children. In 1989, Federation of Associations of Pediatrics Anesthesia (FEAPA) was founded, and Dr. Ljubinko Tonić, who worked at the University Children's Hospital, participated in the founding assembly. From the first day of its establishment, our country is a member of FEAPA. Ten years after the founding of FEAPA, it changed its name to European Society of Pediatric Anesthesia (ESPA).

Robert M. Smith, MD, a Harvard Medical School graduate, significantly contributed to the understanding of how important it is to know the unique anatomy and physiology of the newborn and young infant as they apply to anesthetic care, researched the safety and efficacy of tracheal intubation and muscle relaxants in children [22]. He also trained future specialists, and he wrote the first extensive book of pediatric anesthesia, still current (the newest one is the 10th edition, released in 2021) [23]. Dr. Virginia Apgar merits special attention as a figure from this period: her one- and five-minute Apgar physical assessment scores for the newborn are the standard of care in hospitals throughout the world [24, 25]. The score was designed to define which babies required reanimation.

Some great individuals of the period between 1960s and 1970s investigated and defined many important processes – fetal transitional circulation and metabolism, birth asphyxia, neonatal metabolism, respiratory control, thermoregulation, body fluid volumes, pulmonary surfactant and its absence in the premature infant – thus establishing the scientific impulse for modern anesthesiology and neonatal intensive care [26]. Monitoring vital parameters such as measurement of arterial pH level and blood gas tensions and interventions like mechanical ventilation, the administration of buffers, and infusion of vasoactive drugs became standards of care [24]. Anesthesiologists who worked with pediatricians, surgeons, and researchers who made these discoveries played the central role by implementing these treatments and interventions [24]. The neonatal care was not restricted to nutrition and support with minimal intervention any more. In 1955, Dr. Goran Haglund, a pediatric anesthesiologist, established the first multidisciplinary pediatric intensive care unit at the Children's Hospital of Gothenburg in Sweden [27]. In 1965, a group of anesthesiologists who specialized in the care of children created a committee within the American Academy of Pediatrics (AAP) dedicated to pediatric anesthesia; later, the Committee officially became the AAP Section on Anesthesiology (AAP SOA) [2].

During the period between 1980s and 1990s, pediatric anesthesiology departments or services, training programs and researches in many of the major children's hospitals and university medical centers were founded. It has become expected that the perioperative survival rate is higher in all but the most moribund infants and children, including preterm infants weighing under 1000 g and those with complex structural heart disease. Enflurane and isoflurane were developed in 1970s and 1980s, and had a better safety profile than halothane. However, these agents did not completely replace halothane because of its benefit during inhalation induction of infants and young children. Recently, sevoflurane has replaced halothane [21]. During this period, pulse oximetry, capnometry, oscillometric monitoring of systemic arterial pressure, and intraoperative neurologic monitoring were introduced to clinical practice.

REGIONAL ANESTHESIA

The history of pediatric regional anesthesia began after its introduction in adults, which occurred after the discovery of cocaine in 1884 [28]. In 1898, August Bier tried to induce spinal anesthesia with cocaine: all of his six patients (two children) had postoperative vomiting and headache [28]. Epidurals came into use in children much later. In this period surgeons dominated the scene, as they performed these blocks. Gaston Labat, a French surgeon, wrote a widely referred book titled "Regional Anaesthesia: Its Techniques and Clinical Applications" [29]. The surgical contribution continued for many years, until anesthesia became an established specialty. Caudal blocks were first reported for cystoscopies in children by Meredith Campbell – this work was presented in the paper to the American Society of Regional Anesthesia in 1933 [30]. The discovery of lidocaine (1943) and bupivacaine (1963) and the increasing concern about postoperative analgesia in the 1970–1980s led to the increased use of blocks [28]. After 1980, the interest in regional anesthesia in children increased, but it is still insufficiently used in clinical practice, probably due to the improvement of standards of general anesthesia, as well as insufficiently trained staff.

DEVELOPMENT OF PEDIATRIC ANESTHESIOLOGY IN SERBIA

The development of pediatric anesthesiology as a distinct specialty in Serbia was, as in the rest of the world, associated with the development of pediatric surgery. In the beginning,

the surgical problems of pediatric patients were solved by general surgeons, and the anesthesia of children was performed by the same people who performed anesthesia in adults. Dr. Dimitrije Jovčić was the first teacher of pediatric surgery at the Faculty of Medicine in Belgrade and a member of the Serbian Academy of Sciences and Arts [11]. The development of pediatric anesthesiology and intensive care was longer and more laborious because it was very difficult to find the right understanding in the medical circles, as well as due to the slow development of technology and the pharmaceutical industry. The introduction of modern methods of anesthesia and intensive care required a specialist of anesthesia. For that purpose, at the Department of Pediatric Surgery, the first specialist of anesthesiology in our country, who worked at a military hospital, Dr. Sever Kovačev, remembered as one of the doyens of our anesthesiology, was occasionally hired. He was probably the first to introduce endotracheal anesthesia in children in our country.

The following years proved crucial for the further development of pediatric anesthesia. Dr. Branka Mitrović (the first educated anesthesiologist next to prof. Predrag Lalević) is considered to be the originator of pediatric anesthesiology in our country. Firstly, she founded the Department of Anesthesiology, Reanimation and Intensive Care at the University Children's Hospital (1955), and a few years later (1965), she established the same department in the newly founded the Institute for Health Protection of Mother and Child. Several decades (1994) after the establishment of the Department at the University Children's Hospital, for the first time the Intensive Care Unit was separated as a new department.

In 1985, the first association of pediatric anesthesiologists was formed at the Section for Anesthesia and Reanimation of the Serbian Medical Society, called Pediatric Anesthesiologists Work Group (*Aktiv pedijatrijskih anesteziologa*), which for decades has regularly organized professional meetings dedicated to pediatric anesthesiology, reanimation, and intensive care [31]. Previous presidents of the Section were Prim. Dr. Aleksandar Milenković (wrote the first study guide on pediatric anesthesiology from which the residents learned), Dr. Branka Mitrovic, and Prim. Dr. Božidar Mijomanović (one of the founders of the European Association of Pediatric Anesthesiologists). Today the president is Prof. Dr. Dušica Simić.

The Section of Anesthesiology with Reanimation was established for the first time at the Faculty of Medicine of the University of Belgrade (MFUB), founded by Prof. Predrag Lalević, who also designed the first specialist internship curriculum. At that time, the specialization lasted three years, and within that, two months of education for pediatric anesthesiology. The establishment of the Section at the University of Belgrade was followed by the establishment of specialist sections in Novi Sad, Niš, Kragujevac, and Priština, which had the same curriculum. Since 1990, the specialization in Anesthesiology with Reanimation lasts four years, within which four months are provided for pediatric anesthesiology.

The first professor of pediatric anesthesiology, Dr. Zvonimir Budić, from the Faculty of Medicine in Niš, was promoted in 1997. The first professor from the University of Belgrade is Dr. Dušica Simić (since 2003). She is the author of the textbook titled "Fundamentals of Pediatric Anesthesiology," the first one approved by the Faculty of Medicine in Belgrade [14]. At the University of Novi Sad, the first professor is Biljana Drašković, who was elected in 2012. Today, at MFUB, there is (only) one full professor from the ranks of pediatric anesthesiologists and four assistant professors. At the Faculty of Medicine in Novi Sad, there is one full professor, two associate professors, and two assistant professors, while in Niš, there are two associate professors. There are no pediatric anesthesiologists at the faculties of medicine of the universities of Kragujevac and Kosovska Mitrovica. The Ministry of Health of the Republic of Serbia approved a specialization in pediatric anesthesiology in 2018 [32]. In four years since the establishment of the specialization in pediatric anesthesiology, four anesthesiologists have already been promoted to specialists, and 15 candidates enrolled for specialization.

In Serbia today, there are four specialized clinics for children's surgery and anesthesia – two in Belgrade and one each in Niš and Novi Sad, which is perhaps enough for our small country, but there are child surgical patients in other cities and smaller places as well, and specialists of pediatric anesthesia will play a crucial role in improving the outcome of surgical treatment of pediatric patients.

In the 2012–2016 period, Prof. Dr. Dušica Simić was the President of the Committee for Pediatric Anesthesia in the World Federation of Anesthesia Associations. In 2013 and 2015, pediatric anesthesiologists from Serbia participated in the two largest pediatric studies – APRICOT and NECTARINE. The first ESPA congress in Belgrade was held in 2016. In 2017, the Association of Pediatric Anesthesiologists and Intensivists of Serbia was founded by Prof. Dr. Dušica Simić.

Despite humble beginnings, with an insufficient number of pediatric anesthesiologists, today this is changing and pediatric anesthesiology is experiencing a bloom.

CONCLUSION

Today, even the smallest operation in pediatric population without anesthesia is unimaginable, primary thanks to many pioneers in this field, as well as their students who continued the further development of pediatric anesthesia. Unfortunately, it is impossible to provide a complete history of pediatric anesthesia because so many names and institutions have made us grow as a distinct specialty.

It seems that the defining issue of pediatric anesthesia in the 21st century will be how to respond to the worldwide workforce deficit in the face of the increasing demand for skilled pediatric anesthesiologists, and how to correct it.

Ethics: This article was written in accordance with the ethical standards of the institutions and the journal.

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Историја дечје анестезије

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САЖЕТАК

Почеци педијатријске анестезиологије датирају из средине деветнаестог века, а везани су за сеоског лекара Крофорда Лонга (*Crawford W. Long*), који је 1842. године први пут забележио како је применио диетил-етарску анестезију на осмогодишњем дечаку. Почетком развоја савремене педијатријске анестезије сматра се 1930. година. Од тада се бележе два периода развоја. У првом периоду развијене су технике анестезије и прибор прилагођен различитим узрастима деце. У другом периоду се у свакодневну клиничку праксу уводе савремени анестетички медикаменти и мониторинг како би се што боље заштитили витални органи и њихове функције. Године 1955. основана је прва мултидисциплинарна педијатријска јединица интензивне неге у Дечјој болници у Гетеборгу у Шведској. Др Бранка Митровић се сматра зачетником педијатријске анестезиологије у нашој земљи, јер је 1955. године основала Одељење за анестезиологију и реанимацију Универзитетске дечје болнице. Историја педијатријске регионалне анестезије почела је након њеног увођења код одраслих, што се догодило после открића кокаина, 1884. године. Министарство здравља Републике Србије је 2018. године одобрило ужу специјализацију из педијатријске анестезиологије.

Развој педијатријске анестезије је фасцинантан, јер је потпуно пратио развој дечје хирургије. Савремена педијатријска анестезиологија је потпуно спремна за задовољи потребе најсложенијих хируршких интервенција, као и лечење критично оболеле деце и тиме значајно допринесе бољим исходима лечења педијатријских хируршких пацијената.

Кључне речи: деца; дечја анестезија; историја; развој

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 видео-приказа 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.

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

АДРЕСА:
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