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МЕДИЦИНСКИ ФАКУЛТЕТ · УНИВЕРЗИТЕТ У БЕОГРАДУ

Medicinska istraživanja

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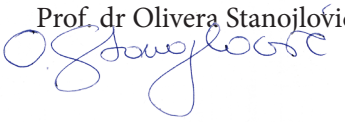

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RESEARCH ARTICLE

The role of active perinatology in the prevention of spontaneous loss of conceptus and birth rate drop

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Summary

Introduction: Modern perinatology demands continuous improvement of doctrines and protocols. The loss of conceptus is unforgivable when the possibility to sustain such pregnancy would elevate the level of birth rate that we aspire as a society. The aim of this study was to show the role of low molecular weight heparin in prevention of poor pregnancy outcomes.

Methods: The study included all women with inherited thrombophilia referred to the Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia between 2016 and 2018 who were followed-up until delivery. The patients were divided into two groups.

Results: The total number of 180 patients were pregnant for the first time, while 178 patients had had previous pregnancies. In 153 out of 178 patients, the previous pregnancy had poor outcome. 12 patients with AC therapy had FMU in previous pregnancies, 49 patients had missed abortion, 54 patients had second trimester miscarriage, 4 patients had both FMU and missed abortion, 9 patients had missed abortion and second trimester miscarriage while one patient had FMU, missed abortion and second trimester miscarriage. In previous pregnancies, 92 babies were born out of 313 pregnancies while in the current pregnancies treated with therapy there were 173 babies from 151 pregnancies.

Conclusions: Patients with anticoagulant treatment in current pregnancy have had significant burden of previous pregnancy losses.

Keywords: pregnancy, pregnancy loss, inherited thrombophilia.

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INTRODUCTION

Modern perinatology demands continuous improvement of doctrines and protocols. The loss of conceptus is unforgivable when a possibility to sustain such pregnancy would elevate the level of birth rate that we as a society wish for.

The recommendations for testing to congenital thrombophilia and antiphospholipid syndrome given by the Clinic for Hematology of the Clinical Centre of Serbia state that congenital thrombophilia is an increased tendency for thrombosis as a result of gene mutation for different factors in the haemostatic syndrome (1).

Within the frames of perinatology, at the moment there is no absolute consensus for testing against congenital thrombophilia. Testing is recommended only for individuals with a previous diagnosis of deep venous thrombosis and venous thromboembolism (VTE) which represent the leading causes of mortality in women (2).

Recently, the indications have been broadened to existing obstetrics history (habitual miscarriages in the second trimester and sudden fetal death). We are striving to improve the process of protocols modernization by scientifically proven data (3–6).

Prompted by obvious birth rate drop, we have analyzed publicly available data (the Institute of Public Health of Serbia) in pre-COVID period. These data show the difference between 2016 and 2017: the number of live births 35,047 vs. 35,564; the number of still births 222 vs. 209; the number of deaths 48,037 vs. 49,402, the number of live births -12,963 vs. -13,838.

If we excluded the population that migrated and delivered in Serbia and concentrated only to the data on population inhabiting Serbia for a longer period of time, it would be possible to obtain even more statistically significant data (7).

The comparison between 2016 and 2017: stillbirths 151 vs. 182. The number of live births against still births per 1,000 people goes from 9.8 to 10. The birth rate per 1,000 people goes from 3.6 to 3.9.

METHODS

The study included all women with inherited thrombophilia referred to the Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia between 2016 and 2018 who were followed-up until delivery. The patients were divided into two groups. The first group included 137 pregnant women with one or more forms of congenital thrombophilia and no use of anticoagulant therapy. The second group included 221 pregnant patients with one or more forms of thrombophilia with administered anticoagulant therapy. The following was examined: demographics, family and personal history, presence of pregnancy complications, type and presence of thrombophilia, perinatal outcome of previous pregnancies, type of anticoagulant therapy, mode of delivery in previous and current pregnancies, laboratory and sonography parameters and perinatal outcome (newborn body weight and Apgar Score at birth). The following pregnancy complications were analyzed: miscarriage (early – up to the 10^{th} week of gestation and late – between the 10^{th} and the 20^{th} week of gestation), preterm deliveries (between the 20^{th} and the 37^{th} week of gestation), intrauterine growth restriction (IUGR), intrauterine fetal death, preeclampsia, placental abruption and deep venous thrombosis.

Exclusion criteria were the following: patient's age over 40, egg donation, joined presence of both congenital and acquired thrombophilia, congenital uterine body anomalies, conditions after gynecological surgeries, perinatal infections (TORCH – toxoplasmosis and others such as syphilis, varicella, mumps, parvovirus and HIV, rubella, cytomegalovirus, herpes simplex), type I diabetes mellitus, chronic hypertension, kidney transplantation, morbid obesity (BMI>40), the use of anticoagulant therapy for other comorbidities, abnormal screening tests in the first trimester (Double and/or Triple test) and pathological karyotype, confirmed fetal anomalies, as well as central placenta praevia and pathological degree of placental nidation (suspected accrete, increta and percreta).

The study was approved by the Ethic Committee (decision No 2650/IV-13) of the Faculty of Medicine, University of Belgrade. A written informed consent was obtained from all study participants.

STATISTICAL ANALYSIS

Descriptive statistics were reported as mean with standard deviation for numerical data. Numbers with percentages were used for categorical data. Differences between groups were analyzed using Pearson Chi Squared test for categorical variables. All tests were 2-tailed. $P<0.05$ was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS, version 21).

RESULTS

The study included 358 pregnant patients with diagnosed trombophilia and mean age 33.67±4.01. The characteristics of the study group are presented elsewhere (6)previous studies regarding LMWH prophylaxis for APO in women with inherited thrombophilia were performed in high risk patients with previous adverse health outcomes in medical, family and/or obstetric history. Therefore, the aim of this study was to investigate the effects of LMWH prophylaxis on pregnancy outcomes in women with inherited thrombophilias regardless of the presence of previous adverse health outcomes in medi-

cal, family, and obstetric history.Prospective analytical cohort study included all referred women with inherited thrombophilia between 11 and 15 weeks of gestation and followed-up to delivery. Patients were allocated in group with LWMH prophylaxis (study group.The total number of 180 patients had their first pregnancy while 178 patients had had previous pregnancies. In 153 out of 178 patients, the previous pregnancy had poor outcome. In the total sample of patients, significantly higher number of patients had poor outcomes in previous pregnancies (χ^2 =36.888; p<0.001). A total number of 129 out of 151 patients with anticoagulant therapy had poor previous pregnancy outcome.

Table 1. Previous pregnancies

Outcome	Total	With AC therapy
Delivery	25 (14.0%)	22 (14.6%)
Poor outcome	153 (86.0%)	129 (85.4%)
Total	178 (100%)	151 (100%)

When comparing previous pregnancies with current pregnancy, 129 out of 151 patients with AC therapy (85.4%) had poor outcomes in the past while they were not present in the current pregnancy. 12 patients with AC therapy had FMU in previous pregnancies, 49 patients had missed abortion, 54 patients had second trimester miscarriage, 4 patients had both FMU and missed abortion, 9 patients had missed abortion and second trimester miscarriage while one patient had FMU, missed abortion and second trimester miscarriage **(Table 2)**.

Table 2. Poor outcomes in previous and current pregnancy, with AC therapy(n=129)

	Past	Current
FMU	12 (9.3%)	0 (0%)
Missed abortion	49 (38.0%)	0 (0%)
Second trimester mis.	54 (41.9%)	0 (0%)
FMU+Missed abortion	4 (3.1%)	0 (0%)
Misc.+Missed	9 (7.0%)	0 (0%)
FMU,Missed ab.,Misc.	1 (0.8%)	0 (0%)

The total number of previous pregnancies was 379 (313 in the group of patients with AC therapy. The total number of losses in the past was 273 (19 FMU, 107 missed abortions, and 147 second trimester miscarriages). The total number of 73 patients had one loss, 51 patients had two losses, 20 patients had three losses, and 7 patients had four losses, while there were 2 patients with 5 previous pregnancy losses. Poor outcomes were statistically significantly more common (72%) in previous pregnancies (χ^2 =73.586; p<0.001). The pregnant patients in the AC therapy group had a total number of 223 (71.2%) poor outcomes in previous pregnancies.

The pregnant patients that received AC therapy had 18 FMU in previous pregnancies(8.1%), 205 missed abortions and miscarriages(91.9%) which was not present in their current pregnancies. In previous pregnancies, 92 babies were born out of 313 pregnancies while in the current pregnancies, where patients were treated, there were 173 babies from 151 pregnancies.

Table 3. Previous pregnancies outcome

Outcome	Total	With AC therapy
Delivery	106 (28%)	90 (28.8%)
Poor outcome	273 (72%)	223 (71.2%)
Total	379 (100%)	313 (100%)

Table 3. Poor outcomes in pregnant patients with therapy, previous and current pregnancy

	Past (n=223)	Current (n=151)
FMU	18 (8.1%)	0 (0%)
Missed ab., miscarriage	205 (91.9%)	0 (0%)

DISCUSSION

In the group of patients where we administered AC therapy for pregnancies burdened by congenital thrombophilia, almost half of the patients could already have had offspring. Half of the patients previously lost a conceptus, had a handicap. The society missed a possible birth rate increase.

If we analyze the available data from the Institute of Public Health of Serbia, by observing birth rate and mortality on the territory of Belgrade only in the past two years, the trend shows drama and a decrease in population. The quality of newborn population is a subject per se, i.e. fetal programming and prevention of adult age diseases through appropriate monitoring of the course and outcome of pregnancy.

Comparing the period of 2016 to the period of 2017, the ratio is as follows: live births 17,967 to 18,000 migrations; still births 88 to 90; deaths 20,803 to 21,768. Birth rate ranging from -2,836 to -3,768. Newborn deaths ranging from 96 to 73. Birth rate in 1,000 people ranging from -1.7 to -2.2.

If we compare the number of deliveries in 2016 and 2017 at the Clinic of Gynecology and Obstetrics of the Clinical Centre of Serbia (Visegradska) only, we come up with the following numbers: in 2016 there were 3,999 vaginal deliveries and 2,298 Cesarean Sections (the total in 2016 – 6,288); in 2017, there were 3,691 vaginal deliveries and 2,230 Cesarean Sections (the total in 2017 – 5,921). In 2018, there were 5,602 deliveries – 3,576 vaginal deliveries and 2,026 Cesarean Sections.

By observing the parameters related to the incidence of diagnosed thrombophilia in women and the effects of administered anticoagulant therapy, we came to an astonishing number of lost conceptuses. Possibilities of increasing birth rate by timely diagnosis of thrombophilia as a possible risk factor for the loss of conceptus and therefore lack of offspring are obvious, both in quantita-

tive and statistical analyses.

The birth rate is evidently dropping. When encouraging an increase in birth rate, not only quantity is important, but quality as well if we want healthy offspring. By losing a conceptus, birth rate decreases. Morbidity (personal, physical and emotional) is increased, as well as social morbidity in relation to family as a societal entity and in relation to the society as a whole.

When observed from the financial aspect, the cost of the loss of potential offspring is high, together with the costs of treatment and late diagnosis. The costs of healthcare system and the burden on it are unreasonably pilling.

Such a stand does not lead to the other extreme that includes unnecessary diagnostic procedures. There are aspects related to sub-specialist perinatology knowledge that are indicators of a possible need for diagnosing congenital thrombophilia and the therapy of certain forms of thrombophilia.

We know that the basic aspect of placental function is its size, but also the intensity of nidation and vascular connection of uteroplacental unit. The size of placenta is determined during the first trimester when definitive chorioallantoic placenta and membranes (chorion leave) are separated before the start of uteroplacental blood flow. By recognizing the phenomenon of chorion regression, with the use of ultrasonography in the second trimester, severe perinatal outcome and thrombotic placental damage are anticipated. Once the definite placenta is formed, invasive extravillous trophoblastic cells transform the spiral arteries in order to establish low-resistance uteroplacental circulation or more efficient flow. This step in the development may be diagnosed by Doppler examination of uterine artery and is the main risk factor for inadequate placentation. In one large study, Franco et al found histological evidence of uteroplacental (maternal) vascular pathology superimposed to placental infarction in 78.7% of cases(8).

From the physiological point of view, placenta has the auto-anticoagulation ability. External area of placental villi is covered by special syncitiotrophoblast layer which is actively involved in the local hemostasis. Decreased placental expression of otherwise physiological glial cells type 1 and poor development of placental villi with defect syncytialization are key characteristics of placental disorder. Invasive extravillous trophoblast normally excludes maternal T-cells by secreting an enzyme indoleamin-2,3-dioxigenase which catalyzes tryptophan. Poor trophoblast invasion and differentiation to secret indoleamin-2,3-dioxigenase or maternal immune overreaction which removes these cells by apoptosis, result in aberrant invasion of maternal T-cells. Maternal T-cells invasion, leading to vitilis, is a further example of abnormal placental development(8).

Iserman et al. conducted a study where they observed animal model pregnancies, pointing to the role of thrombomodulin in the growth and survival of trophoblast. By studying mice with impaired coding of thrombomodulin gene, at the fetal-maternal junction, they observed the thrombomodulin deficit related to embryo abortion. This study showed the basic role of thrombomodulin in the growth and survival of trophoblast. At the feto-maternal junction, thrombomodulin deficit stimulates procoagulant cascade, therefore prompting mass cell death of trophoblast and leading to trophoblast cell growth cessation(9).

In order to properly understand the establishing of correct flow in the uteroplacental unit, the fact that placenta itself has procoagulant characteristics, expressed in trophoblast cells, should not be neglected (10).

However, there are also inhibitory mechanisms, such as endothelial protein C receptor, thrombomodulin, annexin V and tissue coagulation factor inhibitor, which increase starting from the 10th week of gestation (11–14).

According to the literature data, congenital thrombophilia affects 3-11% of the population. Several forms of mutations have been established, classified into most common groups (15–28).

Factor V Leiden (FVL)

1. Factor II (prothrombin) G20210A
2. Protein C deficiency
3. Protein S deficiency
4. Antithrombin deficiency
5. Dysfibrinogenemia
6. Hyperhomocysteinemia, methylenetetrahydrofolate reductase gene, MTHFR 677 T
7. PAI-1 and angiotensin converting enzyme (ACE)

Placental insufficiency is considered to be the cause of the following perinatal complications in pregnancy: preeclampsia, fetal growth restriction (FGR) and still birth. The most common placental lesion is the infarction of placental villi. The frequency of infarction incidence is positively correlated to the perinatological tests for monitoring of uteroplacental circulation, and successive pathologies of the flow through fetal body. Such observations of clinicians perinatologists, as a part of observational studies, prompted the hypothesis and led to testing for thrombophilia in mothers(8).

Thus, it was established that pregnancies destined to end before the 32nd week of gestation with severe preeclampsia or FGR often had abnormal test results for placental function observed between the 12th and the 22nd week of gestation. However, this included false positive results of maternal serum for Down syndrome, smaller placental size and decreased uteroplacental blood flow. In case of two or more abnormal test categories of placental function, placental infarction may be predicted with high certainty. However, maternal thrombophilia was proven as an unusual finding in patients with documented thrombotic placental disorder (8). It is important to mention that the most precise tests and biological credibility of such findings were based primarily on animal models (9).

Adequate placental circulation is necessary for the successful development of pregnancy. Inadequate placental perfusion in conditions surpassing physiological level of coagulability leads to microthrombosis forming and decreases the possibility of trophoblast invasion. Thus, primarily established inadequate perfusion is superimposed to incidence of chronic hypoxia. Clinical manifestations of pathological conditions such as fetal growth restriction, intrauterine fetal death, second and third trimester pregnancy loss, placental abruption and preeclampsia, add to the fact that placental invasion was limited through the process of hypercoagulability surpassing the level of tolerance.

CURRENT GUIDELINES

The lack of strong and consistent evidence base for clinical guidelines has led to different recommendations for clinicians. Regarding thromboprophylaxis, the recommendations of the American College of Chest Physicians (ACCP), compared to recommendations of the Royal College of Obstetricians and Gynecologists (RCOG), do not have absolute consensus(29,30).

Considering the weak correlation between the most common types of thrombophilia and VTE, the incidence of VTE diagnosis in family history has been monitored. ACCP recommendations suggest LMWH prophylaxis in two groups of women: 1) without family history of VTE who are either homozygote FVL or prothrombin gene mutation; and 2) women with family history of VTE in combination with any other congenital thrombophilia.

ACCP guidelines do not recommend prophylactic use of LMWH for those with congenital thrombophilia and with the absence of previous pregnancy complications. This is justified by the lack of evidence to support outcome improvement with LMWH in women with congenital thrombophilia and recurrent pregnancy loss. However, ACCP recommends aspirin for women who are under high risk of developing preeclampsia, regardless their thrombophilia history. This is in accordance with RCOG and supported by a strong evidence base.

Similarly, RCOG guidelines recommend considering antenatal prophylaxis with LMWH in patients who are homozygote FVL and prothrombin G20210A. These guidelines also recommend prophylactic LMWH in women with antithrombin deficiency, proten C or protein S deficiency, despite the lack of family/personal history of VTE, which differs from ACCP recommendations. RCOG further stratifies the risk as per pragmatic accumulation of the risk factors: if FVL heterozygote or prothrombin gene mutation is present with two or three other risk factors, or there is a complex heterozygote, prophylactic LMWH may be administered even before delivery. The other difference is that RCOG guidelines applies stratification of risks to further difference in dosing, pointing to the fact that women with antithrombin deficit and previous VTE should have 50-100% dose of therapy antenatally and 6 weeks postnatally (9).The studies of Gris et al. (31,32)we investigated the effectiveness of enoxaparin, a low-molecular-weight heparin, in preventing these complications. Between January 2000 and January 2009, 160 women from the NOHA First cohort, with previous abruptio placentae but no foetal loss during their first pregnancy and negative for antiphospholipid antibodies, were randomised to either a prophylactic daily dose of enoxaparin starting from the positive pregnancy test (n=80 on the prevention of negative outcomes of pregnancies in women with history of preeclampsia and abruption, treated by LMWH, showed a significant benefit.

ACCP and RCOG are the only two examples of internationally available guidelines. The variations between these two guidelines are only examples of the lack of adequate evidence base

CONCLUSIONS

Previous pregnancy poor outcomes were statistically significantly more common when anticoagulant therapy was not administered (72%).

Pregnancy complications such as preeclampsia, hypertension, placental abruption, and thrombocytopenia were more common in pregnant patients without the anticoagulant therapy, but with no statistical significance.

More pregnancies were delivered by means of surgery, especially in patients with previous pregnancy poor outcomes. The patients with anticoagulant therapy had vaginal deliveries more often, with statistical significance, compared to a higher number of Cesarean Sections in the group without the therapy.

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ULOGA AKTIVNE PERINATOLOGIJE U PREVENCIJI NEPOTREBNOG GUBITKA KONCEPCIJE I PADA NATALITETA

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Sažetak

Uvod: Savremena perinatologija zahteva kontinuirano unapređenje doktrina i protokola. Gubitak trudnoće se smatra neoprostivim, a mogućnost za održavanje rizičnih trudnoća bi mogao da utičena povećanje stope rađanja, kojoj težimo kao društvo. Cilj ovog istraživanja bio je da se prikaže uloga niskomolekularnog heparina u prevenciji loših ishoda trudnoće.

Metod: U istraživanje su uključene sve **žene** sa naslednim trombofilijama upućene na Kliniku za Ginekologiju i akušerstvo, Kliničkog Centra Srbije između 2016 i 2018. godine, koje su praćene do porođaja. Pacijentkinje su podeljene u dve grupe.

Rezultati: Ukupno je 180 pacijentkinja bilo u svojoj prvoj trudnoći, dok je njih 178 imalo prethodne trudnoće. Ukupno je 153 od 178 njih imalo gubitak prethodne trudnoće. 12 pacijentkinja sa antikoagulantnom terapijom imalo je FMU, 49 je imalo missed pobačaj, 54 je imalo spontani pobačaj u drugom trimestru, 4 pacijentkinje sui male i FMU i missed, 9 njih je imalo missed i spontani pobačaj u drugom trimestru, jedna pacijentkinja je imala sva tri nepovoljna ishoda. U svim prethodnim trudnoćama, ukupno je rođeno 92 bebe iz 313 trudnoća, dok je sa antikoagulantnom terpaijom rođeno 173 bebe iz 151 trudnoće.

Zaključak: Pacijenkinje sa antikoagulantnom terapijom imaju značajno visoko opterećenje sa prethodnim gubicima trudnoće.

Ključne reči: trudnoća; gubitak trudnoće; nasledne trombofilije.

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CASE REPORT

Ventricular tachycardia and hypertensive crisis induced by routine neuromuscular blockade reversal – a case report and literature review

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Summary

Introduction: Neuromuscular blockade reversal may provoke cardiovascular events. We present the case of a middle-aged, vascular patient in whom ventricular tachycardia and hypertensive crisis occurred immediately after the initiation of neuromuscular blockade reversal.

Patient Review: A 56-year-old man was admitted to our institution for emergency surgical treatment of left extremity ischemia. Besides hypertension, the patient's medical history was negative for any other significant acute or chronic diseases. Routine preoperative analyzes, ECG, and echocardiography showed normal findings. The patient underwent urgent trans popliteal thrombectomy under general endotracheal anesthesia. Immediately following the initiation of neuromuscular blockade reversal, with a diluted mixture of atropine and neostigmine (1 mg/2.5 mg, respectively), ventricular tachycardia and hypertensive crisis developed. Arterial blood gas analyses and electrolyte values were within the reference limits at the moment. Adequate therapeutic measures were undertaken immediately, and sinus rhythm was restored shortly. Later, serial ECG records showed negative T waves in the precordial leads, with an increasing trend of troponin I values (ranging from 0.59 to 5.45 μg/L). Coronary angiography was later performed and revealed a normal coronary angiogram. During the next three days, ischemic ECG alterations showed resolution and the patient was hemodynamically stable. On the fifth postoperative day, the patient was discharged, in good general medical condition.

Conclusion: A careful administration of the atropine/neostigmine mixture is advised. Malignant arrhythmias must be recognized and treated promptly by an anesthesiologist, in order to achieve positive treatment outcomes.

Keywords: neuromuscular blockade reversal; ventricular tachycardia; hypertensive crisis.

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INTRODUCTION

Neuromuscular blockade reversal (NMBR), along with anesthesia awakening and tracheal extubation, represents one of the most critical points of general endotracheal anesthesia (GETA). Among various complications that may emerge during that phase of anesthesia management, cardiac arrhythmias deserve special attention. Although cardiac rhythm disorders that develop during this period are often transient and benign, more complex dysrhythmias may develop, as well. Some of those arrhythmias, if not treated promptly, may be life-threatening, even in patients without cardiac comorbidities. Ventricular tachycardia (VT), a malign cardiac rhythm disorder, is a wide-QRS-complex tachycardia, with a sudden onset, a regular rhythm, and heart rate (HR) higher than 100 beats per minute (bpm). VT most commonly occurs in the presence of structural heart disease. (1) Still, in up to 10% of patients, an obvious structural heart disease has not been identified. (2)
We present a case of simultaneous development of VT and hypertensive crisis (HC) following a routine NMBR in a middle-aged healthy vascular patient.

CASE REPORT

A 56-year-old male was admitted to our institution, due to pain and coldness in his left leg. Pedal pulses were absent and Color Dopler Sonography of left limb blood vessels showed distally occluded left popliteal artery, as well as its branches, by a hypoechoic mass. The patient's medical history, besides hypertension, was negative for any acute or chronic diseases (including cardiovascular system-related events, such as myocardial infarction, significant arrhythmias, and symptoms of angina pectoris). The patient was a smoker, he denied allergies, previous operations and narcotic consumption. Routine blood, blood gas, and urine analyses showed no disturbances from reference values, except for the deviations related to an acute vascular disease. Preoperative electrocardiogram (ECG) and echocardiography (ECHO) were performed and they showed no disorders either (ECG: sinus rhythm with no changes in the ST segment and T wave; ECHO: structurally normal heart, left ventricle ejection fraction 62%, with no kinetics disorders). **(Figure 1)**

Due to acute left limb ischemia, the patient underwent trans popliteal thrombectomy under GETA. Anesthesia was induced with 5 mg of midazolam, 80 mg of propofol, and 100 μg of fentanyl. Succinylcholine (80 mg) was used to facilitate tracheal intubation and rocuronium-bromide was subsequently added to maintain muscle relaxation. In order to reach adequate anesthetic depth, sevoflurane, in an oxygen–air mixture was administered. Vital parameters were continuously monitored: oxygen saturation, end-tidal CO_2, blood pressure (BP), HR, and ECG. The patient was hemodynamically stable during the whole procedure and the intraoperative course was uneventful. An average heart rate was 75 bpm and mean arterial pressure was 100 mmHg. **(Figure 2)**

Following the initiation of NMBR, by diluted atropine–neostigmine mixture(1 mg–2.5 mg, respectively), ECG showed ventricular tachycardia (HR=157 bpm) with cardiac axis deviation, bizarre wide QRS-complexes and capture beats, accompanied by the hypertensive crisis (BP=235/171 mmHg). **(Figure 3)**

Following a bolus injection of lidocaine (1.5 mg/kg), the continuous infusion was initiated, at the rate of 1 mg/kg/hr. Within two minutes, VT converted to sinus rhythm. Glyceryl nitrate was fractionally administered intravenously and as continuous infusion, with metoprolol boluses, so blood pressure lowered. At the time, arterial blood gas analysis and blood electrolytes revealed normal values. When the patient was hemodynamically stabilized, no other active intervention was done, and he was transferred to the Intensive care unit. Three hours later, a serial 12-lead ECG revealed negative T waves in

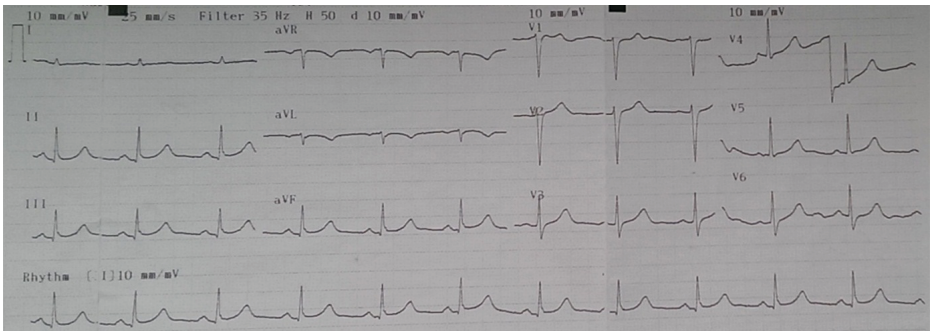

Figure 1. Preoperative ECG

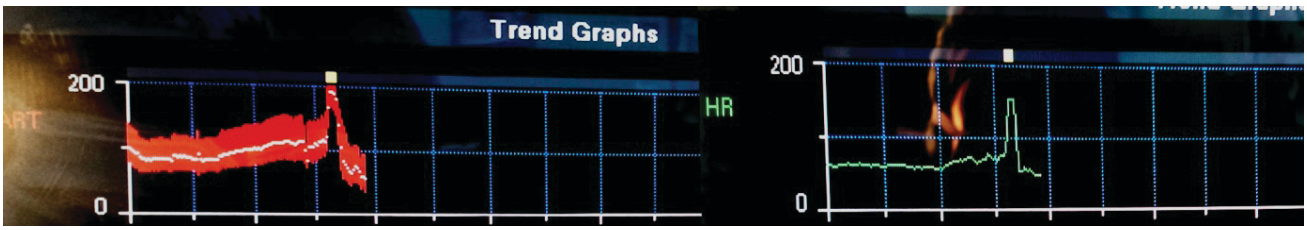

Figure 2. Intraoperative blood pressure and heart rate trend graphs

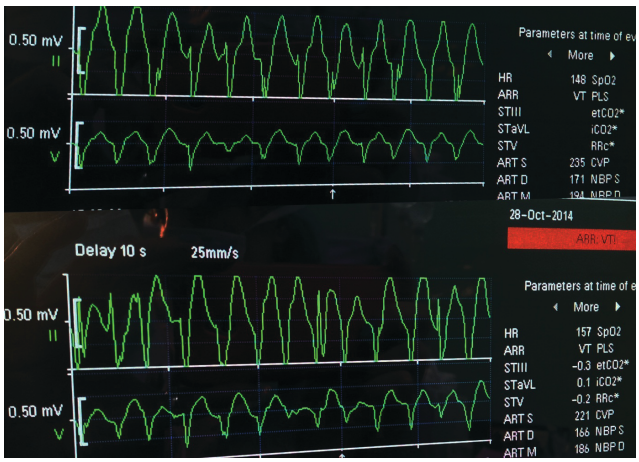

Figure 3. Intraoperative blood pressure and heart rate at the time of the event

precordial leads. Troponin I value showed an increasing trend (from 0.59 up to 5.48 μg/L). Later, coronary angiography was performed and it showed a normal coronary angiogram. **(Figure 4)** During the next three days, negative T waves showed resolution; the patient was hemodynamically stable. On the fifth postoperative day, the patient was discharged, in good general medical condition.

DISCUSSION

Anesthesia emergence and tracheal extubation often provoke hypertension and tachycardia. These cardiovascular alterations may precipitate he occurrence of additional cardiac rhythm abnormalities and may even lead to the development of myocardial ischemia in patients with coronary arterial disease. (3) On the other hand, in patients without structural heart disease, hemodynamic disturbances which develop spontaneously and with no obvious reason during anesthesia awakening may be associated with NMBR.

In an anesthetized patient, without structural heart disease, VT may develop due to many reasons, such as metabolic/electrolyte abnormalities, hypoxia, hypercarbia, anesthetic overdose, myocardial ischemia, and IV use of adrenaline and other catecholamines. Furthermore, life-threatening ventricular arrhythmias may develop in patients without coronary artery disease due to Takotsubo cardiomyopathy. (4) This stress-induced cardiomyopathy which occurs due to the massive release of catecholamines may lead to cardiotoxicity, multivessel coronary vasospasm, and abnormalities in coronary microvascular function. (5) Still, all the above-mentioned factors were ruled out in our patient. Since the cause of this malign arrhythmia may remain unknown, (6) we can only assume that the atropine-neostigmine mixture, along with anesthesia awakening, over-stimulated our patient's cardiovascular system, predisposed the coronary arteries to spasm and thus the autonomic control of the heart was altered. Our assumption is supported by the fact that, although generally considered safe, this anticholinesterase-anticholinergic combination may have a potential proarrhythmic effect. (7)

In order to further investigate the possible cause of this substantial but, fortunately, timely managed cardiovascular event in our patient, we have performed a literature review. Several relevant electronic databases were systematically searched using a combination of the following keywords: "neuromuscular blockade reversal", "atropine and neostigmine", "ventricular tachycardia" and "hypertensive crisis". The results of our review suggest that, although routine NMBR may precipitate significant hemodynamic disturbances, only a few similar cases were described. Back in 1995, Rodríguez J. et al. presented a case of bradycardia and asystole following atropine-neostigmine administration in a patient who underwent a Caesarean section. The authors partially attributed the event to the effects of methyldopa, which was used for the management of pregnancy-induced hypertension, but they believed that NMBR agents might have contributed. (8) In 2004, Liaquat et al. presented the case of successfully managed cardiac arrest induced by routine NMBR. (6) Similar events were also described in children - Tüfek A. et al. published a case of cardiac arrest in a healthy18-month-old child. Besides the immaturity of the parasympathetic nervous system, the authors associated this event to the direct effects of the atropine/neostigmine mixture. (9) The rest of the cases in the available literature which describe similar cases refer to the patients with structural heart abnormalities (10, 11) or to another combination of medicaments used for NMBR. (12) So, to the best of our knowledge, no other report presented the exact case as ours.

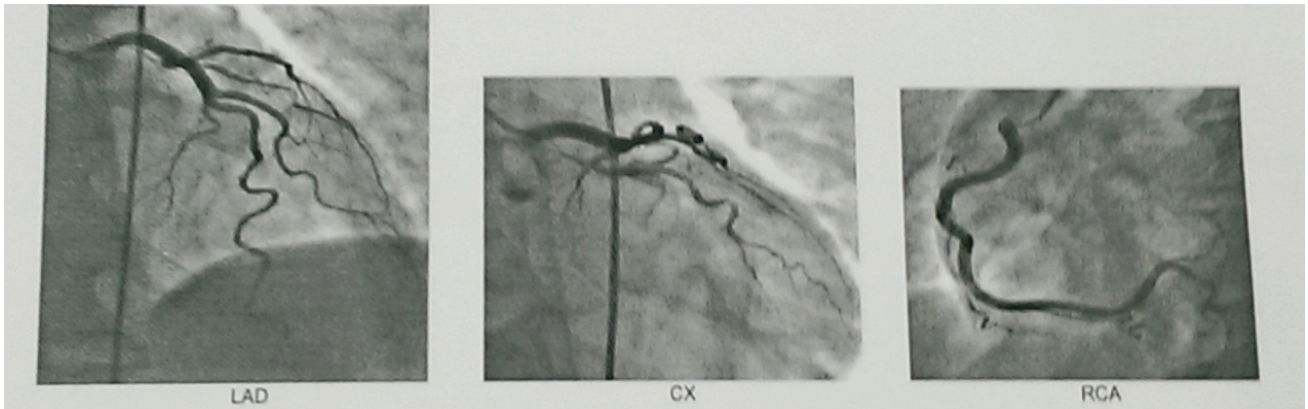

Figure 4. Coronary angiography

CONCLUSION

The report emphasizes the need for careful atropine-neostigmine mixture administration, even in healthy patients, without structural heart diseases. It also suggests that malign cardiac rhythm disorders must be recognized and treated promptly, in order to achieve positive outcomes, which mostly depend on the anesthesiologist's timely intervention.

Author Contributions

1) the conception or design of the work: K.J., R.T., P.M., M.S.; 2) the acquisition: R.T., I.T., P.M., A.D.; 3) analysis, or interpretation of data: AD, MS, IK; 4) preparing the draft of the manuscript: K.J., I.T., M.D., L.D.; 4) interpretation of revised version of manuscript: K.J., I.K., M.D., L.D.

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VENTRIKULARNA TAHIKARDIJA I HIPERTENZIVNA KRIZA IZAZVANE RUTINSKOM REVERZIJOM NEUROMUSKULARNE BLOKADE: PRIKAZ SLUČAJA I PREGLED LITERATURE

Ksenija Jovanović[*1,2], Ranko Trailović[1,2], Perica Mutavdžić[2,3], Ivan Tomić[2,3], Miloš Sladojević[2,3], Andreja Dimić[2,3], Marko Dragaš[2,3], Igor Končar[2,3], Lazar Davidović[2,3]

Sažetak

Uvod: Reverzija dejstva miorelaksanasa može dovesti do nastanka kardiovaskularnih poremećaja tokom buđenja iz anestezije. Prikazujemo vaskularnog bolesnika kod koga je došlo do nastanka ventrikularne tahikardije i hipertenzivne krize, neposredno nakon započinjanja reverzije neuromuskularne blokade.

Prikaz slučaja: Muškarac, star 56 godina, primljen je u našu ustanovu radi hitnog operativnog lečenja ishemije levog ekstremiteta. Osim hipertenzije, bolesnikova anamneza je bila negativna na druga značajna akutna ili hronična oboljenja. Rutinske preoperativne analize, EKG i ehokardiografija pokazale su uredne nalaze. Bolesnik je hitno podvrgnut transpoplitealnoj trombektomiji u uslovima opšte endotrahealne anestezije. Prilikom započinjanja reverzije neuromuskularnog bloka (kombinacijom razblaženog rastvora atropina i neostigmina, u dozi od 1mg, odnosno 2,5mg), dolazi do pojave ventrikularne tahikardije praćene hipertenzivnom krizom. Gasne analize arterijske krvi i vrednosti elektrolita su bile u referentnim granicama u tom momentu. Adekvatne terapijske mere su odmah preduzete, te se kod bolesnika ubrzo ponovo uspostavlja sinusni ritam. Kasnije, serijski EKG zapisi pokazuju negativne T talase u prekordijalnim odvodima, uz trend porasta vrednosti troponina I (u rasponu od 0,59 do 5,45 µg/L). Na učinjenoj koronarografiji nisu postojale značajne stenoze koronarnih krvnih sudova. Tokom naredna tri dana, dolazi do rezolucije ishemijskih promena na EKG-u i bolesnik je hemodinamski stabilan, te je, petog dana posle operacije otpušten iz bolnice, dobrog opšteg stanja.

Zaključak: Savetuje se pažljiva primena kombinacije atropina i neostigmina, a maligni poremećaji ritma moraju biti pravovremeno prepoznati i tretirani od strane anesteziologa, u cilju postizanja zadovoljavajućih rezultata hirurškog lečenja.

Ključne reči: reverzija neuromuskularnog bloka; ventrikularna tahikardija; hipertenzivna kriza.

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ORIGINAL ARTICLE

Multivariate logistic model of hospital length of stay after appendectomy

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Summary

Background: Appendectomies are interesting because they are the most common emergency abdominal operations, they are considered simple procedures, and the imperative is a quick recovery measured by hospital length of stay (LOS). However, this is not always the case in clinical practice, hospitalization can be prolonged, and the question is what factors affect it.

Methods: A multivariant logistic model of LOS predictors analyzed from the clinical data of 446 patients who underwent appendectomy at the Clinic for Emergency Surgery, Belgrade. The patients were divided into Short LOS group (SLOS hospital stay ≤3 days, 157 patients) and Long LOS group (LLOS hospital stay >3 days, 289 patients).

Results: Significant differences were found between SLOS and LLOS groups in age ($p<0.001$), comorbidities ($p=0.001$), preoperative WBC ($p = 0.004$); preoperative CRP ($p < 0.001$); peritonitis ($p < 0.001$), using ≥ 2 antibiotics ($p < 0.001$), complicated appendicitis ($p < 0.001$), surgical time ($P < 0.001$). No significant difference was found concerning gender, postoperative WBC, CRP, and complications ($p>0.05$). Patients who underwent laparoscopic appendectomy (LAP) had a statistically significantly shorter hospitalization time compared to those who underwent Mini-Incision Open Appendectomy (MIOA) ($p < 0.001$). The multivariate logistic model found three statistically significant predictors of longer hospitalization: CRP preoperatively ($B=0.006$, $p=0.047$), $OR=1.006$, the type of surgery ($B=1.199$; $p<0.001$), $OR=3.3$ complicated appendicitis ($B=0.762$; $p=0.003$), $OR=2.142$.

Conclusion: Surgical approach has statistically the most significant impact on LOS. Laparoscopic appendectomy is superior to Mini-Incision Open Appendectomy concerning the hospital LOS.

Key words: Hospital Length of Stay (LOS), Laparoscopic Appendectomy (LAP), Mini-Incision Open appendectomy (MIOA)

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INTRODUCTION

Despite advances in non-operative management of appendicitis, modern antibiotic therapy and precise imaging for monitoring patients, the standard of care for acute appendicitis is appendectomy (1) Appendicitis is one of the most common abdominal emergencies and appendectomy is one of the most common abdominal surgeries (2,3). The advantages of laparoscopic appendectomy (LA) over the open one have made it the gold standard today (4). Open appendectomy (OA) is still an option for cases of severe abdominal inflammation with a presentation of an acute abdomen, for patients with previous multiple abdominal operations due to adhesions, in cases of severe respiratory disorders, in case of technical deficiencies of the hospital, a lack of intensive perioperative care and an inexperienced surgical team. Two important indicators of the success of the treatment are the rate of postoperative complications and the length of hospital stay (LOS). The most common complications after appendectomy are wound infection, intra-abdominal abscess, ileus. Although appendectomy is considered a simple procedure and both LAP and OA are safe and effective techniques, the patient's recovery and the occurrence of postoperative complications depend on various factors (5). Recent studies indicate that laparoscopic surgery vs open appendectomy brings about a quick recovery and a shorter LOS (6).

We designed a study to reassess the treatment quality analyzing the LOS in patients who underwent appendectomy at the University Clinic for Emergency Surgery, considering hospitalization shorter than 3 days as a favorable outcome.

METHODS

This retrospective study analyses the clinical data that could have a significant impact on the hospital LOS of patients with acute appendicitis who underwent appendectomy between April 2020 and June 2022. at the Clinic for Emergency Surgery, University Clinical Center of Serbia, Belgrade. The study was approved by the Ethical committee of the University Clinical Center of Serbia, Belgrade (878/9). LOS was defined as the period of time from hospital admission to patient's discharge. The patients were divided into Short LOS group (SLOS, hospital stay ≤3 days) and Long LOS group (LLOS hospital stay, >3 days). We included 446 adult patients diagnosed with acute appendicitis which was indicative of emergency appendectomy. Diagnostic procedures and treatment protocols were standardized for all the patients including antibiotic therapy, premedication, surgical treatment, analgesia, nutrition. Depending on the admission time, operations were performed at any time during regular 24-hour shifts by surgical teams at the Clinic for Emergency Surgery. Two surgical approaches were used, laparoscopic and open appendectomy. Three Port Laparoscopic Appendectomy (LAP) was performed through one umbilical port (10 mm), suprapubic (5mm) and low left lateral port (10 mm) **(Figure 1 a, b; Figure 2 a, b, c)**. For managing the base of the appendix, we used titanium or polymer ligating clips **(Figure 1 a, b; Figure 2 a, b, c)**. LAP was the first option, but the definite decision about the type of operation was based on surgeons' assessment depending on the local findings of the severity of inflammation, the patient's condition, the status of Covid infection. Mini-Incision Open appendectomy (MIOA) was defined as the right lower quadrant incision, up to 3cm diameter.

The exclusion criteria were the following:

- Patients who were treated by nonoperative management, antibiotics, or percutaneous drainage as the first choice according to guidelines (3, 6).
- Patient who underwent medial laparotomy.

The diagnostic algorithm for acute appendicitis was as follows: clinical finding of abdominal pain, followed by nausea and vomiting, abdominal tenderness with maxi-

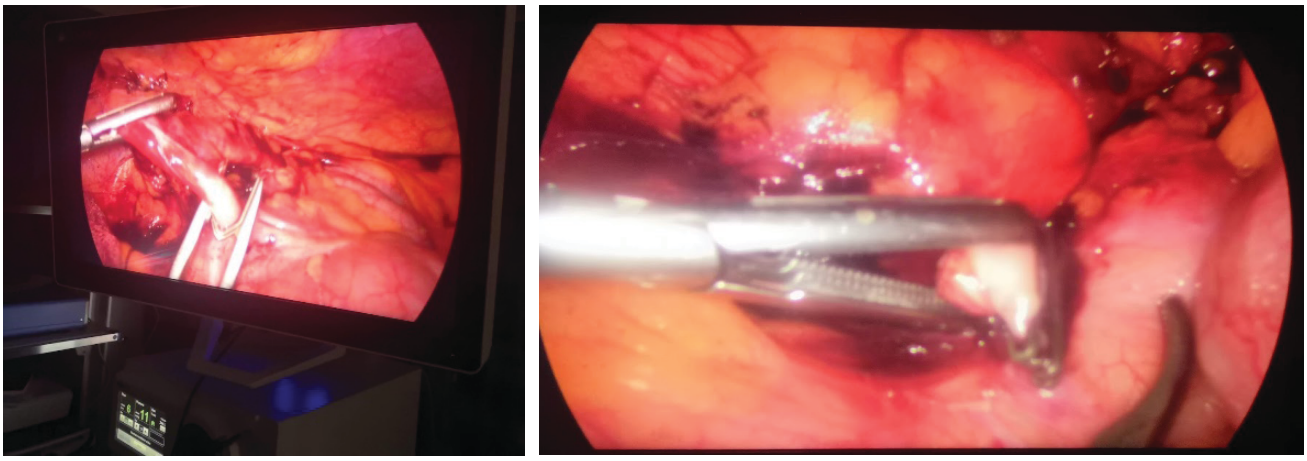

Figure 1. A. LAP-After vascular dissection, holding appendix near the base using a forceps introduced through 5 mm suprapubic port, before appendiceal stump treatment by titanium ligating clips. **B.** LAP- Management of the base of the appendix was completed, the appendiceal stump closure by titanium ligating clips through left lateral port was performed.

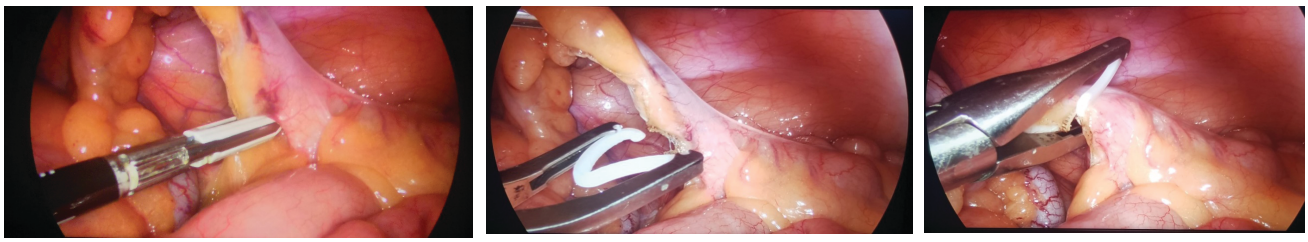

Figure 2.A. LAP -Vascular dissection of appendix. Figure 2. **B.** LAP - After vascular dissection, holding appendix before the appendiceal stump closure by polymer ligating clips. Figure 2. **C.** LAP – The appendiceal stump closure by polymer ligating clips.

mum pain in McBurney point, increased white blood cell (WBC) count, increased C-reactive protein (CRP) and positive ultrasound or abdominal Computed Tomography (CT) suggesting acute appendicitis. All procedures during the treatment were performed in accordance with the current medical and ethical standards. The multivariant logistic model predictors were patients' anonymous clinical data: sex, age, comorbidity, preoperative imaging diagnostics, preoperative laboratory value of WBC and CRP, intraoperative finding of peritonitis, pathological type of acute appendicitis, surgical time, postoperative complications, mono/dual antibiotic treatment. Surgical time represents the duration of the operation from the moment of surgical incision to the end of operation, measured in minutes. Acute appendicitis was defined as uncomplicated or complicated, which was determined by the presence of gangrenous appendicitis or perforated appendix with peritonitis, with or without an abscess. In all the cases of complicated appendicitis, we placed intrabdominal drainage, as the final step after appendectomy. Minor (Clavien-Dindo I, II) complications were postoperative nausea, wound infections, minor stump fistula, abscesses, all treated by non-operative management. Major complication defined as Clavien-Dindo III-IV needed re-intervention or ICU after appendectomy and included the following: postoperative bleeding, ileus, peritonitis (7).

STATISTICAL ANALYSIS.

Depending on the type of variables and the normality of distribution, data description is shown as n (%), mean±sd or median (min-max). Among the methods for testing statistical hypotheses, the following were used: t-test, Mann-Whitney test, chi-square test and Fisher's exact probability test. Univariate and multivariate logistic regressions were used to analyze the relationship between binary outcomes (hospitalization up to and over 3 days) and potential predictors. Multivariate regression models included predictors from univariate models that were statistically significant at the 0.05 significance level. Statistical hypotheses were tested at the statistical significance level of 0.05. The results are presented tabularly and graphically. All the data were processed in the IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software package.

RESULTS

Significant differences were detected between SLOS and LLOS groups in age (30.62 ± 11.09 years vs 35.92 ± 13.60, p<0.001), comorbidities (11.5% vs 24.2, p=0.001), preoperative WBC (12.57 ± 3.23 × 109/L vs 13.63 ± 4.31 × 109/L, p = 0.004); preoperative CRP (31.16 ± 36.88 mg/L vs 53.13 ± 54.11 mg/L, p < 0.001), peritonitis (37.6% vs 60.6%, p < 0.001), using ≥ 2 antibiotics (37.6% vs 60.6%, p < 0.001), complicated appendicitis (55.4% vs 73.7%, p < 0.001), surgical time (45.0 min vs 55.0 min, p < 0.01), type of surgery (p < 0.001) (Table 1). It this study 238 (53.4%) patients underwent LAP and 208 (46.6%) patients underwent MIOA. Patients who underwent laparoscopic surgery had a statistically significantly shorter hospitalization time compared to those who underwent an open surgery (p < 0.001) (Table 1; Figure 1a, b; Figure 2a, b, c). No significant difference was found concerning gender (p=0.432), preoperative imaging (p=0.316), postoperative CRP (p=0.082) and minor or major postoperative complications (p=0.655, p=0.167) **(Table 1)**.

In the multivariate logistic model with the LOS longer than 3 days, those predictors from the univariate models that were statistically significant at the significance level of 0.05 were included. The model contains 8 predictors that were compared to 446 respondents, 289 of which had the outcome of interest. The entire model with all predictors was statistically significant (p<0.001) **(Table 2)**.

In the multivariate logistic model, statistically significant predictors of hospitalization longer than 3 days were:

- CRP preoperatively (B=0.006, p=0.047), OR=1.006, which means that with an increase in CRP for a unit of measure, the chance of hospitalization longer than 3 days increases by 0.6%, while controlling all other predictors in the model.
- Type of surgery (open versus laparoscopic), (B=1.199; p<0.001), OR=3.3 shows that respondents who underwent MIOA had almost 3 times higher chance of hospitalization longer than 3 days, while controlling all other predictors in the model.
- Complicated appendicitis (B=0.762; p=0.003), OR=2.142, respondents who had complicated appendicitis had more than 2 times higher chance of being hospitalized longer than 3 days, with all other predictors in the model controlled.

Table 1. Comparison of characteristics between the two groups.

Characteristic	SLOS group n=157	LLOS group n=289	p
Age (year, mean ± SD)	30.62 ± 11.09	35.92 ± 13.60	<0.001
Sex, male (*n*, %)	80 (51.0%)	136 (47.1%)	0.432
Comorbidities (*n*, %)	18 (11.5%)	70 (24.2%)	<0.001
Preoperative WBC count (10^9/L, mean ± SD)	12.57 ± 3.23	13.63 ± 4.31	0.004
Preoperative CRP level median (range)	18.1 (0.6-240.5)	38.5 (0.6-292.5)	< 0.001
Preoperative US	139 (88.5%)	246 (85.1%)	0.316
Preoperative CT	18 (11.5%)	43 (14.9%)	
LAP	108 (68.8%)	130(45.0%)	< 0.001
MIOA	49 (31.2%)	159 (55.0%)	
Surgical time median (range)	45 (30-110)	55 (30-120)	< 0.001
Peritonitis (*n*, %)	59 (37.6%)	175(60.6%)	< 0.001
Complicated appendicitis (*n*, %)	87 (55.4%)	213 (73.7%)	< 0.001
Dual antibiotic therapy (*n*, %)	59 (37.6%)	175(60.6%)	< 0.001
WBC on the second postoperative day (10^9/L, mean ± SD)	8.016 ±2.09	7.492±2.25	0.016
CRP level on the second postoperative day median (range)	30.6 (0.6-195.0)	35.2 (0.6-210.9)	0.082
Clavien-Dindo I, II complications	10 (6.4%)	23 (8.0%)	0.655
Clavien-Dindo III-V complications	0 (0.0%)	5(1.7%)	0.167

Table 2. The multivariate logistic model for LOS.

Variables	B	p	OR	95% C. I.	
				Lower	Upper
Age	0.017	0.109	1.017	0.996	1.038
Comorbidity	0.225	0.508	1.253	0.643	2.440
Preoperative WBC count	0.008	0.793	1.008	0.951	1.069
Preoperative CRL level	0.006	0.047	1.006	1.000	1.012
Type of surgery	1.199	< 0.001	3.316	2.074	5.300
Peritonitis	0.463	0.053	1.589	0.991	2.547
Complicated appendicitis	0.762	0.003	2.142	1.302	3.526
Surgical time	0.011	0.223	1.011	0.993	1.030

DISCUSSION

Appendectomy is one of the most common interventions in emergency surgery (8,9). Experience from our clinic has confirmed that patients with acute appendicitis are most frequently hospitalized among emergency surgical patients. It is most often a disease of younger adults and an adequate treatment enables their quick recovery and early return to normal life. Elderly patients with appendicitis have a lower rate of complications if the diagnosis is made on time and adequate treatment is carried out (9).

Regardless of the severity of abdominal inflammation or the presence of comorbidity, the goal is always to make the patient's recovery as short as possible and without complications. LOS measured in days is the time elapsed from hospital admission to discharge. In clinical practice, we can expect that a patient's recovery and length of hospitalization may depend on the severity of the diagnosis itself. However, statistical analysis can provide a more accurate insight into the relationship between several clinical parameters and their outcome. LOS is considered as an adequate indicator of the effectiveness of the treatment, the quality of hospital treatment, including both the patient outcome and the cost of treatment (10-12).

In this study three factors were identified as significant predictors of LOS after emergency appendectomy. We made a predictive model based on multivariate regression factors of SLOS and LLOS for 446 patients undergoing appendectomy (Figure 1, 2). Study analyzed the influence of seventeen clinical parameters on the duration of hospital stay, as one of the indicators of the quality of treatment in patients who underwent emergency LAP or MIOA. During the two-year study time, it was not always possible to perform laparoscopy for objective reasons or to perform open surgery in conditions of Covid infection due to Covid protocol. Eight clinical parameters showed

a statistically significant influence on the LOS. Between different variables such as demographic data, laboratory data, pathohistological data, we found that the three most important predictors are: CRP preoperatively, type of surgery and severity of appendicitis. Finally, this statistical model showed that the type of surgery is the most important predictor of the LOS. Patients who underwent laparoscopic appendectomy had a statistically significantly shorter hospitalization time compared to those who underwent an open surgery ($p < 0.001$) **(Table 1, 2)**.

Laparoscopic appendectomy has become a gold standard owing to the results of randomized trials based on the comparison between LAP and open appendectomy (4-6). LAP is associated with lower morbidity, shorter operative time, less postoperative pain, and shorter hospitalization (4-6). However, in not so rare cases of severe neglected abdominal infection and peritonitis-ileus syndrome that occur as a consequence of complicated appendicitis, open appendectomy is still the conventional approach (5).

Although it is considered a simple procedure, it is obvious that in patients who underwent appendectomy, many factors could affect the outcome and LOS.

A large multicenter cohort study of 4618 patients identifies complicated appendicitis, morbidity, conversion, and reinterventions as significant risk factors for longer hospital stay after laparoscopic appendectomy, assuming that the median LOS was 3 days (13). Trunfio et al. showed that complications, severe diagnosis, and patients' age influenced LOS after LAP (14). Crandall et al. excluded a complicated case and the study of variables affecting LOS showed that LOS was significantly influenced by the operative time of day (15). In the study containing 636 patients who underwent LAP, Zhang et al. showed that LOS increased with patients' age, higher preoperative inflammatory markers, operation delay and the rate of complicated appendicitis with appendicolith (16). We also found that patients who underwent complicated appendicitis had more than a two times higher chance of being hospitalized longer than 3 days (Table 2). Similar to our results, but in the pediatric population, Cheong et al. found an association of the length of hospitalization with open appendectomy (17). In patients who underwent appendectomy, some authors have found that patients' demographic characteristics could have an influence on LOS (18).

According to different authors, the length of hospital stay after appendectomy can be influenced by complicated appendicitis, a surgery delay, the time of day when the surgery is performed, the skills of the surgeon or resident, the patient's age, the type of surgery (open vs. laparoscopic) (13-17). This study showed that older age, comorbidities, higher preoperative WBC and CRP, peritonitis, using ≥ 2 antibiotics, complicated appendicitis, longer surgical time, and open surgical approach significantly affect the length of hospitalization. It is important to mention that those predictors are measurable so their identification would help about a better clinical decision-making process.

CONCLUSION

This study was designed with the idea of improving the treatment of many patients hospitalized for emergency surgery due to acute appendicitis. Out of the seventeen analyzed parameters that can influence LOS, multivariant logistic model identified three predictors: CRP preoperatively, the type of surgery and the severity of appendicitis. This result is very close to our clinical experience. Finally, the statistical analysis showed that surgical approach has the greatest impact on LOS. Laparoscopic appendectomy is superior to Mini-incision Open appendectomy concerning the hospital LOS.

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MULTIVARIJANTNI LOGISTIČKI MODEL DUŽINE HOSPITALIZACIJE NAKON APENDEKTOMIJE

Krstina Doklestić[1,2], Zlatibor Lončar[1,2], Zoran Bukumirić[1,3]

Sažetak

Uvod: Apendektomije su zanimljive jer su najčešće hitne abdominalne operacije, smatraju se jednostavnom procedurom, a imperativ je brz oporavak meren dužinom boravka u bolnici (DBB). Ali to nije uvek slučaj u kliničkoj praksi, hospitalizacija se može produžiti, a pitanje je koji faktori na to utiču.

Metode: Multivarijantni logistički model prediktora DBB analiziran je na osnovu kliničkih podataka 446 pacijenata koji su podvrgnuti operaciji slepog creva na Klinici za urgentnu hirurgiju u Beogradu. Pacijenti su podeljeni u kratku DBB grupu (KDBB, ≤3 dana, 157 pacijenata) i u dugu DBB grupu (DDBB, >3 dana, 289 pacijenata).

Rezultati: Utvrđene su značajne razlike između grupa u pogledu starosti (p<0,001), komorbiditeta (p<0,01), preoperativoj vrednosti leukocita (p = 0,04); preoperativnom CRP (p < 0,001); peritonitisu (p < 0,001), primeni ≥ 2 antibiotika (p < 0,001), komplikovane upale slepog creva (p < 0,001), dužini trajanja operacije (P < 0,01). Nije nađena značajna razlika u odnosu na pol, postoperativne vrednosti leukocita, CRP i komplikacije (p>0,05). Pacijenti koji su bili podvrgnuti laparoskopskoj apendektomiji (LAP) imali su statistički značajno kraće vreme hospitalizacije u poređenju sa onima koji su bili podvrgnuti otvorenoj apendektomiji sa minimalnim rezom (OAMR) (p < 0,001). Multivarijantni logistički model je pronašao tri statistički značajna prediktora duže hospitalizacije: CRP preoperativno (B=0,006, p=0,047), OR=1,006, 95% CI (1,000-1,012), tip operacije (B=1,199; p<0,001), OR=3,3 95% CI (2,074-5,300), komplikovanu upala slepog creva (B=0,762; p=0,003), OR=2,142, 95% CI (0,284-0,768).

Zaključak: Hirurški pristup ima statistički najznačajniji uticaj na DBB. Laparoskopska apendektomija je superiornija od otvorene apendektomije sa minimalnim rezom u pogledu DBB.

Ključne reči: Dužinom boravka u bolnici (DBB), Laparoskopska apendektomija (LAP) Otvorena apendektomija sa minimalnim rezom (OAMR)

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REVIEW

Improvement of the psychiatric care through outsourcing artificial intelligence technologies – where are we now?

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Summary

Currently, the world is entering the fourth industrial revolution – marked by artificial intelligence (AI) powered technologies. The growing ubiquity of AI technologies is already present in many sectors of modern society, but caution still prevails in medicine where their application is far from routine, although it is on the constant rise. Psychiatry has been recognized as one of the disciplines where significant contribution of AI technologies is expected for prediction, diagnosis, treatment and monitoring of persons with psychiatric disorders. Nearly half of the world's population live in countries that have fewer than one psychiatrist per 100 000 inhabitants, which is far below the health needs as the prevalence of psychiatric disorders is within the range of 10-20%. Thus, the question arises – whether AI technologies can help to fill the gap in unmet needs in psychiatry? The main types of autonomous technologies currently applied in psychiatry are machine learning and its subsets deep learning and computer vision, alongside natural language processing and chatbots. The present review will focus on the brief history of the concept, the utility of AI technologies in psychiatry, clinicians' attitudes, ethical dilemmas, clinical and scientific challenges. This review emphasizes that the psychiatric community should not be ignorant but could try to leave the comfort zone and do more to raise the awareness of AI technologies development achievements.

Key words: artificial intelligence; machine learning; psychiatry; mental health; ethics

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INTRODUCTION

Currently the world is entering the fourth industrial revolution – marked by artificial intelligence (AI) powered technologies (1). Previous industrial revolutions mostly changed the way we work, while this one will fundamentally alter the way we think and who we are – our identity, sense of privacy, spending patterns, leisure time, the way we develop our careers, meet people and relate to one another. The fourth industrial revolution will mitigate or even eliminate the gap between people and technology, and it is considered that *"in its scale, scope and complexity, the transformation will be unlike anything humankind has experienced before"* (2).

The precise definition and meaning of the AI concept has been the subject of much discussion. It is commonly defined as a scientific discipline that studies and designs computers able to engage in human-like thought processes and behaviors such as learning, reasoning, planning and self-correction (3). What causes a lot of confusion in the existing literature on this topic is when the terms AI and machine learning (ML) are used interchangeably. However, AI is a broader concept referring to creation of autonomous machines that can simulate human thinking capability and behavior, whereas ML represents a subset of AI, increasingly applied in medicine, focused on developing computer systems capable of learning from data (experience) without being explicitly programmed. In other words, the program is not completely predetermined by the given code (i.e. a deterministic algorithm is an algorithm that given a particular input will always produce the same output), but the output can be adjusted based on the input data.

It is important to emphasize that AI is not one technology - but a set of technologies, among which ML, deep learning, natural language processing (NLP), virtual agents/chatbots and computer vision have the most promising applications in medicine. A detailed description of the mentioned AI technologies' technical characteristics exceeds the scope of this review article, which will rather focus on their application in the field of biomedicine - particularly psychiatry, which has been proven to be useful or promising. Psychiatry has been recognized as one of the disciplines where a significant contribution of AI technologies is expected both in the diagnosis and in the treatment of mental disorders. In addition, a brief history of the concept of AI will also be presented, as well as certain ethical dilemmas and challenges, and the application of existing knowledge in everyday practice.

A BRIEF HISTORY OF THE CONCEPT OF AI

The beginnings of the concept of AI date back to 1936 when the brilliant British mathematician and decoder Alan Turing, known as "the father of AI", constructed the so-called Turing machine – a special computer designed to solve a given problem by testing all possible combinations until reaching the correct solution (4). Two decades later, in 1956, the computer scientist John McCarty (who is also considered one of the "founding fathers" of AI) coined the term "artificial intelligence" which he defined as the science and engineering of making automatic computers that simulate the higher functions of the human brain (5).

In the early 1970s AI technologies gradually entered the field of biomedical research and diagnostics, particularly in certain disciplines such as ophthalmology and radiology (6). However, the rest of this decade is a period known as the "winter of AI" – when its development slowed down since previously set high expectations have not been met and funding for this area has been significantly reduced (7).

On the other hand, the 1980s were a period of incredible growth and technological innovation when interest in practical application of AI technologies was renewed. Digital technology has replaced the analog one, and computers and the internet have become the main drivers of social and industrial development (the Third Industrial Revolution began) (8).

The 1997 was historical year when the IBM's chess-playing supercomputer called *Deep Blue* defeated Garry Kasparov – the world chess champion at the time and one of the best chess players ever (9). That was an unprecedented shift in the development of AI technologies that paved the way for further successes.

CHALLENGES IN THE DEVELOPMENT OF AI TECHNOLOGIES

Although we are living in an age of rapid technological changes and development, there are still numerous technical barriers and challenges for the field of AI and related disciplines. Generally speaking, AI-powered technologies are good at things that seem hard for humans, such as solving complex mathematical problems, but they are still not good enough at those things that people find quite simple and natural – like facial recognition or understanding of natural language. Computer scientist Hans Moravec offered a possible evolutionary explanation of the paradox that the easiest things for humans are the hardest ones for AI technologies. In his famous book "Mind children" he stated: *"Encoded in the large, highly evolved sensory and motor portions of the human brain is a billion years of experience about the nature of the world and how to survive in it. The deliberate process we call reasoning is, I believe, the thinnest veneer of human thought, effective only because it is supported by this much older and much more powerful, though usually unconscious, sensorimotor knowledge"* (10). The skills that people find the simplest are the same ones that have been evolving for millions of years, whereby the things that peo-

ple find difficult could be difficult just because they are new. We have been thinking about chess strategy for just over a thousand years, but we have been learning about interaction with the environment since the time our ancestors were single-celled organisms.

AI TECHNOLOGIES IN MODERN MEDICINE

At the mention of AI technologies the first association is most likely some kind of technological innovation that will appear in the distant future, but the fact is that they are already operating all around us – although often behind the scenes. The growing ubiquity of AI technologies is already present in many sectors of modern society, but caution still prevails in medicine where its application is far from routine – given that the risks are also significantly higher than in other fields - but it is still on the constant rise. As the main advantage of AI technologies (particularly ML) is the possibility of rapid analysis of large amounts of data and identifying patterns and regularities in them, the medical disciplines that are currently applying such technologies most successfully are ophthalmology, oncology, dermatology and radiology, where the algorithms of this kind exhibit the same or even better performance as experienced clinicians in assessing images or spotting abnormalities and subtle differences that are otherwise not visible to the human eye (11). The Food and Drug Administration (FDA) recently authorized for the first time an autonomous AI-based diagnostic system designed to detect diabetic retinopathy and macular edema in primary care clinics, with the potential to help prevent vision loss in thousands of people with diabetes annually (12). Although the use of AI technologies in medical practice has increased in recent years, the field of mental health has been slower to accept these innovations, and at the moment they are not routinely applied. The main reason is that psychiatry represents a unique field requiring a more complex integration of cultural and psychosocial factors with medical comorbidities.

DESCRIPTION OF AI TECHNOLOGIES WITH POSSIBLE IMPLEMENTATION IN PSYCHIATRY

About 15% of the world's population lives with some form of mental disorder, with approximately half of them not receiving timely professional help due to treatment-related costs, insufficient number of mental health professionals and the stigma associated with mental illness (13). In recent years, mental disorders top the list of medical conditions in terms of the estimated spending – surpassing even cardiovascular diseases (14).

There are huge unmet needs in mental health care and psychiatry, so the question arises – whether AI technologies can help to bridge this gap? Globally, the median number of mental health workers (including psychiatrists, nurses, psychologists, social workers, and other clinicians) is 9 per 100 000 populations, but there is extreme variation (from below 1 in low-income countries to 72 in high-income countries) (13). Nearly half of the world's population lives in a country with below one psychiatrist per 100 000 (15), but more than half of the world's population owns a smartphone. The increasing use of smartphones and other AI-powered technologies has enabled patients to better monitor their own condition, but also improved their access to mental health care. AI technologies could provide alternative methods that are affordable, available, effective and evidence-based (16). Their application refers to the use of computerized techniques and algorithms for the prediction, diagnosis, treatment and monitoring of mental disorders. AI-powered technologies could have the potential to make significant changes in psychiatry by enabling mental health practitioners to re-define mental illnesses more objectively than currently done in DSM-5 and ICD-11 (17), to identify these illnesses at an earlier stage – when targeted interventions may be more effective (18), and to enable personalized treatment for patients (16).

The main types of AI technologies currently applied in psychiatry **(Figure 1)** are ML and its subsets deep learning and computer vision, alongside NLP and chatbots.

ML has led to numerous breakthroughs in the field of AI, resulting in the outstanding performance of computer systems that in certain domains even surpass human experts (19). Basically, ML represents the ability of a software to improve its performance through exposure to data and gaining experience. A typical ML model first discovers patterns and acquires knowledge from large data sets, and then applies that knowledge to predict future outcomes. For example, these techniques are used in predictive analytics – to anticipate future outcomes

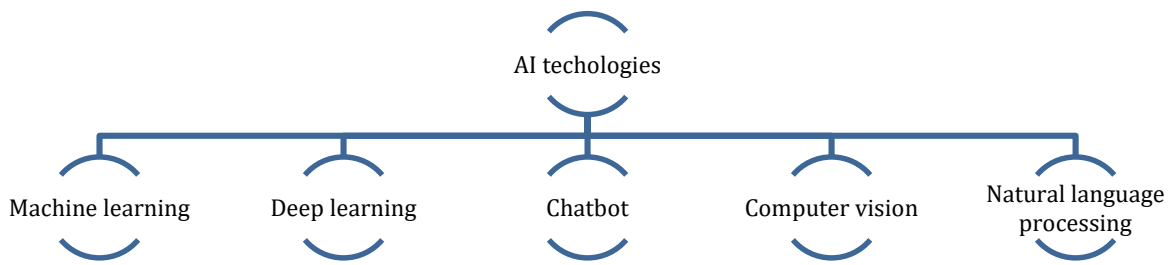

Figure 1. The main types of artificial intelligence (AI) technologies currently applied in psychiatry

based on available data (20). Unlike humans, whose ability to learn is limited by constitutional capacities, access to knowledge and lived experience, ML technologies are able to quickly analyze large amounts of data and spot certain regularities in them - often without *a priori* knowledge of that data, which is their major precedence. Ironically, the lack of classical human intelligence can be an advantage of ML technologies – so they have no prejudices and can detect certain patterns that humans would overlook, and they can also ignore some generally accepted knowledge that is not supported by data (21). Currently there are two main types of ML techniques - supervised and unsupervised. The supervised ML firstly uses the labeled datasets to train the algorithms (the model learns on the set of training data), after which the algorithm is tested on unlabeled data to ensure its accuracy in classifying the target variable (22). On the other hand, unsupervised ML is based on analyzing unlabeled data and discovering hidden patterns in them (unlabeled data are sorted into groups or patterns to identify their underlying structure) (22). Due to the growing availability of data pertaining to an individual's mental health status nowadays, ML technologies are being increasingly applied to improve the understanding of mental health disorders and assist clinicians for improved decision making process (23).

Deep learning is a subset of ML and one of its latest advances which transforms the data through layers of nonlinear computational processing units therefore providing a new paradigm to gain knowledge from complex data (for detailed description see reference 24). Deep learning programs use the so-called artificial neural networks - the computer programs intended to discover latent relationships in raw complex data. This technology has greatly improved the state-of-the-art in speech and visual object recognition, as well as many other domains, thereby bringing breakthroughs in processing images, video, speech and audio data (24).

Computer vision is another AI technology that uses artificial neural networks and ML principles to enable computers and systems to derive meaningful information from visual inputs (images, videos), and make recommendations or take actions based on such information. The model learns key features of the images (edges, curves, etc.) by imposing a grid-like structure on them, after which it is capable of recognizing similar objects. Computer vision can quickly surpass human visual capabilities as it is able to rapidly analyze large amounts of visual data and point imperceptible alterations or defects in them.

NLP is an AI-technology concerned with the computer programs intended to process and analyze large amounts of natural human language data. By extracting the word features (syntax, grammar, semantic meaning) it aims to comprehend human language from transcribed speech. Given that speech and text represent the main real-world data sources in psychiatry, natural language processing holds great potential in mental health research and care (22).

Chatbots (also known as virtual assistants or conversational agents) are AI-powered software programs that simulate human discussion by creating a bidirectional information exchange. Over the past two decades advances in NLP and deep learning have contributed to the development of sophisticated chatbots that are able to analyze verbal/textual inputs and respond appropriately using human audio or textual language (25).

AI TECHNOLOGIES IN PREDICTION OF MENTAL DISORDERS

The effectiveness of AI-based techniques in predicting various psychiatric disorders has been examined in recent years (18). That could be of great importance since the timely implementation of targeted interventions might possibly change the course and outcome of the disorder, and in the most favorable scenario – even prevent symptom exacerbation.

It is generally acknowledged that social cognitive deficits – such as impaired emotion recognition characterize various psychiatric disorders, among which schizophrenia, depression-anxiety and autism spectrum disorders were the most broadly studied to date (26-30). Growing evidence suggests that deficits in social cognition have an important role in the initiation and maintenance of the symptoms and underlie poor functional outcomes in patients with mental health impairments (31). What has been less studied in the literature so far is whether the impaired ability to recognize emotions can be an indicator of susceptibility or increased risk of developing certain mental disorders (the so-called trait-dependent risk marker). The results of a recent study showed that healthy individuals with higher levels of neuroticism – largely innate disposition to experience distress, anxiety and depression (trait-dependent risk marker associated with many forms of psychopathology), have poorer recognition of happiness on other people's faces. That finding indicates that biased processing of positive emotions might represent a useful marker of general susceptibility to psychopathology that could easily be obtained using computerized neuropsychological tests, thus enabling early detection of individuals at risk and timely application of preventive interventions (32).

Prediction of transition to psychosis in persons at clinical high risk has also become the cornerstone of modern preventive psychiatry and there is a need to formulate a more accurate prognostic estimate at the individual level (33). IBM has developed an automated ML speech classifier - comprising decreased semantic coherence and reduced usage of possessive pronouns, that had an approximately 80% accuracy in predicting psychosis onset in high-risk youths (34). This halved the false-negative rate

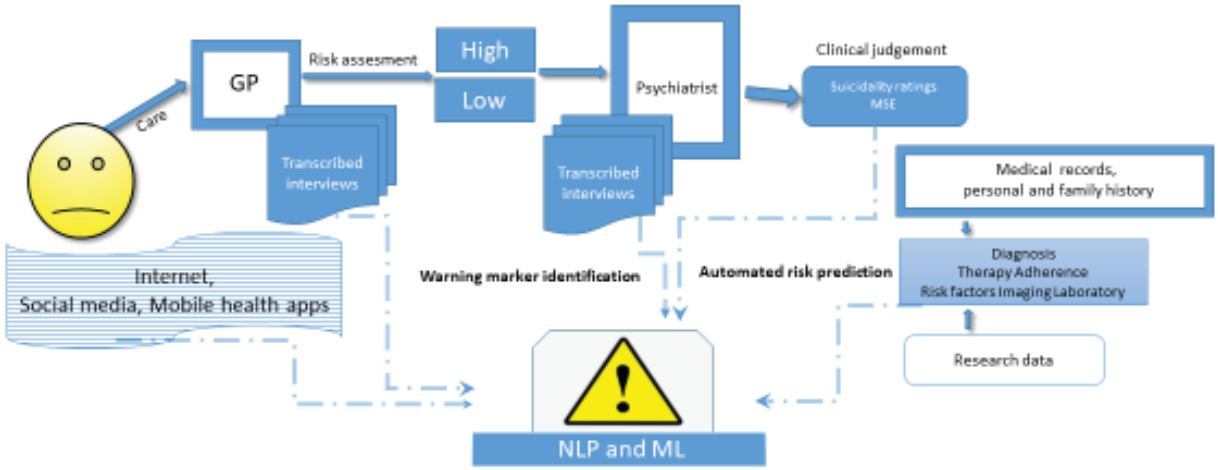

Figure 2. How AI technology might be leveraged to predict a suicide risk by analyzing linguistic patterns
(Abbreviations: GP - general practitioner; MSE – mental state examination; NLP - natural language processing; ML - machine learning; Apps – applications)

in comparison to the clinicians' assessment – which mainly relies on the clinical interview and the patients' motivation to accurately describe their (psychotic) experience.

Another important application of ML algorithms is in predicting suicide in individuals at risk (i.e. with previous suicide attempt or self-injury; see Figure 2). For example, ML algorithms based on linguistic and acoustic characteristics were able to differentiate psychiatric patients who are suicidal from those who are not, as well as from a healthy control group, with an accuracy of 85% (35). By applying ML to electronic health records it is possible to predict future suicide attempts in patients with the history of previous self-harm with the accuracy of 80% for the next two years, and in the next week with the accuracy of 92% (36).

Social media can also become a space where prediction and detection of mental disorders can take place outside the traditional framework. The rationale for that is the mere nature of social networks – where in real-time a huge amount of data that can be linked to the emotional state of the user is available. For example, since 2017 Facebook has been implementing a suicide risk screening around the world (except in the European Union due to stricter data privacy laws) that relies on deep learning algorithms. This new proactive approach scans all users' posts for patterns of suicidal thoughts, and when indicated contacts their friends or local emergency services. A recent study showed that applying these methods enabled prediction of future depression with considerable accuracy up to three months before its overt onset (37). The language predictors of depression have been found to include certain emotional (sadness), interpersonal (loneliness, hostility) and cognitive processes (preoccupation with the self, rumination) (37).

AI TECHNOLOGIES IN THE DIAGNOSIS OF MENTAL DISORDERS

Psychiatry generally lacks specific and reliable biomarkers indicating mental health disorders – that would enable accurate distinction between psychopathology and mental health. For decades and even centuries psychiatric diagnosis has largely relied on the patient's self-reported symptoms, medical history and clinical observations, often leading to subjective and insufficiently reliable symptom assessment (38). Despite recent advances in research in genetics and neuroimaging that are slowly paving the way for improved diagnostics, there is widespread disappointment with the overall pace of progress in detecting and treating mental disorders. AI technologies in psychiatric diagnostics implies the use of advanced computerized techniques and algorithms such as automated speech analysis and ML to assess the mental state of patients beyond self-reporting and clinical observation (39).

In recent decades, neuroscientists and practitioners have increasingly recognized the importance of computerized neurocognitive test batteries and their use has largely become a part of the everyday clinical practice of modern psychiatric centers, especially the academic ones. In such a way, objective assessment of cognition has become an important part of both psychiatric diagnostics and monitoring the course of the disorder, the effectiveness of therapy, and the neuro-rehabilitation progress (40, 41).

One of the promising AI-based approaches in the diagnosis of mental disorders is the use of latent semantic analysis (LSA) – an automated tool for NLP. The basic principle on which LSA relies is that words that are close in meaning will occur in similar pieces of sentences/text (the so-called distributional hypothesis) (42). By applying the LSA in combination with the analysis of speech structure the research team from the National Institute of Mental Health (USA) was able to detect very subtle deviations in speech between probands with schizophrenia, their

unaffected first-degree relatives and unrelated healthy controls and to successfully distinguish the mentioned groups from each other (43). Studies have also shown that ML and NLP algorithms trained to analyze the choice of words and their order in sentences can distinguish between genuine and elicited suicide notes with even greater accuracy than mental health professionals, indicating that they are able to detect signs of distress well (44).

With the aid of computer vision it has recently become possible to detect ADHD or autism spectrum disorder based on the analysis of a person's behavior from a video with high accuracy (of as much as 96%), which might significantly improve the diagnosis of these disorders (45). AI technologies could be a helpful complement to the clinical assessment of psychiatric disorders, which would reduce the number of false-positive and false-negative diagnoses.

The neuroscience technology company Cambridge Cognition recognized voice audios as a rich biomarker of both content (what is said) and acoustic speech properties (how it is said). They recently released the NeuroVocalix - an automated tool for verbal cognitive assessments that brings a fuller understanding of patient functioning through an additional layer of understanding to cognitive assessment (46). One of the major uses of this ML technology is suggested to be in the objective voice-based measurement of pain. The NeuroVocalix is designed to elicit and automatically analyze pain-related signals in human voice therefore providing objective means of measuring pain for use in clinical trials as a more accurate assessment of a drug's effects and eventually in clinical practice where it will support appropriate prescribing.

AI TECHNOLOGIES IN MENTAL HEALTH MONITORING

Early detection and prevention of relapse can have a significant impact on the outcome of psychiatric disorders. Various applications are available for active monitoring of mood, sleep, physical activity and other areas closely related to an individual's mental state, and in recent years the development of AI technologies in combination with different sensors and smartphone applications allowed improved monitoring of psychiatric patients in the community (47). For example, a number of outgoing calls, sent messages, variability in typing dynamics (errors, pauses), walking distance, rate of speech speed and voice modulation have been identified as good predictors of impending depressive or manic episodes (48).

Speech and language analysis have emerged as the two most useful applications of AI technologies in psychiatry, since speech and mental wellbeing are closely related. So monotonous speech may indicate depression, rapid pressured speech may be a sign of mania, and disorganized speech is characteristic of psychotic disorders. When these alterations are sufficiently pronounced – a clinician can spot them, but ML and NLP algorithms can be trained to recognize them even when they are too subtle for humans to spot them.

AI TECHNOLOGIES IN THE TREATMENT OF MENTAL DISORDERS

Overall, the treatment of mental disorders consists of pharmacological and non-pharmacological interventions. Both approaches have already been in the focus of the technology innovations with a lot of examples and ongoing debates. Just a few examples of possible interventions will be mentioned here, followed by the ethical considerations, since the use of treatments based on AI technologies is raising many ethical questions and dilemmas.

Non-pharmacological interventions

Emotion recognition technology finds its application in modern psychiatric practice. The pilot study conducted by the researchers from Stanford university showed that wearing the Google Glass, so-called "smart glasses" with a built-in camera associated with software that detects facial expressions and categorizes emotions, might help children with autism to better understand emotional states and facial expressions of others (49), which is one of core deficits associated with these disorders (26).

Woebot is another digital health technology created by clinical psychologist dr. Alison Darcy (50). It is a virtual assistant or chatbot that simulates conversations that patients have with their psychotherapists – asks the user about his/hers thoughts and mood, "listens" to how he/she feels, learns about him/her, and provides evidence-based psychotherapy based on cognitive-behavioral techniques (CBT). For example: "How are you feeling today?"; "I am panicking"; "Oh, no. I'm sorry. Breathe along with me for a minute, and then we'll talk more about it, OK?" (51). Users can reach the *Woebot* at any time and the chatbot promptly responds to their messages. Although experts agree that it is only a robot that cannot provide a human connection, they also agree that it has many advantages (50).

The advantages of chatbots are that they are affordable and easy to use. Furthermore, they make CBT more accessible to modern generations who are accustomed to being online all the time. Sessions do not have to be scheduled in advance, they are much more frequent than with a human therapist, and chatbots are always available for their users (51). The initial studies examining their effectiveness have yielded promising results. The first randomized controlled trial examining the preliminary efficacy of the *Woebot* for college students who self-identify as having symptoms of anxiety and depression showed that this therapeutic method appears to be a feasible, en-

gaging and effective way to deliver CBT that significantly reduced their symptoms after just two weeks of use. The participants reported that they did not feel condemned while "talking" with a chatbot, and they were more willing to express themselves and to share potentially unpleasant information about themselves without shame, which has been recognized as a significant advantage of virtual therapists (50).

Pharmacological interventions and hybrid-medicines

In 2017, upon the FDA approval of Otsuka's application for digital aripiprazole (ABILIFY MYCITE®) i.e. a combination of the medicine and medical device, psychiatry became the discipline with the first-ever digital drug. Aripiprazole is an antipsychotic drug which has been registered for schizophrenia and bipolar disorder, severe psychiatric conditions frequently associated with therapeutic non-compliance, whose course might be (more or less) improved by the antipsychotic medication. The rationale behind adding the ingestible sensor is to transmit a signal to the web-based portal for professionals and caregivers. When the drug-device combination is exposed to gastric acid in the stomach, the technology will allow for real-time information about medication ingestion and this method has been expected to increase medication adherence, to improve health outcomes and decrease the health care costs (52).

Upon the FDA registration, this innovation raised quite a few questions and ethical debates. For example, whether such a medicine improves medication adherence and improves quality of life was not sufficiently studied and how autonomy of the patients, their privacy and human rights will be protected was unresolved. Not surprisingly, the US approval was not followed by the European approval. In mid 2020, European Medical Agency (EMA) expressed "certain major objections" towards the registration of ABILIFY MYCITE® for schizophrenia and bipolar disorder "which cannot be fully addressed" (53). It could be that "schizophrenia was a difficult indication because patients whose symptoms include paranoia and delusions were likely to reject it", as it was stated in the comment published by "Nature" (54). However, it seems that digital medicines might prove more acceptable to promote adherence and improve the outcomes in non-psychiatric indications (diabetes mellitus, hypertension, hepatitis C virus, etc.).

ETHICAL CHALLENGES

In the field of the non-pharmacological interventions, virtual therapists are anonymous, immune to the prejudices that human therapists might have and more accessible, which could be seen as an advantage compared to human therapists. Also, there is no stigma associated with revealing psychiatric symptoms to a clinician, the cost-effectiveness could be better and so on (51). However, besides the potential advantages, AI-based techniques also have certain limitations. First of all, it is possible to encounter certain technical difficulties. Chatbots are not always able to understand the user and his/her intentions because they do not have their own mind but follow a predefined script. Some experts therefore suggest that they should always be used in collaboration with a human therapist – to ensure something doesn't get missed. Also, therapy chatbots do not include empathy of a human therapist, and for that reason patients are sometimes not sufficiently motivated to keep on their treatment. Another significant shortcoming is that most studies on the effectiveness of these interventions have been conducted by their developers, who have conflict of interest and personal financial gain from the results (39).

One of the important topics of the modern age is privacy, as tracking and sharing personal information has become an integral part of a new way of connecting with people. The so-called 'digital phenotyping' provides a novel, nontraditional route to yield inferences about patients' health status, but also presents a novel challenge to orthodox boundaries of traditional medical expertise (55). In 2018 the European Union enacted its 'General Data Protection Regulation' (GDPR) aimed at ensuring citizens have control of their data, and provide consent for the utilization of their sensitive personal information. However, this model was not accepted everywhere and some countries (for example the US) still have considerably weaker data privacy rules.

A fundamental requirement for the responsible use of AI technologies in biomedicine, including psychiatry, is that the prediction or diagnosis of mental disorders are accurate and reliable, and do not in any way increase the risk to patients (56). In 2017 it was reported that an estimated excess of 10 000 apps related to mental health was available for download. However, the majority of them have not been tested by randomized controlled trials, and many may even provide harmful 'guidance' to users (57). The problem of responsibility is very important, i.e. who is responsible for decisions and actions of AI technologies – their designers, users, or both? One of the crucial differences between intelligent machines and humans is that the former cannot accept responsibility for their own actions or have moral consequences. The machines will not experience humiliation, stress or pain associated with reprimands, loss of professional privileges, license or other legal sanctions.

AI-powered machines might be seen to have advantages over human therapists from the ethical point of view as they are objective, unbiased, have no personal problems that might interfere with their professional competence, and are not subject to other ethical pitfalls

such as inappropriate relationships with patients or their family members. By outsourcing some aspects of medical care to machine learning, physicians could be freed up to invest more time in higher quality face-to-face doctor-patient interactions (58). Although many are concerned about the lack of emotions and empathy in intelligent machines, some also claim that even though it is important to be sensitive to other people's emotions, it is not necessary for a machine to have its own emotions in order to act in accordance with ethical principles. The software could be properly trained to take into account someone's mental state and potential suffering when making a decision in a particular ethical dilemma (59). Being emotional can even interfere with the ability to make the right ethical decisions and act properly in crisis situations because people tend to be blinded by their strong emotions.

However, clinician's contextual, comprehensive assessment of a patient's condition cannot be easily replicated by AI technology. Technology-mediated care is biased due to several reasons, ranging from "decontextualization" to social biases and technical biases. According to a recent report by EU Steering Committee for Human Rights (60), certain restrictions on the use of personal health data in AI-driven analyses could interfere with essential data linkages. Also, social bias could appear by examining the outputs of AI systems for unequal distributions across demographic groups, or when existing biases in society have been learned by an AI system. Critical examination of existing inequalities must be taken into account in order to better control the aforementioned bias.

Last but not least, AI systems might be generating new forms of discrimination. The so-called "digital divide" is a huge ethical challenge - a phenomenon describing a gap between those who have access to digital technology (smart phones, computers, internet) and those who do not, which can cause inequality and deepen the existing gap in the community. Such a gap could be a so-called "digital Berlin Wall". This is why the United Nations considered a "global commitment for digital cooperation" as the key recommendation (61). Such recommendations could be seen as intrusive, and in parallel like as a very humanistic. The obvious reason for such global initiatives, such as the cooperation suggested by the UN, is the fact that in a large number of places around the world people in need for traditional mental health care still cannot access it (13).

PSYCHIATRISTS' OPINIONS ABOUT THE IMPACT OF AI ON PSYCHIATRIC PRACTICE

A recent global study (22 countries) explored mental health professionals' opinions on the future of psychiatry and the likelihood that future autonomous technologies - namely AI/ML, would replace them in performing some of their key responsibilities (62). Four major domains related to AI/ML were surveyed in a large group of professionals from 22 countries: 1. patient-psychiatrist interactions; 2. the quality of patient medical care; 3. the profession of psychiatry; and 4. health systems. Half of the respondents deemed that AI/ML usage will significantly change their job, but the majority was skeptical that it would be able to perform complex psychiatric tasks in the same way or better than human therapists. The respondents generally agreed that AI technologies could fully replace humans only in administrative tasks such as collecting and updating medical records and data consolidation. Only 4% of the respondents thought that AI technologies would make their work redundant, and the vast majority thought it was unlikely that AI/ML would ever be able to provide empathetic care in the same way or better than the average psychiatrist, to assess someone's mental status or aggressive behavior, or to formulate an individual treatment plan. The conclusion is that AI technologies should not be meant to replace doctors, but to complement and augment human capabilities through some kind of hybrid of the traditional way of working and improving psychiatric care by outsourcing the AI technologies - to help and enable doctors do their job in a more efficient and human way (62).

What could be a concern for health workers is the possibility for continuous technological progress to enable the creation of autonomous technologies that would surpass human beings in terms of social and intellectual abilities. An intriguing concept of a super-clinician, an autonomous system that would incorporate different AI technologies, has been recently proposed (56). It would use facial recognition technology to confirm a patient's identity, advanced sensors to observe and analyze nonverbal behavior (facial expression, voice modulation, etc.) and to assess certain parameters that the human eye cannot see – such as detecting changes in body temperature with infrared cameras. The system would be able to access and analyze in real time all available patient data from the electronic health record. It could be trained to use all known therapeutic approaches, and with the use of predictive analytics the intelligent system could know exactly how and when to apply the best treatment or intervention, thereby making it personalized. However, what is inherent for helper professions would be lost – empathy, authentic care and compassion, as well as physical contact through handshakes, comforting lying of a hand on the shoulder of a person who is suffering, and so on.

CONCLUSION

Much has been done so far in the implementation of AI/ML technologies in psychiatry and this review paper aimed to summarize these findings. Experts in the field are divided in their opinions – from the belief that catastrophic consequences for humanity can occur if there is

no control over the development of AI technologies, to the view that such an opinion is paranoid and that any form of their development should be supported due to its boundless potentials (63). We can not foresee which scenario is likely to emerge at this moment, but time will provide us with an epilogue of these debates. However, the assumption is that the role of the doctor can never be completely replaced and that the future of medicine will probably become a "team game" of humans and AI technologies. They will likely be outsourced to help and support clinical decision making, to enable doctors to focus on the human aspects of medicine instead of being stuck in administrative tasks, and allow them more time to truly communicate effectively with their patients and be more compassionate and humane to them (56). We agree with Blease et al. (62) that lacking adequate education on ML technology and its potential to impact the lives of patients, as well as many related ethical issues, future psychiatrists will be ill-equipped to steer mental health care in the right direction. The psychiatric community should not be ignorant but should leave their comfort zone and do more to raise the awareness of AI technologies development achievements among current and future specialists.

Conflict of interest

None to declare

Contributors

SAP analyzed the literature, searched for references and wrote the first draft of the manuscript. NM revised the manuscript, provided figures and other important intellectual content. Both authors wrote and approved the final version of the manuscript.

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TEHNIKE VESTAČKE INTELIGENCIJE ZA POBOLJŠANJE PSIHIJATRIJSKE PRAKSE - GDE SMO SADA?

Sanja Andrić Petrović [1, 2], Nadja P Marić [1, 2]

Sažetak

Svet je zakoračio u četvrtu industrijsku revoluciju koju obeležavaju tehnologije veštačke inteligencije (VI). Tehnologije VI su vrlo prisutne u brojnim sektorima savremenog društva, međutim u oblasti medicine preovlađuje oprez. Primena ovih tehnologija nije postala rutinska, ali jeste u konstantnom porastu. Psihijatrija je jedna od disciplina gde bi se mogao očekivati značajan upliv tehnologija VI. Oko polovine svetske populacije živi u zemljama sa jednim psihijatrom na 100 000 stanovnika, što je značajno ispod zdravstvenih potreba jer se prevalencija psihijatrijskih poremećaja kreće u rangu 10-20%. Stoga, postavlja se pitanje kako bi tehnologije VI mogle da pomognu stanovništvu i struci? Glavne tehnologije koje trenutno nalaze primenu u psihijatriji kao što su: mašinsko učenje i duboko učenje, kompjuterski vid, obrada prirodnih jezika i četbotovi, mogli bi da nađu primenu u detekciji, dijagnostici, tretmanu i daljem praćenju osoba sa psihijatrijskim smetnjama. U aktuelnom revijalnom radu biće predstavljeni kratak istorijat koncepta VI, trenutne mogućnosti primene tehnologija VI u psihijatriji, kao i stavovi kliničara, etičke dileme i izazovi za struku i nauku. Ovim radom se usmerava pažnja na postojeće informacije o dostignućima tehnologija VI u oblasti mentalnog zdravlja i bolesti, kako bi se lakše pratio razvoj oblasti i formirao aktivan odnos prema primeni u praksi.

Ključne reči: veštačka inteligencija; mašinsko učenje; psihijatrija; mentalno zdravlje; etika

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RESEARCH ARTICLE

Autoimmune comorbidities in persons with multiple sclerosis in the population of Belgrade

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Summary

Aim of the paper: To analyze the burden of autoimmune comorbidities in persons with multiple sclerosis (PwMS) in Belgrade, Serbia, using the population-based MS Registry.

Methods: A descriptive epidemiological study was used. The source of data was the Belgrade population MS Registry. The prevalence of different autoimmune comorbidities was calculated as the proportion of persons with a certain comorbidity among the total MS cohort in the Registry and presented with corresponding 95% Confidence Interval (CI). The prevalence date used was December 31st, 2021.

Results: The prevalence of all autoimmune comorbidities was 5.80% (95% CI 4.98-6.73) i.e. the total of 165 autoimmune comorbidities were registered in 2841 PwMS in the Belgrade Registry on December 31, 2021. The highest prevalence was observed in autoimmune thyroid disease (4.26%, 95% CI 3.55-5.07). The highest prevalence was observed in the age groups 50-59 and 60-69 years, with higher values observed in women of all ages. Age-adjusted prevalence of autoimmune comorbidities was 0.05/100,000 in both sexes, 0.03/100,000 in males and 0.07/100,000 in females. In persons with relapsing MS phenotype prevalence of autoimmune comorbidities was 5.5%, while in persons with primary progressive MS phenotype it was 4.9%, however, this difference was not statistically significant ($\chi 2=5.118$; $p=0.163$).

Conclusion: The results of our study showed that the prevalence of autoimmune comorbidities in PwMS in Belgrade, Serbia, is in accordance with that observed in other studies. As expected, the prevalence increased with age and was higher in females. The most common autoimmune comorbidity was the autoimmune thyroid disease.

Keywords: prevalence, registry, autoimmune thyroid disease

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INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that can lead to severe disability and death (1, 2). It is characterized by huge clinical heterogeneity, however the majority of patients experience slow and continuous progression of vision, motor and sensory impairment (2). Disease predominantly occurs in young females at the mean age ranging from 10 to 60 years (2). The MS atlas in 2020 reported that there were 2.8 million people living with MS at the global level (prevalence - 36 cases per 100,000 inhabitants) and that there were 11,972 in Serbia with a corresponding prevalence of 136 MS cases per 100,000 inhabitants (3). This is a significant increase compared to the data from the previous edition of MS Atlas in 2013, when the total of 2.3 million PwMS were registered (3).

Term comorbidity usually refers to those diseases that occur in an individual apart from the index disease and are frequently present in persons with MS (PwMS) (4, 5). In 2015, Ruth Ann Marrie published seven systematic reviews related to comorbidity burden in MS population (6-12). The investigation of comorbidities in this population has been shown to be of particular significance since there is evidence that the presence of these disorders can negatively affect MS course in several ways. First, comorbidities are associated with an increased disability level and a higher mortality rate among PwMS (13-16). Second, the presence of comorbidity can lead to a prolonged time interval in establishing the MS diagnosis (17). Third, these diseases can result in decreased quality of life in PwMS (18, 19). Despite all this, precise measurements of the comorbidity burden in MS are lacking and there are several reasons for it, including different sources of data, various study designs, lack of age-specific and age-adjusted rates of comorbidity frequency and distribution, etc. (6).

According to previous studies it was demonstrated that PwMS most frequently experience hypertension, hyperlipidemia, chronic lung disease, anxiety and depression as comorbid conditions (20). Among different diseases, autoimmune comorbidities are specially important having in mind that MS is considered to be an autoimmune disease in whose pathogenesis cellular immunity (CD4+ and CD8+ cells) plays an important role, through cells directed at myelin antigens in the CNS (21). Furthermore, autoantibodies may also take part in the development of the disease (21). Therefore, it is assumed that MS and other autoimmune disorders can share at least some risk factors. Consequently, elucidating their etiology could be beneficial for revealing MS etiology, yet incompletely discovered.

According to the results of the studies that investigated distribution of autoimmune diseases in MS patients after establishing MS diagnosis, their frequency in this population ranges from 3% to 26.1% (7). Also, studies have shown that the prevalence of autoimmune diseases is higher in the population of PwMS compared to the general population (7). Based on the systematic review from 2015 which included 61 different studies, the most prevalent autoimmune comorbidities in these patients were psoriasis (observed in 0.39%-7.74% of MS patients) and thyroid gland disease (observed in 2.08%-10% MS patients) (7). The prevalence of autoimmune comorbidities in MS population is usually below 5%, with several exceptions including previously mentioned thyroid disease and psoriasis, as well as type 1 diabetes and celiac disease (7). The risk of type 1 diabetes was especially examined in Sardinia whose population is well known for its genetic susceptibility to autoimmune diseases occurrence (22-24). Comparison of the risk between MS and general population on this island resulted in finding that the MS population was five times more likely to develop type 1 diabetes than the general population (22).

Autoimmune comorbidities were also studied in Danish population, which has a long tradition of collecting data on MS patients. According to the obtained data, compared to the general population, patients with MS had an increased risk of developing ulcerative colitis and pemphigoid (25). Also, according to research results, first-degree relatives of MS patients had an increased risk of developing some other autoimmune diseases (25).

Taking into consideration all previously mentioned, the aim of this study was to analyze the burden of autoimmune comorbidities in PwMS in Belgrade, Serbia, using the population-based MS Registry.

MATERIAL AND METHODS

In order to determine the prevalence of autoimmune comorbidities in persons with MS in Belgrade, Serbia, a descriptive epidemiological study was used. The source of data was the Belgrade population MS Registry which contains all the relevant data on each person with confirmed MS diagnosis living in the region of Belgrade. The list of examined autoimmune comorbidities included autoimmune thyroid disease, inflammatory bowel disease, Sjogren's syndrome, vitiligo, psoriasis, rheumatoid arthritis, uveitis, systemic lupus erythematosus, dermatomyositis, systemic sclerosis, pernicious anemia and primary biliary cirrhosis.

The prevalence of different autoimmune comorbidities was calculated as the proportion of persons with a certain comorbidity among the total MS cohort in the Registry. The prevalence date used was December 31st, 2021. The prevalence was presented with corresponding 95% Confidence Interval (CI) for each comorbidity separately as well as for all autoimmune comorbidities combined. In order to allow the comparison of prevalence with similar international studies, the direct age-adjustment method was used with both European and World standard populations. Additionally, the prevalence was calculated in relation to different MS phenotypes (relapsing vs. primary progressive). All analyses were performed using Statistical Package for Social Sciences (SPSS), version 17.0.

RESULTS

The prevalence of autoimmune comorbidities in Belgrade MS cohort is presented in **Table 1**. The prevalence of all autoimmune comorbidities was 5.80% (95% CI 4.98-6.73) i.e. the total of 165 autoimmune comorbidities were registered in 2841 persons with MS in the Belgrade Registry on December 31, 2021. When autoimmune comorbidities were analyzed separately, the highest prevalence was observed for autoimmune thyroid disease (4.26%, 95% CI 3.55-5.07) **(Table 1)**. On the other hand, dermatomyositis, pernicious anemia and primary biliary cirrhosis were the least common diseases (for all three comorbidities the prevalence was 0.04%; 95% CI 0.00-0.20) **(Table 1)**.

Table 2 contains age-and-gender-specific as well as age-adjusted prevalence of autoimmune disorders. The highest prevalence of autoimmune comorbidities in PwMS in Belgrade region was observed in age groups 50-59 and 60-69 years, with higher values observed in women of all ages.

Age-adjusted prevalence of autoimmune comorbidities was 0.05/100,000 in both sexes, 0.03/100,000 in males and 0.07/100,000 in females. The values were the same in both cases when European or World standard population was used **(Table 2)**.

When the prevalence was analyzed in relation to different MS phenotypes it was shown that in persons with relapsing MS phenotype the prevalence of autoimmune comorbidities was 5.5%, while in persons with primary progressive MS phenotype it was 4.9%, however, this difference wasn't statistically significant (χ^2=5.118; p=0.163).

DISCUSSION

Autoimmune comorbidities were present in 5.80% (95% CI 4.98-6.73) of MS patients in our cohort. The most frequent autoimmune disease was thyroid disease (prevalence 4.44%, 95% CI 3.71–5.30). This is in accordance with Marrie et al. and their systematic review combining 61 primary studies in which it was reported that the prevalence of autoimmune diseases in MS patients ranged from 3.0% to 26.1%, (7). A study from Sweden revealed that PwMS were at a greater risk of developing an autoimmune disease compared to the general population (IRR=3.83, 95% CI 3.01-4.87) (27). Hauer et al. demonstrated similar findings of more frequent autoimmune comorbidities among PwMS compared to those without MS, particularly in case of psoriasis, rheumatoid arthritis, and inflammatory bowel disease (28).

The most common autoimmune disorder in our MS cohort was autoimmune thyroid disease (4.44%, 95% CI 3.71–5.30). Systematic review with meta-analysis on this group of comorbid conditions in PwMS observed a higher prevalence of thyroid disease (6.44% (95% CI 0.19–12.7))

Table 1. Prevalence of autoimmune comorbidities in Belgrade MS cohort

Comorbidity	Prevalence (%)	95% Confidence Interval
Autoimmune thyroid disease	4.26	3.55-5.07
Sjogren's syndrome	0.35	0.17-0.65
Inflammatory bowel disease	0.32	0.15-0.60
Vitiligo	0,21	0.08-0.46
Psoriasis	0.14	0.04-0.36
Rheumatoid arthritis	0.14	0.04-0.36
Uveitis	0,14	0.04-0.36
Systemic lupus erythematosus	0.07	0.01-0.25
Systemic sclerosis	0.07	0.01-0.25
Dermatomyositis	0.04	0.00-0.20
Pernicious anemia	0.04	0.00-0.20
Primary biliary cirrhosis	0.04	0.00-0.20
Total	5.80	4.98-6.73

Table 2. Age-and-sex-specific and age-adjusted prevalence of autoimmune comorbidities in Belgrade MS cohort

Age	20-29	30-39	40-49	50-59	60-69	70+	Age-adjusted prevalence*	Age-adjusted prevalence**
Sex								
Male	3.38	2.73	4.99	3.17	1.29	1.69	0.03	0.03
Female	5.76	5.30	7.12	9.08	9.01	3.48	0.07	0.07
Total	4.89	4.54	6.43	7.25	7.00	2.91	0.06	0.06

*according to World standard population
**according to European standard population

in comparison to our sample (7). Many studies have been performed in order to compare the prevalence of autoimmune thyroid disease in PwMS and general population. The results of these studies are conflicting – some studies found an increased prevalence among PwMS while the others found no difference (29-32). However, systematic review combining the results of 61 individual studies regarding autoimmune comorbidities in PwMS reported that the prevalence of autoimmune thyroid disease was in accordance with the prevalence observed in the general population (7). According to a UK study, a greater risk of autoimmune thyroid disease occurrence is expected in the relatives of PwMS (7). The occurrence of autoimmune thyroid disease in PwMS was also examined in relation to immunomodulatory therapy. It was observed that MS patients undergoing the treatment with interferon-β were at a greater risk of developing autoimmune thyroid disease or worsening the existing comorbidity, while a negative impact wasn't observed in patients treated with glatiramer acetate (34-37). Furthermore, it has been shown that autoimmune diseases are the most frequent negative effect of Alemtuzumab treatment and among them Graves' disease is the most common disorder occurring in 16.7-41.0% of MS patients using this therapy (38).

The prevalence of Sjogren's syndrome - 0.35% (95% CI 0.17-0.65) and inflammatory bowel disease - 0.32% (95% CI 0.15-0.60)in our study were also in accordance with previously published findings (0% - 16.7% for Sjogren's syndrome and 0.36% - 4.66% for inflammatory bowel disease) (7). Autoimmune comorbidities with the lowest prevalence in PwMS in the population of Belgrade were dermatomyositis, pernicious anemia and primary biliary cirrhosis (for all three comorbidities the prevalence was 0.04%, 95% CI 0.00-0.20). According to literature, the prevalence of primary biliary cirrhosis in PwMS ranges from 0% to 0.12%, the prevalence of dermatomyositis is estimated to be 0.03% and the prevalence of pernicious anemia ranges from 0% to 2.44% (7).

The results of this study showed that the highest prevalence of autoimmune comorbidities in PwMS in Belgrade was observed at the age of 50-59 and 60-69 years. This is in accordance with the data from earlier research demonstrating that the prevalence of comorbidities increases with MS patients' age (39). Also, in all age groups, the prevalence was higher in female population. This is not surprising having in mind that the majority of autoimmune diseases occur more frequently in women.

The presence of autoimmune comorbidities can potentially negatively influence MS course in several ways. A number of studies showed that the presence of autoimmune comorbidities in PwMS, especially psoriasis and thyroid disease, was associated with considerably worse MRI findings showing significant areas of demyelination (39). In a study based on self-reported data from MS patients, a greater number of comorbidities occurring simultaneously in the same person was associated with poorer quality of life and an increased level of disability (39). Furthermore, the presence of rheumatoid arthritis was associated with a three-fold higher risk, and the presence of anemia with a twofold higher risk of relapse in MS patients (39). A study performed in New York confirmed a negative influence of autoimmune comorbidities on the brain volume in PwMS, and a relationship was observed for type 2 diabetes, psoriasis and thyroid disease (40). Impaired glucose metabolism in PwMS has been previously documented (41). It has been also shown that type 1 diabetes comorbidity in PwMS is related to an increased brain atrophy as a marker of brain damage, specifically in grey matter and cortical grey matter (42). The level of observed brain atrophy was directly correlated with type 1 diabetes duration (42). However, this correlation has not been found in the case of autoimmune thyroiditis and celiac disease (42).

The strengths of our study include population-based study design. Namely, the Belgrade MS Registry was initiated in 1996 and it is being regularly updated. In Denmark, MS Registry was established in 1948 (43). On the other hand, none of the countries in the Southeast Asian region has MS registries, while 20% of African countries and 22% of countries in the Western Pacific region maintain MS registries. The WHO regions with the largest share of countries with MS registries are the Americas (47%) and the region of Europe (46%) (3). The limitations of our study include a cross-sectional study design taking into account only the presence of autoimmune disorder and no other relevant characteristics of these comorbidities. The other limitation refers to the unavailability of data on comorbidity presence in some patients from the Registry. Finally, not all autoimmune comorbidities were included in the analysis.

CONCLUSIONS

The results of our study showed that the prevalence of autoimmune comorbidities in PwMS in Belgrade, Serbia, was in accordance with that observed in other studies. As expected, the prevalence increased with age and was higher in females. The most common autoimmune comorbidity was autoimmune thyroid disease. Since it has been shown that the presence of these comorbidities is associated with many negative outcomes in PwMS it calls for action and development of strategies for early detection and treatment of autoimmune comorbidities in order to preserve brain volume, prevent brain damage and avoid negative impact on different MS outcomes.

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Conflict of interest

None to declare.

Author contributions

Conceptualization, J.D., T.P. and S.M.; methodology, G.M., and T.P.; statistical analysis, G.M. and A.J.; measurement and data acquisition, O.T., N.V., J.I., V.M., M.A., and M. I.; writing—original draft preparation, G. M.; all authors have read and agreed to the final version of the manuscript.

Ethical approval

Study approval statement: This study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine,University of Belgrade, Serbia, approval number [29/III-17].

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KOMORBIDITETI AUTOIMUNIH BOLESTI KOD OSOBA SA MULTIPLOM SKLEROZOM U POPULACIJI BEOGRADA

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Sažetak

Cilj rada: Analiza opterećenja autoimunim komorbiditetima osoba sa multiplom sklerozom (MS) u populaciji Beograda na osnovu podataka populacionog MS registra.

Materijal i metode: Sprovedena je deskriptivna epidemiološka studija. Izvor podataka bio je populacioni registar za MS Beograda. Prevalencija različitih autoimunih komorbiditeta je računata kao proporcija osoba sa tim komorbiditetom među svim osobama u registru i prikazana sa odgovarajućim 95% intervalom poverenja (IP). Prevalencija je određivana za dan 31. decembar 2021. godine.

Rezultati: Ukupna prevalencija svih autoimunih komorbiditeta iznosila je 5,80% (95% IP 4,98-6,73), odnosno ukupno je registrovano 165 komorbiditeta kod 2841 osobe sa MS u registru za područje Beograda na dan 31. 12. 2021. godine. Najviša prevalencija je zabeležena za autoimunu bolest štitaste žlezde (4,26%, 95% IP 3,55-5,07). Najviša uzrasno-specifična prevalencija registrovana je u uzrastu 50-59 i 60-69 godina, sa višim vrednostima u ženskoj populaciji u svim uzrastima. Standardizovana prevalencija autoimunih komorbiditeta iznosila je 0,05/100.000 za oba pola, 0,03/100.000 u populaciji muškaraca i 0,07/100.000 u populaciji žena. Prevalencija autoimunih komorbiditeta kod osoba sa relapsnom formom MS bila je 5,5%, a kod primarno-progresivne forme 4,9%, bez statističke značajnosti ($\chi2=5,118$; $p=0,163$)

Zaključak: Rezultati naše studije pokazali su da je prevalencija autoimunih komorbiditeta kod osoba sa MS u populaciji Beograda u skladu sa onom dobijenom u drugim studijama. Očekivano, prevalencija je rasla sa uzrastom i bila je viša u populaciji žena. Najčešći autoimuni komorbiditet je autoimuna bolest štitaste žlezde.

Ključne reči: prevalencija**,** registar, autoimuna bolest štitaste žlezde

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CASE REPORT

Leser-trelat sign in the diagnosis of occult neoplasms-case report

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Summary

Leser-Trélat (LT) sign (syndrome) is a rare, distinctive clinical phenomenon that is manifested by a sudden, eruptive, appearance of multiple itchy seborrheic keratoses (SK) that sometimes coincide with occult malignancy.

A 73-year-old patient came for examination of numerous, large seborrheic keratoses (SK) on the skin. According to the patient's statement, SK did not occur suddenly and "eruptively". Nevertheless, ultrasound and endoscopic evaluation were suggested to the patient to exclude the Leser-Trélat phenomenon. The patient was then diagnosed with an occult, asymptomatic rectal neoplasm.

The occurrence of numerous seborrheic keratoses (especially if they are "eruptive", large and bizarre in shape), should raise suspicion of LT phenomenon, or internal malignancy in the patient, and result in relevant diagnostic procedures to detect possible latent malignancy. It would be wise for the doctors of all disciplines to be acquainted with the existence of the LT sign (syndrome) and possible clinical implications of it.

Key words: Leser-Trélat sign; seborrheic keratosis; occult tumors; skin

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INTRODUCTION

Leser-Trélat sign (syndrome) is a distinctive clinical phenomenon that is manifested by a sudden, eruptive, appearance of multiple itchy seborrheic keratoses (SK) that sometimes coincide with occult malignancy. [1]

The LT sign is considered to be a rather rare paraneoplastic skin marker of internal malignancy. [2-5]

Seborrheic keratoses (SK) are very common benign skin changes in the population over 40 years old. SK are also found in completely healthy people. [6]

In the majority of published cases that describe Leser-Trélat (LT) syndrome, gastrointestinal adenocarcinoma is predominantly present, but the coincidence of SK has also been described with cancers of the lung, breast, esophagus, urinary bladder, larynx, ovary, prostate, as well as with melanoma, hepatocellular carcinoma, etc. [1,7]

The pathogenesis of the LT sign/syndrome remains unclear and continues to be the subject of prolonged observation. It is suspected that the release of cytokines and growth factors from the neoplasm stimulates the eruptive growth of seborrheic keratoses. In fact, overexpression of EGF-alpha and EGFR (epidermal growth factor receptor) may contribute to the eruptive nature of SK. [1-7]

CASE HISTORY

Patient M.O. 73 years old, came for the first time for a dermoscopic examination of the skin in June 2012 due to a change on the head, which was diagnosed as an intradermal nevus without significant elements. At the same time, in addition to this change, a non-melanocytic skin lesion was detected on the head, which turned out to be basocellular carcinoma (BCC). On that occasion, numerous seborrheic keratoses (31), of different sizes, were detected on the patient's chest. At the same time, according to the patient's claims, seborrheic keratoses occurred successively and without acute exacerbation in the form of eruptive growth. The BCC was then removed in the competent institution using an optimally radical method.

In the middle of January 2018, the patient came for examination again, this time due to the above mentioned seborrheic keratoses. The patient denied changes in number and size, although (by comparing previous pictures), it was clear that they were bigger. Seborrheic keratoses were larger in diameter, some having the form of irregular domes, atypical in appearance **(Figure 1)**. No skin changes that could be considered suspicious of malignancy were found.

Regardless of denying any changes in the SK themselves, the patient was recommended to undergo additional examination of the gastrointestinal tract in order to exclude possible Leser-Trélat phenomenon because of the impression that the SKs were larger and had unusual forms.

Initially, the patient showed no interest in additional examination because he did not see a possible link between skin changes and occult tumors. However, he finally obeyed and a few days after the above mentioned examination, he reported for further examination in a competent institution. On that occasion, the patient underwent ultrasound (US) examination of the abdomen and the results were as follows: 'Liver solid, isoechoic, fatty, pancreas humpbacked, fatty, without focal lesions, gallbladder, kidneys, spleen and retroperitoneum neat, prostate hypertrophic, homogenous with the volume of 63.3 ml. The colon meteoristic, sub-occluded.'

The patient was hospitalized in the first week of March 2018 in a competent institution for further examination, which showed the following:

- gastroscopic examination: 'Esophagus of an appropriate lumen, with mild hyperemia above the cardia. The mucosa of the antral part is hyperemic and slightly edematous with linear non-bleeding erosions confluent towards the pylorus. Pylorus is circular and passable for the instrument, there is DG reflux. Mild hyperemia of the mucosa of the duodenal bulbus. Postbulbar finding neat, bile is present';
- digital rectal examination: 'An uneven polypoid hard infiltration is palpated';
- colonoscopic examination: 'Colonoscope inserted 30 cm into the rectum, 5 cm from the anocutaneous line tm infiltration, polypoid, hard, necrotic, covering 2/3 of the circumference 10 cm long. Taken forceps biopsy. At the exit, a wreath of hemorrhoidal nodules';
- pathohistological finding: Adenocarcinoma scirrhosum invasivum (particulae) ;
- MR of the pelvis: "A circular, irregular, soft-tissue thickening of the rectal wall can be seen, the distal end begins just above the junction of the levator anii and at a distance of about 5 cm from the anus. The cranial thickening of the wall involves the intestine in the length of about 5 cm. The described wall thickening is up to 15 mm in diameter, it shows postcontrast marginal amplification of signal intensity, affects all layers of the wall and is without certain signs of serosa breakthrough and perirectal adipose tissue infiltration. The differential diagnosis primarily corresponds to the infiltrative Neo process. There are no signs of infiltration of seminal vesicles, prostate and bladder. Locoregionally, in the perirectal adipose tissue on the right side at the "9h" position, there is an oval lymph node with a maximum diameter of 9.5 mm and slightly higher, on the left side, at the level of the rectosigmoid junction, two round nodes up to 5 mm in size. The urinary bladder is moderately filled with urine, without wall thickening and without pathological contents. The prostate is enlarged, 40X52X38mm in diameter, slightly lobular contours, heterogeneous internal structure. Seed vesicles symmetrical. There is no free fluid in the small pelvis. No enlarged first nodules were observed along the iliac blood vessels. There are no signs of infiltration on the visible bone structures;

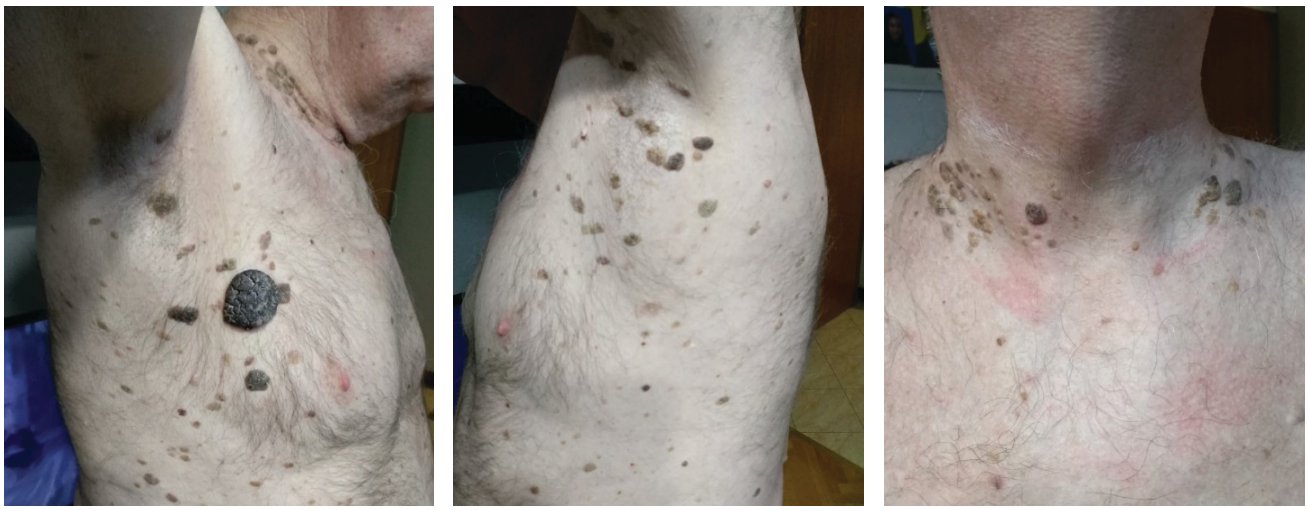

Figure 1. Seborrheic keratosis in patient M.O.

Conclusion: low infiltration of the rectal wall with locoregional lymphadenopathy.

The patient then underwent surgery for the mentioned neoplasm.

DISCUSSION

Seborrheic keratoses (SK) are very common (almost common), skin changes, especially in elderly population. Therefore, many authors suspect the existence of a correlation between SC and malignancies, that is, they believe that it is only a simple coincidence of the occurrence of SK and malignant tumors within Leser-Trélat syndrome (LTS).[8]

Although the pathogenesis of LTS is unclear, the clinical picture indicating LTS requires diagnostic processing to detect possible visceral malignancy.[1]

The case of possible LTS in our patient with rectal malignancy is also indicative, because it can, at least minimally, increase interest for skin changes, especially SK and the possibility of coincidental malignancy elsewhere.

Even when the Leser-Trélat sign (syndrome) is not anamnestically and diagnostically confirmed, it seems that patients affected by suspected SK should be closely monitored, due to potential occult malignancy.[8]

Leser-Trélat sign is usually associated with adenocarcinoma, most often of the colon or stomach, but also the liver, kidneys, pancreas. Then, there was a coincidence with hepatocellular carcinoma, lung, breast, urinary bladder, prostate carcinoma, as well as with malignancies of the esophagus, larynx and ovaries, melanoma, mycosis fungoides, nasopharyngeal carcinoma, etc.[7,8] In over 60% of the cases, the disease was detected in an advanced (metastatic) phase.[1] LTS has been described in woman with osteogenic sarcoma, then in a man diagnosed with germ, etc.[1]

Our patient with asymptomatic malignancy on the rectum was referred for further evaluation, precisely on the basis of suspicion of LTS, despite the possible coincidence of SK with visceral neoplasms. The supplementary evaluation proved to be justified. Namely, it is clear that the patient would only appear later with problems related to malignancy.

Suspicion of LTS should be based primarily on the sudden eruption of SK and/or the size and change in the number of SK.[8]

Probably justifiably, there is a suggestion that the importance of LTS is underestimated, that is, that the importance of the occurrence of multiple SKs is largely minimized.

In everyday clinical practice, multiple SKs may be neglected or misdiagnosed. There is a proposal that in all cases of sudden eruption or intensification of the appearance of SK, an adequate dermatological evaluation is performed, in order to more accurately assess the frequency of association of SK with occult neoplasms.[8]

At the same time, malignant acanthosis nigricans, characterized by velvety, symmetrical hyperpigmentation, anywhere on the body (more often at intertriginous parts), occurs simultaneously in about 20% of cases showing the Leser-Trélat sign and should increase the suspicion of coincidental malignancy.

It has been observed that in many patients who show the Leser-Trélat sign, another paraneoplastic disease occurs at the same time, so that a careful examination and precise anamnesis cannot be assessed.[2-7]

As epidermal growth factor (EGF) receptors are present on basal keratinocytes, it has been suggested that greater importance should be given to combining molecular characteristics of multiple SKs with immunohistochemical analyzes of EGFR proteins to determine the likelihood of Leser-Trélat syndrome and consequently a high risk of disease.[8]

At the same time, it is suggested for EGFR immunohistochemical analysis to be limited, i.e, to indicate the presence of LTS only when some additional clinical manifestations are present, such as: acute morphological changes in long-standing multiple SK, sudden, multiple

"eruption" of SK, association with acanthosis or other paraneoplastic manifestations of the skin, a younger age of the patient at the onset of SK, and malignancies in personal and/or family history.[8]

Experience with our patient has shown that it makes sense to ask for careful observation, ultrasound and endoscopic examination, even when the patient himself denies a sudden increase in volume or number of SKs, if their number and appearance are objectively suspicious.

CONCLUSION

Occurrence of numerous seborrheic keratoses (especially if they are "eruptive", large and bizarre in shape[1-7]), should raise suspicion of LT phenomenon, or internal malignancy in the patient, and result in relevant diagnostic procedures to detect possible latent malignancy. It would be wise for the doctors of all disciplines to be acquainted with the existence of the LT sign (syndrome) and the possible clinical implications of it.

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LESER TRELAT ZNAK U DIJAGNOZI OKULTNIH NEOPLAZMI-PRIKAZ SLUČAJA

Vildana Jahić[1], Jagoda Balaban[2], Đuka Ninković Baroš[2,3], Darko Lukić[3], Darko Jović[3,4], Andrea Stanojević[5], Biljana Pavlovska[6]

Sažetak

Leser-Trelat (LT) znak (sindrom) je rijedak, karakterističn klinički fenomen koji se manifestuje iznenadnom, eruptivnom, pojavom višestrukih svrbećih seboroičnih keratoza (SK), koje ponekad koincidiraju sa okultnim malignitetom.

Pacinet star 73 godine javio se na pregled brojnih, velikih seboroičnih keratoza (SK) na koži. Prema izjavi pacijenta, SK nisu nastale naglo i „eruptivno". Ipak, savjetovana mu je ultrazvučna i endoskopska evaluacija, radi isključenja Leser-Trelat fenomena. Pacijentu je potom otkrivena okultna, asimptomatska neoplazma rektuma.

Pojava brojnih seboroičnih keratoza (naročito ukoliko su „eruptivne",velike i bizarnog oblika), trebalo bi da pokrene sumnju na LT fenomen, ondosno, na unutrašnji malignitet kod pacijenta, te da rezultuje relevantnim dijagnostičkim procedurama radi otkrivanja eventualnog skrivenog maligniteta. Bilo bi mudro da se doktori medicine svih disciplina upoznaju sa postojanjem LT znaka (sindroma) i mogućim kliničkim implikacijama istog.

Ključne reči: Leser-Trelat znak, seboroične keratoze, okultni tumori, koža

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CASE REPORT

Primary Hepatic Neuroblastoma in a 19-month-old Child: A Case Report

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Summary

Introduction. Neuroblastoma in solid organs other than the sympathetic nervous system is extremely rare. The most common site of neuroblastoma is the adrenal medulla. Liver neuroblastomas are usually metastatic lesions, particularly from stage 4S adrenal neuroblastoma. **Patient review.** We report the first case of primary hepatic high-risk neuroblastoma diagnosed in a child older than 12 months. The patient received multimodal oncology treatment, including chemotherapy, surgery, bone marrow transplantation, radiotherapy, and immunotherapy, as well as deep regional hyperthermia. Despite the timely diagnosis, the tumor was refractory to intensive treatment, and the patient died 2.5 years after the diagnosis. **Conclusion.** The differential diagnosis of primary malignant liver tumors in pediatric patients should include neuroblastoma, especially in tumors with atypical clinical presentation. The reports of similar cases in the future may contribute to better tumor biology understanding and facilitate clinical management.

Keywords: liver, hepatic, neuroblastoma, pediatrics.

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INTRODUCTION

Neuroblastoma is the most common extracranial solid malignant tumor in children. It arises from primitive neural crest cells. Neuroblastoma is characterized by biological heterogeneity and various clinical presentations. The most common neuroblastoma sites are the adrenal gland, retroperitoneum, posterior mediastinum, and neck, although theoretically, neuroblastomas could arise anywhere where sympathetic nerves are spread (1). Neuroblastoma arising in solid organs other than the sympathetic nervous system is extremely rare. Here we report on a child with primary hepatic neuroblastoma.

CASE PRESENTATION

A 19-month-old boy was admitted to our hospital with jaundice and acholic stools. He had a 1-month history of itching without apparent skin changes. His previous medical history was uneventful, and the boy was developmentally normal. The family history of cancer predisposition syndrome was unremarkable. He was the second child of healthy unrelated parents.

On physical examination, a tumor mass was palpable in the upper abdomen, and jaundice was noticeable. Initial laboratory findings were as follows: total bilirubin levels 188 μmol/L (ref. <17.1 μmol/L), conjugated bilirubin levels 161 μmol/L (ref. <3.0 μmol/L), ALT 262 U/L (ref. 19–59 U/L), AST 214 U/L (ref. 16–57 U/L), alkaline phosphatase 862 U/L (ref. 103–349 U/L), GGT 685 U/L (ref. <50 U/L).

Abdominal MRI revealed a large, two-component tumor lesion in the liver and pancreatic head **(Figure 1)**. Both adrenal glands were normal in size and appearance. Secondary metastases were not detectable on the chest CT scan.

Regarding tumor markers, serum α-fetoprotein level (AFP) was performed before the biopsy, and it was within the normal range for age. Serum lactate dehydrogenase (LDH) was 2076 U/L (ref. 85–227 U/L).

Histopathological analysis of liver tumor biopsy showed undifferentiated neuroblastoma with *N-Myc* oncogene amplification. Histopathological analysis of bone marrow biopsy revealed no malignant cells. Molecular cytogenetic karyotype analysis from bone marrow cell culture and fluorescence in situ hybridization (FISH) showed a normal male karyotype.

The serum level of neuron-specific enolase (NSE) was greater than 370 ng/mL (ref. 0–16.3 ng/mL). The urine catecholamine levels were within the normal range (the level of urinary vanillylmandelic acid (VMA) was 6.5 mg/g creatinine, and the level of urinary homovanillic acid (HVA) was 31 mg/g creatinine). The ferritin level was normal.

Iodine 123-meta-iodobenzylguanidine (123I-mIBG) scintigraphy showed increased radiopharmaceutical uptake only in the liver.

Based on the tumor site, the boy was classified as stage III (according to the International neuroblastoma staging system (INSS) or stage L2 (according to the International neuroblastoma risk group staging system (INRGSS)), but considering *N-Myc* amplification, he was defined as high-risk neuroblastoma. Soon after the diagnosis, chemotherapy was started according to the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) HR-NBL-1 protocol. Abdominal CT scan after induction chemotherapy showed that the intrahepatic tumor component had shrunk by 50%, and that the extrahepatic component had shrunk by 40%. Having completed the in-

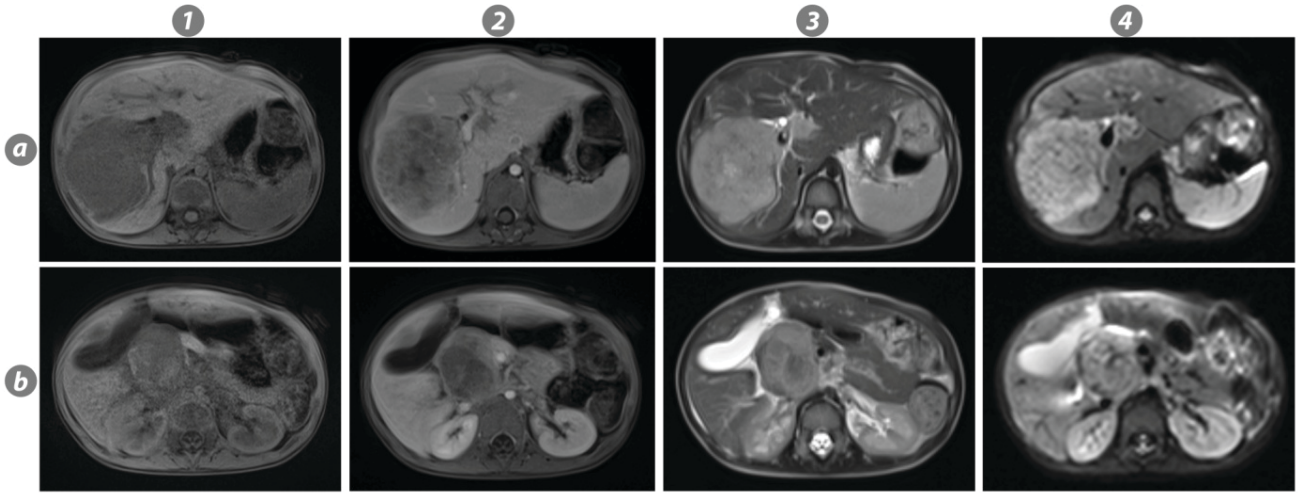

Figure 1. 1) The two-component tumor mass showed hypointense signal to the surrounding liver on T1W MR images, 2) heterogeneous hypervascularity on Gd contrast-enhanced images, 3) moderate signal hyperintensity on T2W, and 4) diffusion restriction on diffusion-weighted images (DWI); a) The first tumor component occupied V, VI, and VIII liver segments measuring 7.8 cm x 7.35 cm x 7 cm; b) The second tumor component had the caudal spread from porta hepatis, between the hepatoduodenal ligament and the pancreatic head, with dimensions 4.5 cm x 5 cm x 5 cm. It exerted pressure on the surrounding anatomic structures, including the common bile duct, duodenum, and inferior vena cava.

duction chemotherapy, the patient underwent trisegmentectomy (segments V, VI, and VIII) to remove the residual hepatic tumor. A separate tumor mass between the hepatoduodenal ligament and the pancreatic head was also completely removed. The resected liver specimen measuring 6.5 x 5 x 4.8 cm contained a vaguely demarcated tumor nodule of irregular shape, which was firmer on the periphery and softer in the central part. The extrahepatic tumor component was resected in two pieces with a maximal size of 2.35 cm and in the form of crumbly granular calcified tissue. The histopathological analysis of the intrahepatic tumor component showed poorly differentiated neuroblastoma with low mitosis-karyorrhexis index (MKI). In the reactive fibrous tumor background, neuroblastoma islets focally showed anaplastic characteristics focally. Lymphovascular invasion was also observed **(Figure 2a, b, c)**. The extrahepatic tumor component also had histology of a poorly differentiated neuroblastoma with infiltration elements into the lymph nodes **(Figure 2d)**.

After surgery, the boy received high-dose chemotherapy with busulphane and melphalan, followed by autologous bone marrow transplantation (BMT). The patient subsequently underwent radiation therapy at the tumor site (21 Gy in 14 fractions).

After irradiation, the boy received immunotherapy with chimeric anti-GD2 monoclonal antibody ch14.18/CHO combined with isotretinoin. After two courses of immunotherapy, the patient developed obstructive jaundice and acholic stools. The boy underwent a surgery, which revealed an obstructing mass surrounding and infiltrating the pancreatic head and common bile duct, leading to a resection of the gallbladder and common bile duct, followed by Roux-en-Y hepaticojejunal anastomosis. Jaundice resolved after surgery, but one month after surgery, tumor relapse was detected on abdominal MRI, and the second line therapy with topotecan, vincristine, and doxorubicin started. Because of further tumor progression, the boy received four courses of hyper-PEI regimen: cisplatin, etoposide, and ifosfamide plus simultaneous 1-h regional deep hyperthermia (41–43°C). After the fourth course of the hyper-PEI regimen, abdominal MRI showed tumor rest in the liver, and 123I-mIBG scintigra-

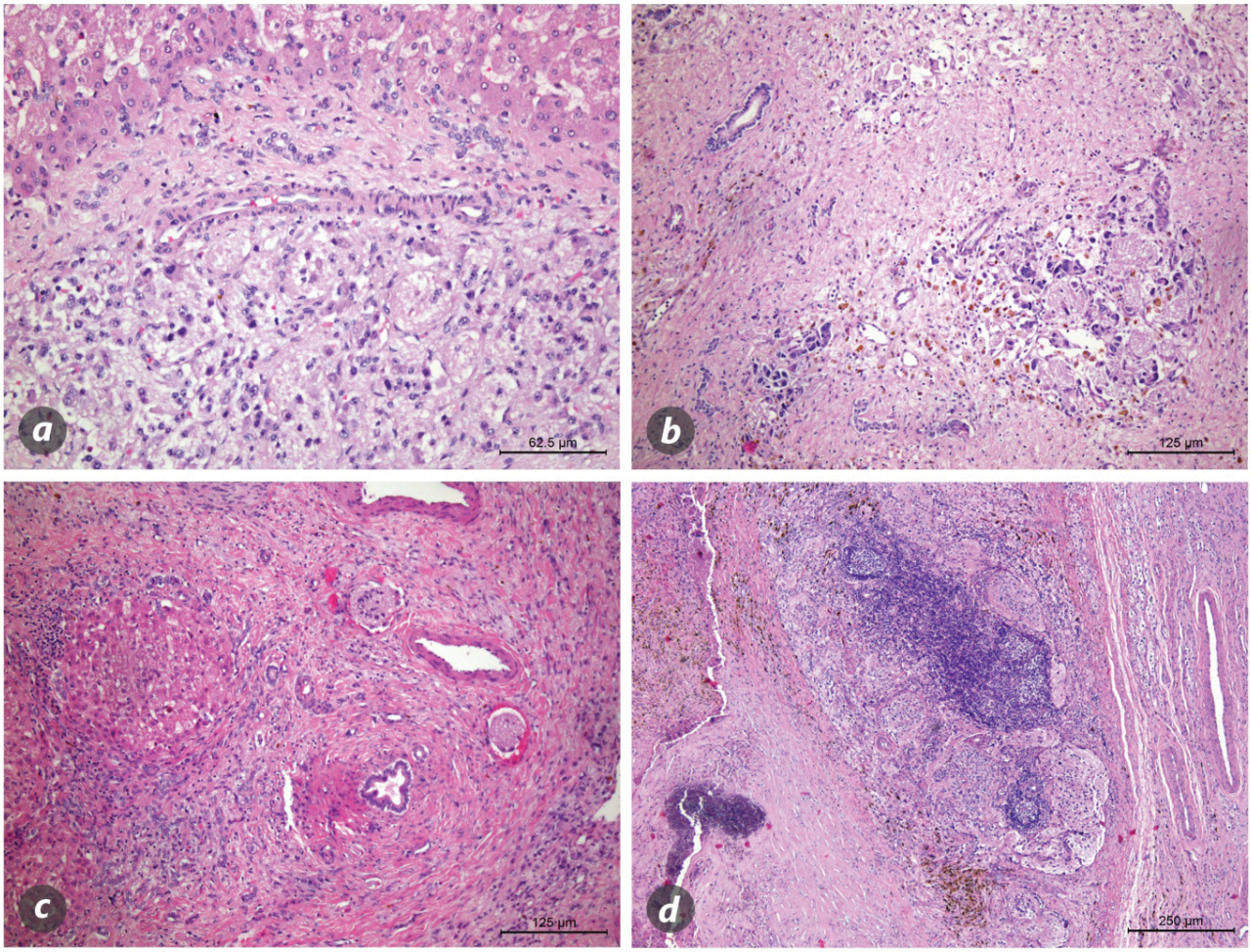

Figure 2. a) Nests of neuroblastic cells immersed in the neuropil matrix are separated from the hydropically degenerated liver parenchyma by a thick layer of reactive, fibrous tissue followed by moderately proliferated bile ducts (HE, x 200); b) In the reactive fibrous tissue, there are two tumor islets composed of non-cohesive and highly anaplastic neuroblastic cells (HE, x 100); c) Neuroblastic emboli in the lymph and venular blood vessels in the fibrous tissue of the liver around the tumor (arrows) (HE, x 100); d) In the extrahepatic part of the tumor, the infiltration of neuroblastoma tissue into the lymph node is recognizable by the partially preserved lymph follicles and accompanied by surrounding hyalinosis, foci of siderophages, and calcification (HE, x 50).

phy showed an increased radiopharmaceutical uptake in the liver and the right thoracic paravertebral space. Finally, the boy was treated with six courses of irinotecan and temozolomide, but due to further tumor progression, he passed away 2.5 years after being diagnosed with neuroblastoma.

DISCUSSION

Primary malignant liver tumors are rare in childhood, with an incidence of about 1.6 cases per million children (2). Hepatoblastoma is the most common malignant liver tumor in early childhood. Other liver malignancies in children include biliary tract rhabdomyosarcoma (BTR), undifferentiated embryonal sarcoma of the liver, rhabdoid tumor, angiosarcoma, and metastatic neuroblastoma (2). Liver neuroblastomas are usually metastatic lesions, particularly from stage 4S adrenal neuroblastoma (1).

In our case, hepatoblastoma was initially suspected because of the tumor site and the patient's age. On the other hand, our patient was admitted with jaundice, an extremely rare presentation of hepatoblastoma. Jaundice is more frequently present in BTR and undifferentiated embryonal sarcoma of the liver (3). Initial work-up included serum AFP level, which was normal. Considering clinical presentation and the fact that AFP is elevated in more than 90% of children with hepatoblastoma (2), we considered other liver malignancies in the differential diagnosis. MRI findings were the most consistent with a BTR, mainly because BTR is often located in or near the porta hepatis. Also, adjacent organ invasion and regional lymphadenopathy are frequent presentations of BTR, and similar findings were present in our case.

Surprisingly, a liver tumor biopsy revealed undifferentiated neuroblastoma. Metastatic neuroblastoma was not initially considered because there was no sign of primary NB in the abdomen. Therefore, urine catecholamines analysis was carried out after a histopathology report was available. The most commonly used tumor markers for NB are urinary VMA and HVA levels, with combined sensitivity of 84% (4). Our patient's urinary VMA and HVA levels were within a normal range. Some studies reported the association between low VMA levels and *N-Myc* amplification (5) and the association between poor prognosis and low urinary VMA levels (6–7) and low urinary HVA levels (7). Also, the urinary VMA/HVA ratio <0.5 is associated with poor outcomes (4). Neuron-specific enolase levels above 200 ng/mL and LDH levels above 2500 IU/mL, both found in our patient, are associated with a worse outcome (5). Regarding the histopathology group, patients with poorly differentiated neuroblastoma, older than 1.5 years, with any MKI have unfavorable histology (8). Also,*N-Myc* amplification is associated with a worse prognosis (9).

There are several possible theories of developmental pathophysiology based on previously reported similar cases. The first theory is that the hepatic tumor is a metastasis of spontaneously regressed primary neuroblastoma. There is one described case of neonatal neuroblastoma 4s with diffuse hepatic metastatic involvement at presentation and without adrenal mass (10). This tumor was *N-Myc* negative, and it is well known that patients with 4s neuroblastoma have a good prognosis and even the possibility of spontaneous tumor regression. Also, there is the case of primary hepatic *N-Myc* negative neuroblastoma in a 29-year-old woman supporting the theory of spontaneously regressed primary adrenal neuroblastoma (11). Also, a possible primary tumor site could be perihepatic retroperitoneal space with *per continuitatem* spreading into the liver (12), but the tumor was not visualized in the retroperitoneal space of our patient. Having the age of our patient and N-*Myc* oncogene amplification in mind, there is a remote possibility that the hypothesis of spontaneous regression can explain the occurrence of liver neuroblastoma. The second theory is the primary pancreatic origin of the tumor because the pancreas has sympathetic innervation. Primary pancreatic neuroblastoma is exceedingly rare and was described only in several cases (13–15). However, the liver tumor component was bigger than the pancreatic component, and the first complaint of our patient was cholestasis which probably developed after the tumor spread from the liver towards the bile duct and pancreatic head. The third theory is that hepatic neuroblastoma may arise from the intrahepatic sympathetic nervous system that innervates the liver and have a role in glucose metabolism and tissue repair (16). Our opinion is that the third hypothesis is the most probable.

CONCLUSION

To the best of our knowledge, our patient is the first reported case of primary hepatic neuroblastoma in a child older than 12 months. Despite the timely diagnosis, our patient had tumor refractory to intensive multimodal oncology treatment. Similar cases should be reported and followed up to reveal clinical and biological tumor features, which should lead to the development of effective diagnostic and treatment strategies.

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PRIMARNI NEUROBLASTOM U JETRI KOD DEVETNAESTOMESEČNOG DETETA: PRIKAZ SLUČAJA

Jovana S. Dimic[1], Dejan U. Skoric[1,2], Aleksandar Lj. Sretenovic[2,3], Slavisa M. Djuricic[4,5]

Sažetak

Uvod. Najčešća lokalizacija neuroblastoma je medula nadbubrežne žlezde. Neuroblastom koji raste u solidnim organima u kojima nema simpatičkog nervnog sistema je veoma redak. Neuroblastomi u jetri su obično metastatske lezije, uglavnom se viđaju u 4S neuroblastomu. **Prikaz pacijenta.** Prikazujemo prvi slučaj visokorizičnog neuroblastoma sa primarnom lokalizacijom u jetri, koji je dijagnostikovan kod deteta starijeg od 12 meseci. Pacijent je lečen multimodalnim onkološkim pristupom, uključujući hemioterapiju, hirurgiju, transplantaciju matičnih ćelija hematopoeze, radioterapiju i imunoterapiju. Takođe, primenjena je i regionalna duboka hipertermija. I pored pravovremene dijagnoze tumor je bio refraktaran na lečenje i dečak je preminuo 2,5 godine nakon postavljanja dijagnoze. **Zaključak.** U diferencijalnu dijagnozu primarnih malignih tumora jetre u pedijatrijskom uzrastu trebalo bi uključiti i neuroblastome, posebno u slučaju atipičnih kliničkih prezentacija. Prikazi sličnih slučajeva u budućnosti bi doprineli boljem razumevanju biologije ovih tumora i poboljšali klinički pristup ovim pacijentima.

Ključne reči: jetra; neuroblastom; pedijatrija.

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RESEARCH ARTICLE

Social and lifestyle characteristics of sports bettors in Serbia

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Summary

Aim: The aim of our study was to examine the prevalence of sports betting in the previous month in Serbia and its association with social and lifestyle characteristics.

Methods: The analysis of the data from the cross-sectional survey National Survey on lifestyles in Serbia: substance abuse and gambling conducted in 2014 was performed. 10% of participants reported sports betting in the past 30 days.

Results: Sports betting was associated with male gender, living in urban areas compared to living in rural areas, having secondary education compared to having primary education, being employed compared to being retired. Sports betting in the previous month was also associated with binge-drinking compared to abstaining from alcohol, non-prescription use of anti-anxiety medications compared to no use of anti-anxiety medications and low/ moderate problem gambling compared to no problem gambling as measured by PGSI. However, it was not associated with a higher risk of tobacco smoking and illicit drug use.

Conclusions: The association of sports betting with risk behaviors among young males should be a concern for public health authorities.

Keywords: sports betting; factors; gambling; problem gambling.

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INTRODUCTION

Sports betting is any placement of money on the outcome of any local, national, or international sports activity (2). Sports betting is becoming an increasingly available type of gambling game in many countries due to more liberal legislation and market developments (3). It has been one of the gambling games which are strongly associated with problem gambling in recent years (2,3). The prevalence of problem gambling is significantly higher among sports bettors compared to the general population, and they have almost 2.3 times higher likelihood for problem gambling (5,6).

Traditional forms of sports betting were organized as the nation-wide lotteries in many European countries, and the bets were placed during the week. This type of gambling was not associated with possibilities for the development of problem gambling (7). Sports betting today is more frequent and more intense and consequently could be associated with gambling disorder (7). A recent increase in participation in on-line odds and live betting can be observed (7). Structural and situational characteristics of on-line and especially live betting (i.e. unlimited availability, gambling in turn, frequency of betting, parallel gambling activities, lack of social control, etc.) provide strong impulses reinforcing urge to play and leading to the development of a gambling disorder (8–10). Young men in particular represent a highly vulnerable group (11).

Advertisers typically present sports betting as a usual form of social interaction among males, which is becoming widely accepted in social and workplace settings and is no longer associated with any social stigma. Following a massive development in the availability of sports betting in the past decade, the 'in-play' betting developed, which allows bettors to place bets during a match (12). Sports betting can now include an outcome of the match, the events in the match, or so-called micro-events. It involves betting on a specific event in the match, such as the outcome of the next point in tennis (12). This all provides constant betting cues and increases the likelihood of problem gambling (13).

The most recent research on demographic characteristics of sports bettors showed that, unlike traditional problem gamblers, they are more often young males (2). The target group for almost all betting advertisements is a young, single, professional male (3,6). This population of young, single, employed, or studying males is at high risk for developing problem gambling associated with sports betting (6). These characteristics differentiate the population who is at risk from problem gambling due to sports betting from the population who receives treatment for problem gambling (i.e. middle-aged, married, with different educational levels, playing most commonly casino games) (6). Some studies showed that sports bettors, although younger, have a higher income than gamblers who engage in other forms of gambling. However, others found that there was a link between sports betting and a lower income, or found no association between income and sports betting at all (13–15). Being single and/ or never being married was also associated with problem gambling among sports bettors as was having an undergraduate degree (2). Sports bettors at risk of problem gambling have a high risk of alcohol use and illicit drug use (16).

The study of gambling participation and problem gambling in Serbia showed that sports betting is associated with more than 35 times higher likelihood of problem gambling (18). To the best of our knowledge, no study has examined socio-demographic, socio-economic, or lifestyle characteristics of sports bettors in Serbia. The aim of our study was to examine the prevalence of sports betting in Serbia in the past month and its association with social and lifestyle characteristics.

METHODS

Data source/sample

The cross-sectional study included 5385 participants, aged 18-64 and was a secondary analysis of the data from the National Survey on lifestyles in Serbia: substance abuse and gambling, conducted during 2014 [18].

A total of 8079 households were eligible to participate (out of 11144 visited households). Exclusion criteria were: age under 18, individuals serving prison sentences, or individuals in other sorts of institutions such as hospitals, therapeutic communities, social care centres, homeless individuals and individuals living in illegal communities.

Sampling was done in accordance with Probability Proportion Sampling – PPS, with the use of multistage cluster sampling (19). The sample was representative of the general working-age population in Serbia (18-64 years). To provide representativity of the sample, small territorial units were selected randomly with probability proportional to the population size. Then, each unit was selected using the National household registry as a sampling frame. The respondents in each of the selected households were selected using the Kish grid. The sample was weighted for the sex, age, educational level, regions, and urban or rural areas.

The procedure of data collection

The data collection was conducted between January and March 2014. Face-to-face interviews were used for data collection with the questionnaire specially developed for the National Survey on Lifestyle in Serbia: Substances Abuse and Gambling, 2014. The questionnaire consisted of 158 items. The first part was on socio-demographic characteristics. The second part was on lifestyle characteristics with Beverage Specific Quantity Frequen-

cy-BSQF Instrument developed during Standardized measurement of Alcohol-related troubles-SMART project (20), Kessler psychological distress scale, Problem Gambling Severity Index (PGSI), use of illicit drugs, and prescription/ non-medical prescription drug use.

Measures

Sports betting engagement was assessed with yes/ no question: 'Have you done sports betting in the past 30 days?' (Yes/No). Participants who answered ,,Yes'' were categorized in the group of sports betting in the past 30 days and participants who answered ,,No'' were classified in the group of ,,No sports betting in the past 30 days''.

The questionnaire also contained yes/no questions on playing casino games and using slot machines: 'Have you played casino games/used slot machines in the past 30 days?'

Self-perceived financial status was assessed with the question: 'How would you describe your financial status?' (very good, good, average, poor, very poor). Then we merged the categories of 'very good' and 'good' in one (good) and categories 'poor' and 'very poor' in another one (poor). Smoking status was assessed with the question 'Have you ever smoked tobacco?', and participants were divided into current smokers, ex-smokers, and non-smokers (Yes, I currently smoke/ I used to smoke, but not anymore/ No, I am not a smoker). The set of questions on alcohol use was developed during the Standardized Measurement for Alcohol-Related Troubles Project (SMART project), funded by the European Union (20). This part of the questionnaire consisted of Beverage Specific Quantity Frequency Instrument with three questions for the assessment of the quantity of each alcoholic beverage (beer, wine, and spirits) drunk and drinking frequency. Drinking frequency for each alcoholic beverage was assessed with the question: 'In the past 12 months how often did you have an alcoholic drink?'(every day/ 5–6 days per week/ 3–4 days per week/ 1–2 days per week/ 2–3 days a month/ 1 day a month/ 6–11 days a year/ 2-5 days a year/ once in the year prior to the study and no drink in the year prior to the study). The quantity was then calculated in milliliters (20). All participants who reported drinking at least once in the past 12 months were classified as 'alcohol consumers'. All participants who reported drinking at least five standard drinks (the amount of 1.5 l of beer= five beers of 0.33l, 0.7l of vine= five glasses of the vine of 0.14l or 0.15l of spirits= five glasses of 0.03l of spirits on one occasion in the year prior to studies) were classified as 'binge drinkers'. Illicit drug use was assessed with the yes/no question 'Did you use any illicit substance in the past 30 days?'

Gambling severity was assessed with Problem Gambling Severity Index- PGSI (21)non-problem, low-risk, moderate-risk and problem gamblers, only the latter category underwent any validity testing during the scale's development, despite the fact that over 95% of gamblers fall into one of the remaining three categories. Using Canadian population data on over 25,000 gamblers, we conducted a comprehensive validity and reliability analysis of the four PGSI gambler types. The temporal stability of PGSI subtype over a 14-month interval was modest but adequate (intraclass correlation coefficient = 0.63. PGSI is a nine-item scale used to screen individuals with high risk for pathological gambling (α=0.97). The PGSI answers are presented on a four-point Likert scale with the possible answers ranging from never (0) to almost always (3). PGSI total scores vary between 0 and 27. Based on the score on the PGSI scale the participants who reported gambling were divided into three categories: 0 = non-problem gambler, 1-7 = low/moderate risk gambler, 8-27 = problem gambler. Some studies showed that there were no significant differences between low and moderate risk gamblers on almost every variable examined, which was also showed in our initial analyses (21–23)non-problem, low-risk, moderate-risk and problem gamblers, only the latter category underwent any validity testing during the scale's development, despite the fact that over 95% of gamblers fall into one of the remaining three categories. Using Canadian population data on over 25,000 gamblers, we conducted a comprehensive validity and reliability analysis of the four PGSI gambler types. The temporal stability of PGSI subtype over a 14-month interval was modest but adequate (intraclass correlation coefficient = 0.63. Accordingly, we merged the categories of low-risk gamblers and moderate-risk gamblers in the category of low/moderate-risk gamblers.

Psychological distress was examined using the Kessler psychological distress scale. The Kessler psychological distress scale is a 6-item questionnaire with questions about anxiety and depression symptoms that a participant has experienced in the past four weeks (24)which we refer to as the K10 and K6, were constructed from the reduced set of questions based on Item Response Theory models. The scales were subsequently validated in a two-stage clinical reappraisal survey (N = 1000 telephone screening interviews in the first stage followed by N = 153 face-to-face clinical interviews in the second stage that oversampled first-stage respondents who screened positive for emotional problems, α=0.87. Answers on the Kessler psychological distress scale are provided on a 5-point Likert scale, varying from never (1) to always (5). According to the score on this scale, our participants were classified into three categories: no risk (≤7 points), moderate emotional distress (8-12 points), and high risk of emotional distress (≥13 points).

The use of anti-anxiety medications was assessed with the following questions: 'Have you taken any anti-anxiety medication in the past 12 months? (yes/ no)' and 'If you have taken any anti-anxiety medication in the past 12 months, how did you obtain the medication? (physician's prescription/ bought it in the pharmacy

without prescription/ obtained it from a friend or family member/ bought them via internet/ obtained it in some other way)'. Based on the answers to these two questions, the participants were classified into three categories: no use of anti-anxiety medications, prescription-only use, non-medical prescription drug use.

The ethical committee of the Republic Institute of Public Health approved the National Survey on Lifestyle: Substance Abuse and Gambling 2014 (No.178/1, January 16th, 2014). The participants were given oral and written information about the study, its processes, and aims and they gave consent for participation.

Variables

The total of 16 variables was analyzed. These variables were: age, gender, place of residence (urban/rural), level of education, marital status, employment status, religiousness, self-perceived financial status, smoking status, alcohol consumption, score on Kessler emotional distress scale, illicit drug use, anti-anxiety medication use, playing casino games, using slot machines, PGSI score.

Statistical analyses

Data were expressed with absolute numbers, means ± SD, and frequencies (percentages). Chi-square test was used to assess differences between participants who reported doing sports betting and participants who reported no sports betting in the past 30 days on all variables (socio-demographic and socio-economic characteristics, lifestyle characteristics, and score on Kessler psychological distress scale). All variables which were shown to be significant were entered in the multivariate logistic regression analysis with sports betting in the past 30 days as an outcome variable. P-values were considered statistically significant if $p<0.05$. All analyses were done in the Statistical Package for Social Sciences SPSS 22.0.

RESULTS

The study included a total of 5385 participants. Almost one-fifth of the participants, 17.2% (927/5385) reported that they had betted on a sports event in the year before the study and 537 participants (10.0%, 537/5385) reported sports betting in the month before the study.

The participants who reported sports betting in the past 30 days and participants who did not report sports betting in the past 30 days differed significantly on majority of socio-demographic and lifestyle characteristics. A significantly higher percentage of participants who reported sports betting in the past 30 days were males (93.7% vs. 44.8%, $p<0.001$), lived in urban areas (70.4% vs. 59.9%, $p<0.001$), were single (59.4 % vs. 39.6%, $p<0.001$), had secondary education (70.0 % vs. 52.9%, $p<0.001$), were binge-drinkers (58.0 % vs. 25.1 %, $p<0.001$), used anti-anxiety medications without prescription in the year before the study (10.6% vs. 3.6%, $p<0.001$), played casino games(4.3% vs. 0.2%, $p<0.001$), or used slot machines in the past 30 days (6.3% vs. 0.2%, $p<0.001$) and were at risk of low/ moderate (14.6% vs. 1.4%) or problem gambling (2.6% vs. 0.1%) $p<0.001$ **(table 1)**.

The socio-demographic, socio-economic and lifestyle characteristics of the participants are presented in **Table 1**.

Table 1. Characteristics of the participants who reported sports betting and participants who did not report sports betting

	Total	Sports betting	No sports betting	p-value
Independent variables	**No (%)**	**No (%)**	**No (%)**	
Gender				
Males	2676 (49.7)	504 (93.7)	2172 (44.8)	
Females	2709 (50.3)	34 (6.3)	2675 (55.2)	**<0.001***
Age (in years) (X±SD)	42.18±13.63	34.45±11.70	43.04±13.56	**<0.001****
Place of residence				
Rural	2103 (39.1)	159 (29.6)	1945 (40.1)	
Urban	3281 (60.9)	379 (70.4)	2903 (59.9)	**<0.001***
Marital status				
Single	2239 (41.6)	319 (59.4)	1919 (39.6)	
Married/permanent relationship	3147 (58.4)	218 (40.6)	2928 (60.4)	**<0.001***
Level of education				
Primary	1418 (26.3)	90 (16.8)	1328 (27.4)	
Secondary	2941 (54.6)	376 (70.0)	2566 (52.9)	
College/faculty	1025 (19.0)	71 (13.2)	953 (19.7)	**<0.001***
Employment status				
Unemployed	1684 (31.3)	133 (24.7)	1551 (32.0)	
Employed	2553 (47.4)	307 (57.1)	2246 (46.3)	

	Total	Sports betting	No sports betting	p-value
Student	449 (8.3)	85 (15.8)	364 (7.5)	
Retired	699 (13.0)	13 (2.4)	686 (14.2)	**<0.001***
Religion				
Not religious	455 (8.4)	59 (11.0)	396 (8.2)	
Religious	4930 (91.6)	478 (89.0)	4452 (91.8)	**0.026***
Self-perceived financial status				
Poor	2155 (40.0)	224 (41.6)	1931 (39.8)	
Average	2661 (49.4)	260 (48.3)	2401 (49.5)	
Good	570 (10.6)	54 (10.0)	516 (10.6)	0.704*
Smoking				
Never	2141 (39.8)	264 (49.1)	1877 (38.7)	
Ex-smoker	993 (18.4)	75 (13.9)	918 (18.9)	
Current smoker	2251 (41.8)	199 (37.0)	2052 (42.3)	**<0.001***
Score on Psychological distress scale				
No risk	4310 (80.0)	450 (83.6)	3860 (79.6)	
Moderate risk	766 (14.2)	71 (13.2)	694 (14.3)	
High risk	310 (5.8)	17 (3.2)	293 (6.0)	**0.015***
Alcohol consumption				
Alcohol consumers	2346 (43.8)	164 (30.6)	2182 (45.3)	
Binge-drinkers	1520 (28.4)	311 (58.0)	1209 (25.1)	
Abstainers	1487 (27.8)	61 (11.4)	1426 (29.6)	**<0.001***
Illicit drug use, last 30 days				
Yes	883 (16.4)	51 (9.5)	832 (17.5)	
No	4502 (83.6)	486 (90.5)	4016 (82.8)	**<0.001***
Use of anti-anxiety medications				
No use	4382 (82.9)	354 (65.9)	4028 (84.8)	
Prescriptions only use	679 (12.8)	126 (23.5)	553 (11.6)	
Misuse	228 (4.3)	57 (10.6)	171 (3.6)	**<0.001***
Casino games				
Yes	31 (0.6)	23 (4.3)	8 (0.2)	
No	5354 (99.4)	514 (95.7)	4840 (99.8)	**<0.001***
Slot machines				
Yes	45 (0.8)	34 (6.3)	11 (0.2)	
No	5340 (99.2)	503 (93.7)	4837 (99.8)	**<0.001***
PGSI score				
No problem gambling	3000 (94.0)	756 (82.8)	2244 (98.5)	
Low/ moderate gambling	165 (5.2)	133 (14.6)	32 (1.4)	
Problem gambling	26(0.8)	24 (2.6)	2 (0.1)	**<0.001***

*According to the Chi-square test
**According to Students T-test

The multivariate logistic regression analysis showed that sports betting in the past 30 days was significantly associated with being male (OR:11.71, 95% CI: 7.95-17.26), age (OR 0.96, 95% CI: 0.95-0.97), living in urban areas (OR: 1.83, 95% CI: 1.43-2.33), having secondary education (OR: 1.45, 95% CI: 1.08-1.96) compared to having only primary education, being employed (OR: 2.37, 95% CI: 1.19-4.72) compared to being retired, having a high risk of psychological distress (OR: 0.43, 95% CI: 0.21-0.90), binge drinking (OR: 1.88, 95% CI: 1.35-2.63), non- medical prescription drug use of anti-anxiety medications (OR: 1.76, 95% CI: 1.21-2.58), and having low/ moderate gambling risk (OR:12.44, 95% CI: 8.24-18.79) or problem gambling (OR: 38.34, 95% CI: 10.50-139.92) compared to no problem gambling.

The results of the multivariate logistic regression analysis can be seen in **Table 2**.

Table 2. Multivariate logistic regression analysis with sports betting as an outcome variable

	OR (95% CI)
Independent variables	**No (%)**
Gender	
Males	**11.71 (7.95-17.26)**
Females	1.0 reference category
Age	**0.96 (0.95-0.97)**
Place of residence	
Rural	1.0 reference category
Urban	**1.83 (1.43-2.33)**
Marital status	
Single	1.15 (0.90-1.48)
Married/permanent relationship	1.0 reference category
Level of education	
Primary	1.0 reference category
Secondary	**1.45 (1.08-1.96)**
College/faculty	0.99 (0.66-1.48)
Employment status	
Unemployed	1.98 (0.96-4.07)
Employed	**2.37 (1.19-4.07)**
Student	2.08 (0.93-4.64)
Retired	1.0 reference category
Religion	
Not religious	0.91 (0.64-1.29)
Religious	1.0 reference category
Smoking	
Never	1.0 reference category
Ex-smoker	0.93 (0.73-1.19)
Current smoker	0.74 (0.54-1.02)
Score on Psychological distress scale	
No risk	1.0 reference category
Moderate risk	1.05 (0.75-1.48)
High risk	**0.43 (0.21-0.90)**
Alcohol consumption	
Alcohol consumers	1.11 (0.80-1.57)
Binge-drinkers	**1.88 (1.35-2.63)**
Abstainers	1.0 reference category
Illicit drug use, last 30 days	
Yes	1.48 (0.66-3.35)
No	1.0 reference category
Use of antianxiety medications	
No use	1.0 reference category
Prescriptions only use	1.14 (0.87-1.49)
Misuse	**1.77 (1.21-2.58)**
Casino games	
Yes	1.71 (10.57-5.16)
No	1.0 reference category
Slot machines	
Yes	**2.14 (0.78-5.84)**
No	1.0 reference category
PGSI score	
No problem gambling	1.0 reference category
Low/ moderate gambling	**12.44 (8.24-18.79)**
Problem gambling	**38.34 (10.50-139.92)**

DISCUSSION

Our study showed that one-tenth of the adult population in Serbia reported doing sports betting in the past 30 days in 2014. Sports betting in the past 30 days in Serbia was associated with being male, age, living in urban areas, having secondary education, being employed, binge drinking, using non-prescription anti-anxiety medications, and having low/moderate or high risk of problem gambling.

Previous studies have shown that problem gamblers who report sports betting are on average 10 years younger compared to problem gamblers who do not report sports betting (6,25). Males under 45 years of age were previously described as a group that is prone to peer influences for risky behavior such as alcohol use, illicit drug use, and gambling (26). Young males are at additional risk as the majority of advertisements for sports betting are directed at this population group (2,7). This group is at a higher risk of placing sports bets more frequently because of the lack of factors that limit gambling activities such as family and other financial responsibilities (6,27).

Participants from urban areas had almost two times higher likelihood of sports betting in the past 30 days in our study. Sports betting market have grown in Serbia in the past two decades and sports betting places are now available in every quarter and every neighborhood in urban areas, but not in rural ones, which might explain these differences (28). The previous studies described sports bettors as highly educated (6), while in our study, sports betting was associated with secondary education only. The reason for the difference between the previously published data and the data from our study lies in the different availability of sports betting examined. Sports betting in our study refers to sports betting at betting places, as online betting was not very common in Serbia at the time the study was conducted (18). It is online betting that is associated with higher education and a more superior professional status (6,29).

Sports bettors were two times more likely to report binge-drinking in the year before the study compared to the participants who did not report sports betting in the past 30 days in our study. Sports betting is now associated with male social encounters as is binge drinking, which is considered a bonding activity, through the joint experience of drunkenness (30). As sports betting is now increasingly associated with possibilities of peer bonding, especially through advertisements (7), males might associate it with power and masculinity, as they do binge-drinking (30). Betting places in Serbia are considered places for friends gathering and betting is accompanied with drinking alcohol, which stimulates binge-drinking.

Even more worryingly, sports betting was associated with non-medical prescription use of anti-anxiety medications in our study, and the participants who reported sports betting in the past 30 days also reported non-medical prescription use of anti-anxiety medications in the year before the study. Both anxiety and depression were previously associated with problem gambling (31), which is linked to non-medical prescription anti-anxiety medication use (32), but to the best of our knowledge, no study examined the association between sports betting and non-medical prescription drug use. From the public health perspective, non-medical prescription drug use and sports betting are a cause of concern. Surprisingly, although sports betting was positively associated with non-medical prescription anti-anxiety medication use, it was negatively associated with a high risk of psychological distress. Sports bettors might see this activity as a social activity and might use it to relieve the pressures of everyday lives.

Sports betting in the past 30 days was associated with more than 12 times higher likelihood of low/moderate risk gambling and more than 43 times higher likelihood of problem gambling based on a PGSI score in our study. Sports betting was previously associated with problem gambling in Serbia (18), mainly due to its wide availability and the tendency for an increasing number of consumers (13). The association between sports betting and problem gambling is therefore important for the public health authorities and measures against problem gambling are now mostly directed at casino games and the Responsible gambling act is mainly directed at casino games and slot machines, not sports betting. Our results indicate that sports betting should also be subject to preventive measures for problem gambling.

One of the limitations of the study is that the participants could report different types of gambling activities they are involved in and the study did not classify the participants in the groups of sports bettors only vs. sports bettors with other gambling games played. The main strength of our study is that it presents one of the rare studies on sports betting done on a national representative sample of the entire adult population.

Our study has shown that sports betting in the past 30 days is highly frequent among adults in Serbia and that, unlike in other studies, it is associated with being a young, adult male. As sports betting is now widely available, and as its market is constantly growing in many countries, the significant association between binge-drinking and non-medical prescription anti-anxiety medication use with sports betting is alarming for the public health professionals. The common association of all these types of behavior with masculinity and social interactions among males should be avoided by advertisers. With an increase in the availability of Internet and online sports betting opportunities, there is a justified concern that there will be an increase in the prevalence of sports betting in Serbia and as online betting provides uncontrolled stimuli for betting there might be an increase in the prevalence of problem gambling as well. The introduction of measures such as setting the limit on both the time spent betting and the amount of money placed on sports betting, development of self-exclusion betting programs, and public health education efforts might be options for countering these issues.

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SOCIJALNE KARAKTERISTIKE I KARAKTERISTIKE STILA ŽIVOTA OSOBA KOJE UČESTVUJU U SPORTSKOM KLAĐENJU U SRBIJI

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Sažetak

Cilj: Cilj ovog istraživanja bio je da se ispita prevalencija sportskog klađenja u poslednjih mesec dana u Srbiji, kao i povezanost sportskog klađenja sa socijalnim karakteristikama i karakteristikama stila života.

Metod: Sprovedena je sekundarna analiza podataka iz Nacionalnog istraživanja o stilovima života u Srbiji: zloupotreba supstanci i kockanje koje je sprovedeno 2014. godine.

Rezultati: 10% učesnika u istraživanju je navelo sportsko klađenje tokom poslednjih 30 dana. Sportsko klađenje je bilo povezano sa muškim polom, stanovanjem u urbanim sredinama, srednjoškolskim obrazovanjem, zaposlenošću. Pored toga, sportsko klađenje je bilo povezano sa teškim epizodičnim opijanjem tokom poslednjih 30 dana, korišćenjem lekova za smirenje bez lekarskog recepta, nisko/umereno rizičnim i problematičnim kockanjem u poređenju sa onima koji se ne kockaju, ali nije bilo povezano sa pušenjem duvana ili korišćenjem psihoaktivnih supstanci.

Zaključak: Povezanost sportskog klađenja sa rizičnim ponašanjima među mladim muškarcima predstavlja znak upozorenja za sve one koji se bave javnim zdravljem.

Ključne reči: sportsko klađenje; faktori; kockanje; problematično kockanje.

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