

TMOČKI MEDICINSKI GLASNIK



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The Bulletin of the Zajecar branch of the Serbian Medical Association

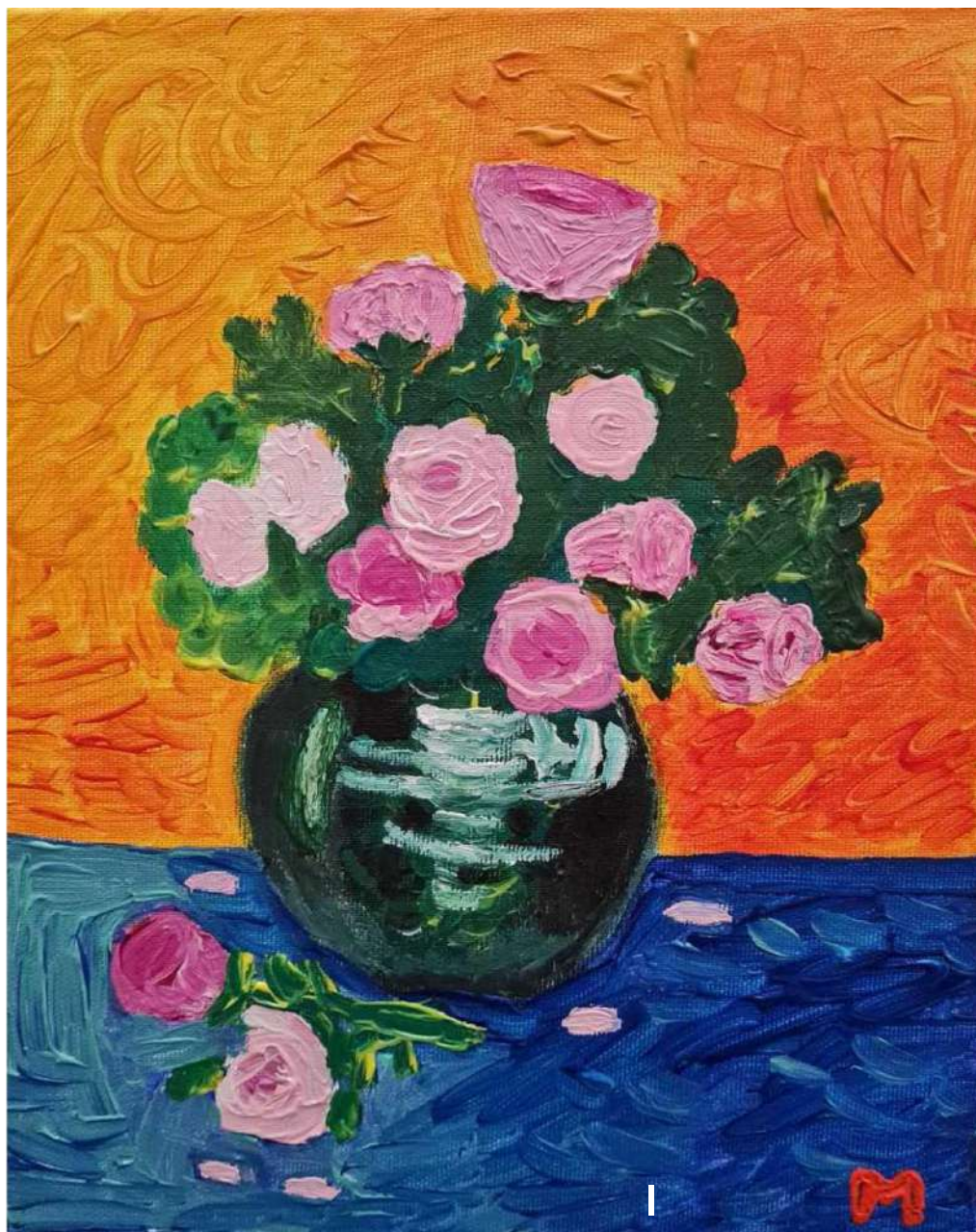
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RELATIONSHIP BETWEEN VARIABILITY OF ARTERIAL BLOOD PRESSURE FROM AMBULATORY 24-HOUR MONITORING OF ARTERIAL BLOOD PRESSURE WITH ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS UNDER ANTIHYPERTENSIVE THERAPY

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Summary: Introduction: Variability of systolic daytime arterial pressure was until recently a controversial parameter but is now recognized as an independent prognostic risk factor for stroke in hypertensive patients. Blood pressure variability is a quantitative index of spontaneous daily and nocturnal variations in systolic and diastolic arterial blood pressure and has been proposed as a risk factor for inducing subclinical damage to target organs in arterial hypertension. Besides varying degrees of left ventricular myocardial hypertrophy (LVH), patients with hypertension also exhibit accompanying diastolic dysfunction of the left ventricle as an early sign of hypertensive damage, even when myocardial hypertrophy does not develop. The variability of pressure over 24 hours in Ambulatory Blood Pressure Monitoring (ABPM) has not been sufficiently studied in terms of correlation with echocardiographic parameters in controlled hypertension. Methods: A total of 196 adequately treated patients with stage 2 hypertension, with a target of achieving normotension less than 140/90, were examined. The total of 196 patients, 109 males and 87 females, with a mean age of 49.3 ± 8.4 years, untreated or inadequately treated patients with stage 2 hypertension (mean BP before treatment 167/106 mmHg) were divided into three groups according to blood pressure variability parameters. Alongside standard methods: medical history, clinical examination, and electrocardiogram (ECG), 24-hour ambulatory arterial pressure monitoring (ABPM, so-called blood pressure holter) was performed with 24-hour, daytime, and nighttime variability of systolic and diastolic blood pressure as well as Color and Tissue Doppler echocardiography after adequate treatment. Results: Elevated blood pressure variability was observed in 66/196 patients (34%) in group V despite good pressure regulation, while 130/169 (66%) had normal variability - group C (control). A subgroup ExtV was particularly highlighted within group V with extreme variability of daytime systolic BP ($SD > 20$ mmHg) - 15/66 patients (8%). Evaluation of left ventricular myocardial mass index (LVMI) showed no difference in the degree of LVH between groups C and V. In the subgroup ExtV (from group V with extreme blood pressure variability), comprising 15/66 patients (8%), a significant difference in the degree of left ventricular myocardial hypertrophy was found between groups C and V regarding extreme variability ($p < 0.01$). There was no difference concerning gender and age structure. Statistical analysis of investigated 24-hour blood pressure parameters and echocardiographic parameters did not show significant correlation through calculation of the linear correlation coefficient between mean arterial pressure measured by 24-hour ambulatory pressure monitoring and standard deviations of daytime and nighttime pressure and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r < 0.20$), as expected. However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, E/E' ratio, and variability of daytime systolic pressure: $r = 0.41$. Only the subgroup with extreme variability ExtV in terms of daytime systolic pressure has a statistically significant correlation with the degree of LVMI myocardial hypertrophy, $r = 0.51$. Conclusion: One-third of the examined patients, 66/196 patients (34%) in group V, had elevated blood pressure variability despite good pressure regulation. There was no significant difference in the degree of left ventricular myocardial hypertrophy between the investigated parameters of 24-hour blood pressure and echocardiographic indices, except in extreme variability ExtV ($P < 0.01$). However, there is a

moderate but significant correlation between the best echocardiographic parameter of diastolic function, E/E' ratio, and variability of daytime systolic pressure: $r=0.41$. Only the subgroup with extreme variability ExtV in terms of daytime systolic pressure has a statistically significant correlation with the degree of LVMI myocardial hypertrophy, $r=0.51$.

Keywords: arterial hypertension, systolic and diastolic blood pressure, daytime and nighttime blood pressure, early morning pressure, left ventricular hypertrophy, mean 24-hour arterial pressure, 24-hour ambulatory blood pressure monitoring (ABPM), 24-hour blood pressure variability, left ventricular myocardial mass index, diastolic dysfunction of the left ventricle, extreme blood pressure variability.

INTRODUCTION

Blood pressure variability refers to changes in blood pressure (BP) values over a certain period of time. By definition, blood pressure variability (BPV) is a quantitative index of spontaneous daily and nocturnal variations in systolic and diastolic arterial BP and has been proposed as a risk factor for inducing subclinical damage to target organs mediated by hypertension (HMOD) [1]. Older studies of ambulatory invasive intra-arterial pressure have shown that BP is highly variable during the day and to a lesser extent at night [2,3] due to the interplay of central neuro factors, humoral influences, local vasoactive mechanisms, and the buffering effect of baroreflexes [4,5].

While it's normal for blood pressure to vary throughout the day, excessive variability, i.e., high blood pressure variability, may be associated with an increased risk of heart disease, stroke, and other complications [1]. It is well known that besides reducing the mean arterial pressure measured by 24-hour ambulatory blood pressure monitoring (ABPM), reducing blood pressure variability under

therapy has prognostic significance as an independent factor in stroke prevention [1]. Episodic elevated blood pressure is associated with more frequent cardiovascular (CV) events.

Short-term BPV is quantitatively related to the level of elevated BP and is therefore greater in arterial hypertension than in normotension [3] and has a detrimental effect on the development of hypertension-mediated subclinical organ damage (HMOD) [6]. Interestingly, significant differences in blood pressure variations exist between human and animal studies, with BPV being much lower in experimental animals [7]. Non-invasive studies with ABPM have shown that 24-hour BP variability has a detrimental effect on CV outcomes, independent of 24-hour mean BP [8,9,10,11].

Left ventricular hypertrophy (LVH) as one of the most important HMODs is a sensitive index for the level of elevated mean arterial pressure (MAP) [12]. LVH and aortic dilation are also sensitive indices for the level of blood pressure variability MAP [12].

Table 1. Models and mechanisms of elevated blood pressure variability (BPV). [4,5]

variability model	region/tissue	clinical example
increased variability at rest	baroreflex afferent nerves brain stem centers	autonomic dysfunction age morning BP surge
increased vasoreactivity	endothelium vascular muscle	dyslipidemia, insulin, resist hypertension
behavioral response (fear, anger)	hypothalamus brain stem centers	

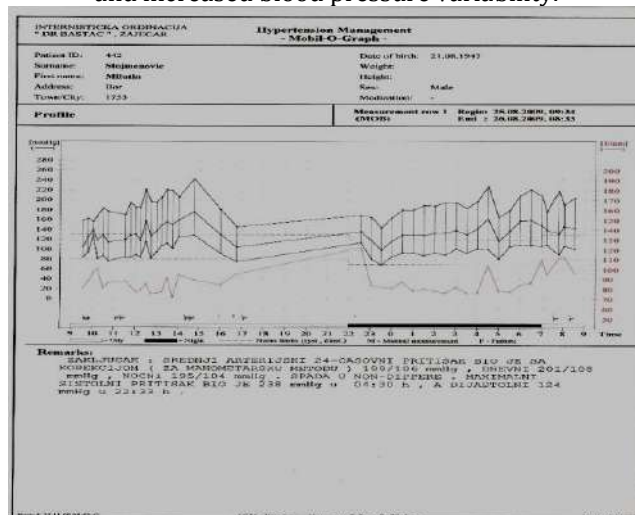
The complex topic of short-term and long-term blood pressure variability (BPV) is a factor that introduces some confusion in the diagnosis, classification, and treatment of hypertension. The true pathophysiological variation in blood pressure is associated with heart rate, respiration, complex sympathetic nervous system responses, vascular reactivity, and arterial stiffness [4,5]. Measurement errors

(systematic and random errors) further complicate the analysis of BPV. Most studies use serial clinical blood pressure values in the office, 24-hour ambulatory blood pressure monitoring (ABPM), or home blood pressure values (HBPM) with standard statistical indicators (standard deviation, variance, or coefficient of variation) (Figure 1 and 2).

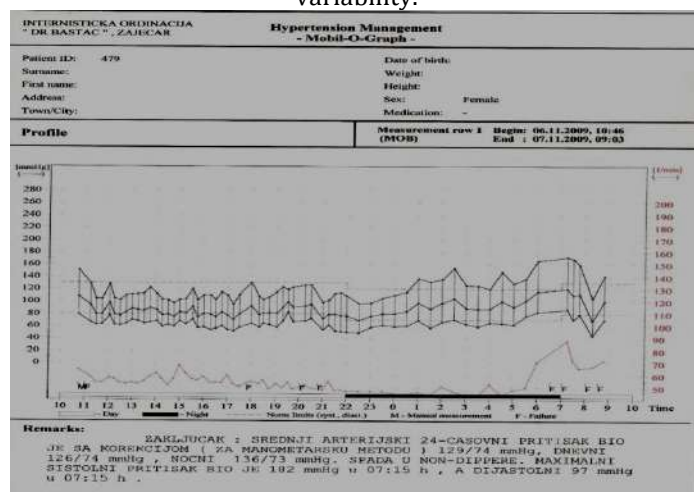
Various studies have found that BPV is reduced to a small extent with calcium antagonists and diuretics therapy and even increased with ACE inhibitors, beta-blockers, and alpha-blockers [13,14], but no interventional study has addressed whether reducing blood pressure variability provides protection from cardiovascular disease risk [11]. BPV is not specifically mentioned in the latest ESH guidelines and practical recommendations from 2023 [15], but it is tacitly confirmed by recommendations for repeated blood pressure measurements, standardization of techniques, and confirmation of hypertension diagnosis by home or ambulatory blood pressure monitoring

to explain the "white coat effect," masked hypertension, time spent in normotension during treatment, and to avoid problems in hypertension classification. There is no formal consensus on how to quantify or treat elevated blood pressure variability despite the real need for better diagnostic and therapeutic guidelines. Therefore, doctors should focus on controlling mean blood pressure using combinations of medications that improve cardiovascular disease (CVD) outcomes. Future consensus guidelines should directly address blood pressure variability and should include educational materials for both physicians and patients [15].

Picture 1. Example of elevated mean 24-hour blood pressure on ABPM graph with stage 3 hypertension and increased blood pressure variability.



Picture 2. Ambulatory 24-hour ABPM monitoring of blood pressure under antihypertensive therapy that is well-regulated shows normal average arterial 24-hour BP, but there is still increased blood pressure variability.



PATIENTS AND METHODS

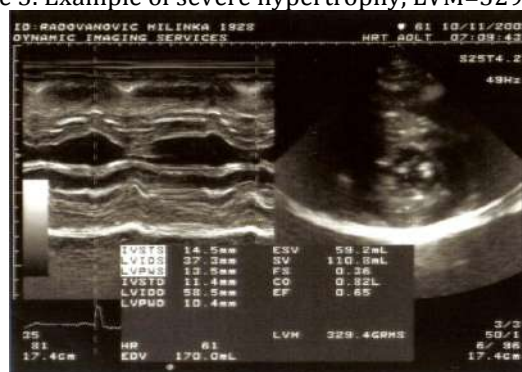
This retrospective cross-sectional study included 196 hypertensive patients under adequate therapy who underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean 24-hour arterial pressure for the entire group was normal at 123/76 mmHg on ambulatory blood pressure monitoring. A total of 196 patients were examined, 109 males and 87 females, with a mean age of 49.3 ± 8.4 years, untreated or inadequately treated patients with stage 2 hypertension (mean BP before treatment 167/106 mmHg) who were divided into three groups according to blood pressure variability parameter. Elevated blood pressure variability was present in 66/196 patients (34%) - group V despite good pressure control, while 130/169 (66%) had normal variability - group C, control. A subgroup ExtV was specifically identified within group V with extreme blood pressure variability ($SD > 20$ mmHg) - 15/66 patients (8%). In addition to routine clinical methods, ECG, office blood pressure measurements, and 24-hour ABPM, all patients underwent echocardiography using a GE Vivid 7 DIMENSION PRO machine with an emphasis on myocardial hypertrophy: left ventricular mass (LVM) and left ventricular mass index (LVMI) and parameters of left ventricular diastolic function via pulse (PW), continuous (CW), and tissue (TDI) Doppler.

Normal geometry assumes normal LVMI (less than 134 g/m² for males and 110 for

females), normal relative wall thickness (RWT less than 0.45), normal left ventricular end-diastolic dimension index (LVDDI less than 3.1 cm/m²), and normal septal eccentricity index (less than 1.3). Two-dimensional echocardiography was performed for precise measurements on M-Mode and qualitative analysis of standard two-dimensional (B-mode) cross-sectional planes. All parasternal longitudinal and transverse sections, apical sections with two and four cardiac chambers, as well as subcostal and suprasternal sections, were routinely performed. Visual analysis of the appearance of valvular echo apparatus, endocardium, and pericardium was performed. Regional myocardial motion analysis was also performed: presence or absence of hypokinesia, akinesia, or dyskinesia, and motion nonuniformities, taking into account normal variations. Diastolic parameters were determined by PW and TDI Doppler, including the E and A wave velocities ratio (E/A), the deceleration time of the A wave (DTA) representing myocardial relaxation, and the E wave transmitral velocity/mitral annulus E' velocity ratio on tissue Doppler representing left ventricular compliance and indirectly left ventricular filling pressure.

Statistical analysis was performed using the Statgraphics computer program, and the following parametric tests were used to test the hypothesis: Student's t-test, linear correlation coefficient, and nonparametric chi-square test.

Picture 3. Example of severe hypertrophy, LVM=329 grams.



Increased blood pressure variability is represented as the standard deviation ($\pm SD$) of blood pressure values in mmHg. Reference

threshold values for increased blood pressure variability are categorized according to blood pressure standard deviation ($\pm SD$).

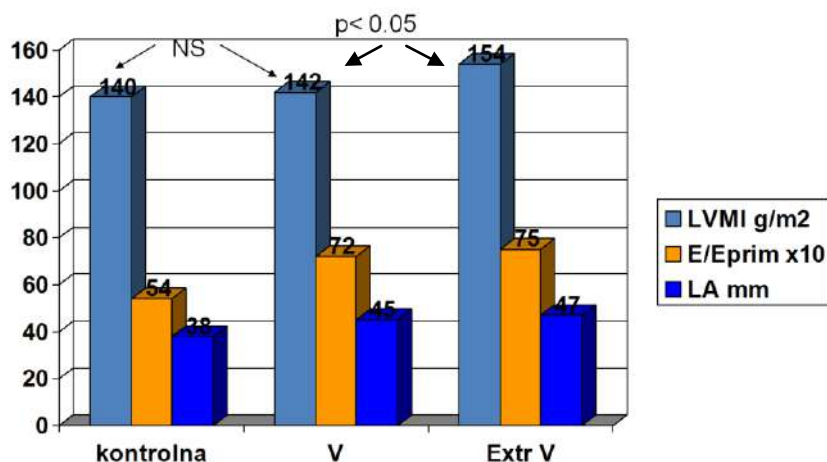
- daily systolic: >17 mmHg,
- daily diastolic: >13 mmHg,
- nocturnal systolic: >13 mmHg,
- nocturnal diastolic: >10 mmHg,
- extreme daily systolic variation: >20 mmHg.

RESULTS:

One-third of the examined patients, 66 out of 196 (34%), had increased blood pressure variability - group V despite good pressure control, while two-thirds of the patients, 130 out of 169 (66%), had normal variability - group C, which served as the control group. A subgroup ExtV was specifically identified within group V with extreme blood pressure variability - consisting of 15 out of 66 patients (8%). Left

ventricular mass index (LVMI) was elevated in groups C (140 g/m²) and V (142 g/m²) but without statistically significant difference (NS). Only in the group with extreme variability of daily systolic blood pressure, the left ventricular mass index was significantly higher compared to groups C and V ($p < 0.05$) (Graph 1). There was no difference regarding gender and age structure.

GRAPH 1. Myocardial mass and diastolic function



The mean left atrial (LA) dimension, as a parameter of cardiac diastolic function, was normal in the control group C (LA=38 mm, normal up to 40 mm), and statistically significantly higher ($p < 0.01$) in groups with increased blood pressure variability (group V - LA=45mm and ExtV - LA=47mm), but without significant differences between them. The diastolic function, expressed as the ratio of transmitral early diastolic filling velocity E to the average mitral annulus velocity E' (E/E'), was normal in group C (E/E' = 5.4 x 10) and statistically significantly higher in groups V (E/E'=7.2) and ExtV (E/E'=7.5) compared to the control group C ($p < 0.01$), although all mean E/E' values were within the normal range.

Statistical analysis of the examined parameters of 24-hour ambulatory blood pressure monitoring and echocardiographic parameters did not reveal significant correlation

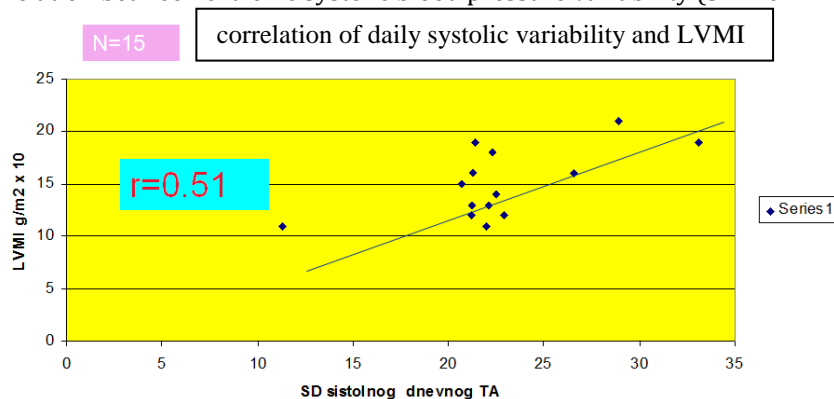
through calculating the coefficient of linear correlation between mean arterial pressure measured by 24-hour ambulatory blood pressure monitoring and standard deviation of daily and nocturnal blood pressure, and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r < 0.20$), as expected. However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, the E/E' ratio, and the variability of systolic daily blood pressure: $r = 0.41$. A weak correlation was found between the E/E' ratio and the variability of nocturnal diastolic blood pressure ($r = 0.30$). There is no correlation between E/E' and the variability of diastolic daily blood pressure ($r = 0.01$) and nocturnal systolic blood pressure ($r = 0.16$).

Early morning systolic pressure determined by ambulatory blood pressure

monitoring, as an important prognostic factor, only has a weak correlation with LVMI ($r=0.39$). Only the subgroup with extreme variability ExtV in terms of daily systolic blood pressure has a

statistically significant good correlation with the degree of left ventricular myocardial hypertrophy LVMI, $r=0.51$ (Graph 2).

GRAPH 2. Correlation between extreme systolic blood pressure variability ($SD>20$ mmHg) and LVMI



DISCUSSION

The pronounced variability in arterial blood pressure (ABP) is intertwined and overlaps with the diagnosis of hypertension, presenting a challenge for clinicians, as standard antihypertensive drugs only modestly reduce ABP fluctuations, as they are a consequence of pathophysiological changes or behavioral factors. Clinically, ABP variability is classified into 4 main types based on the duration of monitoring: ultra-short-term (beat-to-beat), short-term (within 24 hours), medium-term (within a few days), and long-term (over one month or year). Blood pressure variability is a strong risk factor for cardiovascular disease, chronic kidney disease, cognitive decline, and mental illness. The diagnostic and therapeutic value of measuring and controlling blood pressure variability can provide critical targets alongside reducing average blood pressure in hypertensive populations. [14].

Although some studies have shown that treatment reduces 24-hour blood pressure variability (BPV), there are no studies to date demonstrating that lowering BPV through treatment reduces cardiovascular risk. [8,9,16,17].

Numerous studies have focused on other types of BPV. Conflicting results have been published regarding the prognostic value of BP variability in-office between physician visits (inter-visit variability) [18], while some studies have reported an association between day-to-day variability when BPV was assessed through

home blood pressure monitoring (HBPM) and the risk of cardiovascular outcomes [19,20]. However, the largest body of evidence for BPV relates to office BP variability, from visit to visit over the course of one or more years (long term). Post-hoc analyses of antihypertensive treatment studies have shown that long-term BPV, measured as differences between office BP readings at 6 or 12 months, is associated with cardiovascular risk in treated hypertensive patients. In a post-hoc analysis of three studies, an increased number of physician visits resulting in office BP being lowered to recommended levels was associated with a proportional reduction in cardiovascular outcomes and mortality, independent of the average office BP achieved during the treatment period. [21-23].

Furthermore, in studies or treated cohorts of patients with various demographic and clinical characteristics, BP variations between physician visits are associated with cardiovascular and renal risk, independent of mean BP values over years of treatment [24-26]. In one study, combining the mean BP during treatment with BPV between physician visits identified a safer cardiovascular risk profile in treated hypertensive patients than any individual measurement [27]. These data suggest that in treated patients, protection depends on the time spent under controlled pressure, as evidenced by the recent confirmed relationship between cardiovascular events and the calculated time spent within the therapeutic BP range (TTR) or other BP burden ratios in

patients undergoing renal denervation and treated diabetics, respectively. [28,29].

From a clinical practice perspective, these data justify recommendations to pay attention to the consistency or regularity of BP regulation in patients on therapy, as the absence of regulation in a given physician visit does not represent "innocent" BP elevation without consequences, as it indicates a prolonged period of high pressure in previous months. Evidence from the ELSA study shows that inconsistent BP regulation is common in treated hypertensive patients [30]. Few studies have explored the relationship between blood pressure variability and echocardiographic parameters of myocardial mass, systolic and diastolic function indices [31,32,33]. Multivariable logistic regression showed that the trend of 24-hour systolic blood pressure burden on ABPM acts independently as a critical risk factor for LVH development [31]. A correlation was observed between systolic blood pressure burden and the severity of LVH in pediatric patients with hypertension, and 24-hour SBP burden acts as a critical early prognostic parameter for LVH [31]. Shin et al. [32] found that patients with higher blood pressure variability showed a significantly increased left ventricular myocardial mass index (LVMI) and late mitral inflow velocity (A), as well as a reduced E/A ratio (early mitral inflow velocity/late mitral flow velocity) compared to those with lower BP variability (LVMI: $p = 0.02$; velocity: $p < 0.001$; E/A ratio: $p < 0.001$). Additionally, increased blood pressure variability was associated with higher pulse wave velocity (PWV) and augmentation index ($p < 0.001$). Even among patients whose blood pressure was well controlled, blood pressure variability correlated with LV mass, diastolic dysfunction, and arterial stiffness [32]. Increased blood pressure variability was associated with LV mass and dysfunction, as well as arterial stiffness, suggesting that blood pressure variability may be an important determinant of target organ damage in patients with hypertension [32].

Variability in systolic blood pressure from visit to visit is associated with increased cardiac events [33]. Recent advances in imaging deformation via speckle tracking allow analysis of left atrial volume at various phases (2-DSTE) and easy measurement of left atrial phase function (LA). However, the relationship between BP variability and left atrial functional

deformation with patient clinical outcomes has not been sufficiently explored. Findings by Tanaka et al. [33] suggest that high VVV-SBP is associated with cardiovascular risk, including worsening LA function in clinical practice.

Recent technological advancements through practical ambulatory systems without cuffs will enable continuous, non-invasive monitoring of blood pressure (BP), heart rate, and cardiac rhythm on both longitudinal 24-hour measurement scales and high-frequency blood pressure variability from beat to beat, along with synchronous heart rate variability (HRV) and changes in baseline heart rhythm[11,34].

CONCLUSION:

Variability in daytime systolic arterial blood pressure is now recognized as an independent prognostic risk factor for stroke in hypertensive patients. One-third of the examined patients, 66 out of 196 (34%), had elevated blood pressure variability (BPV) - group V despite good pressure regulation. Comparing the examined parameters of 24-hour ambulatory pressure and echocardiographic indexes, no significant difference was found in the degree of left ventricular myocardial hypertrophy, except in extreme variability (ExtV) ($P < 0.01$).

The left ventricular myocardial mass index (LVMI) was elevated in groups C (140 g/m²) and V (142 g/m²) but without statistically significant difference (NS). Only in the group with extreme variability of daytime systolic blood pressure was the LVMI significantly higher compared to groups C and V ($p < 0.05$). The mean value of left atrial dimension (LA) as a parameter of cardiac diastolic function was normal in the control group C (LA=38 mm, normal up to 40 mm), but statistically significantly higher ($p < 0.01$) in groups with elevated BPV (group V - LA=45mm and ExtV - LA=47mm), although without significant difference between them.

Diastolic function, represented by the E/E' ratio (the ratio of early diastolic transmitral velocity to early diastolic mitral annulus velocity), was normal in group C ($E/E' = 5.4 \times 10$) but statistically significantly higher in groups V ($E/E'=7.2$) and ExtV ($E/E'=7.5$) compared to control group C ($p < 0.01$), although all mean values of E/E' were within normal limits.

However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, the E/E' ratio, and the variability of daytime systolic blood pressure: $r = 0.41$. Only the subgroup with extreme variability (ExtV) regarding daytime systolic blood pressure has a statistically significant strong correlation with the degree of left ventricular myocardial hypertrophy (LVMI), $r = 0.51$.

Statistical analysis of the examined parameters of 24-hour ambulatory pressure and echocardiographic parameters did not find a significant correlation through the calculation of the linear correlation coefficient between the mean arterial pressure measured by 24-hour ambulatory pressure monitoring and the

standard deviation of daytime and nighttime blood pressure and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r < 0.20$), as expected.

Arterial blood pressure variability has a strong correlation with a representative echocardiographic parameter of diastolic function derived from tissue Doppler: the E/E' ratio $r = 0.41$, which best represents left ventricular diastolic dysfunction as subclinical organ damage. Only the subgroup with extreme variability (ExtV) regarding daytime systolic blood pressure has a statistically significant strong correlation with the degree of left ventricular myocardial hypertrophy (LVMI), $r = 0.51$.

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SELF-LIMITED EPILEPSY WITH CENTROTEMPORAL SPIKES - AN OLD ACQUAINTANCE IN A NEW GUISE

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Summary: The International League Against Epilepsy (ILAE) in 2017, in its latest classification, lists Self-limited epilepsy with centrotemporal spikes (SeLECTS) among childhood focal epilepsies. The cardinal feature of rolandic epilepsy is focal epileptic seizures. Seizures can manifest in various ways, usually classified into groups of symptoms: 1) unilateral facial sensory-motor symptoms (30% of patients); 2) oro-pharyngo-laryngeal symptoms (53% of patients); 3) speech impairment (40%); 4) hypersalivation (30%). There is a clear influence of sleep, drowsiness, and sleep deprivation on seizure frequency. Three-quarters of seizures occur during nonREM sleep, mostly at the beginning of sleep or just before waking up. Febrile convulsions are often encountered in personal history (5-15%). A positive family history is often found in SeLECTS, indicating a genetic etiology. EEG findings: High-voltage spike-wave complexes activated during drowsiness and sleep are a striking feature of this entity (essential for diagnosis). The initial part of the graph element is usually described as a spike, although precise measurements often show it to be a sharp wave. The site of occurrence is typical, and most earlier names for this syndrome referred to that site. Furthermore, it has been shown that the frequency of spike-wave complexes depends on the state of wakefulness, i.e., they occur more often during sleep. Moreover, in repeated EEG registrations, the site of occurrence can change, so the epileptic focus often appeared in a different location compared to previous registrations ("spike migration"). This also involved a change of hemisphere, which was strong evidence against a structural lesion, i.e., indirect evidence that this is the entity in question. With the expansion of knowledge about benign childhood epilepsy with centrotemporal spikes, it is generally accepted that there are small but statistically significant abnormalities in the cognitive, behavioral, and emotional fields of children with this type of epilepsy.

Keywords: epilepsy/classification; self-limited epilepsy with centrotemporal spikes, electroencephalogram, high-voltage spike-wave complexes, focal epileptic seizures

INTRODUCTION

The International League Against Epilepsy (ILAE) in its 2017 classification includes Self-Limited Epilepsy with Centrotemporal Spikes among pediatric focal epilepsies [1].

The clinical manifestation typical of Self-limited epilepsy with centrotemporal spikes (SeLECTS) according to van Hufflen was first described by Martinus Rulandus in the 17th century (639/1989) [2].

In mid-20th century the first descriptions of epilepsy specific to children emerged, characterized by certain types of seizures and identifiable findings in EEG [3]. This type of epilepsy has proven to have an excellent prognosis, adding a third key characteristic to the clinical and neurophysiological findings: a benign course.

In attempts to make the name as precise as possible, authors included three or four terms in

the name, each individually describing the key characteristics of this entity.

In early works addressing this issue, the emphasis was placed on distinguishing this from other types of epilepsies. This approach led to the formation of a unique entity that clearly stands apart from other epilepsies [3].

With the increasing adoption of knowledge, this epilepsy became more recognizable in clinical practice and better described. Initially, authors gave various names to this type of epilepsy, namely there was not a single term used by all authors.

Problems with determining the name of the syndrome

Different names have been used for this type of childhood focal epilepsy. One group of authors used the eponym "Rolandic," while others employed a descriptive term, aiming to encapsulate the main characteristics of this

entity and provide a more precise definition of this type of epilepsy. In their attempts to be more precise, authors included three or four terms in the name, individually describing the key features of this entity:

- 1) The most important characteristic is a benign prognosis, so the term "Benign" is usually placed first in the name.
- 2) The determining point related to the time of onset of this syndrome is child's age. In the names, "children's or "childhood" is used.
- 3) In the third position is the determining point related to focal occurrence (focal, partial). Some authors omit this determining point, assuming it is implied when specifying the location of interictal epileptiform graphoelements in EEG.
- 4) The next determining point is the location of interictal specific graphoelements (spike, EEG focus). The location is determined in two ways: by neurophysiological criteria (centrotemporal, based on electrodes placed according to the international 10-20 system in EEG) or by an anatomical model, i.e., the part of the brain where epileptic discharge is presumed to occur – the Rolandic region, around the Rolandic fissure. American authors used the term "mid-temporal"

to describe these discharges [4,5], while French authors preferred "Rolandic spikes" [6,7,8,9].

It has been observed that an identical EEG finding characteristic of this type of childhood epilepsy also occurs in children without seizures. In such cases, terms like BFEDCs (Benign Focal Epileptiform Discharges of Childhood) [10,11,12], or BEDs (Benign Epileptiform Discharges) [13] are commonly used.

Childhood benign focal epilepsies form a group of epilepsies or epileptic syndromes sharing common features. According to the ILAE recommendation [14], these epilepsies are collectively termed Self-limited focal epilepsies of childhood (SeLFE), previously known as BCFE - Benign Childhood Focal Epilepsy [12] or Idiopathic focal epileptic syndromes (IFE) [15]. Self-limited epilepsy with centrotemporal spikes (SeLECTS) is the most common syndrome in this group, and this term was recommended by the ILAE in its new nomenclature in 2017 (275-2022). Throughout history, this type of epilepsy has had various names and abbreviations. The used names, abbreviations, authors, and publication years are listed in Table 1.

Table 1. The used names, abbreviations and publication years for Childhood epilepsy with centrotemporal spikes

BECCT	Benign Epilepsy of Children with Centro-Temporal EEG Foci[17]	1972
BFEC	Benign Focal Epilepsy of Childhood[16]	1975
BECT	Benign Partial Epilepsy with Eentrottemporal Spikes [18,19]	1988
BERS	Benign Childhood Epilepsy with Rolandic Spikes[20]	1990
BECCT	Benign Epilepsy of Chidhood with Centrotemporal Spikes[21]	1991
BECTS	Benign Epilepsy with Centrotemporal Spikes[22,23,24,25]	1992
BECCTS	Benign Epilepsy of Childhood with Centrotemporal Spikes[26]	1994
BECRS	Benign Epilepsy of Childhood with Rolandic Spikes[27]	1996
BREC	Benign Rolandic Epilepsy of Childhood[29]	1996
BCECTS	Benign Rolandic Epilepsy[28]	1997
BCSSS	Benign Childhood Seizure Susceptibility Syndrome[30]	2008
BRE	Benign Rolandic Epilepsy [31]	2009
ECTS	Epilepsy with CentroTemporal Spikes[32]	2019
CECTS	Childhood Epilepsy with Centrotemporal Spikes[33]	2021

The three main characteristics that constitute this entity (SeLECTS) are: Clinical manifestation, specific EEG findings, and a favorable prognosis, i.e., a benign course.

Clinical manifestation

The cardinal feature of Rolandic epilepsy is focal epileptic seizures, which can manifest in various ways typically categorized into symptom groups [34]:

- (1) Unilateral facial sensory-motor symptoms (30% of patients),
- (2) Oro-pharyngeal-laryngeal symptoms (53% of patients),
- (3) Speech impairment (40%),
- (4) Hypersalivation (30%) [30].

In addition to focal seizures, generalized tonic-clonic seizures also occur, commonly considered secondary generalized.

Beyond the seizure semiology and classification in this syndrome, anamnesis can provide other relevant data. There is a clear influence of sleep,

drowsiness, and sleep deprivation on the frequency of seizures. Three-quarters of seizures occur during non-REM sleep, mainly at the onset of sleep or just before waking up [30].

Febrile seizures are often encountered in personal history (5-15%) [1,35].

A positive family history is also frequently found in children with BECT, indicating a genetic etiology [36].

Specific EEG findings

High-voltage spike-wave complexes activated during drowsiness and sleep constitute a distinctive finding in this entity (essential for diagnosis) [1].

The initial part of the graphoelement is commonly described as a spike, although precise measurements often reveal a sharp wave.

The location is typically specific, and most of the earlier names of this syndrome were related to this location.

Furthermore, the frequency of spike-wave complexes has been shown to depend on the wakefulness state, occurring more frequently during sleep [34].

In repeated EEG recordings, the location of occurrence can change, so the epileptic focus often appeared in a different place compared to previous registrations ("spike migration") [37]. This included a change in the hemisphere, a strong indication that it wasn't a structural lesion, providing indirect evidence of this entity. The frequency of spikes in the EEG was not related to the frequency of seizures, which was a perplexing factor for clinicians. On the other hand, it was observed that some children with such EEG findings during nocturnal sleep exhibited almost continuous discharges. This led to the formation of a new entity (Epilepsy with continuous spike-and-waves during slow-wave sleep), separating this type of epilepsy from BECT (216/2001).

Regarding the location, most spikes are found in centro-temporal regions, but spikes in BECT can also be found outside these regions. Even though, in some cases, spikes in this entity may appear in other regions, it is not sufficient reason to exclude it from this syndrome ([38].

Many researchers have attempted to demonstrate different subtypes of this syndrome, but over time, this has been established only for spikes located in the occipital region. Only in correlation with the clinical description of seizures, two new types of

epilepsy with clear clinical-neurophysiological distinctions were recognized: Gastaut's type and Panayiotopoulos' type of childhood occipital epilepsy. According to the ILAE definition from 2022 [39], Panayiotopoulos syndrome is called Self-limited epilepsy with autonomic seizures, and Gastaut's type of occipital epilepsy is called Childhood occipital visual epilepsy (COVE).

Panayiotopoulos then introduced the concept of the susceptibility syndrome [35], a continuum of childhood benign focal epilepsies. The concept consists of a unique nosological entity with phenotypic variations. According to this concept, the central and largest part is BECT, while at the milder end is Panayiotopoulos syndrome, and at the other end is epilepsy with continuous discharges during sleep.

When it comes to the EEG findings, it has been observed that identical spike-wave complexes seen in BECT also appear in children without seizures. Genetic studies have shown that this trait is inherited, but the type of inheritance and the responsible gene (or genes) remain unknown. Many genes have been associated with this trait [40], but there is no consensus on the inheritance pattern. Inheritance has been found not to be gender-related since such discharges in healthy children (children without seizures) occur equally in boys and girls, unlike in BECT where there is a clear male predisposition. It can be concluded that BECT discharges are a necessary but not sufficient condition for the development of BECT. Only the second one (gender-related inherited condition) allows seizures to occur in children with predisposition (i.e. spike-wave complexes in EEG).

The nature of the spike in EEG remains unknown. Despite advances in medicine and science in general, it is still unclear which neurophysiological processes in the brain lead to the appearance of spikes in EEG.

Benign course

The third key characteristic of this syndrome is a favorable prognosis, i.e., the resolution of seizures during development [16]. While crucial for the entity, from a clinician's perspective, this characteristic lacks significant diagnostic value. It requires a sufficiently long period to confirm the benign nature of the epilepsy. Consequently, a definitive diagnosis can only be made retrospectively, once the child outgrows the age when this epilepsy occurs, and since this period

is defined differently in the literature, the final diagnosis can only be established after a prolonged, vaguely defined period.

On the other hand, the favorable prognosis holds significant prognostic value, for it reassures parents that their child's epilepsy will likely resolve over time, making it crucial for clinicians to have the first two elements present (clinical and EEG findings) to determine the third (favorable course), similar to how, in mathematics, two angles in a triangle can determine the third one.

However, the concept of benignity has been reevaluated and has been completely removed from the name following the ILAE recommendation [39]. This action is based on numerous studies indicating various changes in these children, mainly on a cognitive, behavioral, and psychological level. These changes were detected through carefully designed and precisely conducted studies, reaching statistical significance. Since the term benignity could imply "insignificance" across all aspects of this entity due to its broadness, it has been replaced with the term "self-limited," indicating a time-limited occurrence of seizures. In other words, by removing the term "benign" from the name, the favorable course of epilepsy remains acknowledged.

The term "benign" is eliminated from the title while retaining the concept of a favorable course.

Classification

International League Against Epilepsy (ILAE) provided a classification of epileptic seizures in 1981 [41], and in 1989, they published a classification of epilepsies and epileptic syndromes [42]. Both classifications proved to be highly valuable for both practitioners and researchers, operating at both clinical and scientific levels.

The 1989 classification of epilepsies and epileptic syndromes [42] lists two entities among idiopathic focal epilepsies of childhood:

Benign childhood epilepsy with centro-temporal spike

Childhood epilepsy with occipital paroxysms

In the report of the ILAE Commission on Classification and Terminology in 2001 [38], presented by Engel, five axes were proposed for diagnosing patients with epilepsy.

1. The first axis involves the description of seizures (ictal semiology).

2. The second axis involves the type of epileptic seizure. The ILAE Commission provided a list of accepted seizure types, categorized into self-limited seizures, continuous seizures, further divided into generalized and focal seizures.

3. The third axis is the syndromic diagnosis, including a list of accepted epileptic syndromes.

4. The fourth axis consists of specific etiology when known.

5. The fifth axis is optional and relates to the degree of impairment resulting from epilepsy.

Idiopathic childhood epilepsies (Axis 3), besides Benign Childhood Epilepsy with Centrotemporal Spikes, recognize two additional syndromes: Benign Childhood Occipital Epilepsy with Early Onset (Panayiotopoulos type) and Childhood Occipital Epilepsy with Late Onset (Gastaut type). It's notable that the term "benign" remains in the name of two syndromes in this group of epilepsies.

In 2010, ILAE issued a revision of terminology and the concept of organizing seizures and epilepsies [43]. The concept of electroclinical syndrome was introduced, referring to complex clinical data, signs, and symptoms that together define a distinct and recognizable clinical disorder. There are specific disorders identified by features such as the age of onset, specific EEG findings, types of seizures, and other characteristics that, when considered together, allow a specific diagnosis. A syndromic diagnosis, in turn, impacts the treatment, management, and prognosis of epilepsy.

The recommendation related to Rolandic epilepsy in this revision pertains to the use of the term "Benign Epilepsy." The recommendation is not to use the term "benign." The reasons are manifold. Firstly, it has been shown that childhood focal benign epilepsies are not as "benign" as initially thought. Increased knowledge indicates a connection between epilepsy and a broad spectrum of brain disorders such as cognitive, behavioral, and psychiatric disorders. The term "benign" may mislead both professionals and patients and their families to underestimate and neglect these associated conditions. On the other hand, the term "benign" has not been completely eliminated from the names of these epileptic syndromes, so in the category of childhood electroclinical syndromes, the following names have remained:

Panayiotopoulos syndrome Benign epilepsy with centrotemporal spikes (BECTS)

Late onset childhood occipital epilepsy (Gastaut type)

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)

Landau-Kleffner syndrome (LKS)

In 2017, the ILAE introduced a new classification of epileptic seizures [44] with an attempt to facilitate its use in clinical practice [45]. This classification is operational (practical) and is based on the 1981 classification and its expansion in 2010.

Significant progress in understanding epilepsy and its mechanisms was summarized in a noteworthy classification, the first after the one in 1989. This classification provides diagnostic guidelines for clinicians divided into three steps: First, the diagnosis of the type of epileptic seizure. The second step is determining the type of epilepsy, including focal epilepsies, generalized epilepsies, combined generalized and focal epilepsies, and the unknown epilepsy group. The third step is determining the epileptic syndrome, where a syndromic diagnosis can be established. Regarding the cause, instead of the terms idiopathic, cryptogenic, and symptomatic, the etiology of epilepsy can be (1) genetic, (2) structural, (3) metabolic, (4) immunological, (5) infectious, and (6) unknown.

The term "benign" has been replaced with "self-limited" or "pharmacoresponsive." This recommendation also extends to the name of the electroclinical syndrome, so "Benign epilepsy with centrotemporal spikes" is now called "self-limited epilepsy with centrotemporal spikes."

The change in the name of the most common childhood epilepsy after decades of using the word "benign" as a key element in the name stems from the imprecision of the term "benign." With the increased knowledge about benign childhood epilepsy with centrotemporal spikes (BECT), it has been widely accepted that there are small but statistically significant abnormalities in the cognitive, behavioral, and emotional areas in children with this type of epilepsy. Consequently, BECT is no longer

entirely "benign," leading to the replacement of the term "benign" with "self-limited." This new term is more precise and clearly indicates one of the main characteristics of this electroclinical syndrome, namely the mandatory cessation of seizures upon entering adolescence (i.e., with the completion of nervous system maturation).

However, while gaining precision, there is a loss on the other side. The name of this syndrome was already awkward and often replaced with abbreviations, which, on the other hand, were not always standardized. The term "self-limited" is not commonly used in everyday language, requiring additional mental effort to understand its meaning. Instead of one widely accepted word ("benign"), a compound term ("self-limited") is introduced, usually requiring further explanation. In the end, instead of a name consisting of five words, we now have a name with six words. In the professional community, confusion may arise, leading to the perception of a new entity when encountering this term. The key word in the old name ("benign") is now missing and replaced by a new compound term ("self-limited").

Attempts to precisely define an entity in its name inevitably lead to a name that can be awkward and unwieldy can create difficulties in its acceptance in clinical practice.

CONCLUSION

The concept of epileptic syndromes and the dynamics of renaming certain diseases depend on the rapid progress of scientific knowledge in medicine. Recommendations from ILAE contribute to terminology standardization and a better understanding of the essence of epilepsy. Given the dynamic nature of this field, ILAE will continue to monitor new achievements in epileptology and update classifications to reflect the latest knowledge. Clinicians are urged to not only formally but also substantively follow developments in their medical field to provide the best and most contemporary assistance to their patients.

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FOREIGN BODIES IN THE URINARY BLADDER - CASE REPORT

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Abstract: INTRODUCTION Pathological substances produced by the body and entering the urinary bladder cannot be considered foreign bodies. They are more common in women than in men, with a ratio of 100:1 according to some statistics (Sonntag). They can be of animal, plant, or mineral origin. Medical foreign bodies remain after certain surgical interventions, either in the bladder itself or on surrounding organs, due to negligence, carelessness, incorrect use, or poor quality of materials. **CASE REPORT** Patient C.R. from the vicinity of Donji Milanovac, aged 30, presented to our clinic complaining of frequent urination, burning sensation during urination, and occasional sudden cessation of urination. Anamnestic data were very scarce, except for the mentioned symptoms. Urine sediment showed a significant number of pale red blood cells and rare bacteria. Urine culture yielded sterile cultures. Descending cystography revealed an ellipsoid contrast defect. Subsequent urethrocystoscopy showed a urethra easily passable for a Ch 20 cystoscope sheath, with a short prostatic urethra of about 2 cm. **CONCLUSION** Operative findings revealed: A round dark-brown formation, the size of a pigeon's egg, was observed in the bladder lumen. A "stone" was extracted from the bladder lumen with stone forceps and placed in a kidney basin. After completing the operation, the image showed a foreign body. Three snake-like objects, twisted, with a length of about 10 cm and a thickness of about 10 mm, were found in the kidney basin. They were candles.

Keywords: urinary bladder foreign body, Cystoscopy, candles, quackery

INTRODUCTION

Pathological substances produced by the body and entering the urinary bladder cannot be considered foreign bodies. They are more common in women than in men, with a ratio of 100:1 according to some statistics (Sonntag). They can be of animal, plant, or mineral origin. Medical foreign bodies remain after certain surgical interventions, either in the bladder itself or on surrounding organs, due to negligence, carelessness, incorrect use, or poor quality of materials.

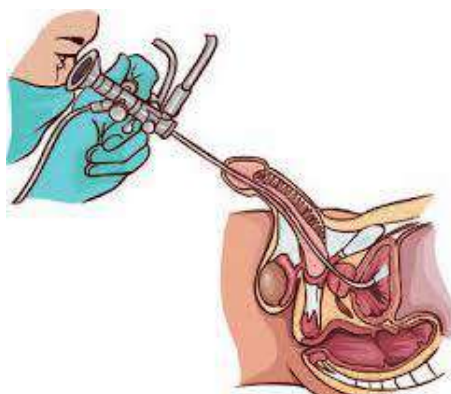
Foreign bodies introduced through the urethra can be residual parts of tools used for diagnostic purposes (parts of catheters, bougies, probes). These are most commonly gauze, swabs, parts of drains, catheters, or probes, and very rarely surgical instruments. Objects introduced into the urethra for masturbation or sexual perversion purposes (needles, hairpins, thermometers, candles, grain spikes, grass, worms) enter the urinary bladder via antiperistalsis. Objects used to close the urethral meatus to prevent conception (candles, textile tampons, rubber). Objects used for criminal

abortions (plant roots, wooden objects) mistakenly inserted into the urethra instead of the vagina. Injuries from firearms, more common in war and less so in peacetime conditions, can create a foreign body due to a retained projectile in the bladder itself or migration from the surrounding area.

CASE REPORT

Patient C.R. from the vicinity of Donji Milanovac, aged 30, presented to our clinic complaining of frequent urination, burning sensation during urination, and occasional sudden interruption of urination. Anamnestic data are very scarce, except for the mentioned symptoms. Urine sediment analysis revealed numerous pale red blood cells and occasional bacteria. Urine culture showed sterile growth media. Descending cystography revealed an ellipsoid defect in contrast. Subsequently, urethrocystoscopy was performed (Figure 1): the urethra allowed easy passage for the sheath of the 20 Fr cystoscope, with the prostatic urethra measuring approximately 2 cm in length.

Figure 1. Urethrocytoscopy Cystoscopy (taken from:http://cdn.futura-sciences.us/builds/images/thumbs/4/41b85c2a84_cystoscopie-c-hakan-corbac-305-fotoliacom.jpg)



The bladder neck is normal. A round dark-brown formation, the size of a pigeon egg, is observed within the bladder lumen. Suspecting a calculus, attempts were made to perform electrohydraulic lithotripsy with Urat-I. However, stone disintegration was unsuccessful, leading to a recommendation for surgical stone removal.

Operative findings: Under general endotracheal anesthesia, the surgery was performed. A Pfannenstiell suprapubic incision was made. After fascial incision, the rectus

muscles were separated, and the bladder wall was dissected and transversely opened. The "stone" was removed from the bladder lumen using stone forceps and placed in the kidney. The bladder was irrigated with warm saline solution, sutured in two layers, a drain was placed in the Retzius space, the rectus muscles were approximated, skin closure performed, drain fixation, wound dressing with gauze. Following completion of the surgery (Figure 2), foreign bodies were observed.

Figure 2. Foreign bodies - candles, surgically removed from the bladder



To our astonishment, three snake-like objects, curved, approximately 10 cm in length and 10 mm in diameter, were found in the kidney. They turned out to be candles.

Then our professional struggles began. The patient stubbornly refused to disclose how the candles ended up in the bladder. After a patient, persistent, and even ultimative conversation, here is his story: Fearing he had "been infected," he turned to a witch doctor. She suggested that for three days he should apply fresh cow dung around his genitals. To prevent the dung from entering the canal, the witch

doctor instructed him to insert a candle into it. The next day, there was no candle in the canal during the new application, so he inserted another candle, and the next day, one more. This is how his "treatment" ended. Three to four months later, urinary problems arose, prompting him to see a urologist.

DISCUSSION

In most cases, foreign bodies in the urinary bladder occur in individuals with psychopathological, mentally impaired, or intoxicated states. Small children, in innocent

play, often insert various objects into natural orifices. Women may accidentally or due to negligence or lack of knowledge insert contraceptive devices or abortion aids into the urethra instead of the vagina. Medical foreign bodies may remain accidentally due to carelessness, negligence, incorrect use, or poor material during a surgical intervention in the bladder itself or on surrounding organs. Even surgical suture materials can act as a nucleus around which a stone forms. Firearm injuries, more common in war and rarer in peacetime, can create a foreign body due to a retained projectile in the bladder or its surroundings. Cases of projectile migration from the abdomen into the urinary bladder have been described.

Symptomatology is dominated by persistent, recurrent, and antibiotic-refractory cystic complaints. Cystic complaints result from irritation of the mucous membrane due to mechanical pressure. Painful hematuria may also occur. Retention occurs depending on the shape and size of the foreign body, due to closure of the internal opening of the urethra. Complications may include fistulas due to prolonged mechanical pressure on the bladder wall, septic conditions, and even kidney function damage.

Diagnosis is easy if there is a history of foreign body insertion into the urethra. However, the true reasons are often concealed due to shame or fear. Diagnosis is also challenging in mentally retarded individuals and small children. Patients typically consult a doctor due to persistent cystic complaints after prolonged use of antibiotics.

In the urine sediment, signs of nonspecific inflammation predominate, with the presence of fresh erythrocytes and leukocytes. Ultrasonography shows a hyperechoic lesion

(with shadowing), while intravenous pyelography on descending cystography reveals a contrast defect. The most reliable diagnostic method is URETHROCISTOSCOPY. It detects the foreign body, shows its shape and size, and determines the possibility of elimination. A very small percentage of foreign bodies (about 3%) can be spontaneously eliminated per urethra. Depending on the shape and size of the foreign bodies, endoscopic extraction or cystolithotomy methods are used in therapy.

CONCLUSION

Patient C.R. from the vicinity of Donji Milanovac, aged 30, presented to our clinic complaining of frequent urination, burning sensation during urination, and occasional sudden interruption of urination. On descending cystography, an elliptical contrast defect was observed. Subsequently, urethrocystoscopy was performed, revealing a urethra easily passable for the sheath of a size 20 cystoscope, with a prostatic urethra approximately 2 cm in length.

In the bladder lumen, a round dark-brown formation the size of a pigeon egg was noticed. Suspecting a calculus, attempts were made at electrohydraulic lithotripsy with Urat. However, stone disintegration failed, leading to a recommendation for surgical stone removal.

Operative findings: A "stone" was extracted from the bladder lumen using stone forceps and deposited in the kidney. After the completion of the surgery, the image showed a foreign body. In the kidney, three coiled objects, approximately 10 cm in length and 10 mm in diameter, were found. They were candles.

Quackery exists in eastern Serbia. Here is an example. It was our intention to point this out so that it does not happen again and is not forgotten!

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ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) ASSOCIATED WITH TICS - CASE REPORT

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Abstract: Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder in children and adolescents, with estimated global prevalence ranging between 5% and 12%. The frequency of ADHD comorbid with tics is significantly higher than expected. Children diagnosed with ADHD are much more likely to have chronic tics compared to those without ADHD. When ADHD occurs alongside tic disorders, treatment can be challenging. Through this case report, we aim to shed light on the unique challenges and potential treatment strategies for this comorbidity. A nine-year-old boy was admitted to the Department of Psychiatry due to hyperactivity, poor concentration, attention, and motor tics such as frequent blinking, grimacing, and head nodding. He was admitted for additional diagnostic procedures and possible initiation of differential psychopharmacotherapy. Psychological testing revealed that his overall intellectual achievement was average, but there was a discrepancy between verbal and manipulative abilities. During hospitalization, observation, comprehensive psychological testing, and the use of tests (SNAP-IV borderline scores) did not directly indicate the presence of hyperkinetic disorder. Therefore, a recommendation was made for a six-month follow-up and continuation of speech therapy and defectology treatment. Meanwhile, he was followed up by a psychiatrist, and based on psychodiagnostic assessments, attention deficit with hyperactivity was diagnosed. After ruling out contraindications, methylphenidate therapy was initiated at a dose of 18mg, titrated to 36mg after two months when a satisfactory therapeutic response was achieved. The introduction of methylphenidate had no significant effect on tics but did not worsen them either. Behavioral disorders and functional impairments associated with ADHD have negative impacts on academic, social, and family aspects. Unlike individuals facing only with Tourette's syndrome (TS), those with both TS and ADHD have more pronounced difficulties in areas such as planning, working memory, inhibitory function, and visual attention. Clinicians treating patients with tics and ADHD may consider using methylphenidate to address ADHD symptoms. However, it is important for clinicians to discuss this issue with caregivers when prescribing the medication and carefully monitor patients due to precautions listed in the drug information.

Keywords: methylphenidate; ADHD; comorbidity; tics; treatment

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder in children and adolescents, with an estimated global prevalence ranging between 5% and 12% [1]. ADHD is a condition with a diverse symptomatology characterized by symptoms of hyperactivity, impulsivity, and disrupted attention.

Tics are characterized by repetitive, structured, and non-rhythmic movements or sounds that are inappropriate in a given context. Tourette's syndrome (TS), a relatively common neurodevelopmental disorder that begins in childhood, is diagnosed when a person exhibits

a combination of at least two motor tics and at least one vocal tic for more than a year. It is observed in approximately 1% of school-aged boys [2].

Undoubtedly, ADHD is significantly influenced by heredity through polygenic susceptibility and various environmental risk factors. However, there are inconsistent data regarding the extent to which early upbringing and development influence ADHD, the extent to which gene-environment interactions contribute to inheritance, and how gene-environment correlation explains additional risk factors. Therefore, the actual causes of ADHD remain insufficiently understood [3].

The frequency of ADHD comorbid with tics is significantly higher than expected [4]. Children diagnosed with ADHD are much more likely to have chronic tics (chronic tic disorder, CTD) compared to those without ADHD. In fact, up to 30% of children diagnosed with ADHD simultaneously have chronic tics. These involuntary movements, often in response to an urge, present an additional layer of complexity in the clinical management of ADHD [5], leading to significant increases in additional psychiatric and functional challenges [6].

Possible explanations for the significant overlap between these conditions include a fundamental lack of inhibition associated with dysfunction of frontal-striatal and frontal-parietal networks within cortico-striatal-thalamo-cortical pathways. Visual diagnostic imaging studies show increased activity in the basal ganglia in individuals with tics, leading to increased motor, cognitive, and emotional disinhibition. This is exacerbated by frontal hypoactivity observed in ADHD [7]. The observation that both disorders typically improve over time may be attributed to enhanced myelination of frontal brain regions [8].

When ADHD occurs alongside tic disorders, treatment can be challenging. Medications commonly prescribed to manage ADHD symptoms include stimulants such as methylphenidate and amphetamines, non-stimulants such as atomoxetine, tricyclic antidepressants, and alpha agonists [9]. These alpha agonists are also used as tic medications. Considering the impact of ADHD symptoms on children with tic disorders, ADHD treatment often takes priority over direct medical management of tic symptoms. However, clinicians have historically been hesitant to use stimulants in children with both ADHD and tics due to concerns about potential exacerbation of tic symptoms.

This case report aims to contribute to existing research by presenting a detailed case of ADHD with tics. Through this case report, we hope to illuminate the unique challenges and potential treatment strategies for this comorbidity.

This research was approved by the local Ethics Committee following the Helsinki Declaration.

Presentation of the patient

The nine-year-old boy was admitted to the Psychiatry Clinic due to hyperactivity, poor concentration and attention, as well as motor

tics manifested as pronounced blinking, grimacing, and head nodding. He was admitted for additional diagnostic procedures and the possible introduction of alternative psychopharmacotherapy. He was hospitalized for two weeks. The symptoms began with his school attendance, exhibiting immature behavior, refusal to cooperate, poor attention, and concentration, prompting a psychologist to advise a consultation with a psychiatrist who recommended hospitalization.

Psychological testing revealed that his overall intellectual achievement was average, however, there was a discrepancy between his verbal and manipulative abilities. His verbal skills were at the age-appropriate level (IQ=90), while his manipulative abilities were above average (IQ=140). His attention was decreased, as well as his understanding of social situations. He achieved exceptionally high scores in visual and spatial abilities, as well as in distinguishing between relevant and irrelevant information. When faced with problematic situations, he tended to rely on others, showing dependency. Only in prolonged, unstructured testing conditions, was impatience and mild hyperactivity observed. Significant emotional immaturity and introverted characteristics were noted in his personality development. Impulsivity was not observed during the assessment.

An electroencephalogram (EEG) and neurological examination were performed, revealing nonspecific findings indicating mild to moderate cerebral dysfunction, manifested electrocortically, occasionally indicating generalized sharpened high-voltage waves. During the first hospitalization, based on observation, psychological testing, and the use of the Swanson, Nolan and Pelham questionnaire (SNAP-IV borderline values), direct evidence of hyperkinetic disorder could not be established, thus, a six-month follow-up and continuation of logopedic-defectological treatment were recommended. SNAP is a standardized validated questionnaire consisting of nine questions related to symptoms of impulsivity, nine questions related to attention deficit symptoms, and eight questions based on oppositional defiant behavior. At that time, no therapy was initiated. He was discharged with a diagnosis of F95.8 (tic alius, according to the International Classification of Diseases ICD-10), which he had previously, with suspected attention deficit and activity disorder. During this period, the problems with attention and activity continued and intensified.

In the meantime, he was monitored by the responsible psychiatrist, during which based on psychodiagnostic assessments, it was concluded that there was attention deficit with hyperactivity. Additionally, certain stereotypical behaviors were noted, such as twisting of the hands, touching objects, and rocking, along with persistent pronounced blinking. He exhibited low frustration tolerance, oppositional behavior, and defiance.

High scores were now recorded on the SNAP-IV questionnaire, both by parents and school staff. After excluding contraindications, methylphenidate psychostimulant therapy was introduced at a dose of 18mg. The dose was titrated after two months to 36mg when a satisfactory therapeutic response was achieved. The introduction of methylphenidate resulted in a reduction of symptoms of attention and activity disorders, noticeable improvement in attention, longer periods of remaining calm during school lessons, and reduced movement. Although occasional aggression occurred when faced with frustration, overall behavioral improvement was evident both to parents and school staff.

The introduction of methylphenidate did not have a significant impact on tics, but it also did not worsen this type of problem.

Discussion

This case illustrates the treatment of a child with ADHD and tics, as well as the challenges in diagnosing ADHD. Based on a cross-sectional analysis of children whose parents reported ADHD, it is clear that most of them did not receive medication for ADHD and never received mental health care as outpatient patients. Therefore, there is a need to develop approaches that will improve the recognition of children with ADHD in clinical settings and improve their access to appropriate treatments.

CTD often accompanies ADHD in children. Children who have both ADHD and CTD are more likely to have comorbid anxiety and obsessive-compulsive disorder compared to those with only ADHD. CTD is significantly more common in children with ADHD, four times more common at the age of 7 and almost six times more common at the age of 10, compared to children without ADHD. The presence of concurrent CTD symptoms contributes to increased rates of internal disorders, greater difficulties in peer relationships, and reduced quality of life in children with ADHD.

Behavioral disorders and functional impairments associated with ADHD have

negative impacts on academic, social, and family aspects. Unlike individuals facing only Tourette syndrome (TS), those with both TS and ADHD have more pronounced difficulties in areas such as planning, working memory, inhibitory function, and visual attention.

Guidelines for stimulant medications advise against their use in individuals with tics, a concern still shared by many clinicians. However, significant evidence has emerged to challenge the assumption that stimulants are not suitable for children with tics. In a year-long randomized trial in children diagnosed with ADHD, clinically significant tics occurred equally in children receiving methylphenidate or placebo. Interestingly, tics improved during treatment in approximately two-thirds of children with a previous history of tics. A significant randomized controlled trial in children with Tourette syndrome (TS) and ADHD showed moderate but significant improvement in tics with methylphenidate. A meta-analysis concluded that methylphenidate does not worsen tic symptoms.

Although clinicians occasionally notice patients for whom stimulants appear to induce or worsen tics, the above-mentioned year-long study reported that 23.6% of children using the active drug developed moderate to severe tics for the first time, while 22.2% of children on placebo also had such symptoms. Therefore, while there is a possibility that methylphenidate exacerbates tics in some children, on average, it is more likely to improve tics. Any worsening of tics during medication use is likely coincidental. Clinicians treating patients with tics and ADHD may consider using methylphenidate to address ADHD symptoms. However, it is important for clinicians to discuss this issue with caregivers when prescribing the medication and carefully monitor patients for precautions listed in the product information..

CONCLUSION

Methylphenidate can be an important choice when selecting medication for patients with ADHD and tics. Considering that this case report is based on a single case, further research is needed to determine whether methylphenidate can indeed be an effective and safe option for treating ADHD associated with tics in different age groups. Additionally, this case highlights the common practice of individualized treatment rather than standardized approaches, especially in addressing complex neurodevelopmental

conditions such as ADHD, often accompanied by additional health issues.

Conflict of interest: Maša Čomić: none. Dragana Ratković: none. Vladimir Knežević:

none. Aleksandra Dickov: none. Svetlana Ivanović-Kovačević: none. Jovan Milatović: none. Darja Šegan: none.

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INFECTION AFTER OPEN FRACTURE OF THE TIBIA IN POLYTRAUMATIZED PATIENT

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Summary: Open fractures of the shinbone are the most common open fractures of long bones, typically resulting from direct or indirect exposure to strong force. Open fractures of the shinbone are often encountered in the context of polytrauma. This case presents a 58-year-old patient who experienced polytrauma after falling from a crane at a height of approximately four meters, resulting in an open fracture of the shinbone classified as Gustilo grade III B and a head injury. Upon admission to the hospital, diagnostic and preoperative preparations were carried out. The patient underwent a surgical procedure, during which the open fracture of the shinbone was stabilized with an external skeletal fixator, and the wound was closed with primary sutures. Due to the head injury, the patient was transferred to the neurosurgery clinic. During postoperative treatment, the patient developed a high fever, prompting a consultation with the orthopedic specialist. Upon removal of the dressing and gauze, purulent secretion was observed between the primary sutures of the wound. Following suture removal, soil was found in the depth of the wound along with purulent secretion. The wound was thoroughly irrigated, and foreign material, including the soil, was removed. The wound was left open, and antibiotic therapy was prescribed (amp. Ceftriakson a 2,0 gr/24 h, amp. Amikacin a 1,0/gr, Metronidazol a 500mg/8h). The patient underwent daily dressing changes, leading to improvement. The wound healed by secondary intention. After the fracture healed and completion of physical therapy, the patient returned to their work and daily activities.

Key words: open fracture, lower leg, bleeding, extremity

INTRODUCTION

Open fractures of the shinbone occur as a result of direct or indirect force and belong to the most severe fractures of the musculoskeletal system. In open fractures of the shinbone, damage to surrounding soft tissues creates highly unfavorable biological conditions for fracture healing. Due to the impairment of both intramedullary and periosteal vascularization, open fractures of the shinbone are predisposed to delayed healing and the development of pseudoarthrosis, with a constant risk of infection and osteitis [1].

The treatment of open fractures of the shinbone is challenging due to the extent of the injury. External skeletal fixation is commonly employed in the treatment of open fractures today. When using external skeletal fixation for the treatment of open fractures, good stability is achieved with minimal additional damage to the soft tissue envelope of the shinbone. The pins of the external skeletal fixator are placed away

from the fracture site, minimizing additional damage to the intramedullary and periosteal vascularization of the bone in the fracture zone, which is crucial for fracture healing [2].

The treatment of open fractures of the shinbone involves removing all foreign bodies from the open fracture wound, thorough irrigation of the wound with saline and hydrogen peroxide, debridement of damaged tissues, fracture stabilization, and delayed closure of the open fracture wound

Open fractures of the shinbone occur as a result of direct or indirect force and are among the most severe fractures of the locomotor system. In open fractures of the shinbone, there is damage to surrounding soft tissues, creating very unfavorable biological conditions for fracture healing. Due to damage to both intramedullary and periosteal vascularization, open fractures of the shinbone are predisposed to slow healing and the development of pseudoarthrosis, with a constant threat of

infection and osteitis [1]. Treating open fractures of the shinbone is accompanied by significant difficulties due to the extent of the injury. External skeletal fixation is now used in the treatment of open fractures. When applying external skeletal fixation in the treatment of open fractures, good stability is achieved with minimal additional damage to the soft tissue envelope of the shinbone. The pins of the external skeletal fixator are placed away from the fracture site to avoid further damage to intramedullary and periosteal vascularization in the fracture zone, which is crucial for fracture healing [2]. Treatment of open fractures of the shinbone involves removing all foreign bodies from the wound, thorough irrigation of the wound with physiological solution and hydrogen peroxide, debridement of damaged tissues, fracture stabilization, and delayed closure of the open fracture wound.

OBJECTIVE OF THE STUDY

The aim of our study is to present the treatment of a polytraumatized patient with an open fracture of the shinbone using external skeletal fixation with the Mitković unilateral

external fixator. The treatment goal is to avoid primary amputation and to restore full function of the injured limb.

MATERIAL AND METHOD OF WORK

The study depicts a polytraumatized patient with an open fracture of the shinbone, who underwent primary wound management followed by external skeletal fixation, and closure of the open fracture wound with primary sutures. However, during the subsequent course of treatment, the patient developed severe infection and sepsis.

CASE REPORT

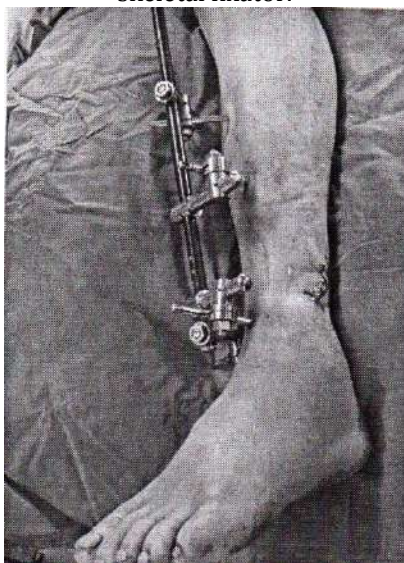
A 58-year-old patient sustained an open fracture of the shinbone by falling from a height of approximately 4 meters, landing on stacked logs.

Upon admission to the hospital, the patient was prepared for surgical intervention, and a reduction and external skeletal fixation of the shinbone were performed. The open fracture wound of the shinbone was primarily sutured (see images 1 and 2).

Fig. 1 and 2. X-ray images of the open fracture of the shinbone after the realignment of bone fragments and stabilization of the fracture with an external skeletal fixator.



Fig. 3. Condition after stabilization of the open fracture of the distal third of the shinbone using an external skeletal fixator.



Due to a head injury, the patient was hospitalized in the neurosurgery clinic. During the treatment, the patient developed high fever. A follow-up examination was conducted, during

which the primary sutured wound of the open fracture of the shinbone was observed, with inflammation and purulent discharge between the wound sutures.

Fig. 4. The wound of the open fracture of the shinbone is inflamed, and there is purulent discharge present between the wound sutures.

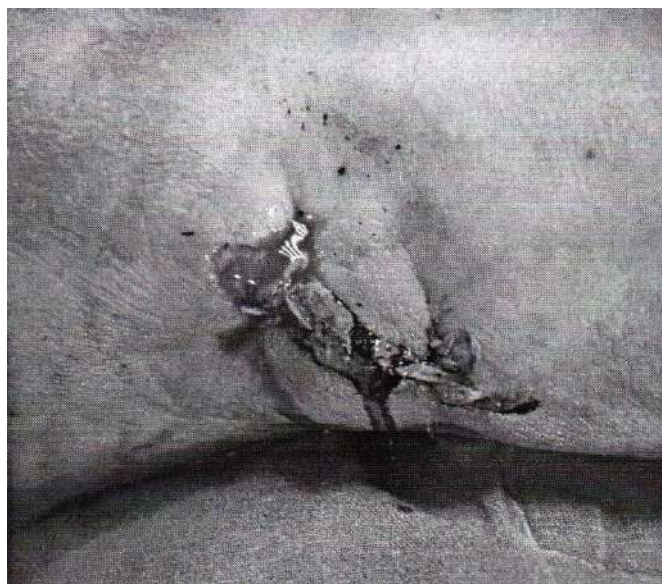
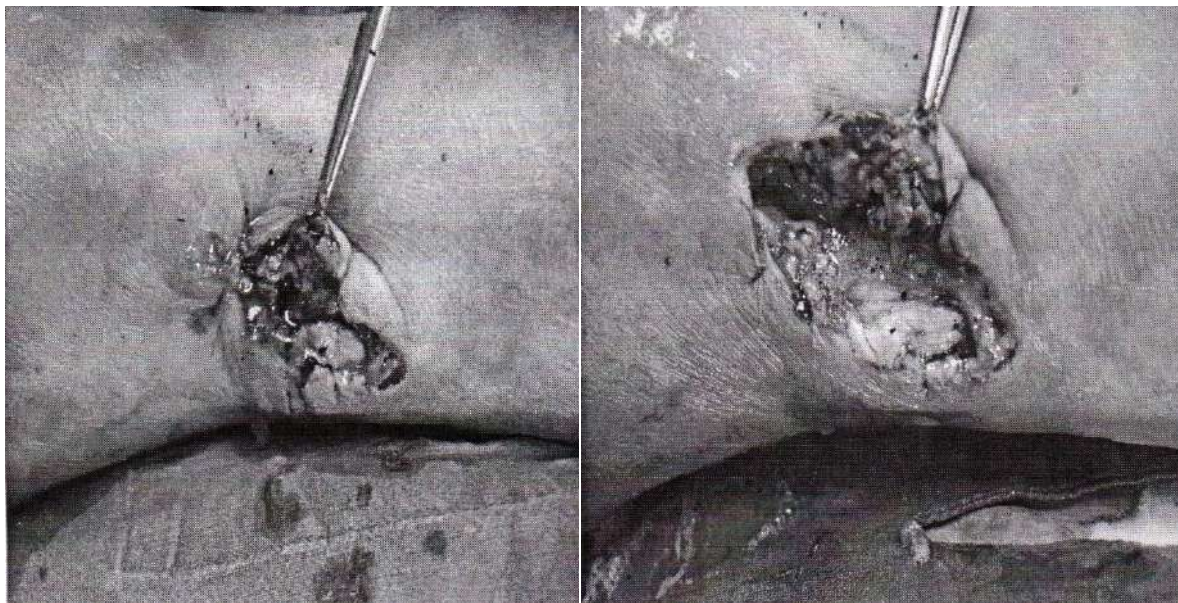


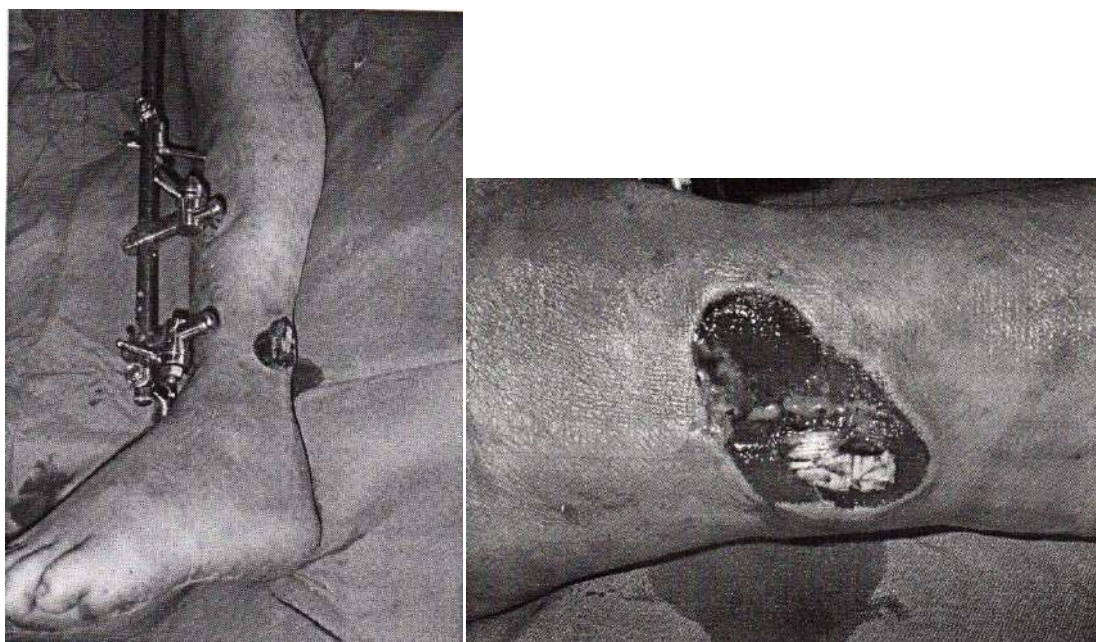
Fig. 5 and 6. The sutures used to close the open fracture wound initially were removed from the wound, and foreign material, soil, and pus were found within the wound..



The wound was thoroughly irrigated, and wound debridement was performed layer by layer for the open fracture of the shinbone. Foreign material was removed, and the wound

was extensively irrigated again. Following the debridement of the open fracture wound, the wound was not sutured but left open (see images 7 and 8).

Fig. 7 and 8. The condition of the wound after debridement and thorough irrigation. Following debridement, the open fracture wound was left open.



The patient was prescribed antibiotic therapy (amp. Ceftriakson 2g/24h, amp. Amikacin 1g/24h, and Metronidazol 500mg/8h).

Following the wound debridement and antibiotic therapy, the temperature normalized, and the wound healed. After the fracture healed

and physical therapy, the patient returned to their work and daily activities.

DISCUSSION

Open fractures of the shinbone are the most common open fractures of long bones. They occur as a result of direct or indirect force. Direct mechanisms of injuring the shinbone typically occur in traffic accidents, during agricultural work, falls from great heights, gunshot wounds to the shin region, and so forth. Indirect mechanisms of injury lead to the majority of shinbone fractures during sports activities such as skiing, falls, or other sports-related activities. Damage to the soft tissues of the shinbone usually occurs due to high-intensity force or displacement of sharp bone fragments that penetrate the soft tissues from within. In open fractures, there is communication between the fracture site and the external environment. Open fractures are primarily contaminated with microorganisms from the external environment.

In the clinical presentation of an open fracture of the shinbone, there is communication of the fracture site with the external environment, pain, deformity, bleeding, hematoma, local swelling, pathological mobility, and loss of function of the injured limb. Due to the potential injury to major blood vessels, it is necessary to check pulses such as the dorsalis pedis artery, anterior tibial artery, and posterior tibial artery. Radiological diagnostics (conventional X-rays, MSCT, magnetic resonance imaging) are the most significant and precise methods to gain insight into the shape of the shinbone fracture, the degree of displacement, and the location of the fracture. X-ray imaging of the diaphysis of the injured shinbone in two directions with the knee and ankle joints should be conducted to avoid missing associated fractures at the joint levels.

Upon admission of the patient with an open fracture of the shinbone, a clinical examination and X-ray diagnostics should be performed if the patient's condition allows or after resuscitation. Inspect the open fracture wound and take a wound swab for culture and antibiotic susceptibility testing. In the operating room, irrigate the wound with physiological saline and hydrogen peroxide (sometimes it may be necessary to use up to ten liters of fluid for wound irrigation), and remove all visible foreign bodies from the wound. After that, prepare the surgical field in the standard manner. One of the

most important procedures in combating infection in open fractures is the primary surgical wound management (debridement, removal of damaged and devitalized tissues), which provide a good substrate for the development of bone infection, osteomyelitis, or specific infections such as gas gangrene and tetanus. Debridement is performed from the surface to the deeper layers of the wound. Firstly, debride the skin. The skin is resistant to trauma, and caution should be exercised during debridement to avoid creating a large defect unnecessarily. Only remove damaged and avascular parts of the skin. Skin vitality is assessed based on capillary bleeding. Skin that bleeds upon incision is vital and should not be removed. Subcutaneous fat tissue is poorly vascularized and avascular parts should be removed. Damaged fascia is also removed. If necessary to facilitate repositioning and irrigation of the wound, the fascial opening can be extended longitudinally proximally and distally with a longitudinal incision [5]. It is crucial to perform meticulous (good) debridement of muscle tissue. During muscle debridement, we use the 4K rule (color, consistency, bleeding, contractility). Muscle that does not have a nice pink color is likely avascular, necrotic. Crushed muscle that tears when grasped with forceps is likely avascular. Muscle that does not bleed when incised and does not contract when grasped with forceps or touched with diathermy is likely avascular. During muscle debridement, small portions of muscle with a diameter of about 1cm are removed piece by piece to avoid creating a large defect in vital tissue indiscriminately. It is necessary to remove all avascular, necrotic tissues. If we are unsure about the tissue's vitality, debridement can be repeated after 24 hours or 48 hours when avascular, necrotic tissues will demarcate (primary, secondary, tertiary, etc., debridement). Debridement should be repeated until all avascular, necrotic tissues are removed from the wound. After debridement of the open fracture wound, it should be irrigated again [6].

After the realignment of fractured fragments of the shinbone, the fracture is stabilized with an external skeletal fixator or an Ilizarov apparatus. Vital structures such as major blood vessels, nerves, and bone tissue are covered with vital muscle tissue if possible. Other structures such as fascia, skin, and

subcutaneous tissue are not closed. The wound of the open fracture is not primarily closed but managed with methods such as delayed primary closure, secondary closure, skin grafting, fasciocutaneous flap, or another method, once it is ensured that there is no wound infection [7,8].

Antibiotic therapy is initiated immediately after wound swab collection but before the surgical procedure. It is crucial that antibiotic therapy is administered to the patient as soon as possible. A cephalosporin and an aminoglycoside antibiotic are prescribed (Ceftriakson 2g/24h, Amikacin 1.0g/24h) to cover both gram-positive and gram-negative flora. If the open fracture is contaminated with agricultural soil, metronidazole 500mg/8h is also prescribed to prevent gas gangrene. Tetanus prophylaxis is administered according to the standard protocol [8,10]. Good debridement is the best prevention against infection, gas gangrene, and tetanus.

Complications in the treatment of open fractures of the shinbone include infection of the open fracture wound, infection around the pins or wires of the external skeletal fixator, deep bone infection (osteomyelitis), gas gangrene,

tetanus, delayed healing, healing in poor position, nonunion, limb amputation, etc. [11].

CONCLUSION

Treatment of open fractures of the shinbone includes removing all foreign bodies from the wound, thorough irrigation of the open fracture wound with saline and hydrogen peroxide, debridement of damaged tissues until there is no avascular necrotic tissue remaining in the wound, stabilization of the fracture with an external skeletal fixator, antibiotic therapy, and tetanus prophylaxis. The wound of the open fracture is closed when it is ensured that there are no signs of infection, either with delayed primary closure or secondary closure, using skin grafts, fasciocutaneous flaps, microvascular flaps, etc.

Complications in the treatment of open fractures of the shinbone include delayed healing, infection of the open fracture wound, infection around the pins of the external skeletal fixator, osteomyelitis, nonunion (septic or aseptic), limb amputation, and so on.

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THE DEAFNESS OF LUDWIG VAN BEETHOVEN

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Abstract: Ludwig van Beethoven (1770-1827) began experiencing hearing loss in his thirties, which eventually progressed to profound deafness. Physicians and historians have sought for centuries to interpret the original sources from Beethoven's letters, medical documents, and autopsy reports to determine the causes of his deafness and systemic illnesses. This article reviews the current literature on the theories surrounding Beethoven's deafness and medical conditions. It is based on a PubMed® search spanning from 1958 to 2023 and provides a critical analysis of these theories.

Key words: deafness/history, history of medicine, Beethoven.

INTRODUCTION

Ludwig Van Beethoven (1770-1827) began to face hearing loss in his thirties. By the age of forty-two, people had to shout in order for him to understand them [1]. His last public performance was at the age of forty-four when he started using writing for conversation. At forty-seven, he could not hear his own music, and after the premiere of his Ninth Symphony, he couldn't even hear that the concert had ended [2].

The initial symptoms started at the age of 27, first in his left ear, interpreted by scholars today as tinnitus and high-frequency hearing impairment, associated with poor speech discrimination and recruitment. Initially, these symptoms were temporary and unilateral, but after a year, they became permanent, bilateral, and progressive [3]. It has been described that Beethoven occasionally used a wooden horn, holding one end in his teeth while pressing the other end against the piano, suggesting possible conductive deafness [3,4]. Findings from the autopsy conducted the day after his death in 1827 describe the following (Figure 1): "The Eustachian tube (and)...facial nerves are unusually thick. The auditory nerves are convoluted and devoid of medulla. Auditory arteries are dilated with cartilaginous walls. The left auditory nerve is thinner... the right one with a thicker root, the brain substance in the region of the fourth ventricle is denser and more vascular than the nerves originating there" [5,6].

In summary, most doctors agree that his hearing loss was bilateral. Initially, hearing impairment affected high frequencies, the discomfort with loud sounds was later interpreted as recruitment and cochlear damage, while speech incomprehension was attributed to poor speech discrimination. Beethoven experienced progressive hearing loss, leading to complete deafness twenty years after the initial symptoms.

There are no records of hearing problems or ear infections in Beethoven's early childhood or youth. Since puberty, he suffered from episodes of asthma, headaches in winter months, most likely due to sinusitis [5].

Beethoven died from liver failure due to cirrhosis on March 26, 1827. Throughout his life, he suffered from abdominal colic, episodes of diarrhea, rectal bleeding, rheumatism, rheumatic fever, various skin changes, abscesses, and recurrent infections, eye disorders (uveitis), inflammatory artery degeneration, melancholia (depression), behavioral disorders, jaundice, anemia, and progressive hearing loss [8].

In line with modern medicine, many scholars sought connections between these symptoms and illnesses, aiming to establish a proper diagnosis, using autopsy findings, data from his letters, and available medical documentation. From 1920 to 1970, otolaryngologists was the group most interested in this field (67%), while since 1971, most authors belonged to non-otolaryngological subspecialties (81%) [7].

Figure 1. Postmortem autopsy protocol of Ludwig van Beethoven conducted by Dr. J. Wagner [7].



In the literature, it's noted that autoimmunity could be linked to digestive issues and hearing loss [8]. Abdominal problems are explained by autoimmune bowel inflammation (ulcerative colitis or Crohn's disease). There's documentation suggesting an association between both conditions and sensorineural hearing loss, all attributed to autoimmunity [18,19,20]. An autoimmune condition within the inner ear could realistically be the cause of his deafness.

Given that Beethoven's mother and brother died from tuberculosis, it's possible that he was also infected with Koch's bacillus. His gastrointestinal and neurological symptoms could be explained by miliary tuberculosis, a condition that had a prolonged course over thirty years. The likelihood of Beethoven suffering from tuberculous pachymeningitis, which would have affected the eighth cranial nerve, is low due to the high

mortality rate of this condition during that time [4].

A substantial number of authors suggest that Beethoven's initial jaundice might be explained by viral hepatitis, while his final disease could be attributed to alcoholic cirrhosis [4]. However, there are conflicting reports about Beethoven's inclination toward alcoholism among his contemporaries and friends [21,22].

Systemic lupus erythematosus is proposed as a potential diagnosis due to Beethoven's episodes of rheumatism, eye pains (uveitis), and facial scarring. Isolated deafness in the early stages of lupus or liver cirrhosis isn't described. Symptoms like alopecia, lymphadenopathy, pericarditis, and a tendency to bleed aren't documented in Beethoven's medical records, despite often accompanying a diagnosis of systemic lupus erythematosus [23].

A recent genetic study of Beethoven's hair samples didn't provide a genetic explanation for his hearing disorder or gastrointestinal problems. However, it revealed a genetic predisposition to liver disease. Metagenomic analysis also showed evidence of Beethoven having a hepatitis B infection a month before his death, explaining the cirrhosis that led to his demise [24].

AIM OF THE STUDY

Presentation of published literature on possible causes of Beethoven's deafness and a critical review thereof.

METHODS

This paper provides a literature review of Beethoven's illnesses and the possible etiology of his deafness through a PubMed® search from 1958 to 2023.

RESULTS AND DISCUSSION

Beethoven's Deafness and Systemic Conditions

Kubba and Young [4] suggest a possible diagnosis of chronic otitis media. Beethoven's letters do not mention any ear discharge or pain. His hearing loss is interpreted as sensorineural damage, while chronic ear inflammation predominantly leads

to conductive deafness. Autopsy findings did not describe a perforated eardrum or the presence of a cholesteatoma [9].

Stevens and Hemingway [3] consider otosclerosis as a possible cause of Beethoven's deafness. Otosclerosis predominantly affects the bony labyrinth capsule, leading to conductive hearing loss, mixed impairment, or, rarely, pure sensorineural hearing loss. It often starts in one's twenties as conductive hearing loss with slow progression. Patients hear better in noise and do not complain of discomfort with loud tones or recruitment. "Cochlear otosclerosis" as a possible cause of Beethoven's sensorineural deafness is also plausible, but isolated otosclerosis of the bony labyrinth capsule without involvement of the stapes plate has not been found in literature, making this cause less likely [8].

In his letters and notes, Beethoven does not mention experiencing dizziness or balance loss, excluding vestibular neuritis, Ménière's disease, and labyrinthitis as potential causes [10].

McCabe [11] attributed Beethoven's deafness to syphilis. Deafness due to congenital syphilis presents at birth, in late childhood, or middle age, accompanied by vertiginous symptoms. Autopsy findings did not indicate skull deformities, palate issues, or other pathological changes typical of congenital syphilis. Acquired syphilis is also ruled out because other characteristic signs such as tabes dorsalis, paresis, dementia, gumma, were not described. Hearing loss in syphilis may occur but within neurosyphilis alongside other neurological deficits. Traces of mercury, a treatment for syphilis in the early 19th century, were not found in tissue samples, suggesting Beethoven did not receive it, despite its prevalent use.

The hypothesis of Paget's disease as the cause of Beethoven's deafness is based on his large head and thin bones described in the autopsy report. Paget's disease manifests in one's forties, affects other bones in the body, and causes mixed deafness with a

predominantly conductive component. Both Jasserer and Bankl [12], after histological analysis of Beethoven's skull fragments, exclude the presence of Paget's disease.

Drake [13] states that sarcoidosis caused Beethoven's deafness, dysesthesia, depression, diarrhea, pulmonary edema, and death. Although sarcoidosis causes sensorineural hearing loss, most cases are accompanied by facial nerve paralysis, which he did not have. Granulomatous hepatitis due to sarcoidosis causes hepatomegaly, and not cirrhosis found in Beethoven's autopsy. Therefore, it is unlikely that Beethoven suffered from sarcoidosis.

Walsh et al. [14] discovered a high concentration of lead in Beethoven's hair, attributing his abdominal issues to lead poisoning. Cirrhosis is rare in patients with lead poisoning. Chronic lead intoxication has no toxic effect on the inner ear, and its association with hearing loss is not documented. However, Cohen et al. [16] believe that prolonged exposure to lead can lead to slow, progressive high-frequency hearing loss likely due to axonal degeneration of the cochlear nerve. Stevens explained Beethoven's chronic lead exposure through his long-term consumption of wine, which might have started at the age of 17 after his mother's death. Lead was added to wine at that time to enhance the taste of cheaper wines, such as the Hungarian ones Beethoven favored [17].

CONCLUSION

For centuries, physicians have attempted to unravel the mystery of Beethoven's deafness. Is it an isolated condition or part of a complex disease? Can all the symptoms and signs be attributed to one illness, possibly unrecognized in his time? The exact cause of his hearing loss, one that most scientists and doctors would agree upon, has yet to be established. Modern times and contemporary medicine bring new methods and hypotheses.

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ACADEMICIAN PROF. DR. ISIDOR PAPO - LIFE AND WORK OF THE MOST FAMOUS YUGOSLAV CARDIAC SURGEON

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(1) HOME OF HEALTH ŽABALJ; (2) HOME OF HEALTH KULA; (3) HOME OF HEALTH ODŽACI; (4) HOME OF HEALTH NOVI SAD; (5) HOME OF HEALTH KANIŽA; (6) HOME OF HEALTH SREMSKA MITROVICA

Summary: Prof. Dr. Isidor Papo is our academician, general and one of the pioneers of cardiac surgery in Yugoslavia. He was the first to perform open heart surgery in 1951. With his tireless work, persistence and curiosity, he saved the lives of many people, enhanced Yugoslav surgery to one of the best in the world, and encouraged his students to continue his path and overcome it.

Key words: Isidor Papo, academician, cardiac surgeon

INTRODUCTION

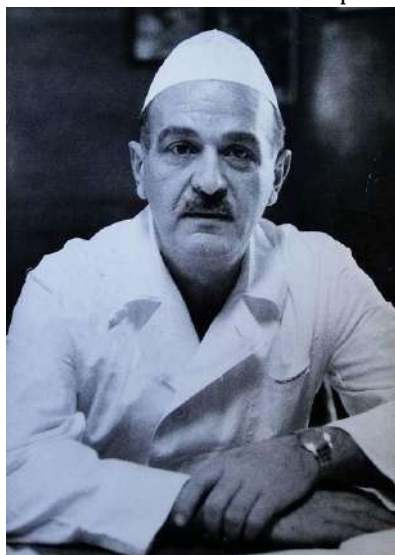
Prof. Dr. Isidor Papo was one of the most respected doctors in the former Yugoslavia. He was born on December 13th 1913 in a small town in Herzegovina, Ljubiško. He was the third child of municipal clerk Jozef Papo, a Sephardic Jew, and his wife Klara, born Levy. [1,2,3] When he was fit for school, his family moved to Mostar, where young Isidor finished high school. According to the testimony of prof. Papo, his childhood in Mostar will remain in his fondest memory, and he will cherish the friendships he made in that city for the rest of his life [5]. In December 1932, he went to study at the University of Zagreb. He passed all his exams in record time and with the best grades- all tens. During his studies, the young Papo was most influenced by prof. Dr. Drago Perović (one of the most famous anatomists of that time) and prof. of surgery, Dr. Julije Budisavljević, who fueled in him the desire to practice surgery. Papo was "obsessed" with the perfect surgical technique, which in periods of imperfect anesthesia was the decisive factor in the patient's survival. After college, he completed his mandatory internship and military service in Sarajevo. In 1939, a strong fascist influence was already felt in the Kingdom of Yugoslavia and it was difficult to get a job. For Jews, "numerus clausus" was implemented when vacant positions were available in public institutions. When a vacant position for a doctor in the Sarajevo hospital was announced, the Minister of Health from that period, Budisavljević, chose young Papo over the candidate that Prince

Pavle himself had exhorted. [1,2] Thus begins Papo's career as a surgeon, which lasted 42 years. He was granted a specialization for gynecology, but soon the war started, which interrupted all of that. Papo is mobilized into the surgical team of the Zeta Division. After the signing of the capitulation, there was a general disunity among the soldiers and he was captured by the Italians in Nikšić. He manages to persuade them to let him go and flees to Sarajevo. Thanks to Home-guard colonel Dr. Dinko Cvitanović, he got a temporary job at the Sarajevo Hospital, where he also lived in the attic. At that time, Sarajevo was under the administration of the NDH and the Ustaše demanded that all Jews be identified with a yellow ribbon, which Papo refused. Raids begin in Sarajevo and the Gestapo sends an invitation to the Papo to come forward. It is then when he decides to flee to Mostar, where Dr. Koporoc employs him in the hospital there. Mostar was then under the occupation of the Italians, who did not persecute the Jews. Jews could move freely in Mostar and its surroundings. Dr. Dinko Cvitanović does not forget him and invites him to flee with him via Split to Abyssinia, but Papo still decides to stay in the captured country. Through his friend Salko Fejić, he came into contact with the communists on September 26th 1941 and becomes a doctor-surgeon of the Mostar battalion. Dr. Gojko Nikoliš, who at that time was the head of the medical department of the Supreme Headquarters of the Partisan Army, transferred him to his surgical team. [1,2] Together with Dr. Mešterović, they form a team

that will take care of tens of thousands of wounded over the next three years. There were a lot of improvisations at that time: sewing was done with parachute thread, there was a lack of medical equipment, instruments, anesthetics, medical personnel... When they took over a settlement, the most important thing for Papo would be to collect food and medical equipment so that they could help wounded soldiers and civilians. He operated tirelessly, sometimes continuously for 72 hours. That war surgery regime left its mark on young Papo. Namely, he begins suffering from insomnia, which will follow him throughout his life. In Jajce, where the Supreme Headquarters was, he carried out operations even during the bombing. Papo did not leave the patients on the table even during the fiercest forays of "Stukas" in order to hide. He participated in both the battle on the Neretva and the battle on the Sutjeska, during which he treated wounded and sick civilians from typhus, and carried some to the nearby hospital on his back. Papo was in the column of wounded that was protected by the 3rd proletarian division under the command of Sava Kovačević. During the battle on the Sutjeska, he escaped death and wandered for two weeks, surviving, as he used to say, by "emasculating young boars in villages". During the war, he also experienced a personal tragedy when the Ustaše killed over 50 members of his family, including his brother and sister. [1,2,3,4,5]

In 1944, he was sent to Bari as a member of a delegation with Dr. Nikoliš in charge with intent of cooperation and training with allied English and American doctors. There, he will meet his lifelong companion, a surgical nurse, Anastasija, Asja Salakin. He also gained a lifelong friend, Lord Rodney Smith,

Picture 1. Prof. Dr Isidor Papo



who in 1969 proposed him for a member of the Royal College of Surgeons. After returning from Italy, he went to Novi Sad, and then to the Srem Front, where he treated the wounded. After the end of the war, from 1945 to 1948, he stayed at the University Clinics in Moscow and Leningrad, where he acquired knowledge from prominent surgeons A. N. Bakunjev, A. A. Visnyevski, B. V. Petrovski and S. S. Judyn. [1,2] He passed the specialist exam for surgery in 1947. Prof. Dr. Papo gained significant experience in esophagus reconstruction, he later modified his professor's method, which is still called Judyn- Papo's method in the literature. Back then, caustic injuries to the esophagus caused by household cleaners such as baking soda and hydrochloric acid were common. According to Medical Military Accadamy (VMA) data, until 1967, Professor Papo performed 425 reconstructive procedures with a mortality rate below 4%. He received numerous international awards for this technique. [2,5] He returned to Yugoslavia in 1948, where he became the head of the Second Surgical Department of the Main Military Hospital in Belgrade, which later grew into the Surgical Clinic of the VMA. He will spend the next 30 years in that position. In 1950 he was elected assistant professor, in 1953 he became an associate professor, and in 1956 he became a full professor of surgery, head of the department and chief surgeon in the Yugoslav National Army (JNA). In 1950, he spent his training in the USA, at clinics in New Orleans, Baltimore and Houston, where he collaborated with Dr. Cooley, gaining knowledge in heart, lung and blood vessel surgery. In 1951, he became the first surgeon in Yugoslavia to perform heart surgery.

In the 1950s, "closed heart" operations were performed. In most cases, these were procedures on patients with congenital heart defects, such as closure of the residual aortopulmonary canal in children, bridging of congenital narrowing of the aorta, arteriopulmonary bypasses, as well as closed commissurotomies of the pulmonary artery valve in children with congenital cyanotic defects. In addition, closed mitral valve commissurotomies and pericardiectomies are regularly performed in adults with acquired heart diseases. Prof. Papo and his team at VMA

from 1960-1961 begin to perform new, exciting operations on the "stopped and open heart" in extracorporeal blood flow and hypothermia, using extracorporeal circulation.

From 1962, catheterization and angiography become a regular part of diagnostics. [2,4]

He manages to surgically treat more and more complex congenital heart defects. Thus, in 1965, he performed the first operation to replace a heart valve with an artificial prosthesis. The professor was proud of that, because those operations were performed a few years after they were performed in the USA, successfully, with few complications and with better equipment than in some European countries. Patients did not have to go abroad for expensive operations. The period from 1960-1981 was the most dynamic for prof. Papo. He did 5 surgeries a day. By his own admission, he had performed 20.000 operations, of which about 10.000 were heart operations, 3.500 congenital heart defects and 3.500 contracted ones. 1.850 people received two or three artificial valves each. [2,4,5]

During the earthquake in Skopje, he organized an "air corridor". The seriously injured were flown to the VMA for surgery. At that time, the professor, together with his team, worked tirelessly for over 20 hours to take care of all the patients. [4,5]

He was Comrade Tito's personal physician, to whom he was bound by war camaraderie. During the three-month trip on the "Seagull", they visited Tunisia, Libya, Morocco and Egypt together. During the trip, prof. Dr. Papo operated on a sailor in the ship's operating room. He was invited to many countries to operate and give lectures, to name just a few: Washington 1973, Barcelona 1973, Los Angeles 1973, Chicago 1974, Buenos Aires 1974, Lima 1974, La Paz 1979, Gothenburg 1983, Houston 1987, etc., as well as great number of lectures in SFRY. [4,5]

At the same time, he progressed in military service. He was promoted to the rank of general-colonel of the medical service in 1975. He was a member of many medical associations such as: Association of Surgeons of Yugoslavia, Austrian Society of Traumatologists, International Society of Hydatologists, American Society of Cardiologists, American Society of Military Physicians (honorary member), Los Angeles Surgical Society, International Society of Surgeons, English Society of Surgeons, British

Society of Chest Physicians, Royal College of Surgeons of England (Honorary Member), German Society of Surgeons, Thoracic Surgery Society of Bolivia, Society of Surgeons of Paris (Honorary Member), International Society of Digestive Surgery, Member of the Academy of Surgery of Paris, Honorary Member of the Academy of Medical Sciences of Peru, Honorary Member of the Academy of medical sciences SLD, corresponding member of ANU in Sarajevo, corresponding member of JAZU in Zagreb, regular member of SANU in Belgrade, member of the Federation Council in Belgrade, honorary doctor of the University of Mostar. In the period from 1963 to 1966, he was president of the Surgical Section of the SLD. He was the winner of numerous awards and high recognitions. Some of them are the AVNOJ Award, the Zavnobiha Award, the "22. December JNA" Award, October Award of the City of Belgrade, Seventh of July Award of the Republic of Serbia, Award of the City of Mostar, Vishnevsky Award in Moscow. [2,4,5]

He wrote over 218 professional papers, 13 of which were published in foreign journals. The papers were cited 285 times. His first paper was published in 1939 in "Physician's courier" no. 11 under the title "Haemangioma medullae spinalis", and the last one was "Experience in heart valvulae replacement" printed in 1995 in the SANU bulletin No.14; pp1-7. Bibliographically, professional papers can be divided into: a group of papers related to the issues of war surgery, a group of papers from the domain of surgical treatment of the esophagus, a group of papers in which all aspects of cardiovascular surgery are discussed, as well as the problems that have arisen and their improvement, and a heterogeneous group of works with rare clinical cases of various diseases in human medicine. He became a corresponding member of the Serbian Academy of Sciences and Arts in 1961, and a regular member in 1968. He was one of the main editors of the Military textbook "Wartime Surgery" from 1953. [3,4,5]

He was well informed about international matters and even wrote a book about the knowledges from the Korean War he had gathered. He encouraged his students to engage in experimental surgery. It is known that 4 associates of Dr. Papo wrote dissertations in that field. Their findings were incorporated into the doctrine of treatment of war injuries in our army's medical system. Prof. Papo was diligent in following

international medical literature, he noticed the shortcomings of the methods and would modify them in order to have a better survival of the patients. He had a special interest in postoperative complications. Friends and associates state that he was hardworking, disciplined, honest and conscientious. If 500 operations were successful and one was not, he would be deeply sad about that one failed operation. Although he advised patients to take a break from work and rest more, he himself never had that balance. He was at the Clinic every day from 5:30 am to 2 pm, and in the evening he would visit his patients. He also loved philately, collected rare birds, was engaged in beekeeping, but he would often be found in the operating room helping his

colleagues in demanding parts of operations even during his breaks. He had a beautiful marriage with his wife Asja, but unfortunately, no children. In his free time, he would go to his native Mostar, and his greatest satisfaction would be when a villager would thank him with "Thank you General, may God give you health". [4,5] He himself underwent major heart and aortic surgery, performed by his friend Dr. Cooley in Houston. Although he wanted to, after the operation he could no longer work. He retired in 1981. He spent his retirement days peacefully, engaged in scientific work. He died on October 14, 1996 at the age of 83. He was buried at the Jewish cemetery in Belgrade.

Picture 2. - Professor Dr. Isidor Papo with his wife Asija in 1946



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DOCTORS AWARDED IN 1915

Goran Ćukić

HOME OF HEALTH BERANE

The orderlies keep watch over them,
 To prevent them from leaping through the window.
 Doctors visit them with trepidation.
 Every hour, someone is carried out.

As he, too, succumbs to a recurrence,
 For so many days now,
 Yet he hasn't sought a replacement,
 For now is not the time for such matters.
 In the scarcity of doctors.

Summary: Since 1925, there has been a recognition that the Chief of the Serbian Military Sanitary Service, Colonel Dr. Genčić, was criticized for untimely and inadequate measures against epidemics and extensive suffering. The main reason for the failure remained unknown. There was no appropriate tactic, and thus timely suppression did not commence. The tactical means and procedures were yet to be promoted. Dr. Subotić found a solution in "scientifically unknown to medicine." Evaluating the events of ten years prior, during the war, as presented by Dr. Genčić, aligns with the war decorations awarded to foreign and domestic doctors in June 1915. These dedicated Serbian doctors, seasoned fighters against typhus and relapsing fever, served as a support to Dr. Genčić, as they later became leaders in the sanitary work of Serbia and the Kingdom of SHS.

Keywords: Military Sanitary Service, Col. Dr. Lazar Genčić, Col. Dr. Viljem Hunter, decorated in 1915, Dr. Vladimir Stanojević.

INTRODUCTION

Dr. Hunter's work, according to medical historians, in combating the epidemic was generally unsuccessful. The same historians examined the work of the Serbian sanitary service [1]. Evaluations made in 1915 and 1925 were also reviewed. After the discovery of the causative agent of plague and Nikola's Nobel Prize, earlier uncertainties needed resolution. Dr. Vuksic noted in 1989 that Dr. Hunter played an impressive role as a leader in combating the plague in Serbia. He pointed out the contribution of Dr. Hunter and his team [2]. This alone indicates the unsustainability of denying the success of 1915. At that time, no significant action by the Serbian sanitary service was noted; instead, it was considered to be within the scope of Dr. Hunter's and other foreign missions' activities.

Chief Sanitary Officer Dr. Genchic insisted to the Serbian government on January 15, 1915, that "the profession needed to be strengthened." The government adopted the

proposal, resulting in success. Regarding Dr. Genchic's address on January 15 in his new methodological approach to studying the Great War through archival material, Dr. Nedok states: "This report concludes the reporting of the Chief Sanitary Officer Dr. Genchic to the Chief of Staff of the Supreme Command, Vojvoda Putnik..." after which "the epidemic waned... By the end of May 1915, a period of respite and recovery will occur..." Dr. Nedok concludes his evaluations with biographical data on Dr. Genchic, who is "criticized" [3].

In his discussion (attached to Dr. Subbotic's presentation), Dr. J. Berry (James Berry) emphasizes the possibility of uncertainty regarding the success of epidemic control. The success of control after the plague epidemic gained momentum is also questioned, i.e., that it is not the same as control that was "timely initiated" [4:38]. No answer is given as to why the epidemic gained momentum..

Measures in combating the epidemic by the Serbian sanitary service were achieved

through the implementation of administrative measures - interruption of railway traffic. The first measure was requested on March 10 - "it came into force on March 16 and lasted for two weeks... it was supposed to expire on March 30."

The second measure, the suspension of other traffic, followed the first and lasted until April 16 (according to the Gregorian calendar). Dr. Hunter takes over a significant portion of medical responsibilities from the Serbian sanitary service starting from March 16, thus beginning the "English side" of combating the plague epidemic and return [5].

Some assessments of the work of the Serbian sanitary service in 1925 were disagreed upon by contemporary Dr. Žarko Ruvidić (war sanitary general). The criticisms he pointed out in 1947 were primarily methodological. Due to insufficient argumentation, he disagreed with the given assessments of former chiefs [6]. It has already been shown that Dr. M. Pecic, who combated the epidemic, successfully ended it in its epicenter, in Valjevo [7]. Dr. Pecic and Dr. Ruvidić were awarded in 1915. This was a new reason to doubt the correctness of the negative assessments pronounced in 1925 regarding the work of the Serbian sanitary service. Re-examining the defeatism of the actors [10], assessments of the outbreak of the epidemic are primarily the result of the impotence of medicine exacerbated by war, i.e., "war typhus," and plague.

A way to combat it was sought, and incidentally, the main reason for the outbreak was implicitly found. It was the initial contribution of Dr. Subbotić, i.e., his "buried furnace" [8,9]. Who supported the Serbian sanitary service? How can this be proven today? The hypothesis is that those who were awarded in 1915 contributed to it. Negative assessments of the work of the sanitary service expressed in 1925 call into question the honor of the awarded doctors. A retrospective analysis of the success of the awarded officers of the Serbian sanitary service will be made. Historians' conclusions about medicine are subject to scientific verification. The assessment by the strength of arguments can be confirmed, modified, or rejected.

Are general measures sufficient? Why were they not properly implemented? The increase in the epidemic led to unrest. Fear of failure had already gripped the doctors of Serbia since January and February, hence the request

for assistance from the allies. As the response was uncertain, Serbia contemplated the epidemic that had befallen them. They did not give up. Isolating the sick alone needed to be reconsidered as a strategy.

If the actors after the Great War were correct in seeking the reorganization of military and civilian sanitation, it does not mean they pinpointed the correct cause of the high mortality rate in the epidemic. The cause was not the organizational weakness of Chief Dr. Genchic. He contributed to the special epidemiology of typhus by combating the lice infestation [3,12]. The problem was how to solve the advancing epidemic, as seen by Dr. Berry while working with his wife in Vrnjačka Banja. The uncertainty of success in combating the epidemic emphasized by Dr. Berry in the conditions of epidemic spread raises the question: were there conditions for timely suppression? Did the English mission and Serbian sanitation reflect on the same?

It is noticeable that there are differences in the activities of the Serbian sanitation during the epidemic and what Colonel Dr. Subbotić wrote about it in his presentations in Paris and London [4]. There is an inconsistency in interpreting the same events. It's as if one truth applied to foreign countries, where Dr. Subbotić was presenting, and another in the homeland. Therefore, despite the dominance of memories in 1925, the published literature dealing with the issue of epidemics in Serbia during the Great War, such as the works of Strong, Hunter, Subbotić, etc., is not utilized. Despite these weaknesses, the chief of sanitation is attributed with the following: "Dr. Genchic was a participant in liberation wars and a member of the Supreme Command. His work was criticized due to untimely and inadequate measures against the epidemics of typhus and dysentery, resulting in massive losses in the army and among the people." [12;13:190]. By automatism, the writer-doctors, as actors, have also assessed themselves. If so, because of the plague (and that was a criticism), the question is whether the doctors deserved the awards given in 1915.

Engagement of the Royal Mission's sanitation in combating the epidemics. Dr. Hunter found an advanced epidemic upon arrival, as indicated by the number of hospitalized patients. The peak was reached one

month after his mission's arrival. This corresponds to Dr. Berry's observations.

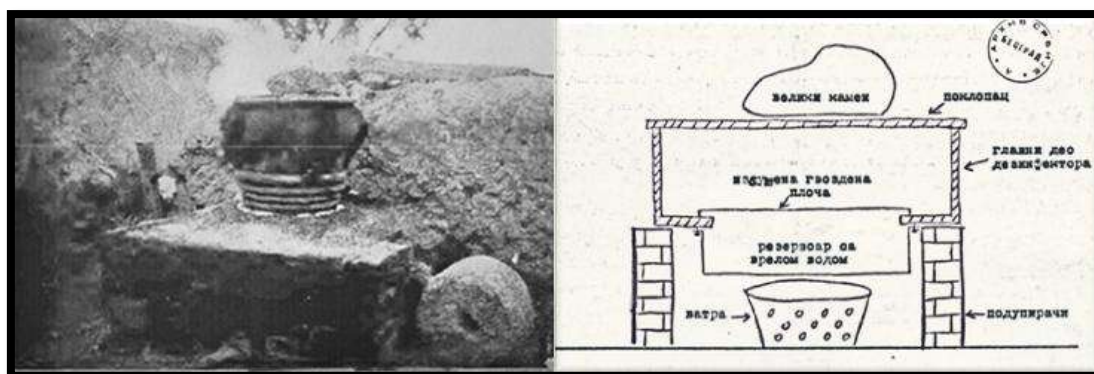
The untimely activity of the Serbian sanitation - The consequence of the untimely implementation of measures is registered by Dr. Hunter in his book. He was familiar with the period preceding the arrival of the mission. Several facts will be presented as he noted them: "There were two types of problems - a clinical problem concerning the improvement of accommodation. The other... a preventive problem to stop further spread of infection to the healthy." [5:108]. Hunter believes that "seeking help from doctors from our government and others, it is undoubtedly, in my opinion, that the guiding thought of the Serbian authorities was to obtain as much of the much-needed clinical help as possible" [5:237-8]. The basis was seen: "Hospital conditions were indescribably poor; overcrowded, without any sanitation plan; without disinfection measures..." The urgent need was for beds, mattresses, bedding, pajamas, clothing for a mass of 15,000 infectious patients [5:99]. The summary would be: "The state in hospitals was

overcrowded and shockingly unhygienic" [5:238]. Other reasons were present: poverty, untimely provision of money, total war, etc.

The English Royal Sanitation Mission of Dr. Hunter proposed measures in nine points, including the use of the "improvised autoclave": a wooden chamber placed above a boiler. A stationary fire heats the water (principle of moist hot air) - (Figure 1) [12]. Then they supplemented them with a new proposal for the interruption of passenger railway traffic [5:113,119,121].

Protich believed that Stamer's improvisation was applied in the Russo-Japanese War of 1905 [14]. Dr. Genchic appointed him as the representative of the Serbian sanitation during the testing of Stamer's improvisation. An order was issued for the production of these chambers at the Military-Technical Institute (VTZ) in Kragujevac [5:219]. The next change was proposed by Stamer: a metal barrel was used instead of a wooden crate, so this was the definitive variant of the improvisation made by VTZ, known as the "Serbian barrel" [12]

Image 1. Left: The furnace used in Japan in 1905 (found according to Dr. Đ. Protić's references) [12:104]; Right: Sketched prototype of Stamer's proposal for an improvised autoclave made of wood: a) box (drawn) and b) "barrel" (notated) [12:101]



Upon arrival, Dr. Hunter was briefed on the preceding events of the epidemic. As these activities in 1919 are partially depicted, predominating are the pieces of information about the epidemic's growth, while activities of the Serbian sanitation to resist the infection are unknown to him.

Assessments of the success during the war - The assessment from 1915 is "astonishingly thorough," although unofficial.

Primarily, it referred to Hunter's work in Mladenovac. The route from the war zone of Valjevo led by narrow-gauge railway to Mladenovac. Other traffic was not functioning. In Mladenovac, Hunter implemented a disinfection station: quarantine and a cleansing center (bathing and delousing), as well as treatment by bringing in mobile hospitals (under tents). The progression of the epidemic was successfully halted by traffic bans and

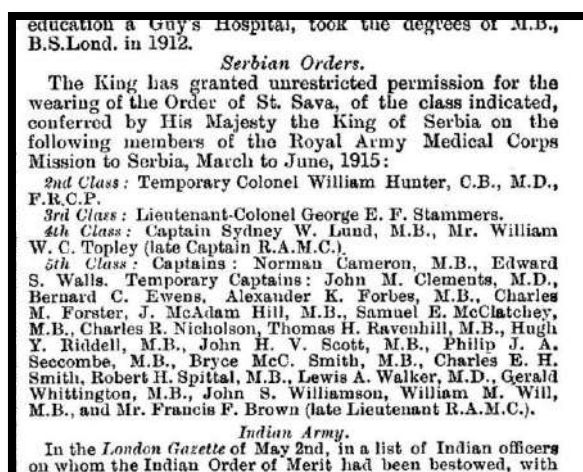
finding ways to protect healthy soldiers from typhus spreading from Valjevo, known as an "epidemic focus" [15]. The Serbian sanitation also had its judgment about the significance of Hunter's team's work - expressed by the chief. It wasn't just courteous, but more than that - a substantial assessment, which would be agreed upon today.

On May 25 (June 7), 1915, Colonel L. Genchic sent a congratulatory letter to Dr. Hunter for leaving Serbia and embarking on a new task: "Although you and your mission have worked only for a short time, exceptional results have been achieved. The assistance your

mission provided us in every aspect, under your experienced leadership, will stand at the forefront of all the foreign aid we have received in this war... (emphasized, GC)" [5:248,251]. This assessment did not differ from Dr. Vuksic's assessment expressed in 1989 and was not sufficiently emphasized.

These commendatory assessments debunked the assessment from 1925 about the importance of warmer weather. Consequently, the decisive activity of the doctors was supported, justifying the proper awarding of honors to members of the English Royal Mission. [16:735].

Figure 2. Decorations of Serbia awarded to members of the Medical Mission of the Royal Army in Serbia [16:735]



The assessments of Hunter's contribution are commendable, but domestic successes have been neglected.

Dr. Subbotić's work was published in 1918. Hunter, in 1919, does not cite this work, although it was presented in English. In his published presentation, he mentions his "underground stove," as well as the use of other chambers with warm dry air and bathing facilities. This seems inadequately emphasized, somewhat clumsily expressed. This is not the case when he points out the advantage of the dry chamber compared to the "Serbian barrel." He also discusses the endemic nature of typhus and the possibility of its importation from neighboring countries such as Albania and Bosnia. Initially, differential diagnosis of typhus posed difficulties.

It is interesting to note the participation of the Berry couple in the discussion, who were in Serbia during the epidemic. The use and description of the chamber with warm dry air, similar to a dugout, is highlighted more clearly than what Dr. Subbotić did. This was first seen and presented in Russia. Supported is also Dr. Subbotić's experience that a deloused patient is non-infectious to the surroundings, and the procedure is outlined as to how this conclusion was reached when the disease is discovered among hospitalized patients [4:38-9]. This is significant evidence that the human body is crucial in transmitting the causative agent of typhus, thus supplementing Nikolay's observations based on experiments on monkeys.

Chapter on the engagement of Serbia's sanitation in combating epidemics will be explored through questions:

a) experience with freckles before the 1915 epidemic;

b) the importance of a mild climate, warm weather, on stopping the epidemic;

c) the interrelationship between the actors of the writers (1925), Hunter (1919) and Subbotić (1918).

The essence of the necessary reorganization of Serbia's sanitation was different from the perspectives of the actors. General preventive measures were insufficient. They had to be replaced by "specific measures". The strategy for combating typhus was deliberation. This insight is valuable for the future Nobel Prize awarded to S. Nikola. Dr. Genčić personally contributed to this direction of Serbian sanitation, as seen in his address to Vojvoda Putnik on January 15 [3,12]. Dr. Subbotić elaborated on the reasons why a certain number of actors did not consistently accept that lice transmitted typhus [4:38]. They could not consider delousing useful for either the sick or the healthy – it just needed to be proven or accepted as having epidemiological significance. So, until then, they were just pests to be removed like any other dirt (unhygienic condition).

At the beginning of the epidemic, a set of facts was noticed that contributed to the spread of typhus. The first is essential: typhus was an unknown disease in medicine. There was a lack of tactical means for mass use. The second fact builds on the previous one, namely the "conditions for the development of such a massive epidemic created by a severe war."

Chapter on the engagement of Serbia's sanitation in combating epidemics will be addressed through questions:

a) Experience with typhus before the epidemic of 1915 - Borjanović in his thesis in 1977 believes that "typhus in Serbia before the First World War was not a health problem, as there were no endemic foci of this disease." He declaratively states the existence of typhus in 1836 in Kragujevac, the then capital of Serbia, without offering arguments on how it was recognized [17:193]. Thus, ambivalence is spoken about the endemicity, as much as it existed, as it was not [18].

It was believed that typhus in Serbia persisted in a chain of acute cases in specific

groups. That it "... appeared only among Gypsies without a permanent residence and in a few cases in prisons" [19]. Criticism was raised due to one-sidedness, for supporting only the teaching that preceded the establishment of the existence of recurrent typhus, "for which explanations had to be found," such as permanent beds [18]. Such an approach was not taken by Dr. Kuzelj. He was more correct as he was more biological, insisting on similarities among people rather than differences.

The occurrence of the epidemic among guardsmen in 1836 in Kragujevac has not been studied more studiously. Therefore, it has not been proven which "typhus" was present; or if a type was specified, arguments were not given for such naming [18]. The typhus that appeared in the Topčider prison in 1906 was not even described, so crucial judgments as experience were not drawn [20]. There was also double reporting of the disease. Official statistics collected data recorded by priests in death books. Until the end of the First World War, combating infectious diseases fell within the jurisdiction of district, county, and city doctors – physicians [21:17]. Physicians sent their reports on the movement of infectious diseases to the Ministry of Health, Sanitary Department. This issue was "resolved" by wartime events. In 1913, the last annual report for 1907 and 1908 was published [22,20,23], while for 1909 and subsequent years they were not even published..

b) Mild climate, spring, warm weather - During the Balkan Wars, the experience was: "...During the winter of 1912/13, when our Serbian Army units crossed Albania to the sea and reached Durrës... the first cases of this disease appeared among them and became much more frequent than in other units. Deaths were not lacking. At first, we attributed them to fatigue, exhaustion, and shortages, but soon it was noticed that we were dealing with a very characteristic disease face to face with an enemy previously unknown to us. These were typhus and relapsing fever, two diseases endemic in Albania. The number of those who contracted these diseases was relatively small; only a relatively small number of doctors knew about them. As soon as the weather became nice, these diseases disappeared on their own." [24:3; 4:32].

It is noted that the spread of typhus is contributed to by its difficult detection, differential diagnosis with other diseases or

conditions. It was emphasized: fatigue, abdominal typhus, etc. This is what doctors in contact with patients in basic units had to pay attention to, and it is important for the entire sanitation.

Antic states how the "authorities" who did not spare us with countless "orders" missed to inform us of one similar order, ordering us to know that soldiers spread typhus. There is no doubt that there was such a conviction among doctors, as well as among the rest of the army, that the number of victims of typhus in the army and among the people would have been significantly lower. [25:322]. Antic believed that the epidemic was stopped by the arrival of spring, naturally; and not by the influence of measures [25:319].

Like Subbotić, Antic also points out that there were doctors who doubted the correctness of the truth that soldiers spread typhus. According to him, neither Dr. Hunter believed in all of this, as he wore a handkerchief instead of a protective mask, thus showing that the transmission of the typhus pathogen is possible through the air. But, others also thought the same. In the article "Serbia, Land of Death," Reid described Serbia as: "...the land of typhus - abdominal, relapsing fever, and mysterious and cruel typhus (in English, he is "typhus"; and "typhoid" is abdominal, G. Ch.), which kills fifty percent of its victims and whose bacillus had not yet been found by that time. Most doctors thought that it was spread by white lice, but a lieutenant of the British Royal Army Medical Corps, who traveled with us, was skeptical. I was there for three months - he said - and I have long ceased to take any precautionary measures except for daily bathing. And as for lice, a man gets used to spending a pleasant evening brushing them off one by one... The truth about typhus is this: no one knows anything about it, except that one-sixth of the Serbian people died from it... Warm weather and the cessation of spring rains had already begun to stop the epidemic - and the virus weakened. Now there were a hundred thousand sick people with typhus in the whole of Serbia and only a thousand deaths per day - except for cases of horrible typhus gangrene." [26,9].

Events in the Great War were memorable and unforgettable. In a commemorative brochure reflecting on that time, it was noted: "The epidemic of typhus in

Serbia, which during the First World War placed us in an unfavorable position in the history of medicine, could not be thoroughly studied or described... Today, there are few doctors in life who served in the sanitation service of Serbia during the First World War, but those last witnesses of the great typhus epidemic of 1914 and 1915 still vividly remember the sudden appearance and dramatic spread of this serious disease among the ranks of soldiers and civilian population. The catastrophic consequences of that epidemic left a mark in their memories as one of the most painful events of that difficult time. Typhus was introduced by the Austrian army and masses of enemy prisoners from Bosnia into Serbia, where all the conditions for the development of such a massive epidemic were created by a hard war." [20:34]. With the departure of the actors from the world stage, Serbian doctors were supposed to complete the description of the "typhus epidemic in Serbia".

From the foregoing, it can be seen that in Serbia, in peacetime, the people's activities prevented typhus from becoming a problem that imposed itself with its special significance. At the beginning of the epidemic, it persisted because it was difficult to diagnose. It was believed that "typhus, as it came, would also go", spontaneously without major casualties. Experience provided evidence that typhus would not be a bigger problem, and those rare cases (sporadic ones) would incapacitate by the first spring [12:19]. In the archives of the sanitation department of the Supreme Command, evidence supporting such thinking was not found. Contrary to this...

Memories from 1925 indicate that such expectations prevailed among physician writers, as seen in their final conclusion explaining the end of the 1915 epidemics: due to the upcoming warm season, they ceased naturally, rather than through undertaken efforts to combat them [12:29,135].

Capur is probably closest to the truth as he believes in 1875 that the medical personnel's imperfections stem from "a lack of patience and perseverance stem for deeper and more thorough immersion in certain matters, or specific fields... This is a common occurrence among people taking their first steps towards cultural development. They simply don't yet have the need to be thorough scholars. Practical knowledge, useful for their current needs, is entirely sufficient for them at first" [11:49].

Serbian doctors were aware of these facts. They advocated for the establishment of a medical faculty. Poor personnel preparedness was emphasized not only in terms of quantity but also regarding specialization. Trouble ignites a spirit whose scope is difficult to measure accurately in wartime conditions, with the presence of a not insignificant number of "scientific unknowns."

Unlike the stance of the actors, Dr. Genčić, with the Infection Control Commission at the Supreme Command, as well as the State Committee for Infection Control, advocated for undertaking activities that respected the body's resilience. The only question was - how to manage them. Dr. Subbotić pointed this out in 1916 [24], which was published in 1918 [4].

c) The interaction between the actors, the writers (1925), Hunter (1919), and Subbotić (1918), shows that Dr. Hunter acted as a scientist, which simultaneously connected him to the history of medical science. He commented on the scientific contribution arising from improvisation: "The problem of providing a simple and effective method of disinfection, accessible to everyone and for the needs of the railway, has been solved, not only now, but for all times (emphasized by V.H.)." [5:248]. Therefore, the "Serbian miracle" emerged. With such actions, there were conditions that could provide a solution, which Dr. Hunter utilized as an organizer. Dr. Subbotić also acted in this direction, solving the impotence through improvisation, offering his "buried stove" (for dry warm air) [4,12]. (Figure 3))

Image 3. Distinguished doctors (left) Official Military Gazette. (35) No. 16 dated 08.06.1915. p. 328. and (right) Official Military Gazette. (35) No. 15 dated 04.06.1915. p. 315-6.



Serbian medical services did not emphasize their scientific contribution. Patriotic and military virtues were valued, and military awards were received for them. Stammers was also promoted [26,5], and Serbia honored him. (Figure 2). The great efforts of Serbian doctors were respected, demonstrating selflessness and dedication to the Serbian soldier (Figure 3 and 4). Improvements in the Serbian army followed the same year.

Dr. Hunter also acted as a scientist. He published his contributions in The Lancet and in a monograph on typhus in Serbia [12]. His achievements were recognized by the British community, and he was awarded an honorary doctorate.

Hunter and Subbotić mention the buried stove in their works in its most primitive initial form, when it did not represent anything significantly preventive [5:106; 12]. Subbotić points out the applied teachings of Nikola in the Great War, but not in the Balkans. They indicate that Nikola's hypothesis needed to be proven because practice imposed misunderstandings. They sharply point out problems that were later proven as hypotheses: that the unknown cause of typhus "is not transmitted only by flea bites," as was then believed, but that it can also occur through other means, such as inhalation or contact with "dejecta and vomitus." They mention the experience of disinfection in hospitals, which is insufficiently emphasized in

the literature about the year 1915. Disinfection was performed using sulfurization, as was routine in Serbia before the war, and systematically during the war in Valjevo, according to the instructions of Hirschfeld, Pecić, and Savić [6]. They present their observations, which are more interesting to surgeons, regarding the frequency of typhus complications that require surgical intervention, such as "parotitis," gangrene, etc.

The authors in 1925 were deeply influenced by emotions for a long time. In support of this, there is a retrospective in the jubilee memorial book of 1969, where the prevailing current rationale of the actors is still presented. Checking the attitudes was as much in line with major discoveries: the awarding of the Nobel Prize in 1928, or the hypothesis of the existence of late relapse of typhus in 1934. Also significant was what was written about the same events, especially before the publication of the memories of 1925: Hunter's work from 1919 was not considered, nor what Subbotić and Strongitd published.

There are assessments of the "unenviable position of the medical service," as well as criticism of the chief's "management of the medical service," despite Dr. Stanojević only considering it as "unexplored." It is noted that the public debate began in 1921, and the question was reopened in 1925 that "our medical experience, however, remains unexplored to this day" [1:foreword]. The unexplored nature was directed through the mortality, and therefore, the culprit for its occurrence was sought...

In the considerations of 1989, the medical historian Dr. Vukšić clearly expressed disagreement with Dr. V. Stanojević as the editor, and he explained this. In evaluating Hunter's work, Vukšić did not differ from Genčić; both emphasized - the success of Hunter's mission was emphasized. The collaboration between Dr. Hunter and Dr. Genčić is enough to assess the successful engagement of the Serbian medical service. But it should be noted that Dr. Nedok proves the existence of

archival material. Based on the documentation found, which he considered the final report of Dr. Genčić, the suppression of the epidemic occurred. Therefore, in addition to Dr. Hunter, Dr. Vukšić, and Dr. Nedok consider the assistance of medical teams that came to Serbia as crucial. This leaves unaddressed the assessment of Dr. Hirschfeld, which obviously does not refer to Dr. Subbotić's "buried stove" because of its modest capacity but rather to the most significant activity of the Serbian medical service, described by the words: "Serbian doctors, with superhuman effort, without means and assistance, began to organize, or rather to improvise devices for dry disinfection, achieving more than all foreign missions combined." [27].

If we accept the fair assessment of Dr. Hunter's work and consider the contribution of the Serbian medical service in proportion to its involvement, along with the correct attitude of Dr. Genčić as the leader, then it becomes evident that Serbian doctors deservedly received the mentioned honors for their patriotic and professional actions in 1915 (Figures 3,4). This is confirmed by the studies of Vukšić, Nedok, Zorić, Stanković, Čukić, and others..

The Chief's actions were manifested in several ways as correct: a) as a physician, he offered a correct solution consisting of applying Nikolov's teachings, by determining a good strategy for disinfection, for which he proposed factory-made autoclaves; b) as the chief, i.e., the leader, he supported all those who offered arguments that their stance was valid, including doctors (domestic: Subbotić, Batuta, etc., foreign: Hunter, Morrison, etc.) and the State Committee for the Suppression of Contagious Diseases, headed by Eng. Vuković; c) he highlighted proactive individuals (e.g., Infantry Major Sretenović); and d) in the Supreme Command, he founded the Commission for the Suppression of Contagious Diseases, which made a significant contribution by publishing brochures and numerous other activities [12]. The contribution of Serbia's medical service in 1915 was significant for world medicine [28].

Picture 4. Decorated doctors. Official Military Gazette. (35) No. 15, June 4, 1915, p. 293-4.



Although the list of honorees was not final, among them were: 4 sanitary generals; 12 brigade generals; 13 colonels, who could be or were the heads of the highest rank, such as sanitary chiefs; then, senior officers - 4; other distinguished doctors who continued their careers in civilian life (academics, faculty professors, civilian sanitary chiefs, ambassadors, physicists, specialists, etc.) - 12. This group engaged in the suppression of epidemics in 1915 provides a general assessment that the honored were successful war doctors who overcame all the wartime trials and were the backbone of Serbia's medical service.

Dr. Genčić, although "criticized," remained spiritually strong, considering himself "neither guilty nor obligated" because of his contributions, for which others were honored with exceptional recognition [8]. The recipients of the same honor include: Tesla, Pasteur,

Batuta, vojvodes. Undoubtedly deserving and recognized, Dr. Hunter received the same honor (Figure 2), having successfully collaborated with Dr. Genčić. The highest-ranking honor awarded to Dr. Genčić in 1929, as the head of the medical service in 1915, ranks him among successful citizens, about whom their homeland must care..

CONCLUSION

- There is no foundation found for the assessment by the medical historian - actors from 1925 that the suppression of the 1915 typhus epidemic was generally unsuccessful and that the epidemic stopped on its own, naturally.
- It has been proven that through the work of Dr. Hunter's mission with the engagement of the Serbian medical service and other foreign missions, the epidemic was suppressed. Therefore, English and Serbian doctors rightfully received their honors in 1915.

- Dr. Genčić deserves a reevaluation of the publicly stated assessment that his work was "criticized." Such an assessment is scientifically unfounded. There are oversights by critics who did not give importance to the results of the Serbian medical service, which are of

particular significance to the world of medicine.

- The existing archival material must be studied in more detail. Whether Dr. Genčić's address to Voivode Putnik on January 15, 1915, was his last, the reason for it, and Dr. Hirshfeld's assertion, are separate topics.

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The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions.** Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the level of significance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion.** For other types of papers the summary has no specific structure.

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The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, or image, there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: <http://www.nlm.nih.gov/>. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. *Biol Reprod.* 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet.* 2000; 355: 451-5.

No authors listed:
Coffee drinking and cancer of the pancreas [editorial]. *BMJ.* 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. *Pharmacol Res Commun.* 1988; 20 Suppl 5: 75-8.

Books and other monographs

The author is a person (s):
Carlson BM. *Human embryology and developmental biology.* 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. *Medical physiology.* New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. *Equalities and inequalities in health.* 2nd ed. London: Academic Press; 1976. p. 165-78.

Meeting announcements: Harris AH, editor. *Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia.* Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. *Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.*

Dissertation:

Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in an internet magazine:
Aboud S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htm>

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:

Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: <http://www.nap.edu/books/0309074029/html/>.

Website:

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: <http://www.cancer-pain.org/>.

Part of a website:
American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: <http://www.ama-assn.org/ama/pub/category/1736.html>

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect

the quality of the articles and the regularity of the publication of the journal.

For any additional information, please contact the address and email below.

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