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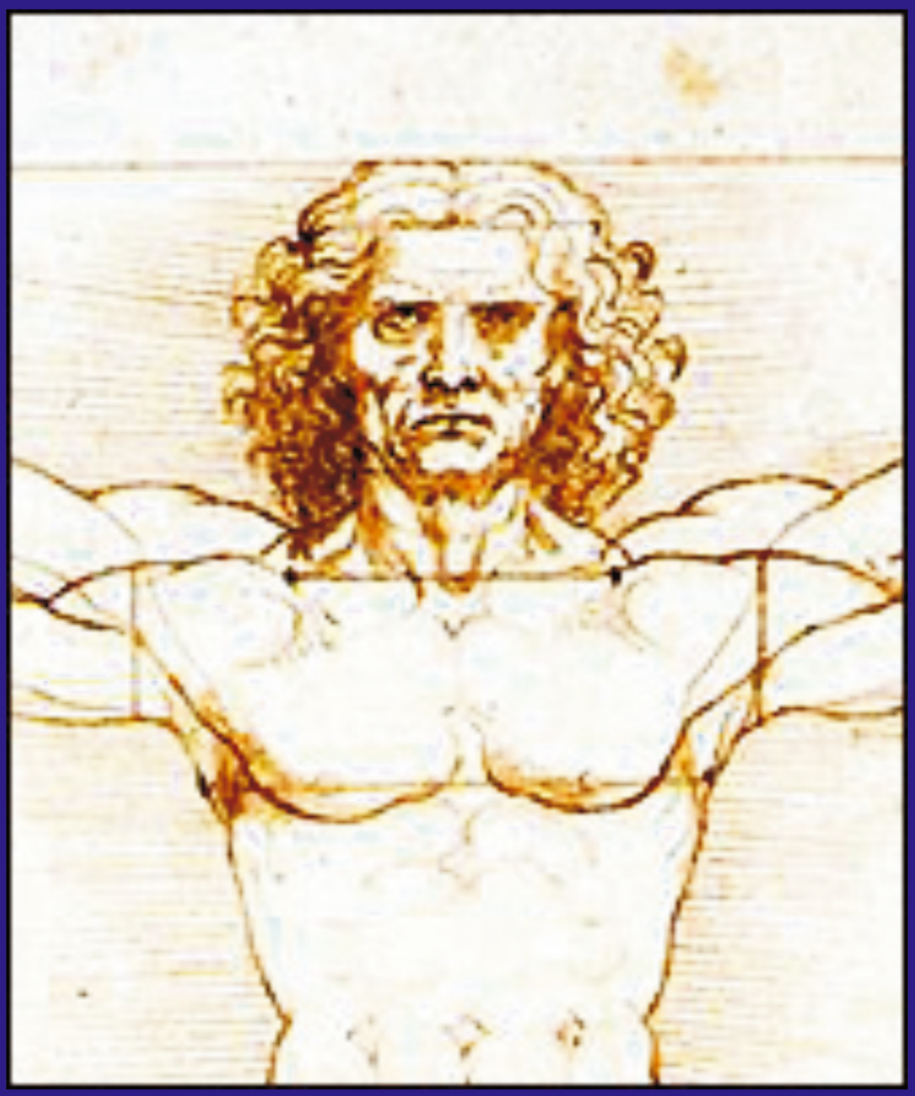

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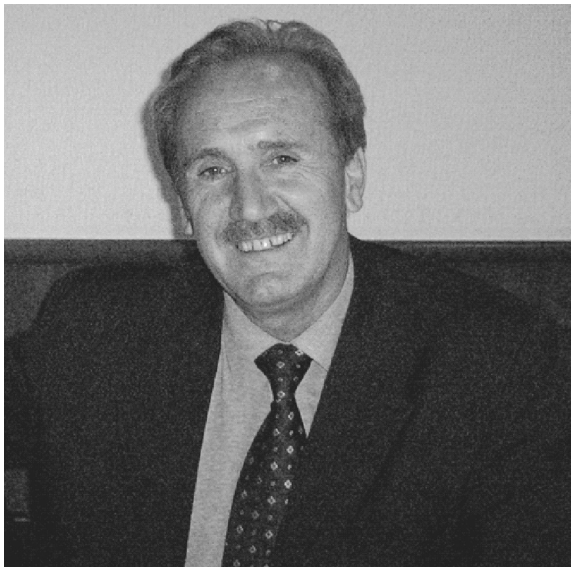
SADRŽAJ

Riječ urednika

Poštovani,



treću svesku ovog broja za 2016-tu godinu, kao što znate jubilarnu, jer je deset godina kako časopis izlazi, obeležavaju dvije stvari. Prva stvar je potvrda uspješnosti rada na ovom časopisu i potvrda zrelosti ekipe koja ga je uređivala svih ovih deset godina. Vodili smo računa prvenstveno na kvalitet i ozbiljnost. Veliki je značaj svih naših saradnika širom svijeta koji su nam svesrdno pomogli u tome. Pratili su naš rad i tamo gdje se to od njih očekivalo, otklanjali sve manjkavosti kako bi „SANAMED"-u dali ozbiljniji i stručniji karakter.

Druga stvar je što pred sobom imamo jedan potpuno standardizovan i uspješno sazreo časopis koji u sledeće godine svog rada ulazi kao uspješno predstavljen naučnoj eliti stručnjaka medicinskih nauka koja se družila svih ovih deset godina i omogućila da ga mnogi širom svijeta upoznaju i useli se u vitrine mnogih biblioteka.

Obe ove stvari su utabale siguran put za lakši budući rad koji će i dalje zahtijevati energiju, znanje i istu efikasnost kako bi časopis, sada sa mjesta blizu vrha, stigao na vrh ili među prvima sa vrha.

Bez obzira na trud da se naš časopis popne još više na lestvici priznatih, neke od onih koji su odlučivali o njegovoj kategorizaciji je čudilo to otkud baš ovaj časopis iz jedne male oaze da se pojavi i takmiči sa časopisima sa mnogo dužom tradicijom i iz velikih univerzitetskih centara, i za koje je bilo logično da sa manje truda zauzmu mesto na tronu. Uputio bih i zamerku onima koji su čak bili hrabri da pitaju kako to da i Novi Pazar, odnosno lekarski esnaf ovog malog grada, ima tako jedan ozbiljan časopis. Ne bih se ovog puta bavio time, ali ih podsjećam da slijedeći put budu objektivniji i ne gledaju odakle je časopis, već šta sadrži i koji kvalitet nosi. Istakao bih takođe i to da baš ove godine je proslavljena jubilarna desetogodišnjica Državnog Univerziteta u Novom Pazaru, što je još jedan razlog da smo ponosni na tu činjenicu zajedničkog sazrijevanja i visokog uspjeha, bez namjere bilo kakvog upoređivanja.

Raditi sve ove godine zahtijevalo je trud i vrijeme, crpeći znanje ljudi od struke širom svijeta, ali bez novca to ne bi moglo baš da se uspješno ostvari. Na svu sreću svi oni koji su vezani za naš časopis su volonteri, a onaj dio koji je vezan za štampanje i elektronsko oglašavanje i održavanje na sajtu ipak zahtijeva novac. Ponekad se javi i neki sponzor, ali vrlo često finasiranje ide iz kase uređivačkog tima. Zadnjih par godina se oko 65% troškova samofinansira preko korisnika časopisa.

Ovim putem htio bih da pozdravim, prije svega najuži tim ljudi u uređivačkom tijelu i sve one širom svijeta koji su dio velikog tima i bez kojih ne bi mogli biti uspješni i da im čestitam Novu 2017 godinu. Želim im pre svega da su zdravi, živi i da im čitav radni i životni vijek protekne u sreći i blagostanju. Srećni i zdravi bili i dočekali novi jubilej od dvadest godina rada.

Prim. dr Avdo Ćeranić
Glavni i odgovorni urednik

A word from the editor

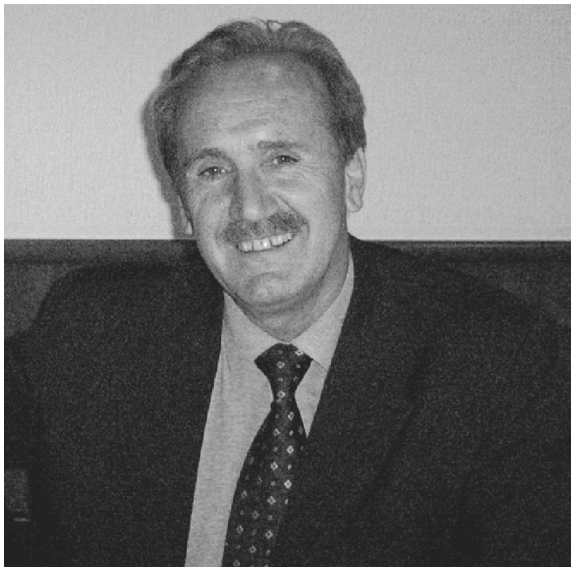
Dear readers,

This year's third volume is, as you all know, the jubilee issue, due to the 10 years of publishing the Journal. This jubilee issue is marked by 2 things. First one is the confirmation of success of working on this journal and the confirmation of maturity of the Editorial Board, which put a great effort in making it possible for the last 10 years. A great amount of attention was paid on the quality and the earnestness of the journal. We have to highlight the importance of the collaborators worldwide, in achieving our goal. They have devoted themselves in each and every step along the way. They corrected the deficiencies in order to give Medical Journal žSanamed' more serious and professional character.

The second thing is that now in front of us stands one fully standardized and successfully matured journal, which will be introduced to the medical scientific elite of experts in the following years. These same elite helped us in achieving our goal all these years and enabled us to become a part of many libraries worldwide.

Both of these previously stated things, paved a safe path for easier work in the future, which will still require energy, knowledge and the same efficacy to put the Journal on the top of the scale of recognized.

Regardless of the effort put in improving our Journal and rising on the scale of recognized, some people that were deciding on its categorization were curious about the origins of this Journal. žSanamed' is competing with journals with longer tradition and journals coming from the great university centers and with ones that was more logical to sit on the throne, without putting a lot of effort. I would like to state a remark to ones who were brave enough to ask, how is it possible that one small environment like Novi Pazar and the guild of doctors of this small town can produce such earnest journal. I would not be commenting it any further at this occasion, but I would like to kindly ask them to be more objective next time and not to watch the origins of the journal, rather what it contains and the qualities it bears. I would point out also that just this year we celebrated the tenth anniversary of the State University of Novi Pazar, which is one more reason to be proud on the common maturing and high success, with no intention of comparisons of any sort.



Working all these years required effort and time, drawing on the knowledge of professionals around the world, but without money it would not be successfully to achieve. Luckily, all those who work for our journal are volunteers, and the part, concerning the print, electronic advertising, as well as the maintenance of the site does require money. Sometimes sponsor appears, but very often the financing is going from the cash register of the editorial team. The last couple of years, about 65% of the costs went via users self-financing.

Hereby, I would like to express my gratitude towards the core team of people in the editorial board and all those people worldwide, who represent a major part of the team and without whom, we would not be successful as we are today. In addition, I would like to wish everyone a Happy New Year 2017. I wish everyone to live healthy lives, welfare and a one more prosperous working year. Be happy, stay healthy and let's greet the next jubilee of 20 years of publishing this Journal.

Prim. Dr Avdo Ceranic
Editor in Chief

Reč gostujućeg urednika / A word from the guest editor

Poštovani čitaoci,

sa posebnim zadovoljstvom sam se odazvala na poziv uredništva časopisa „Sanamed“ i prihvatila da budem gostujući urednik u decembarskom broju koji je pred Vama.

Ovo nije početak naše saradnje. Već nekoliko godina pratim napredak časopisa i divim se entuzijazmu i naporima uredništva da podstaknu što veći broj lekara za publikovanje naučnih i stručnih radova. Ono što polako postaje prepoznatljiv „pečat“ časopisa „Sanamed“ jesu upravo gostujući urednici, kojih je do sada bilo iz više različitih država. Ovo posebno pomaže široj promociji ovog medicinskog časopisa.

U ovom broju donosimo tri rada sa Univerziteta u Kragujevcu, sa željom da se ova vrsta saradnje nastavi. Moram istaći da je saradnja sa uredništvom iznad svega profesionalna i odgovorna, ali je protekla i u prijateljskoj, pozitivnoj i srdačnoj atmosferi.

Uzimajući u obzir kvalitet časopisa, njegovo kotiranje i potencijal, pozivam kolege da publikuju svoja naučna dostignuća u časopisu „Sanamed“ i uključe ga u svoje reference.

Na kraju, zahvaljujem se uredništvu na ukazanom poverenju i iskreno Vam želim napredak i uspeh u daljem radu.

Prof. dr Mirjana A. Janićijević Petrović
Univerzitet u Kragujevcu
Fakultet medicinskih nauka

* * *

Dear Readers,

with great pleasure I have responded to the invitation of the Editors of Sanamed Journal and accepted to be a Guest Editor in December 2016 issue of Sanamed.

This is not the beginning of our cooperation. I follow the progress of the Journal for several years and I admire the enthusiasm and efforts of the Editors that they invest to encourage a greater number of doctors for publishing scientific papers. Visiting editors are something that is slowly becoming a recognizable "signet" of Sanamed Journal. They were, so far, from several different countries. This is especially helpful for the general promotion of this medical Journal.

In this issue we present three papers from the University of Kragujevac, wishing this kind of cooperation to be continued. I must point out that cooperation with the Editors was, above all, professional and accurate, but also it has passed in a friendly, positive and cordial atmosphere.

Considering the quality of the Journal, its impact and potential, I urge colleagues to publish their scientific achievements in Sanamed Journal and to include it in their references.

Finally, I thank the Editors for their trust and I sincerely wish them prosperity and success in future work.

Prof. dr Mirjana A. Janicijević Petrović
University of Kragujevac
Faculty of medical sciences

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

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Original article

DIFFERENTIAL HISTOMORPHOMETRIC CHANGES IN NORMAL AND INFLAMED GINGIVAL EPITHELIUM

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Abstract: **Introduction and aim:** In recent decades, many factors such as smoking, unhealthy diet as well as high alcohol intake were marked as risk factors that can lead to increased incidence of malignant alterations, gingivitis, periodontal disease and other oral epithelium pathological changes. Having in mind that in the group of non-malignant and non-dental oral pathology gingivitis and periodontal disease are the most common oral mucosa alterations aim of our research was to investigate histomorphometric characteristics of healthy and altered oral and gingival epithelium.

Material and methods: Tissue samples of 24 oral and gingival mucosa specimens were collected. Samples were fixed in 10% buffered paraformaldehyde, routinely processed and embedded in paraffin blocks. From each block sections 5 micrometer thin were made and standard H/E staining as well as immunocytochemical detection of Ki-67 proliferation marker and CD79a lymphocyte marker were performed. Measurements and image analysis was performed with Image Pro Plus software (Media Cybernetics, USA) and Axiovision (Ziess, USA).

Results: We showed that inflamed gingival epithelium is increasing its thickness in proportion to the severity of adjacent inflammation. Furthermore, mitotic index is rising (up to 132%) in the same manner as well as basal lamina length (up to 70%) when normal and inflamed gingiva is compared. Architecture of epithelial ridges is changed from straightforward to mesh-like.

Conclusion: Assessment of the free gingival epithelium thickness is directly related to the severity of the inflammation process in gingiva.

Keywords: histomorphometry, gingiva, Ki-67, gingivitis.

INTRODUCTION

Oral epithelium belongs to the stratified squamous type, with or without keratinization. Although one name is used for the whole epithelial lining of the mouth, there are several subtypes of this tissue, according to their specific site (1). Relatively quick turnover rate of this epithelium and exposure to various agents makes it vulnerable and susceptible for disease onset (2, 3). In recent decades, many factors such as smoking, unhealthy diet as well as high alcohol intake were marked as risk factors that can lead to increased incidence of malignant alterations, gingivitis, periodontal disease and other oral epithelium pathological changes (4, 5, 6). World health organization statistical data shows that periodontal disease is found in 15-20% middle aged adults while the incidence of oral cancer ranges from one to 10 cases per 100 000 people in most countries (5). Furthermore, it is well established fact that oral diseases in children and adults are higher among poor, older and disadvantaged population groups (2). Review of literature reveals that, for many of oral diseases, among the first changes there is an alteration of the morphometric characteristics of the oral epithelium (3, 4). Pejcic et al. (7), Villar et al. (8) and Bulut et al. (9) reported that smoking and Cyclosporine A-induced inflammation affects thickness of oral and gingival epithelium as well as degree of the keratinization while Birajdar et al. (10) stated that expression of keratinocyte proliferative marker is a significant prognostic factor for the oral leukoplakia and oral squamous cell carcinoma. Having in mind that in the group of non-malignant and non-dental oral pathology gingivitis and periodontal disease are the most common oral mucosa alterations and the fact that changes of epithe-

lial tissue are, in many cases, the first sign of oral pathology, the goal of our research was to thoroughly investigate histomorphometric characteristics of healthy and altered oral and gingival epithelium such as overall thickness, basal cell count as well as mitotic index of the basal keratinocytes.

MATERIALS AND METHODS

Tissue samples of 24 oral and gingival mucosa specimens (14 male and 10 female, aged from 42-67 years) were collected during the various dentistry procedures at the Department for Preventive and Pediatric Dentistry from September 2015 through March 2016. Ethical approval for the research protocol was issued by Ethics Committee of the Dentistry Department, Health Centar Kragujevac. All patients were fully informed and gave their consent. Histomorphometric analysis was performed at the Histology Institute, Faculty of Medical Sciences, Kragujevac. Specimens were divided into three groups: normal buccal mucosa, normal gingiva and inflamed gingival according to the clinical status. All tissue samples were fixed in 10% buffered paraformaldehyde for 24 hours, routinely processed and embedded in paraffin blocks. From each block sections 5 micrometer thin were made and standard H/E staining as well as routine immunocytochemical staining of the Ki-67 proliferation marker and CD79a lymphocyte marker were performed. Staining for Ki-67 and CD79a was performed with a streptavidin-biotin (SAB) complex method using the Histofine SAB-PO kit (Nichirei Co., Tokyo, Japan) according to the manufacturer's directions. Images of tissue sections were captured with digital camera attached to the Olympus BX51 microscope. Measurements of the epithelial thickness, ridges length and basal lamina/epithelial surface length (BLL/ESL) were performed with Axiovision (Ziess, USA) and Image Pro Plus software (Media Cybernetics, USA). Mitotic index was assessed by two independent researchers marking the number of the dividing basal keratinocytes. Results were presented as mean ± SD. Statistical analysis was done using the SPSS software. Estimation of statistical significance between mean values was performed with student T-test. Level of significance was set at $p < 0.005$.

RESULTS

Based on the histopathological features, in our series, 8 samples were characterized as normal buccal mucosa, 6 samples as a normal gingival mucosa and 10 samples as inflamed gingival mucosa from which 6 specimens were marked as mild gingivitis and 4 cases as a severe gingivitis. The degree of lymphocyte infiltration (assessed by virtue of immunochemical staining) was the determining factor for the classification of the gingivitis-affected samples. Normal buccal mucosa showed classic characteristics of non-keratinized stratified squamous epithelium. Overall thickness of this epithelium was 396 ± 41 μm while epidermal ridges comprised just 89.88 ± 7 μm. Basal lamina length was 133% larger than epithelial surface length (BLL/ESL). Immunochemical detection of Ki-67 antigen showed that percentage of dividing basal cells was 7.1 ± 1.6. Healthy gingival oral epithelium showed mild orthokeratinization. Overall thickness of this epithelium was 478 ± 27 μm, while epidermal ridges comprised significant 251 ± 38 μm. BLL/ESL ratio was 305%. Percentage of dividing cells was 8.0 ± 0.6. Tissue specimens with mild gingivitis showed orthokeratinization very similar to the healthy gingiva. Overall epithelium thickness was 508 ± 27 μm, while pretty strait epidermal ridges (Figure 1a) comprised 351 ± 58 μm. BLL/ESL ratio was 504%. Per-

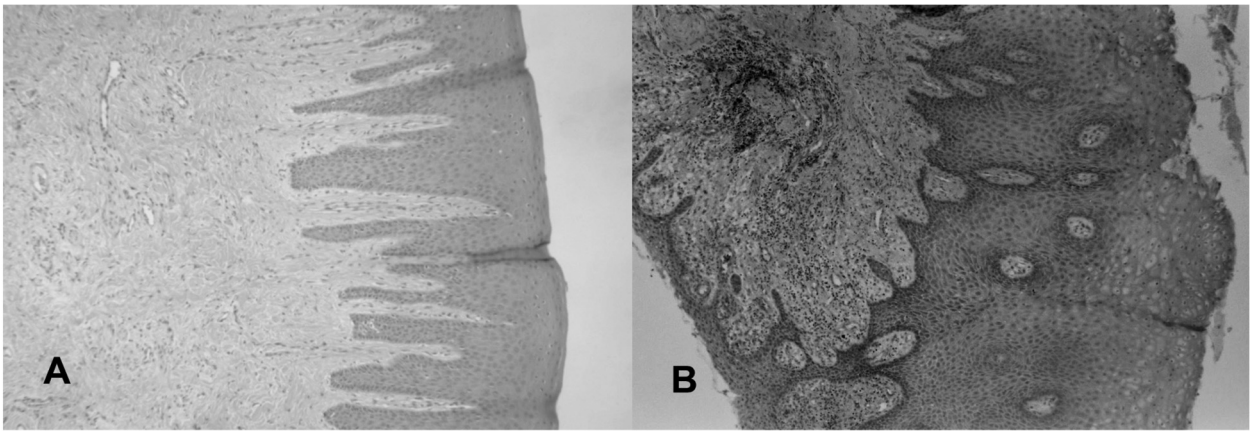

Figure 1. *Epithelial ridges architecture in normal (A) and severe gingivitis (B) cases. Fig B showing the complex epithelial ridges structure (H/E staining, magnification x100)*

Table 1. *Histomorphometric epithelial measurement data*

	Ep. Thickness (μm)	Ridges length (μm)	BLL/ESL ratio (%)	Mitotic index
Normal buccal	396 ± 41	90 ± 7	133	7.1 ± 1.6
Normal gingival	478 ± 27	251 ± 38	305	8.0 ± 0.6
Mild gingivitis	508 ± 27	351 ± 58	504*	8.7 ± 0.5
Severe gingivitis	581 ± 23*	–	355	9.4 ± 0.3*

centage of dividing basal keratinocytes was similar to the healthy gingival epithelium (8.7 ± 0.5%). Severe gingivitis (edging the periodontal disease), in our series, led to increased overall thickness of free gingival epithelium compared to normal and mild cases. Furthermore, keratinization process was altered and layer of orthokeratinized cells on the surface of the epithelium was disrupted and somewhere almost missing. Average thickness was 581 ± 23 μm while epithelial ridges showed complex intertwined pattern (Figure 1b) which prevented us to precisely assess its morphometric features. The same thing happened when BLL/ESL ratio was measured. Our results showed that this ratio was 355% but, again, due to complex epithelial ridge-dermal papillae architecture values must be interpreted carefully. The percentage of dividing basal cells was significantly higher than in normal, but insignificantly compared to the mild gingivitis cases (9.4 ± 0.3%). All measurements were presented in Table 1 where statistical significance compared to normal tissue was marked with asterisk (*). Hence, our study showed that thickness of the epithelium and mitotic index in severe gingivitis cases were significantly higher than in normal mucosa, while basal lamina length to epithelium surface length was significantly higher in mild gingivitis cases compared to control.

DISCUSSION

According to the WHO statistical data, incidence of the diseases of oral mucosa is increasing (5). This is mostly due to exposure to the risk factors such as unhealthy diet, smoking, alcohol intake as well as increased average age of the human population (6, 11, 12). In the group of non-malignant oral mucosa-related diseases, inflamed gingiva and periodontal disease is the most common (6) but, although whole-thickness oral mucosa is affected, the main changes are located in epidermal layer. Furthermore, the first signs of gingiva-related diseases are also in squamous stratified epithelium as proved in study of Prakash P et al. (13). These signs include morphometric features such as epithelial thickness, layer representation, epidermal ridges length and architecture as well as mitotic index of the basal keratinocytes. Available literature data concerning histomorphometry of normal and inflamed oral and gingival epithelium shows that mild inflammation causes epithelium thickening, and severe ones induce epithelial thinning (2, 8). Nevertheless, plethora of these data is related solely to the junctional and sulcar part of the gingival epithelium, but there are very scarce results concerning marginal gingival epithelium characteristics. Our study was designed to reveal changes only in this specific tissue. For the verification of the degree of inflammation we used immunocytochemistry staining with antibody raised against CD79a antigen. We showed that marginal gingival epithelium is increasing its thickness in proportion to the severity of adjacent inflammation. This finding is in a collision with results of Lukandu (14), but their findings are related to the sulcar, not marginal epithelium . In our study mitotic index of basal keratinocytes is rising in the same manner as proved in our study by immunostaining against the Ki-67 antigen. This is similar to the findings of Bulut et al. (9). In their study on cyclosporin-A induced gingivitis they stated that the number of PCNA labeled mitotic cells raises two-fold in gingivitis compared to normal gingival. Our results also showed increased number of dividing basal cells but the degree is much smaller (about 18%). Tissue specimens with severe gingivitis in our study showed altered epidermal ridges architecture. In normal gingiva and mild gingivitis cases ridges were prominent and numerous, but with straightforward manner in the lamina propria. In severe cases (bordering periodontal disease) ridges showed mesh-like structure with significant basal lamina length. This fact is important because the length of the basal lamina is directly related to the overall number of basal cells that participate in epithelium renewal e.g. the longer the basal lamina bellow the epithelium surface, greater is the number of the basal cells that can enter mitosis. This fact can be a good explanation for the thickening, not the thinning of the marginal epithelium. Having in mind previously mentioned facts our study clearly showed that distant inflammation significantly affects morphometric features of the marginal gingival epithelium. Although changes of sulcar and junctional gingival epithelium are thought to be more important for the clinical expression of inflamed gums and periodontal disease, signs of morphometric changes of oral side should be carefully esti-

mated. This is important because, as shown by Prestin S et al. (15), by virtue of OCT (Optical Coherence Tomography), relatively novel method in dentistry, epithelial thickness can be assessed with ease and the most accessible spot for this analysis is free gingival epithelium. Having in mind that precise estimation of the depth and severity of the inflammation process in gingiva is still a significant clinical problem in dentistry, we think that our findings, combined with possibilities of the OCT will bring a novel approach for the assessment of the severity of the gingival inflammation process.

Conflict of interest

The authors declare that there is no conflict of interest.

Abbreviations

H/E — Hematoxylin /eosin
WHO — World health organization
ESL — Epithelial surface length
BLL — Basal lamina length
PCNA — Proliferating cell nuclear antigen
OCT — Optical Coherence Tomography

Sažetak

HISTOMORFOMETRIJSKE PROMENE EPITELA KOD NORMALNE I INFLAMIRANE GINGIVE

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Uvod i cilj: U poslednjim decenijama su pušenje, nezdrava ishrana i konzumiranje alkohola doveli do povećane incidence bolesti usne duplje kao što se kanceri, gingivitis, parodontopatija i dr. Imajući u vidu da su van grupe malignih bolesti i oboljenja zuba gingivitis i parodontopatija najučestalije bolesti usne duplje, mi smo želeli da uporedimo histomorfometrijske karakteristike normalnog i obolelog epitela bukalne sluznice i slobodne gingive,kao i gingive zahvaćene blažim i težim formama zapaljenja.

Materijal i metode: Uzorci tkiva normalne oralne sluznice i obolele gingive su uzeti od 24 pacijenta. Tkivo je fiksirano u paraformaldehidu, rutinski histološki obrađeno i kalupljeno u parafinske blokove. Isečci debeli 5 mikrometara su bojeni H/E metodom i imunohemijskom metodom uz upotrebu anti-Ki-67 i anti-CD79a antitela. Morfometrijsko merenje i analiza slika histoloških preparata je obavljena uz pomoć Image Pro Plus softvera (Media Cybernetics, USA) i Axiovision (Ziess, USA) programa za obradu slike.

Rezultati: Naše istraživanje je pokazalo da udaljena inflamacija izaziva zadebljanje epitela slobodne gingive i to proporcionalno težini zapaljenskog procesa. Raste u istom smislu i mitotski indeks bazalnih keratinocita (do 132%), kao i dužina bazalne lamine (do 70%).

Zaključak: Utvrđivanje debljine slobodnog gingivalnog epitela je dobar pokazatelj uznapredovalosti inflamatornog procesa gingive.

Ključne reči: histomorfometrija, gingiva, Ki-67, gingivitis.

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BENEFICIAL EFFECTS OF LEVOTHYROXINE IN THE TREATMENT OF SUBCLINICAL HYPOTHYROIDISM

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Abstract: **Introduction:** Increased cardiovascular risk in thyroid dysfunction is associated with disorders of lipid and lipoproteins, endothelial dysfunction, metabolic, hormonal, hemodynamic changes and coagulation disorders.

Subclinical hypothyroidism is characterized by a supra normal level of TSH with normal levels of thyroid hormones. The correlation between subclinical hypothyroidism of the lipid profile and cardiovascular outcomes remains unclear. Several intervention studies assessed the effect of levothyroxine therapy on the lipid profile of patients with subclinical hypothyroidism and obtained conflicting results.

The aim of the research is to determine whether subclinical hypothyroidism is associated with the atherogenic lipid profile and whether these changes are reversible after the introduction of the L-thyroxine replacement therapy.

Method: The study included 51 patients over 50 years of age with subclinical hypothyroidism. All the participants were subjected to an examination program which included a detailed anamnesis and physical examination; laboratory tests (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, T3, T4, TSH). After eight weeks of levothyroxine therapy, the same laboratory parameters were determined in the patients.

Results: Subjects with subclinical hypothyroidism had high average values: TSH (12.77 + 2.78 mIU/ml), total cholesterol (7.55 ± 0.79 mmol/l), LDL cholesterol (5.03 ± 0.61 mmol/l), triglycerides (2.48 ± 1.01 mmol/l); and the average value of HDL cholesterol was within reference values (1.12 ± 0.21 mmol/l). After eight weeks of levothyroxine replacement therapy, there was a statistically significant reduction of average values ($p < 0.0001$): TSH (3.83 ± 1.33 mIU/ml), total cholesterol (6.28 ± 0.96 mmol/l), LDL cholesterol (4.03 ± 0.70 mmol/ mmol/l l), triglycerides (1.98 ± 0.87 mmol/l); and the average value of HDL cholesterol increased significantly ($p < 0.0001$) (1.32 ± 0.22 mmol/l).

Conclusion: Subjects with subclinical hypothyroidism have the atherogenic lipid profile which is corrected after the levothyroxine treatment. Subclinical hypothyroidism can be considered a disorder that leads to increased cardiovascular risk.

Key words: subclinical hypothyroidism, levothyroxine, lipids, cardiovascular risk.

INTRODUCTION

The correlation between hypothyroidism, lipid disorders and coronary heart disease was observed as far back as 1960. Elevated levels of total cholesterol, LDL cholesterol and triglycerides as well as reduced levels of HDL cholesterol are classified in the group of risk factors for ischemic heart disease.

Subclinical hypothyroidism (SH) is defined by elevated levels of TSH in the serum with normal levels of thyroid hormone (1). Factors that lead to an increased risk of developing cardiovascular disease in subclinical hypothyroidism are not entirely clear but this correlation is partly associated with high blood pressure, atherogenic lipid and lipoprotein status, proinflammatory conditions, endothelial dysfunction and hypercoagulability (2-10).

Although in the last 20 years several studies have examined the association between subclinical hypothyroidism (SH) and lipid levels, the exact correlation between the SH lipid profile and cardiovascular outcomes remains unclear (3-5, 11-16).

Several intervention studies assessed the effect of levothyroxine therapy on the lipid profile of patients with subclinical hypothyroidism and obtained different results. (7, 8, 11, 17-22).

Different results obtained by the above-mentioned observational studies may be attributed to many rea-

sons, such as different age of the observed subjects, ethnicity, gender, degree and duration of hypothyroidism.

THE AIM OF THE RESEARCH

The aim of the research is to determine whether subclinical hypothyroidism is associated with the atherogenic lipid profile and whether these changes are reversible after the introduction of the levothyroxine replacement therapy.

METHODS

The research included 51 subjects over 50 years of age with subclinical hypothyroidism.

The research was carried out according to the following protocol:

1. Signing of the informed consent. Before any study procedure, a patient was informed on study design, and upon reading the informed consent, he/she signed it.

2. Obtaining history data. History data were obtained by means of structured history questionnaire.

3. Physical examination.

4. Laboratory tests: biological samples were collected: 1 test-tube with citrate for SE, 1 test-tube containing EDTA (5ml) for complete blood count, 2 test tubes for serum separation (10ml each) for biochemical analyses (cholesterol, triglycerides, LDL cholesterol, HDL cholesterol) and immune-metric analyses (T3, T4, TSH).

The study included patients who met all the inclusion criteria and had none of exclusion criteria.

Inclusion criteria were as follows:

1. The informed consent signed

2. The patients over 50 years of age

3. Each of them diagnosed with subclinical hypothyroidism.

Exclusion criteria:

1. Evidence on acute infection in the last 2 weeks.

2. Positive bio-humoral inflammatory syndrome (accelerated SE and leukocytosis).

3. Use of medicaments that may interfere with studied parameters (glucocorticoids, iodine preparations, amiodarone, diuretics, lithium, cytostatics, anti-depressives, estrogens, androgens).

4. Chronic diseases that may have effect on studied parameters (systemic autoimmune diseases, malignant diseases, chronic renal failure, liver insufficiency, acute cardiovascular and cerebrovascular insults and insults within the last 6 months).

5. Recent use of radioactive iodine, surgical interventions of thyroid gland and external neck radiation.

6. Pregnancy and breast feeding.

The initial study phase involved the collection of history data and thorough physical examination. Blood samples collected after 12-hour fasting were used for the following measurements: cholesterol, triglycerides, LDL cholesterol, HDL cholesterol (colorimetric method based on end-point principle). TSH was determined by immunochemical method – chemiluminescent procedure including chemiluminescent substrate. The method was automated (IMMULITE® DPC). Reference values: TSH: 0.27-4.20 mIU/ml; Variation coefficient: 5.50%.

T3 is done on the principle of a competitive immunoassay by a 30-minute incubation, analytical sensitivity of 0.54 nmol/L, and measurement range of 0.61 to 9.2 nmol/L; Reference values: 1:10 to 3:10 nmol/l.

T4 is done on the principle of a competitive immunoassay by a 30-minute incubation, analytical sensitivity of 5 nmol/L, and measurement range of 13 to 309 nmol/L; Reference values: 58-161 nmol/l.

After eight weeks of levothyroxine treatment the same laboratory parameters were determined in patients.

Group formation: The decision criterion for the placement of patients in the group with subclinical hypothyroidism was TSH value: > 4.2 IU/mL, and patients were divided according to age group: 18 patients aged 50 to 55, 17 patients aged 56 to 60 and 16 patients aged over 60.

Before beginning a statistical analysis, laboratory reports with the results of the analyses of patients were anonymised and granted a research code (to protect the privacy of patients, the code is known only to the researcher). An electronic database was created in the SPSS version 20.0. The mean value, standard deviation (SD), median, minimum and maximum values were determined. Univariate methods were used in testing significance of differences: χ^2 test, Student's t-test. Rank correlation was used to test parallelism. The p value of < 0.05 is statisticaly significant, with the calculation of 95% confidence interval.

RESULTS

The study included 51 subjects over 50 years of age with subclinical hypothyroidism.

The average age of patients was 58.32 ± 5.80. Statistically, in gender representation, there were significantly more female patients, i.e. there were 42 female (82.35%) and 9 male patients, or 17.65%, for $\chi^2 = 11.842$, $p < 0.001$.

The average values of T3 and T4 before and after eight weeks levothyroxine therapy remained within reference values (Table 1).

Table 1. *Average values of T3 and T4 in relation to the age of the patients before and after treatment*

Age - intervals		Before treatment			F test	After treatment		F test
		N	Average	SD		Average	SD	
T4 nmol/l	Up to 55	18	103.15	21.78	F = 2.413 p < 0,05	128.63	25.4	F = 3.113 p < 0,05
	56 to 60	17	85.00	20.32		106	25.92	
	Over 60	16	99.88	18.95		114.98	20.69	
	Total	51	96.56	21.11		117.89	25.17	
T3 nmol/l	Up to 55	18	1.93	0.51	F = 0.046 p = ns	2.44	0.44	F = 0.321 p = ns
	56 to 60	17	1.87	0.67		2.64	0.53	
	Over 60	16	1.84	0.25		2.16	0.4	
	Total	51	1.88	0.49		2.43	0.47	

T3- triiodothyronine; T4 – thyroxine;

Average values of TSH in all age groups were reduced after eight weeks of levothyroxine treatment (Table 2).

Table 2. *Average values of TSH in relation to the age of the patients before and after treatment*

Age - intervals		Before treatment			F test	After treatment		F test
		N	Average	SD		Average	SD	
TSH mIU/ml	Up to 55	18	12.60	3.67	F = 0.457 p = ns	3.65	2.2	F = 1.591 p = ns
	56 to 60	17	12.00	1.69		3.72	0.45	
	Over 60	16	**13.72**	2.98		**4.12**	1.35	
	Total	51	**12.77**	2.78		**3.83**	1.33	

TSH: thyroid stimulating hormone

Average values of lipids by age group before and after treatment are given in Table 3.

Table 3. *Average values of lipids before and after treatment in relation to the age group of patients*

Age - intervals		Before treatment			F test	After treatment		F test
		N	Average	SD		Average	SD	
Cholesterol mmol/l	Up to 55	18	7.13	0.61	F = 1.539 p = ns	6.06	1.15	F = 0.339 p = ns
	56 to 60	17	7.73	0.67		6.38	0.46	
	Over 60	16	**7.80**	1.10		6.39	1.27	
	Total	51	**7.55**	0.79		**6.28**	0.96	
Triglycerides mmol/l	Up to 55	18	2.15	0.64	F = 0.643 p = ns	1.94	0.62	F = 0.561 p = ns
	56 to 60	17	2.55	1.13		**2.08**	0.97	
	Over 60	16	**2.75**	1.26		1.91	1.01	
	Total	51	**2.48**	1.01		**1.98**	0.87	
LDL-ch mmol/l	Up to 55	18	4.60	0.56	**F = 3.726 p < 0,05**	3.87	0.59	F = 0.299 p = ns
	56 to 60	17	5.03	0.72		4.10	0.53	
	Over 60	16	**5.47**	0.57		**4.14**	0.99	
	Total	51	**5.03**	0.61		**4.03**	0.7	
HDL-ch mmol/l	to 55	18	1.19	0.25	F = 0.446 p = ns	1.38	0.21	F = 0.769 p = ns
	56 to 60	17	1.08	0.18		1.37	0.24	
	Over 60	16	1.11	0.22		**1.23**	0.22	
	Total	51	**1.12**	0.21		**1.32**	0.22	

Table 4. *PAIRED T TEST- total all patients*

Total patients Before/after	Correlation	Sig.	t	df	Sig. (2-tailed)
T4 v.s. T4 control measurement	0.876	0.001***	-7.633	18	0.0001***
T3 v.s. T3 control measurement	0.711	0.001***	-6.448	18	0.0001***
TSH v.s. TSH control measurement	0.650	0.001***	17.374	18	0.0001***
Cholesterol vs. Chol. control measurement	0.715	0.001***	7.841	18	0.0001***
Triglycerides vs. Triglycerides control measurement	-0.564	0.01**	9.988	18	0.0001***
LDL-ch vs. LDL-ch control measurement	0.640	0.003**	7,174	18	0.0001***
HDL-ch vs. HDL-ch control measurement	-0.734	0.001***	-5,536	18	0.0001***

The average values of total cholesterol, triglycerides and HDL cholesterol did not, statistically speaking, significantly differ among age groups either before or after treatment (p = ns).

The average value of LDL cholesterol before treatment was significantly different among age groups ($p < 0.05$), but after treatment the average value of LDL cholesterol was not significantly different among age groups (p = ns).

The results of correlation and the paired Student's T test before and after treatment are shown in Table 4.

The analysis of the values of TSH, total cholesterol, LDL cholesterol and triglycerides before and after treatment showed a highly significant direct correlation, and the paired T test showed that the values of TSH, total cholesterol, LDL cholesterol and triglyceride levels significantly decreased after the patients received treatment, total ($p < 0.0001$).

The analysis of the value of HDL cholesterol before and after treatment showed a highly significant inverse correlation, and the paired T test showed that the value of HDL cholesterol increased after the patients received treatment in total, statistically significant ($p < 0.0001$).

DISCUSSION

This study shows that in patients with SH there was the atherogenic lipid profile, which was corrected significantly after the application of levothyroxine. The results of this study suggest that the levothyroxine replacement in the examined groups (aged over 50 and with an average TSH > 10 mIU/ml) is completely justified.

Subclinical hypothyroidism is defined by elevated levels of TSH in the serum with normal levels of thyroid hormones. Patients with subclinical thyroid dysfunction are not identified on the basis of signs and symptoms even when they are discreetly present. A typical population-based study in the district of Whickham in England found the prevalence of 75 per 1000 women and 28 per 1000 men (23); similar findings are presented in other studies (24). A higher incidence of subclinical hypothyroidism in women than in men and in the older age group than in the younger one is parallel to the higher incidence of thyroperoxidase and thyroglobulin antibodies in women and the elderly (25, 26). In our study, of the 51 patients with SH, 42 (82.35%) were women.

A disturbed lipid profile is a well-known manifestation of thyroid dysfunction. Results from observational studies that followed the level of serum lipids in patients with subclinical hypothyroidism are inconsistent (1, 4, 5). A large epidemiological study showed a positive correlation between serum TSH and dyslipidemia, and also showed that subclinical hypothyroidism is an intermediate state between euthyroid and clinical hypothyroidism when it comes to lipid profiles (27). In the Colorado study from 2000 which was carried out on 25 862 participants, Canaris et al. found that people with impaired thyroid function in terms of subclinical hypothyroidism have significantly higher levels of total cholesterol, LDL-cholesterol and triglycerides (27). In the Busselton study from 2002, Walsh et al. on a sample of 2108 Australian participants found that TSH is positively correlated with total cholesterol, triglycerides, LDL-cholesterol (12). EPIC-Norfolk prospective study showed a statistically significant increase in the concentration of total cholesterol, LDL cholesterol and triglyceride levels only in women with subclinical hypothyroidism (28). In 2011, Lai et al. among 1534 Chinese adults found that people with subclinical hypothyroidism have higher levels of triglycerides and low HDL cholesterol compared to euthyroid people (15). There are studies that show different results. In 2004, Hueston et al. processed data about 8,586 adult subjects from the The National Health and Nutrition Examination Survey III database and concluded that subclinical hypothyroidism is not associated with the disorder of the levels of total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol (29). In our study subjects with subclinical hypothyroidism had

significantly higher levels of total and LDL cholesterol before the introduction of L-thyroxine as compared to the results obtained eight weeks after its replacement. Triglyceride levels were significantly higher in patients with subclinical hypothyroidism before treatment compared to the results after treatment. In the group of subjects with subclinical hypothyroidism HDL was within reference values and after levothyroxine therapy its value was increased. Our study established a direct correlation between TSH and the levels of total and LDL cholesterol.

Several intervention studies assessed the effect of levothyroxine therapy on the lipid profile of patients with subclinical hypothyroidism and obtained different results (20-22, 26). Tzotzas et al. found that the lipid profile of patients with subclinical hypothyroidism does not differ from euthyroid controls and that levothyroxine therapy does not lead to significant changes in lipid levels (30). Razvi et al. carried out a randomized, double-blind study, and after 12 weeks of levothyroxine treatment the patients had significantly lower levels of total and LDL cholesterol, while there was no significant effect on HDL cholesterol and triglycerides (8). Most studies show a beneficial effect of levothyroxine treatment with basal TSH values above 10 mIU/l (20, 31). This was confirmed in the subjects observed in our study. In our study, the average value of TSH before treatment was 12.71 mIU/l. These results are consistent with our results. It is believed that higher TSH levels (> 10mi/l) are associated with the atherogenic LDL cholesterol fraction and increased cardiovascular risk (20, 32).

In conclusion we can say that the results of this study suggest that subjects with subclinical hypothyroidism have the atherogenic lipid profile which is corrected after levothyroxine treatment and that subclinical hypothyroidism can be considered a disorder that leads to increased cardiovascular risk. In assessing the introduction of levothyroxine therapy in these patients, in addition to the determination of serum TSH levels, an individual cardiovascular risk should be determined, which is essential in making decisions about the treatment of these patients.

Conflict of interest

Authors confirmed that no actual or potential conflict of interest exists in relation to this article.

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There were no external funding source for this study.

Abbreviations

TSH — thyroid stimulating hormone
T3 — triiodothyronine
T4 — thyroxine;
LDL — Low density lipoproteins
HDL — High density lipoproteins s
SH — ubclinical hypothyroidism

Sažetak

KORISTAN EFEKAT LEVOTIROKSINA U TRETMANU SUBKLINIČKE HIPOTIREOZE

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Uvod: Povećan kardiovaskularni rizik u disfunkciji štitaste žlezde u vezi je sa poremećajima metabolizma lipida i lipoproteina, endotelijalnom disfunkcijom, metaboličkim, hormonskim, hemodinamskim promenama i poremećajima koagulacije.

Subklinička hipotireoza karakteriše se supranormalnim nivoom TSH uz normalne vrednosti tireoidnih hormona. Udruženost subkliničkog hipotireoidizma lipidnog statusa i kardiovaskularnog ishoda je i dalje nejasna.Više interventnih studija je ocenjivalo efekat terapije levotiroksinom na lipidni profil pacijenata sa subkliničkom hipotireozom i dobijeni su konfliktni rezultati.

Cilj ispitivanja je da se utvrdi da li je subklinička hipotireoza udružena sa aterogenim lipidnim profilom i da li su ove promene reverzibilne nakon uvođenja supstitucione terapije levotiroksinom.

Metod: Istraživanjem je obuhvaćen 51 ispitanik uzrasta iznad 50 godina sa subkliničkom hipotireozom. Kod svih ispitanika sproveden je program istraživanja koji uključuje: detaljnu anamnezu i fizikalni pregled, laboratorijska ispitivanja (ukupni holesterol, LDL holesterol, HDL holesterol, trigliceridi, T3, T4, TSH). Nakon osmonedeljne terapije levotiroksinom kod bolesnika su određivani isti laboratorijski parametri.

Rezultati: ispitanici sa subkliničkom hipotireozom imali su povišene prosečne vrednosti: TSH (12.77 ± 2.78 mIU/ml), ukupnog holesterola (7.55 ± 0.79

mmol/l), LDL holesterola (5.03 ± 0.61 mmol/l), triglicerida (2.48 ± 1.01 mmol/l); a prosečna vrednost HDL holesterola bila je u referentnim vrednostima (1.12 ± 0.21 mmol/l). Nakon osmonedeljne supstitucije levotiroksinom kod ovih ispitanika dolazi do, statistički značajnog, sniženja prosečnih vrednosti (p < 0,0001): TSH (3.83 ± 1.33 mIU/ml), ukupnog holesterola (6.28 ± 0.96 mmol/l), LDL holesterola (4.03 ± 0.70 mmol/lmmol/l), triglicerida (1.98 ± 0.87 mmol/l); a prosečna vrednost HDL holesterola je, statistički značajno, porasla (p < 0,0001): (1.32 ± 0.22 mmol/l).

Zaključak: Ispitanici sa subkliničkom hipotireozom imaju aterogeni lipidni profil koji se koriguje nakon tretmana levotiroksinom. Subklinička hipotireoza može se smatrati poremećajem koji vodi povećanom kardiovaskularnom riziku.

Ključne reči: subklinička hipotireoza, levotiroksin, lipidi, kardiovaskularni rizik.

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THE CHARACTERISTICS OF THE HEALTH STATE POPULATION IN CENTRAL SERBIA

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Abstract: The aim of this study was to analyze the health status of the population in Central Serbia, in order to identify priority health problems. For data source, authors used reports about diseases, conditions and injuries, recorded in services for the health care of preschool children, services for school health, health care services for the adult population and services for the health care of women's health centers in Central Serbia in 2015. On the territory of Central Serbia, leading cause of morbidity in children of preschool and school age are diseases of the respiratory system. Cardiovascular diseases and respiratory diseases dominate in the structure of morbidity in the adult population, as well as high blood pressure as a single disease, while in the female population the most common are diseases of genitourinary tract.

Key words: health status, morbidity, Central Serbia.

INTRODUCTION

Assessment of the health status of the population is socio-medical procedure that allows us to obtain the objective picture of the health status of population using indicators.

More precisely, population health must be considered as the relation with indicators of the mortality, morbidity, disability, anthropometry and the quality of life.

Assessment of health status should be the first stage and a prerequisite for continued systematic and planned work to improve health, as well as the overall health system. Testing and evaluation of population health is not only the foundation of a modern health care planning and health services, but also a prerequisite for the planning and programming of work and development of health services on planning grounds, as well as the health promotion and further development of the health system. Today, almost all countries of the world are doing assessments of health, as a prerequisite and basis for the work on the reform of the health system (1).

AIM

The aim of this article was to analyze the health status of the population in Central Serbia, with the idea of identifying the priority health problems. This will ensure the implementation of the proper measures in addressing these problems.

METHOD

For data source, authors used the reports about diseases, conditions and injuries of services for the health care of preschool children, services for school health, health care services for the adult population and services for the health care of women's health centers of Central Serbia in 2015. The results are presented in tables.

RESULTS AND DISCUSSION

The population group of preschool children belongs to the birth time up to 6 years age. The proper attention should be paid in order to protect the health of this population group, not only because of special sensitivity to the effects of different factors, which may endanger their health, but also due to the fact that poor health and unhealthy lifestyles in childhood may result in poor health throughout their lives, which for the company means the health, financial and social consequences (2).

In health care services for preschool children in the territory of Central Serbia were registered in 2015, 138 074 illnesses. Five of the most common groups of diseases are diseases of the respiratory system with

50.5%, followed by the factors influencing health status and contact with health services with 17.2%, diseases of the ear and mastoid process with 5.5% and symptoms, signs and abnormal clinical and laboratory findings to 7.4% (Table 1). The leading diagnoses in a group of diseases of the respiratory system are acute inflammation of the throat and tonsils (43.2%) and upper respiratory tract infections (27.5%). These diseases are a short stream of good forecast and with greater socio-medical significance. Diseases of middle ear and mastoid disease is the most common diagnosis from a group of diseases of the ear and mastoid process with a share of 93.4% (Table2).

Population group of school children and youth belonging to school children aged 7 to 14 years and school youth (teenagers) from 15 to 19 years. School children and youth indicators of health are considered as the healthiest of all other age groups. However, this period of life is characterized by rapid sexual and psychosocial development as well as the risk for the formation of various risk behaviors, which may endanger the health at given time and/or later in life (3).

The most common causes of morbidity of school children on the territory of Central Serbia, in 2015 were respiratory diseases, accounting for 38.6% of the total morbidity.

The most common diagnosis in this group of diseases was acute inflammation of the throat and tonsils, which makes 42.9% of all diagnoses of diseases of the respiratory system.

Table 1. *Leading groups of diseases in health care services for preschool children on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE	Number	%
Respiratory system diseases	69791	50.5
Factors influencing of health status and contact with health service	23724	17.2
Symptoms, signs and abnormal clinical and laboratory findings	10249	7.4
Diseases of the ear and mastoid process	7620	5.5
Other diseases	26690	19.3
Total	138074	100

Table 2. *The main diseases in health care services for preschool children in the territory of Central Serbia, in 2015.*

GROUP OF DISEASE		Number	%
Respiratory system diseases		69791	100
1	Acute inflammation of the throat and the tonsils	30134	43.2
2	Upper respiratory tract infections	19174	27.5
3	Acute bronchitis and bronchiolitis	10857	15.6
4	Other diseases	9626	13.7
Factors influencing of health status and contact with health service		23724	100
1	Persons who seeking of health services for examination and testing	11934	50.3
2	Persons in health services for other reasons	8972	37.8
3	Other persons of potentially compromised of health contagious disease	2029	8.6
4	Other diseases	789	3.3
Symptoms, signs and abnormal clinical and laboratory findings		10249	100
1	Other symptoms, signs and laboratory findings	4858	47.4
2	Febrile conditions	4539	44.3
3	Pain in the abdomen and pelvis	801	7.8
Diseases of the ear and mastoid process		7620	100
1	Diseases of middle ear and mastoid disease	7121	93.4
2	Other diseases of middle ear and mastoid disease	493	6.5
3	Other diseases	6	0.07

Table 3. *Leading groups of diseases in the services for school health on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE	Number	%
Respiratory system diseases	61228	38.6
Factors influencing of health status and contact with health service	45771	28.9
Symptoms, signs and abnormal clinical and laboratory findings	11163	7.0
Skin and subcutaneous tissue disorders	6355	4.0
Other diseases	34117	21.5
Total	158634	100

Table 4. *The main diseases in health care services for school children on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE		Number	%
Respiratory system diseases		61228	100
1	Acute inflammation of the throat and the tonsils	26255	42.9
2	Upper respiratory tract infections	12236	20.0
3	Acute bronchitis and bronchiolitis	6473	10.5
4	Other diseases	16264	26.6
Factors influencing of health status and contact with health service		45771	100
1	Persons who seeking health services for examination and testing	35229	77
2	Persons in health services for other reasons	6929	15.1
3	Other persons of potentially compromised of health contagious disease	3582	7.8
4	Other diseases	31	0.06
Symptoms, signs and abnormal clinical and laboratory findings		11163	100
1	Other symptoms, signs and laboratory results	6446	57.7
2	Febrile conditions	2693	24.1
3	Pain in the abdomen and pelvis	2024	18.4
4	Other diseases	601	10.1
Skin and subcutaneous tissue disorders		6355	100
1	Other diseases of skin and subcutaneous tissue	4499	70.8
2	Infections of skin and subcutaneous tissue	1856	29.2

Upper respiratory tract infections are on the second place among the leading diagnoses of acute bronchitis and bronchiolitis. This acute disease has a short course, a good prognosis without greater social and medical importance. In second place are the factors influencing health status and contact with health services with 28.9% and third in total registered morbidity of this population group - the symptoms, signs and abnormal clinical and laboratory findings with 7%. Disorders of skin and subcutaneous tissues are in fourth place in the overall morbidity of school children (Table 3, Table 4).

Women's health is due to the high sensitivity of this population group and the fact that women take care of their own health but also the health of their children, parents and other family members, certainly of particular importance. Women's health involves an emotional, social and physical well-being, and is determined by the social, political and economic context in which women live, as well as the biological aspect. Women's health is not just her personal problem but also a problem of respective societies and the international community. Improving the health and quality of life of women has the very positive impact on the entire family (4).

In health care services for women in the territory of Central Serbia in 2015, more than half of the total mortality (60.7%) is a group of diseases of urinary tract. Factors influencing health status and contact with health services are represented with 27.1% of the morbidity of this service. The total morbidity of this service showed that 3.7% of a group had problems concerning - preg-

Table 5. *Leading groups of diseases in the area of women's health care on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE	Number	%
Diseases of the genitourinary system	29981	60.7
Factors influencing of health status and contact with health service	13395	27.1
Tumors	1968	4.0
Pregnancy, childbirth and puerperium	1836	3.7
Othr diseases	2240	4.5
Total	49420	100

Table 6. *The main diseases in health care services for women on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE		Number	%
Diseases of the genitourinary system		29981	100
1	*Cervicitis uterii*	9363	31.2
2	Other inflammation of female pelvic organs	6204	20.7
3	The menstrual disorders	3325	11.1
4	Other diseases	11000	36.7
Factors influencing of health status and contact with health service		13395	100
1	Persons who seeking of health services for examination and testing	9680	73.3
2	Care and inspection after childbirth	1357	10.1
3	Other diseases	2358	17.6
Tumors		1968	100
1	*Leiomioma uteri*	671	34.0
2	*Neoplasmus benigna ovarii*	479	24.3
3	Malignant tumors of connective and soft tissue	214	10.9
4	Other diseases	604	30.7
Pregnancy, childbirth and puerperium		1836	100
1	Other complications of pregnancy and childbirth	578	31.5
2	Complications in confinements and other conditions which complicate pregnancy and childbirth	394	21.5
3	Other diseases	972	53

nancy, childbirth and confinements. The most significant group due to chronic course, the possibilities of secondary prevention and high participation in mortality, make tumors, whose share in the total morbidity services for the health care of the women in Central Serbia with 4.5% (Table 5, Table 6).

In general medicine of health of Central Serbia, in 2015, a total of 459 055 illnesses were recorded. The leading place in the structure of morbidity in the general medicine on the territory of Central Serbia in 2015 occupying diseases of the circulatory system with 19.8%, which, like other chronic, mass, non-communicable diseases to progressively flow often lead to absenteeism, disability and shortening the length of the quality of life.

Leading diagnoses within this group of diseases is essential (primary) arterial hypertension (67%). In second place are the diseases of the respiratory system to the proportion of the total morbidity of 19.4%, which have the higher socio-medical significance, because it is an acute disease with a short course and the possibility of effective treatment. The leading diagnoses in this group of diseases are acute inflammation of the throat and tonsils, acute bronchitis/bronchiolitis and upper respiratory tract infections. Factors' influencing health status and contact with health services are ranked third with a share of 8.8%. Diseases of the musculoskeletal system and connective tissue are represented with 7.9% of morbidity in general medicine services. A group of diseases of urinary tract is in fifth place with a

Table 7. *The main diseases in health care services for women on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE	Number	%
Circulatory system diseases	90798	19.8
Respiratory system diseases	88955	19.4
Factors influencing of health status and contact with health service	40498	8.8
Diseases of the musculoskeletal system and connective tissue	36191	7.9
Diseases of the genitourinary system	33928	7.4
Other diseases	168685	36.7
Total	459055	100

Table 8. *The main diseases in general medicine on the territory of Central Serbia, in 2015.*

GROUP OF DISEASE		Number	%
Circulatory system diseases		90798	100
1	Essential (primary) arterial hypertension	60799	67
2	Disorders of the conduction system of the heart and heart arrhythmias	7471	8.2
3	Other ischemic heart diseases	6467	7.1
4	Other diseases	16061	17.7
Respiratory system diseases		88955	100
1	Acute inflammation of the throat and tonsils	38832	43.7
2	Upper respiratory tract infections	15172	17.1
3	Acute bronchitis and bronchiolitis	13199	14.8
4	Other disesases	21752	24.5
Factors influencing of health status and contact with health services		40498	100
1	Persons who of seeking health services for examination and testing	25209	62.3
2	Other persons of potentially compromised of health contagious disease	8602	21.2
3	Persons in health services for other reasons	5836	14.4
4	Other diseases	851	2.1
Diseases of the musculoskeletal system and connective tissue		36191	100
1	Other diseases of the back	20211	55.9
2	Degenerative diseases of the joints	6218	17.1
3	Inflammation of the joints	2621	7.2
4	Other diseases	7141	19.7
Diseases of the genitourinary system		33928	100
1	Inflammation of the bladder	20343	60
2	Prostatic hyperplasia	4440	13.1
3	Other diseases of urinary system	3211	9.5
4	Other diseases	5934	17.5

share of 7.4%. Within this group inflammation of the bladder with an incidence of 60% is the most common diagnosis in an adult population (Table 7, Table 8).

Similar results were found in our neighborhood countries. In Croatia in 2015, in the structure of morbidity of the adult population were the most common respiratory diseases and diseases of the heart and blood vessels. For children of preschool and school age usually are diseases of the respiratory system, followed by infectious and parasitic diseases, ear, skin and subcutaneous tissue. The most common reasons why women went to the gynecological clinic and used the services of chosen gynecologist within primary health care of women in Croatia in 2015 were diseases of the urinary

and sexual organs, pregnancy, childbirth and confinement, followed by tumors, infectious and parasitic diseases (5).

CONCLUSION

On the territory of Central Serbia, one leading cause of illness in children of preschool and school age are diseases of the respiratory system. In the structure of morbidity in the adult population are dominated cardiovascular diseases and respiratory diseases, while the high blood pressure is taken as a single disease.

Among females, the most common diseases are diseases of genitourinary tract. Intensifying promotional and preventive measures and activities, as well as educating the population of risk factors and diseases prevention is certainly the priority, in order to achieve improvement and preservation of health of the population in Central Serbia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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There were no external funding source for this study.

Sažetak

KARAKTERISTIKE ZDRAVSTVENOG STANJA STANOVNIŠTVA CENTRALNE SRBIJE

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Cilj rada je analiza zdravstvenog stanja stanovništva u Centralnoj Srbiji radi identifikacije prioritetnih zdravstvenih problema. Kao izvor podataka korišćeni su Izveštaji o oboljenjima, stanjima i povredama - službi za zdravstvenu zaštitu predškolske dece, službi za zdravstvenu zaštitu školske dece, službi za zdravstvenu zaštitu odraslog stanovništva, službi za zdravstvenu zaštitu radno aktivnog stanovništva i službi za zdravstvenu zaštitu žena Domova zdravlja Centralne Srbije za 2015. godinu. Na teritoriji centralne Srbije vodeći uzrok oboljevanja kod dece predškolskog i školskog uzrasta su bolesti sistema za disanje. U strukturi morbiditeta kod odraslog stanovništva dominiraju bolesti sistema krvotoka i bolesti sistema za disanje, dok su u populaciji žena najzastupljenije bolesti mokraćno-polnog sistema.

Ključne reči: zdravstveno stanje, morbiditet, centralna Srbija.

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Case report

ECTOPIC CHORIOCARCINOMA IN A PRETEEN IN OGBOMOSO, SOUTH-WEST NIGERIA. A CASE REPORT

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Abstract: Ectopic Choriocarcinoma is an extremely rare occurrence. The case of ectopic choriocarcinoma discussed here involved a 12 year old girl who presented with lower abdominal pain and dizziness following a short period of amenorrhea after attaining menarche. A provisional diagnosis of ruptured ectopic gestation was made based on the clinical evaluation and patient had emergency laparotomy. Histopathology report revealed a choriocarcinoma of the ovary. Patient defaulted on subsequent follow up care. This case is presented as an eye opener on the need to also focus on the reproductive health challenges, early sex education in preteen and rare occurrence of the disease amongst the Pre-teenage groups. It is also important to deal with the possibility of a non gestational choriocarcinoma of the ovary which has a worse prognosis.

Keywords: Ectopic Choriocarcinoma, Preteenage, ruptured ectopic gestation, departed against medical advice.

INTRODUCTION

Trophoblastic tumours like choriocarcinoma rarely occurs, it can be gestational or non gestational. Gestational choriocarcinoma usually follows a molar pregnancy, normal pregnancy, spontaneous abortion or an ectopic pregnancy unlike the non gestational type in which there is no convincing evidence of pregnancy. Interestingly, choriocarcinoma is a distinctly rare occurrence in an ectopic gestation. It's incidence is one in 533 of tubal pregnancies and one in 1.6 million normal intra uterine pregnancies (1, 2). In fact, only 0.76-4% of choriocarcinomas has been reported in ectopic location (3, 4).

CASE REPORT

Miss AO, A twelve year old girl was referred to our hospital with a history of amenorrhea of 16 weeks following an unprotected sexual intercourse with a 16 year old male teenager. She had complained of lower abdominal pains of 1 week and dizziness in the duration of 2 days; having just attained menarche and had only menstruated twice prior to her presentation in our hospital. Her urine pregnancy test before presenting at our facility was positive and two attempts were made to evacuate the uterus in different private hospitals. However, pelvic ultrasound was not performed, prior to presentation in our hospital.

On examination in the emergency room, she was pale, her pulse rate was 112 beats per minute and blood pressure was 90/60 mmHg. The abdomen was full and moved with respiration, there was generalized tenderness and a mass was felt in the right lower half of the abdomen. Further examination of the mass was hampered due to severe abdominal tenderness. Vaginal examination revealed a grossly normal cervix, cervical examination tenderness was positive and pouch of Douglas was full. Culdocentesis yielded altered non clotted blood.

A provisional diagnosis of rupture ectopic pregnancy was made to rule out perforated uterus following voluntary termination of pregnancy via uterine evacuation. Investigation result includes Packed Cell Volume 22%, Blood Group O positive, Serum electrolyte profile was within normal limit. She had an emergency exploratory laparotomy, and intra operative findings revealed haemoperitoneum of about 500 millitres of fresh and altered non clotted blood, grossly intact fallopian tubes bilaterally, grossly normal left ovary, an enlarged right ovary with multiple cystic appearances and areas of rupture and active bleeding seen. The uterus was normal with no evidence of perforation. Right ovariectomy was performed and post operative recovery was uneventful; she was consulted to abstain from sexual intercourse and the use of contraception. Patient's histopathology report was choriocarcinoma of the ovary. Serum β hCG was > 100,000 IU. Patient and her relatives were counselled on the need to take chemotherapeutic agents and continuous medical follow up care. However, efforts by the managing team and the social workers to keep patient in the hospital for proper care proved abortive she departed against medical advice (DAMA) due to financial reasons. She represented in our hospital six (6) months later with a history of chronic cough and weight loss suggesting a possible metastasis. Following the initial evaluation and on plan to request for investigations and probably work her up to obtain chemotherapeutic agents. Relatives again declined and subsequently departed against medical advice to seek for care with Traditional Care Givers.

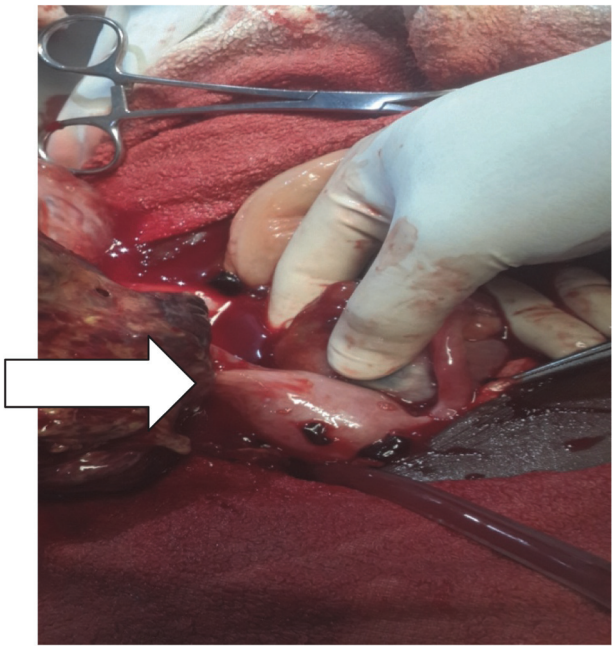

Figure 1a. *Arrow showing ovarian mass at surgery*

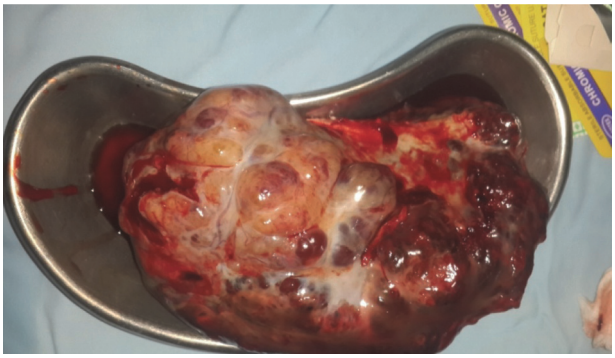

Figure 1b. *Specimen in a kidney dish following its removal at surgery*

PATHOLOGICAL FINDINGS

Gross features

We received 1 kg formalin fixed lobulated, gray, soft to firm mass of 18 x 13 x 10 cm dimension. Cut surface is hemorrhagic, variegated, partly cystic and partly solid. The cysts contain mucoid secretion (Figure 1a, 1b and 2).

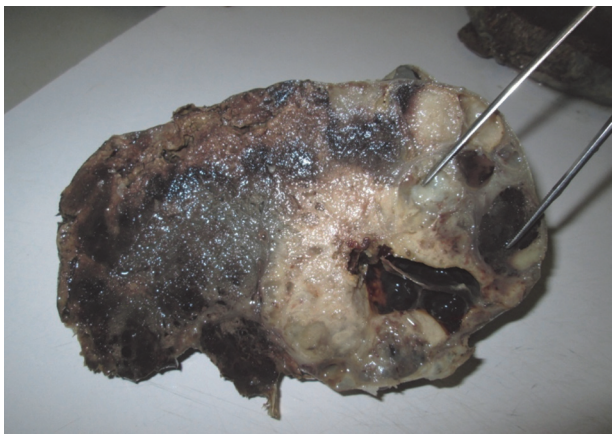

Figure 2. *Cut surface of formalin fixed ovarian mass, showing mucoid containing cyst*

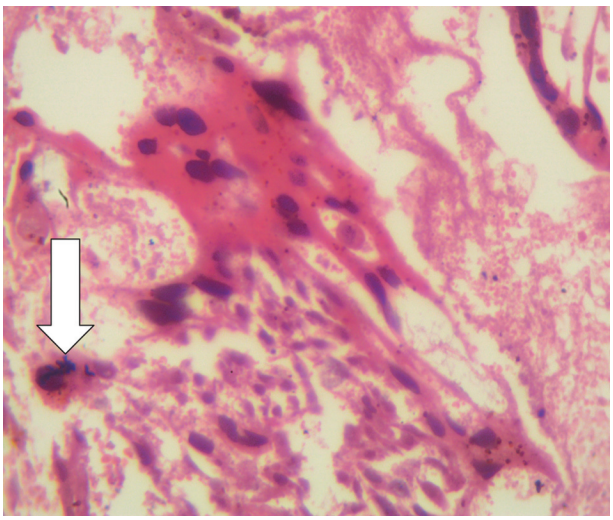

Figure 3. *X 100 showing malignant syncytiotrophoblast and cytotrophoblast cells and bizarre mitotic figure (arrow) in pool of hemorrhagic necrosis*

Microscopic features

The sections show scanty foci of malignant syncytiotrophoblastic and cytotrophoblastic cells and bizarre mitotic figures in pools of extensive hemorrhagic necrosis (Figure 3).

DISCUSSION

Although, ectopic pregnancy can be diagnosed clinically based on common presenting complaint like amenorrhea associated with abdominal pain, minimal vaginal bleeding and dizziness (5). Choriocarcinoma presenting with the clinical features similar to those of ruptured ectopic pregnancy is an extremely rare event and the diagnosis is usually confirmed histologically (6). Choriocarcinoma is a malignant proliferation of cytotrophoblast and syncytiotrophoblast without the presence of chorionic villi. The usual presentation of choriocarcinoma is in the uterine body, it may stem from chorionic villi following a normal or abnormal gestation. In most instances, choriocarcinoma of the ovary are gestational in origin in contrast to non-gestational choriocarcinoma of the ovary which is an exceedingly rare primary germ cell neoplasm of the ovary with poor prognosis due to its resistance to chemotherapy and metastasis to other organs at the time of diagnosis (7). In the case presented patient had just attained menarche and menstruated only twice before she had a sexual intercourse. However, this is not an enough evidence to classify as gestational choriocarcinoma, because of the inability to differentiate gestational and non gestational choriocarcinoma clinically or histologically. Individuals below 18 years and above 40 years are at greatest risk of developing choriocarcinoma (8). Furthermore, development of the tumour has been shown to vary between 5 weeks and 15 years after gestation or even after menopause (9). Therefore, based on her age and inexperience, it was difficult for her to know the symptoms and signs of early pregnancy, let alone relate her distended abdomen to gestation. When pregnancy was eventually suspected attempt to procure uterine evacuation was made on the assumption of the presence of an intrauterine gestation. This would have been avoided by performing an ultrasound examination.

The peculiarity of our case report is that it is a rare form of an extrauterine malignant trophoblastic disease in a preteenage girl who just attained menarche. Although, it is a treatable disease with good prognosis, the prevailing socioeconomic circumstances like age, poverty, lack of education on the part of the parent(s) and ignorance on reproductive health issues could affect the quality of life of preteenage female children. Furthermore, studies have shown that teenagers become sexually active in early puberty without using any form of contraceptives (10, 11).

CONCLUSION

There is the need to ensure that reproductive health education and awareness is not only limited to our secondary schools. There is an urgent need to expand this frontier of knowledge to the family, primary school teachers and the community at large. The rarity but possibility of both gestational and non gestational choriocarcinoma should be entertained by all healthcare providers. There is a need for synergy between professional health care givers and traditional health practitioners in patient care in order to ensure a proper referral system. Advocacy should be made for youth friendly clinics which will take care of young people including the pre-teenagers, social welfare in our hospital and community must create means of taking care of patients with terminal illness like cancer, so that those with curable diseases can be assisted.

CONFLICT OF INTEREST

No author has any conflict of interest to declare.

FUNDING

None

ETHICAL APPROVAL

Patient’s consent was obtained from her mother before they departed against medical advice. Ethical committee approved the work only after demonstrating that the patient was lost to follow up the second time with proposal for the social workers to trace the child and offer treatment at subsidized rate.

Sažetak

EKTOPIČNI HORIOKARCINOM KOD PREADOLESCENTA U OGBOMOSO-U, JUGO-ZAPADNA NIGERIJA: PRIKAZ SLUČAJA

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Ektopični horiokarcinom je izuzetno redak tumor. Slučaj koji se razmatra u ovoj studiji odnosi se na 12-godišnju devojčicu, koja je imala bolove u donjem delu abdomena i vrtoglavice, praćenje kratkotrajnom amenorejom, nakon menarhe. Privremeno postavljena dijagnoza, rupture ektopične trudnoće, načinjena je na osnovu kliničke evaluacije. Nakon toga pacijentkinja je hitno podvrgnuta laparoskopskoj operaciji. Histopatološki nalaz potvrdio je dijagnozu horiokarcinoma jajnika. Pacijentkinja je podvrgnuta naknadnom kontrolnom praćenju. Ovaj slučaj ukazuje na neophodnost fokusiranja na izazove u vezi sa reproduktivnim sistemom, kao što su rana edukacija o seksualnoj aktivnosti u adolescentnom periodu, kao i na pojavu retkih bolesti kod mladih. Bitno je posvetiti pažnju i na mogućnost pojave negestacionog horiokarcinoma jajnika, koji ima lošiju prognozu.

Ključne reči: ektopični horiokarcinom, preadolescentni period, rupturirana ektopična gestacija, napuštanje zdravstvene ustanove uprkos medicinskim savetima.

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Case report

MULTIPLE CEREBRAL TUBERCULOMAS WITHOUT FOCAL NEUROLOGICAL DEFICIT IN AN IMMUNOCOMPETENT ADULT NIGERIAN: A CASE REPORT

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Abstract: Multiple cerebral tuberculomas complicating miliary tuberculosis are a rare occurrence. It is rarer still for multiple cerebral tuberculomas to present without focal neurological deficits. We report the case of a middle-aged Nigerian male with the co-morbidity of miliary tuberculosis and multiple cerebral tuberculomas who presented without focal neurological deficits, but had complete resolution of symptoms and signs following a 6-month course of antituberculous therapy. This unique case emphasizes the need for a high index of suspicion in the diagnosis of atypical presentations of cerebral tuberculomas, while also further illustrating the place of computed tomographic scan of the brain in diagnosis. The case also illustrates the place of therapeutic trial in management.

Keywords: Multiple cerebral tuberculomas,index of suspicion, therapeutic trial, Nigeria.

INTRODUCTION

Worldwide, tuberculosis (TB) remains a serious public health problem (1, 2, 3). Challenges in management occur, especially with the advent of the HIV/AIDS scourge and emergence of multi-drug resistant TB (3, 4). Although the causative organism, *Mycobacterium tuberculosis*,can affect many organs, it most commonly affects the lungs (1, 5). However, central nervous system (CNS) involvement in the form of tuberculous meningitis, tuberculous abscess or tuberculomas is not uncommon, especially in immune-compromised individuals (1). Tuberculous meningitis is the most common CNS manifestation of TB. While an isolated cerebral tuberculoma is rare (6), multiple cerebral tuberculomas associated with pulmonary miliary TB is rarer still (7).

Most cases of cerebral tuberculomas present with focal neurological signs (5-8) and have been reported from various regions of the world (5-13). However, in spite of the high burden of tuberculosis in the West African sub-region which is made worse by the scourge of HIV/AIDS and multi-drug resistance, there is a paucity of information on cerebral tuberculomas from the sub-region. We report the case of an immune-competent Nigerian male with multiple cerebral tuberculomas associated with pulmonary miliary TB, who presented without focal neurological signs, and recovered fully following anti-tuberculosis therapy.

CASE REPORT

A 56-year-old farmer was referred to the Department of Medicine, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria, in July, 2000 on account of intermittent fever and neck pain of 4 months' duration, weight loss and reduced appetite of 2 months' duration, urinary incontinence of 1 week's duration and altered level of consciousness of a few hours' duration. He had associated headache and tremulousness but no blurring of vision, photophobia, vomiting or seizures. There was also no history of weakness in any of the limbs. In the 3 months before presentation, he was noticed to have a non-productive cough that was not asso-

ciated with pleurisy or haemoptysis. He had paralytic poliomyelitis in childhood with residual right lower limb deformity. He neither smoked cigarette nor drank alcohol and had no history of contact with an individual known to have pulmonary tuberculosis. The rest of the history was not remarkable.

Physical examination showed a chronically ill-looking middle-aged man, who was drowsy and responded to commands and questions inappropriately. He was febrile with an axillary temperature of 38.8 °C and had signs of some dehydration. He was neither pale nor jaundiced. There were no enlarged peripheral lymph nodes. His pupils were round, normal-sized and briskly reactive to bright light while the optic fundi were normal bilaterally. There was neck stiffness, but he had no other signs of meningeal irritation such as Kernig's and Brudzinski's signs. Aside from the right lower limb deformity probably due to childhood paralytic poliomyelitis, he had no focal neurological deficits. His pulse rate was 112 beats per minute, and supine blood pressure 120/80 mmHg. The heart sounds were normal. The respiratory rate was 30 cycles per minute. Aside from reduced air entry in the lungs globally, the chest examination was unremarkable, as was the abdominal examination.

He had a postero-anterior chest radiograph which showed widespread miliary nodules, suggestive of pulmonary military TB. A clinical impression of pulmonary miliary TB complicated by TB meningitis was made. Cerebrospinal fluid (CSF) analysis, including microscopy and culture and smear for acid and alcohol fast bacilli (AAFB) were normal. Cough was not productive of sputum, so analysis of sputum for mycobacteria could not be done. The erythrocyte sedimentation rate (ESR) was 30 mm/hr. The complete blood count, serum electrolytes, urea and creatinine, blood glucose

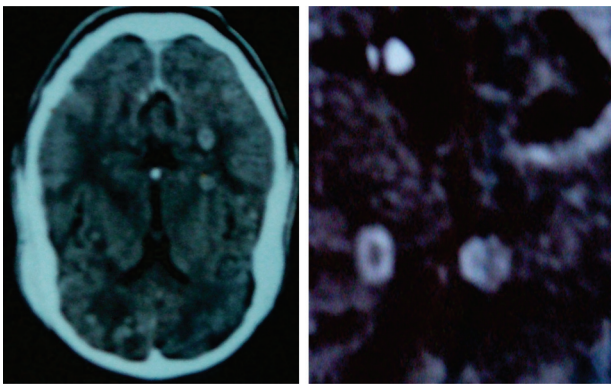
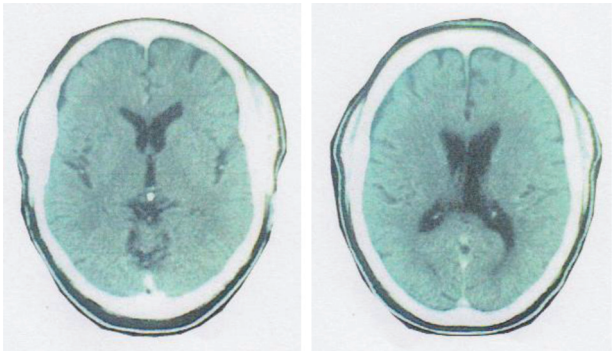


Figure 1a *(left) shows pre-treatment CT Brain scan showing multiple ring-enhanced lesions suggestive of cerebral tuberculomas.* ***Figure 1b*** *(right) shows caseation in lesions in a magnified image of the CT Brain scan*



Figures 2a and 2b. *9 years post-treatment CT scan showing complete resolution of tuberculoma lesions*

and liver function tests were within normal limits. No malaria parasites were seen on blood smear, and HIV I and II screens were negative. A computerised tomographic (CT) scan of the brain showed numerous, irregular, contrast-enhanced, small, widespread brain lesions with minimal surrounding oedema and no evidence of shift of midline brain structure or cerebral collection (Figures 1a and 1b). The findings were suggestive of cerebral tuberculomas.

With the above history, and chest radiographic and CT brain scan findings, a diagnosis of pulmonary miliary TB with multiple cerebral tuberculomas was made and the patient commenced on a 6-month course of anti-tuberculosis therapy. The initial phase of 8 weeks was with 4 drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) followed by a continuation phase of 16 weeks with 2 drugs (rifampicin and isoniazid) in standard daily doses under the DOTS strategy.

The patient made remarkable clinical progress as evidenced by weight gain and the resolution of fever and other symptoms, and was discharged home, after 26 days on admission, with no neurological sequelae. On follow up for more than sixteen years, he remained healthy and free from neurological sequelae, and has been able to continue with farming. For financial reasons, he was unable to repeat the CT brain scan soon after treatment. However, a repeat CT brain scan 9 years after treatment showed complete resolution of the cerebral tuberculomas (Figures 2a and 2b), thus confirming the response to therapy.

DISCUSSION

Cerebral tuberculoma is an important differential diagnosis in patients with focal neurological signs in areas endemic for TB (7, 8), not only in immune-compromised patients (14, 15), but also in immune-competent patients with miliary pulmonary TB, when TB meningitis has been excluded.

CNS tuberculosis can present clinically in many ways, but tuberculous meningitis is the commonest

manifestation (1). While tuberculomas can present without meningeal involvement (5, 6), as was the case with our patient, most often, however, brain TB lesions commonly complicate TB meningitis (12). Cerebral tuberculomas have been reported in 8-17% of patients with TB meningitis (12, 16).

CNS TB is not uncommon in developing countries (16), but multiple cerebral tuberculomas are rare (15), especially in association with miliary pulmonary TB (7) in immune-competent patients. Multiple cerebral tuberculomas are more often associated with miliary TB in children (17) although some reports in adults also show this association (5, 14).

The clinical features of cerebral tuberculoma depend on the size and location of the tuberculoma, and are similar to the neurological presentation of many other space occupying lesions. Aside from TB, the differential diagnoses of space occupying lesions, which causes may involve the lungs in immunocompetent individuals in developing countries, include pyogenic abscess, cysticercosis, and toxoplasmosis. Lymphoma is another possible differential but the chest radiograph usually shows intrathoracic lymphadenopathy when the lung parenchyma is involved.

Our patient presented with drowsiness, urinary incontinence and inappropriate response to command, features that could have been due to encephalopathy from a myriad of causes, but are not typical of a space-occupying lesion. The lack of focal neurological signs in our patient is in contrast to reported cases (5-8, 14).

CT brain scan is useful in the diagnosis of cerebral tuberculoma (7, 13, 15, 16). However, since some other space occupying lesions may have similar features (6, 8), the findings may be non-specific for intracranial tuberculomas, except when the 'target sign', thought to be characteristic of cerebral tuberculoma, is present (18). Therefore advanced MRI techniques, which are scarce in many developing countries, may be required to differentiate cerebral tuberculoma from other space occupying lesions, if invasive procedures are to be avoided.

Although the definitive diagnosis of TB remains the isolation of *Mycobacterium tuberculosis*, culture and/or Ziehl-Nielson (AAFB) staining of tissues from excision or biopsy may not identify the organism in some cases (7). Thus, even at autopsy or with surgical biopsy specimens, the isolation of *Mycobacterium tuberculosis* is possible in only 50% of cases (19). However, most of the developing countries which bear the greatest burden of tuberculosis lack adequate resources and often times have to rely on good clinical judgement. As typified by our patient, a high index of suspicion is important in areas of high TB endemicity, as some patients with cerebral tuberculomas may not have signs of focal neurological deficit at presentation.

Treatment of intracranial tuberculoma may be surgical when the lesions are large and few, and are causing focal neurological deficits, as in the cases reported by Muin and Zurin (7), or medical when the lesions are small and numerous like in our case and that of Innocenti et al (5) and Gasparetto et al (14). The complete resolution of lesions on medical therapy alone which has been documented previously (14, 20, 21), is supported by our report.

CONCLUSION

Our case report demonstrates the presentation of multiple cerebral tuberculomas without focal neurological deficits and the need for a high index of suspicion. Cranial CT scan is invaluable in unravelling the aetiology of such enigmatic cases where patients show signs of diffuse brain parenchymal involvement but no lateralizing signs. Our case also supports the place of therapeutic trial, with response to therapy used retrospectively to confirm the diagnosis of intra-cerebral tuberculosis.

Conflict of interest

The authors have no conflict of interest to declare.

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We are grateful to the patient for giving his permission for the publication of this paper.

Abbreviations

DOTS — Directly Observed Therapy Short course
HIV — Human Immunodeficiency Virus
AIDS — Acquired Immune Deficiency Syndrome
MRI — Magnetic Resonance Imaging

Sažetak

MULTIPLI CEREBRALNI TUBERKULOMI BEZ FOKALNIH NEUROLOŠKIH ISPADA KOD IMUNOKOMPROMITOVANE ODRASLE OSOBE U NIGERIJI — PRIKAZ SLUČAJA

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Multipli cerebrali tuberkulomi predstavljaju jednu od komplikacija miljarne tuberkuloze i izuzetno se retko javljaju. Još je ređi slučaj pojave milijarnih moždanih tuberkuloma bez fokalnog neurološkog deficita. Ovom studijom mi prikazujemo slučaj srednjovečnog Nigerijca sa milijarnom tuberkulozom i multiplim cerebralnim tuberkulomima, koji su se javili bez neuroloških ispada, uz kompletno povlačenje simptoma i znakova bolesti nakon šestomesečne antituberkulozne terapije. Ovaj jedinstven slučaj daje na značaju povišenom indeksu sumnje na tuberkulozu kod atipične prezentacije simptoma, kao i ulozi metoda vizuelizacije u postavljanju dijagnoze, kao što je kompjuterska tomografija (CT). Slučaj takođe prikazuje značajnu ulogu terapije u daljem lečenju pacijenta.

Ključne reči: multipli cerebralni tuberkulomi, indeks sumnje, terapeutski slučaj, Nigerija.

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Case report

OCCIPITAL LOBE EPILEPSY OR MIGRAINE HEADACHE

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Prihvaćen /Accepted 25. 08. 2016. god.

Abstract: **Introduction:** Occipital lobe epilepsies are rarely met in clinical practice, but when they occur, they can be misdiagnosed as migraine-like headache. Their prevalence ranges from 5% to 10% of all epilepsies. Seizures can occur at any age; etiologically speaking they can be symptomatic, cryptogenic and idiopathic (most often onsetis in childhood). Clinical symptomatology is manifested by partial epileptic seizures in the sense of visual elementary and/or complex manifestations, palinopsia, amaurosis, tonic head deviation, bulbus, nistagmus and headache. Propagation discharge to neighbour areas (temporal, parietal and frontal) is a frequent occurrence appearing with complex partial seizures frequently finishing with secondary generalized tonic-clonic (GTC) seizures. **Case report:** We are presenting a17-year-old male patient who has suffered from attacks of visual problems with headache since 10 years of age. All the time it is treated as a migraine headache. During the last attack of headache the patient also had a loss of consciousness, EEG that was performed for the first time evidenced epileptic discharges of the occipital area.The therapy also included treatment with antiepileptic drug pregabalin resulting in seizure withdrawal. **Conclusion:** The appearance of visual symptoms followed by headache is most frequently qualified as migraine triggered headache. However, when antimigraine therapy does not give favorable results epileptic headache should be suspected, with obligatory performance of EEG recording. Occipital lobe epilepsy often presents diagnostic dilemmas due to clinical manifestations that are similar to that of non-migraine headache.

Key words: headache, migraine, epilepsy, occipital epilepsy, dilemma, diagnosis, EEG recording.

INTRODUCTION

Epilepsies with seizures generated from the occipital lobe (occipital epilepsies) represent a rare clinical manifestation. Their prevalence rates from 5%-10% of all epilepsies (1). Etiologically speaking they can be symptomatic, cryptogenic occurring in all ages, and idiopathic that as a rule occur in childhood (1). Seizures are the most often simple partial, while the occurrence of complex seizures is frequently the sign of extra-occipital propagation discharges (temporal, parietal or frontal lobe). A short duration of seizures lasting from a few seconds to one minute and sometimes even three minutes is characteristic, but very rarely longer. Seizures occur frequently, sometimes every day. Clinical semiology of seizures involves visual and oculomotor symptoms. Visual symptomatology is predominated by elementary, rarely complex visual hallucinations, illusions, palinopsia and amaurosis. Visual hallucinations often appear in the form of small colorful circles that move within the visual field or are rarely shining and of twinkling pulsating lights (2). Elementary visual hallucinations are often followed by oculomotor symptoms with a contralateral tonic deviation of the eyes and head, and epileptic nistagmus with pulsating movements. Headache is often associated with seizures deriving from the occipital area that can be ictal or postictal and often has migraine characteristics. Visual hallucinations are the key symptom that suggests the occipital focus. If the visual symptoms are not expressed, semiology of seizures and standard EEG can be often the cause of misdiagnosed type of epilepsy, because they express more the propagation discharge and less initial locality (3). The occurrence of ictal discharge propagation to neighbor areas is very frequent in symptomatic etiology, but very rare in idiopathic etiology (3). Spreading of seizures can lead to the occurrence of complex partial seizures (temporal and frontal lobes), hemiclonic and GTC seizures. Epileptic seizures of the occipital lobe occur more frequently in the awake than in the sleeping state, the interictal EEG shows occipital spikes and/or the spike-and-wave complex in 57% of cases, unilaterally or bilaterally (4). Bioccipital discharges of the spike-and-wave complex occur both in symptomatic and idiopathic etiology. In symptomatic epilepsies of the occipital lobe various samples predominate, beginning from congenital mal-

formations, vascular lesions (infarction, periventricular leukomalacia, porencephaly, hemorrhagic types) systemic diseases, metabolic disorders, infections and neoplasms (4). Prognosis is favorable in the idiopathic and unfavorable in the symptomatic epilepsy where it essentially depends on the type and size of lesion cause. Pharmacoresistance is seen in most symptomatic cases with a disorder of cortical development or occipital lobe tumor where surgical treatment is the method of choice. As the consequence of focal affection of any occipital lobe, visual elementary hallucinations with associated headache can occur that often results in diagnostic dilemma, regardless if it is the case of occipital lobe epilepsy or migraine (5, 6). Migraine (hemicrania) is a vascular, unilateral, gradual, most often throbbing and pulsating headache followed by vomiting, photophobia and phonophobia, and which is of various duration ranging from 4-72 hours. Migraine is most frequently a neurological disease with the prevalence of 6%-16%. Two major clinical types are migraine without aura (80%) and migraine with aura (20%) (7, 8). The migraine aura is most often expressed by twinkling lights, scotomes, including black-and-white zig-zag lines or amaurosis in duration of 15-60 minutes that is followed by headache. Migraine, and particularly a migraine with aura, is frequently difficult to differentiate from the epilepsy of the occipital lobe due to their similar clinical symptomatology (9, 10).

CASE REPORT

We present a 17-year male patient born at term and with normal early psychomotor development, without data on hereditary epilepsy, and who had attacks of short-lasting visual problems (shiny color spots, poor vision or complete loss of vision followed by unilateral back head headache. Seizures occurred 2-3 times per week with associated headache of various duration, 1/2-4 hours, and sometimes longer. Standard biochemical and biohumoral laboratory analyses of blood and urine were performed, as well as neurological and ophthalmological examination, CT and MRI that were within the range of normal referent values. Having all this in mind, the diagnosis of migraine with aura was made. All the time the patient was treated with standard antimigraine medications (sumatripan, pizotiphen, propanolol, naproxen, aspirin) but without significant therapeutic effects. It was at this point of time, when during headache loss of consciousness occurred (GTK seizure), that the first EEG was done which showed epileptic discharges of the occipital area (1-3 seconds unilateral spike and spike - wave discharge), apropos occipital epilepsy. The treatment also included antiepileptic pregabalin (150 mg + 0 + 150 mg), resulting in complete remission seizures.

DISCUSSION

Epilepsies of the occipital lobe are a typical representation of focal epilepsies that are characterized by ictal aura (subjective ictal phenomenon) with predominant visual symptomatology associated with headache. The specificity of occipital epilepsies is elementary visual hallucinations in the form of small multicolor moving circles that increase and multiply, their rapid occurrence and short duration from a few seconds to 3-4 minutes (1, 5). Beside the short-lasting visual aura attacks, occipital epilepsies are characterized by ictal or postictal migraine triggered headache (unilateral or bilateral, pulsating, nausea) that is various in duration, lasting from several minutes to several hours or longer. Identical clinical symptomatology can be also seen in migraines with aura, with the migraine aura developing slowly, lasting longer (≥ 5 minutes) and is mostly followed by colorless visual symptoms in the sense of black-and-white zig-zag lines or scotoma. Migraine headache follows the migraine aura mostly lasting 4-72 hours (7, 8). Migraine and occipital epilepsies have a paroxysmal beginning and a great number of common symptoms that often creates a problem of their diagnostic differentiation. Therefore, in practice it is quite frequent that epilepsy of the occipital lobe is to be proclaimed as a migraine with aura, and more rarely the opposite. These diagnostics mistakes are not rare and can be found in numerous reports by many authors (5, 6). Although the visual aura and headache have their specificities both in the speed of their development and the time of duration, they cannot be often significant parametric differentiating factors between epilepsy and migraine (8). The thing, that can clearly differentiate occipital epilepsies from migraine is the manifestation of ictal oculomotor symptomatology in the sense of the deviation of the head, eyes, nistagmus or hemiconvulsions, GTC seizures and EEG epileptic discharges (5). EEG is the main and irreplaceable diagnostic test for disorders which in occipital epilepsies interictally often register unilateral and/or bilateral occipital epileptic discharges in the appearance of spike and/or spike-and-waves. Therefore, it is necessary to perform EEG in all atypical, persistent headaches, migraine that does not react to standard analgesics and antimigraine medications. In migraines EEG most often shows unspecific, non-epileptiform changes, however if specific grapho-elements are registered it is clear that there is the presence of epileptic headache (7, 8). The term “migralepsy”, which is still used today in the terminology of headaches, and indicates the epileptic seizure during or after the migraine aura, is increasingly often changed by the term epileptic headache – hemicrania epileptic, which suggests that the headache

is, for example, primarily of epileptic and not of migraine etiology (6, 11). Headaches are often nonspecific clinical manifestations of epilepsy; they frequently develop as the result of general organism and brain fatigue after GTC seizure. In relation to the epileptic seizure, in epilepsies headaches are classified as preictal (prodrom seizures), ictal, postictal and interictal (10, 11). In the epilepsies of the occipital lobe, headache is a frequent manifestation showing characteristic of seizures; inctalare of shorter duration, while the postictal last longer and have the characteristics of migraine. Investigations have shown that migraine and epilepsy use common pathophysiological mechanisms and genetic factors which make them clinically similar and diagnostically difficult to differentiate (12). It is clear that the onset of the occipital lobe epilepsy is not essentially different from the migraine with aura, however other clinical manifestations, EEG, CT and MRI findings and response to drug treatmentcan be of significant help in the differentiation between epilepsy and migraine. Our case report also confirms that epileptic seizures (epilepsy of the occipital lobe) are frequently misdiagnosed as migraine. Beside the frequent practice of epileptic seizures being pronounced as an epileptic seizure (event) there are also the opposite situations. About 20% -30% of cases that are hospitalized in the specialized institutions for epilepsy do not have epilepsy, and instead have an epileptic seizure, mostly in the form of a syncope, vertigo, transitory ischemic attack, migraine, parasomnia, dyskinesia or psychogenic nonepileptic seizure (13, 14, 15).

CONCLUSIONS

Clinical occurrence of visual symptoms and the associated headaches are more frequently qualified as migraine triggered headache. However, if the migraine therapy does not yield favorable results it is also necessary to suspect epilepsy of the occipital lobe. The epilepsy of the occipital lobe often leads to a diagnostic dilemma due to clinical manifestations which are similar to non-migraine type of headache. Visual symptomatology and headache characterize both clinical entities. However, the knowledge of further symptomatology with the application of the necessary examination protocol (EEG, MRI) considerably helps in their diagnostic differentiation and exact diagnosis.

Conflict of interest

Authors confirmed that no actual or potential conflict of interest exists in relation to this article.

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There were no external funding source for this study.

Abbreviations

GTC — generalized tonic-clonic
EEG — electroencephalography
CT — computed tomography
MRI — magnetic resonance image

Sažetak

EPILEPSIJA OKCIPITALNOG REŽNJA ILI MIGRENSKA GLAVOBOLJA

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Uvod: Epilepsije okcipitalnog režnja se retko sreću u kliničkoj praksi, a kada se pojave mogu biti pogrešno dijagnostikovane kao migrenska glavobolja. Prevalencija im se kreće od 5% do 10% svih epilepsija. Napadi se mogu javiti u svakom uzrastu, a etiološki mogu biti simptomatske, kriptogene i idiopatske (najčešči početak u detinjstvu). Klinička simptomatologija se manifestuje parcijalnim epileptičkim napadima u smislu vizuelnih elementarnih i/ili složenih halucinacija, palinopsije, amauroze, tonične devijacije glave, bulbusa, nistagmusa i glavobolje. Propagacija pražnjenja na susedne regione (temporalni, parijetalni i frontalni) je česta pojava, pri čemu dolazi do složenih parcijalnih napada koji se često završe sekundarnim GTK napadima. **Prikaz bolesnika:** Prikazali smo muškog pacijenta, uzrasta od 17 godina, koji od svoje 10. godine ima napade vizuelnih smetnji sa glavoboljom. Sve vreme tertian je kao migrenska glavobolja. Kada je tokom poslednjeg napada glavobolje imao i gubitak svesti urađen je prvi put EEG snimak koji je ukazao na epileptička pražnjenja okcipitalnih regiona. U terapiju je uključen antiepileptic pregabalin i napadi su prestali. **Zaključak:** Pojava vizuelnih simptoma sa pratećom glavoboljom se najčešće kvalifikuje kao migrenska glavobolja. Međutim, kada antimigrenska terapija ne daje povoljne rezultate, potrebno je posumnjati i na epileptičku glavobolju uz neophodno EEG snimanje. Epilepsije okcipitalnog režnja često prave dijagnostičke dileme zbog kliničkih manifestacija koje su slične migrenskoj glavobolji.

Ključne reči: glavobolja, migrena, epilepsija, okcipitalna epilepsija, dilema, dijagnoza, EEG snimanje.

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Review paper

MALNUTRITION IN THE SURGICAL PATIENTS

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Abstract: The term "malnutrition" is a broad term used to describe any imbalance in the diet. In 2009 it was confirmed that malnutrition is an urgent health problem. The reasons for which malnutrition may develop are different. Loss on cellular, physical and physiological level happens as a consequence of malnutrition. Studies show that in surgical practice there is malnutrition in 50% of patients and that there is an association between inadequate nutritional status and surgical result. It leads to prolonged treatment, increasing of the level of morbidity and mortality, increased hospital costs, etc. Sometimes malnutrition is unrecognised, untreated and worsened in hospitals. For this reason this paper will elaborate: nutrition and a surgical patient, assessment of a nutritional status, assessment of energy requirements, and enteral and parenteral nutrition in order to determine the conditions and procedures that affect the appearance, recognition and treatment of malnutrition.

Key words: malnutrition, surgical patient, nutritional assessment, assessment of energy requirements, enteral nutrition, parenteral nutrition.

IINTRODUCTION

The term "malnutrition" is a broad term used to describe any imbalance in the diet, ranging from over nutrition to under nutrition. According to the Declaration of ENHA of June 2009, it was confirmed that malnutrition is an urgent health problem throughout Europe. The reasons for which malnutrition may develop are different: scarce food intake, increased requirements related to the stage of a disease, complications of the primary disease expressed in reduced absorption or excessive loss of nutrients, or a combination of all (1, 2). Loss on cellular, physical and physiological level occurs as a consequence of malnutrition (2). This loss is determined by the age of the patient, type, severity and duration of illness, and the current nutritional intake.

Studies show that in surgical practice there is malnutrition in 50% of patients and that there is a connection between the nutrition and surgical result. It leads to prolonged treatment, increasing of the level of morbidity and mortality, increased hospital costs, etc. (3). Professor Claude Pichard's opinion, in this context, says that: "Malnutrition has a high prevalence and it leads to poor clinical outcomes. Solution exists and an effective nutritional support improves the clinical expectations, and it is economically worthwhile. Now it is the time for action." Concerning the seriousness of the problem a conclusion has been made in order to undertake a series of complementary activities under the motto: STOP for the diseases related to malnutrition and for the diseases leading to malnutrition (4)!

Considering the previously mentioned, this paper will elaborate the following issues in order to determine the conditions and procedures that affect the appearance, recognition and treatment of malnutrition:

- Nutrition and a surgical patient,
- Assessment of a nutritional status,
- Assessment of energy requirements,
- Enteral and parenteral nutrition.

The paper will systematize everything that has been published and obtained by searching the data bases such as: Medline (OVID, 1948 - till now), Cochrane Central Register of Controlled Trials, Pub Med, and everything connected to the problem of malnutrition in a surgical patient.

MALNUTRITION AND THE SURGICAL PATIENTS

Surgical patients are a heterogeneous population, with differences in primary diseases. Although differences exist separate in all patients, there is a similarresponse to stressfrom the surgical intervention which is represented with a complex of serial reactions involving the endocrine and inflammatory system. These reactions play an important role in the development of metabolic changes and in the development of postoperative complications.

With the start of the surgery, the patients get increased counter-regulatory hormones like cortisol, glucagon and catecholamines leading, among others, to increased energy consumption and start of protein catabolism. With the progress of molecular biology it has become clear that pro-inflammatory cytokines such as necrosis tumour factor - alpha TNF-α and interleukins IL-1, IL-6, IL-8 are important mediators of early protein catabolism concerning an injury and sepsis. The impaired balance between them and anti-inflammatory cytokines also plays a role in the occurrence of malnutrition or anorexia, pyrexia, and fat catabolism (5).The greater the stress is, the more catabolism gives reactions and influence, and as a consequence reduction in the normal insulin anabolic effect and development of insulin resistance may occur. An intensive catabolic response is difficult for the human organism, it is associated with a destruction of muscle tissue and reduction of energy supplies and it prolongs the recovery (6). Therefore, it is necessary to undertake measures to reduce the stress as a result of surgery and to support the anabolism during the surgical treatment (7).

In the pre-operative phase, the traditional and strict rule "nothing by mouth from midnight to the day of surgery" is applied in order to ensure an empty stomach. The preoperative diet is intended to reduce the risk of regurgitation, nausea and vomiting in patients with anaesthesia, and thus to prevent aspiration of stomach contents (8). Starvation is also important from surgical aspect, especially in stomach and intestines operations or in laparoscopic interventions where there is an increased intra-abdominal pressure and an increased chance of regurgitation.

The optimal time of starvation is questionable. There is consensus that clear solutions can be taken two to three hours before the intervention, and concerning the question of intake of solid food and milk, experiences vary between four and eight hours. According to recent studies, four to six hours for solid food and milk are recommended, and four hours for breastfeeding milk. According to Green C. R et al. excessive starvation will not provide optimal gastric environment, but it can lead to dehydration, electrolyte imbalance, nausea, malnutrition, hypothermia, and irritability (9).

Recommendations are given by ESPEN for intake of carbohydrates instead of starving overnight. This recommendation is supported by the fact that the excessive starvation causes a rise in the inflammatory markers in the acute stress response phase, while the use of oral carbohydrate supplements two hours before the surgical intervention can have an effect on this reaction. The effects of this recommendation have been confirmed in the study by Zelic. According to this study the patients undergoing surgery on intestines due to a malignant disease should receive a carbohydrate drink in the evening and two hours before the surgery because reduction of postoperative thirst, hunger, dehydration, headache, nausea and vomitus have been noticed in all adult groups (10). In gastrointestinal operations the extended and reduced food intake is the cause of malnutrition, which of course is emphasized by the tumour cachexia and the reduced absorption as a result of intestinal obstruction or previous resection (5).

In the postoperative phase, the normal oral nutrition or nutrition through a tube should start within the first 24 hours. There are strong evidences that oral nutritional supplements (200 ml twice daily) given on the day of the surgical intervention up to the normal food intake give positive benefit (11). The early postoperative nutrition decreases the response to stress and consequently decreases the insulin resistance and reduces the nitrogen loss and muscle mass loss (12).

The assessment of gastrointestinal function and tolerance of the patient is extremely important for the application of postoperative nutrition. In patients operated electively by resection of gastrointestinal tract, who take substances through the mouth reduction of infections and hospital stays has been determined opposite to the same group of patients who were not administered substances through the mouth (13). The positive effects of the early nutrition on reducing the incidence of anastomotic dehiscence, infection of a wound, pneumonia and intra-abdominal abscess is confirmed by Lewis et al. They pointed out the conclusion that there is no benefit to keep patients without oral nutrition after surgery (14).

Nutrition may be postponed in the postoperative period due to postoperative complications that have a negative effect on postoperative nutrition. Problems with intestines or postoperative ileus are the most common complication in surgical patients. It compromises postoperative nutrition, which leads to increased postoperative catabolism, worse wound healing, and greater possibility for infection (14, 15). Haemodynamic instability is another reason for the delayed start of en-

teral nutrition. Trophic nutrition is recommended in those conditions (16).

ASSESSMENT OF A NUTRITIONAL STATUS

The assessment of a nutritional status is of particular importance because it affects the postoperative clinical results. The early recognition of malnutrition enables planning of nutrition therapy, prevention of inadequate nutritional status, as well as its cessation or correction so that the postoperative complications can be avoided (17).

For the diagnosis of malnutrition, the American Society of Parenteral and Enteral Nutrition (ASPEN) have recommended methods for assessing the nutritional status of hospital patients. These methods include criteria and data for nutritional needs, food intake, clinical picture of the patient, and anthropometric and laboratory parameters (18). Some of the parameters are: common and current weight, percentage of current loss of weight, height, body mass index (BMI), the upper arm circumference, the upper arm muscle mass, skinfold thickness at the level of triceps, total lymphocyte count, and serum albumins (19). There is no unique standard for identification of malnutrition. ASPEN (2002) proposes the Subjective Global Assessment (Subjective Global Assessment - SGA) for detection of malnutrition prevalence, and the European Society - ESPEN proposes nutritional risk screening - 2002 (NRS-2002).

The simplest and oldest way to measure nutritional status is the body weight, compared to the previous or the ideal weight. The use of weight value as a single one for the assessment of nutrition as a method is considered to have characteristics with limiting estimate. In any case, the weight loss greater than 10% is a poor prognostic indicator (20).

The body mass index (BMI) is a more optimal nutritional indicator. Namely, in each scenario when BMI is less than 15 kg/m^2 the increase in morbidity is significant (21). The hospital patients with a BMI less than 18.5 kg/m^2 have longer stay in the unit for intensive care, increased frequency of postoperative complications, delayed start of oral nutrition etc (22). However, BMI, as a measure of evaluation, has low sensitivity in overweight patients. The increased BMI is associated with a heart disease, diabetes, hypertension, and an increased morbidity during surgery. Hence, a question arises whether the increased morbidity in the perioperative period is actually a result of malnutrition or of comorbidities in these patients. Accompanying diseases in these patients led to a change in water balance, oedema, and ascites that affects the estimations. All in all, BMI is a useful tool for assessment of nutrition in surgical patients who have a need and benefit from nutritional intervention.

Anthropometric methods are used in the general assessment of the nutritional status, but for acutely injured patients they showed as nonspecific.

Another method is the method of functional capacity and muscle power. With this method, which was first introduced by Klidijian in the 1980s, the reduction of muscle power is a better predictor of malnutrition and the complications in the postoperative period than the methods of weight loss and some anthropometric measures. The method of functional capacity and muscle power is useful, but its use is limited to the need for patient cooperation, which as a parameter is variable and subject to change under the influence of drugs (23).

Furthermore, in a prospective study of 100 patients undergoing major surgery of the gastrointestinal tract, Sungurtekin et al. concluded that 44% of the patients have malnutrition according to SGA, a 61% have malnutrition according to NRS (24).

SGA is a marker that integrates data received from the disease history, the clinical examination and image. Five characteristics received from the history of the disease and four characteristics received from the clinical examination enable assessment of nutritional status. The score obtained by applying this method ranks the patients as:

1. Well nourished (Grade A),
2. Moderately malnourished or at risk of malnutrition (Grade B), and
3. Severely malnourished (Grade C).

SGA and albumin are values that are useful to differentiate high risk from low risk patients. Detsky assesses these values as useful techniques for nutritional assessment of patients who need to undergo a major gastrointestinal surgery as a way to predict postoperative complications in nutrition (25).

NRS - 2002 is the method that assesses the weight loss, BMI, food intake, and severity of the disease. Based on this screening the patients can be classified with:

- No risk of malnutrition with value 0,
- Mild risk of malnutrition with a value of 1-2,
- Moderate risk of malnutrition with a value of 3-5,
- Severe risk of malnutrition with a value > 5 (26).

The other marker or the so called nutritional risk index (NRI) is determined by serum albumin and the change in weight. Both markers, NRS and NRI, correlate with the extent and severity of postoperative complications in gastrointestinal surgery patients. Some studies show that patients, who suffer from serious illness and have serious nutritional risk as SGA- level B

and NRS 2002 more than 3 points, would benefit from a perioperative nutritional support in the postoperative recovery and in their clinical results (27).

Reduced synthesis of negative proteins in the acute phase will result in decreased levels of serum albumin, transferrin, prealbumin and retinol which are a potent indicator of a poor result. Hence, it is advisable that albumin and prealbumin should not be used as isolated markers to assess the nutritional status because they are essential markers for the inflammatory metabolism and reflect the water balance. Positive acute phase proteins, such as CRP are also a potent predictor of morbidity and mortality and are increased and present in the period of inflammation (28).

In the evaluation of malnutrition, ESPEN protocols specify the nutritional risk screening 2002 (NRS-2002) and albumin below 30 g/l. In Jie's study it is found that patients who have a score of 5 or more, according to NRS scale for malnutrition benefit more from the perioperative nutritional support (29).

As it can be seen, there are many markers, methods or combination of methods having certain characteristics that may occur as advantages or disadvantages in certain situations. Nutritional status is determined by them which on the other hand is a marker itself for determination of the status of the disease.

ASSESSMENT OF ENERGY REQUIREMENTS

About patients who receive nutritional support there is always a question: are being fed appropriately? Studies in surgical patients have been reviewed to determine the 'optimal' energy and protein requirements of these patients. Uncomplicated surgery has energy requirements of 1.0-1.15 x BMR while complicated surgery requires 1.25-1.4 x BMR in order to meet the patient's needs (30). Identifying the optimal requirements of ICU patients is more difficult because of the heterogeneous nature of this population. In general, 25 kcal/kg/separate considered as an appropriate target for surgical patients, but patients with sepsis or trauma may require almost twice as much energy (31). The measurement of energy expenditure is the most accurate method to assess energy needs. It can be done directly by putting a person in a calorimeter and measuring the amount of heat produced by the body mass but this is not very practical. Predictive equations are routinely used to determine energy needs in patients. There are nearly 200 published energy expenditure formulas dealing with various conditions, disease states, age, presence of obesity and other additional factors (32). One of the most frequently used formulas for predicted energy expenditure is the Harris-Benedict equations and they take into account gender, age, height and weight. Harris-Benedict Equations (calories/day):

Male: (66.5 + 13.8 X weight) + (5.0 X height) – (6.8 X age)

Female: (665.1 + 9.6 X weight) + (1.8 X height) – (4.7 X age)

weight in kilograms, height in centimetres, age in years (33).

Unfortunately there is no consensus about which predictive equation is the most accurate in surgical patientand the substantial error, when compared to indirect calorimetry is in the range of 7–55%, leading to over- and underestimation of energy needs. The reasons are because many of the equations are based on static variables, and the surgical patients are known to show wide day-to-day fluctuations in metabolic rates. Another limitation of predictive equations is the failure to account for potential nutrient losses through diarrhea, wounds, fistulas, and haemodialysis. Another difficulty with energy determinations arises in the obese surgical patients and there is a question of which weight to use in predictive equations. Body composition consists of fat mass and fat-free mass which is the metabolically active component. The concern is that use of the actual body weight (ABW) in the obese patientswill overestimate energy needs, as much of the excess weight is metabolically inactive fat mass and that leads to overfeeding.That is why some practitioners prefer to use adjusted body weight (AjBW) or ideal body weight (IBW) in their calculations, but unfortunately there is still no consensus about this (34).

The gold standard for determining energy expenditure and requirements in the clinical setting is indirect calorimetry. This method calculates rest energy expenditure (REE), the amount of energy in calories required for basic metabolic processes of the body during a non-active period of 24-hours. It is measured indirectly with a indirect calorimetry equipment (metabolic cart) by analysis of respiratory gases (usually expired) to derive volume of air passing through the lungs, the amount of oxygen extracted from it and the amount of carbon dioxide, as a by-product of metabolism, expelled to atmosphere all computed to represent values corresponding to 1 minute time intervals.

With these measurements except REE, the respiratory quotient (RQ) can be also calculated. The abbreviated Weir equation is used to calculate the 24-hour energy expenditure.

Abbreviated Weir Equation:

REE = [3.9 (VO2) + 1.1 (VCO2)] 1.44

VO2 = oxygen uptake (ml/min)

VCO2 = carbon dioxide output (ml/min).

Respiratory quotient (RQ) = VCO2/VO2 (35).

The amount of lean body mass is the primary determinant of REE, but multiple other factors can influence REE such as age, sex, presence of fever or inflammation, thyroid function etc. Sedation, analgesics, and neuromuscular blocking agents reduce REE, while pressors raise REE. The respiratory quotient (physiologic range 0.67–1.2) reflects substrate oxidation and has different values such as 1.0 for glucose, 0.81 for proteins and 0.69 for lipids. It is theoretically useful in assessing a nutrition regimen, as overfeeding or excessive carbohydrate administration increases VCO2 and leads to an RQ > 1.0, while underfeeding with associated lipolysis decreases the RQ. According to some specialists despite the theoretical usefulness of the RQ in nutrition titration, it has a low sensitivity and specificity as an indicator of over- and underfeeding. A number of confounding factors can increase or decrease the RQ, including acid-base disorders, hypo- or hyperventilation, and body habitus (36).

It is clear that the most important measurement for REE is VO2 but it needs indirect calorimetry equipment ("metabolic cart") which is expensive. That is why some specialists tried to find some equation to calculate the REE measuring only VCO2 with ventilator devices. The modified Weir equation (REE, kcal/day = 5.5 × VCO2L/min) × 1440 using a fixed RQ of 0.89) waslater improved by Sandra Stapel and colleagues who proposed an even more sophisticated approach to achieve better accuracy using VCO2 alone in ventilated surgical patients, extracting RQ from the nutrition regimen for each evaluation and not using a fixed value (37).

However, while the use of complicated mathematics resulted in good precision and low bias, the concept does not reflect the complexity of physiology in the surgical patient. First the administered nutrients are only partially absorbed in these patients. Thus, small intestine glucose absorption is markedly impaired, independently of duodeno-cecal transit time while lipid absorption is reduced by almost half when compared with healthy volunteers. Secondly, endogenous glucose production is not depressed despite nutrition administration, adding a load of endogenous carbohydrates to the nutrient administration and autophagy provides endogenous lipids, carbohydrates and protein. Third, secondary to stress, there is significant insulin resistance as well as obligatory lipolysis and severe proteolysis which nutrients are unable to inhibit. Finally, body substrate oxidation obtained by indirect calorimetry is far from the nutrient administration, making the correlation between the prescription and the respiratory quotient more difficult. In addition, indirect calorimetry equipment ("metabolic cart") is expensive, requires technical expertise to operate, and is often unavailable in many institutions. It is inaccurate with $F_{IO2} \geq 60\%$, PEEP ≥ 12 cm H_2O, air leakage in the respiratory circuit (leaking chest tube or endotracheal cuff, bronchopleural fistula), haemodialysis, extreme pain or agitation, and with calibration errors. Inaccuracies inherent in these types of calculations or measurements may explain why some interventional nutrition studies fail to achieve positive clinical outcomes (38).

PARENTERAL NUTRITION

The first attempts of parenteral and experimental nutrition implemented on animals date back to the seventeenth century, but the actual development was recorded in twentieth century, which is identified as the era of development of parenteral nutrition. Namely, the research and practices of a group of doctors from Chicago presented in the study "Prolonged and carefully timed intravenous sugar" in 1915 emphasized the importance of carbohydrates, which opened the door for further research concerning amino acids, polypeptides, lipids and their use.

According to ESPEN the parenteral nutrition is favourable for malnourished patients for whom the enteral nutrition is not possible or is not tolerated and for patients with postoperative complications and loss of gastrointestinal tract function, where it is impossible for patients to receive and absorb sufficient quantities of food, either orally or enterally, more than 7 days. Routine use of parenteral nutrition has not proved beneficial for patients with good nutritional status and patients with adequate oral intake in the first week after surgery (39, 40).

Several studies show that parenteral nutrition 7-10 days before surgery improves postoperative results in patients with severe malnutrition. As a consequence of a direct venous administration, the parenteral nutrition can rapidly improve the nitrogen balance. It enables fast lymphocyte recovery and healing of wounds as well as reduction of infectious and non-infectious complications from 42.9% to 5.3% (41).

In the majority of patients the oral use of carbohydrates before surgery is recommended, which may be used by the intravenous route if oral intake of fluids and food is not allowed. Infusion of glucose of 5 mg/kg per minute and 20% solution can affect insulin resistance, protein metabolism, post-operative nausea and vomiting (42).

The question of whether the diet should be standard or customized remains open. It is known that cardiac patients could benefit from concentrated solutions of small volume, the patients with chronic renal failure require a reduced concentration of sodium, potassium and total volume, and the patients with gastrointestinal disorders, with metabolic and electrolyte imbalances require addition of electrolytes, vitamins and trace elements (43).

Certainly, it should not be overlooked that the use of parenteral nutrition carries risks with itself, such as: volume overload with respiratory compromising, excessive carbohydrate infusion with elevated triglycerides, hepatic steatosis and hyper-glycaemia with immune disorder, feeding with azotaemia, hypertonic dehydration, metabolic acidosis, as well as hyper-capnia and refeeding syndrome as a result of the aggressive nutrition.

Science has been ambivalent towards parenteral nutrition and its use in surgical patients. If by 1988 the importance of parenteral nutrition and its impact on mortality was emphasized, after 1989 the results of the research have given a different answer. According to recent studies the parenteral nutrition does not show a significant benefit for surgical patients.

ENTERAL NUTRITION

Enteral nutrition means intake of food or commercial products through a tube or a stoma in the stomach, duodenum or jejunum. Preserved integrity of the small intestine mucous membrane and colon is necessary for its use. According to recent research on the gastrointestinal tract, intestinal mucosa and its integrity may be endangered by lack of food and it may in fact lead to atrophy of the intestinal mucosa and suppression of local immune response, to bacterial translocation and even to sepsis and multiorgan weakness. The basic rule in clinical nutrition says: "If the gastrointestinal tract works, use it".

Lesions of the central nervous system, anorexia, cancer, hyper metabolic conditions, burns, severe infections, and even intestinal inflammatory conditions are examples where enteral nutrition is indicated (44).

Immunonutrition is a new approach in diet. It is nutrition with added nutrients (immunoregulators) such as arginine, glutamine, omega 3 fatty acids, nucleotides, and antioxidant vitamins and minerals. Immunoregulators act favourably on the secretion of trophic hormones, on the synthesis of anti-inflammatory cytokines, on the reduction of immunosuppressive pro-inflammatory cytokines, on the improving of mesenterial circulation, on the wound healing, on protein synthesis, and also affect the reduction of proteolysis thus preventing bacterial translocation and subsequent infectious complications concerning extended hospital stays.

M. Braga's et al., study is in favor of this context. It was conveyed on 206 patients with gastrointestinal malignancy, where the group administered immunonutrititon through jejunal tube showed significant reduction of infectious complications (14% vs. 30%) and also in the length of hospital stays (11.1 vs. 12.9 days) (45). In his study, Senkal M et al., included 164 patients with cancer on the upper gastrointestinal tract and analysed and compared the complications between patients receiving postoperative immunonutrition through jejunostoma and those treated with standard nutrition. It was noted that the early postoperative complications were similar in both groups, while the complications after the 5th day were significantly reduced in patients with immunonutrition (46).

The quantity and time of enteral nutrition are also important factors. In some cases a minor amount in the intestinal lumen (< 200 ml/24 h) may prevent atrophy of the intestinal villi and affect reduction of bacterial translocation as well as of other complications. These are cases of so called minimal enteral nutrition (47).

Regarding the time of giving, according to a study by Payne J. et al., where patients with abdominal operations (gastrectomy, colon resections) were involved, the group of patients who received enteral nutrition 4 hours after surgery showed significantly lower number of postoperative infections compared to the group with placebo (48).

However, despite the advantages, complications in enteral nutrition may occur. They are divided into mechanical, metabolic and gastric-intestinal. Mechanical complications are: setting a tube into respiratory paths, its displacement, blockage and relegation. Metabolic complications occur in 30-40% of patients and are in a form of disturbance of water electrolyte balance, such as: hypophosphatemia or hyperphosphatemia, magneziemia, glucose, and metabolic acidosis. Gastric intestinal complications include distensia, sickness, nausea, vomiting, and diarrhea. It is considered that diarrhea occurs in 10-15% of the patients.

ENTERAL VERSUS PARENTERAL NUTRITION

Good nutrition must include adequate intake of energy, nitrogen, vitamins and trace elements (49). Enteral nutrition is considered to be the most adequate and superior way of nutrition. More facts support this stance. Namely, the enteral nutrition is considered to have a wide spectrum of applications by which it provides nutrition in different clinical conditions. It is more cost effective, more secure, with simpler and safer maintenance of nutrition, metabolic and immune function, with maintenance of gastrointestinal barrier and preserving the integrity of enterocytes and colonocytes as well as with preventing bacterial translocation (50).

Complications such as intra-abdominal abscess and pneumonias are more common in patients having parenteral nutrition compared to patients with enteral nutrition. The number of lymphocytes in the intestinal mucosa and the respiratory and intestinal IgA levels were reduced in patients receiving parenteral nutrition. Enteral nutrition is a well-known factor in the healing of intestinal anastomoses (51). However, some patients

prefer parenteral nutrition instead of enteral nutrition through tubes, and others despite having a functioning gastrointestinal tract, are unable to tolerate oral or enteral nutrition as a result of anorexia, dysphagia, etc. For these and other reasons parenteral nutrition is an affordable choice of nutrition in some cases.

THE COMBINATION OF ENTERAL AND PARENTERAL NUTRITION

Enteral nutrition cannot always meet the energy needs of patients. According to ESPEN, the combination of enteral and parenteral nutrition should be considered for patients who need nutritional support, and where more than 60% of the requirements cannot be met by the enteral route. The benefit of enteral parenteral combination is unclear.

According to Heidegger et al. the use of parenteral nutrition as a supplement, after the 4-th days of admission is considered to cause a reduction of nosocomial infections and improving of clinical results in patients where the enteral nutrition does not achieve the energy target (52). In a small retrospective study it was showed that the combination of enteral-parenteral nutrition in patients with acute pancreatitis affects not only the evolution of the disease but also the complications and the overall result of the treatment.

In a multicentre study involving more than 4,000 critically ill patients, Casaer MP., reported that an early use of parenteral nutrition as an addition to enteral nutrition, causes an increase in infections and an increased incidence of cholestasis (53). In another retrospective study done by Hsu in a surgical intensive care unit, it was shown that the patients fed enterally by an increased amount of 10% of the total estimated calories, better clinical results were achieved (54). According to the results of these studies and the results of other researchers, it can be concluded that enteral nutrition should be always administered when it is possible.

CONCLUSION

Malnutrition is a well-known major risk factor for poor postoperative results. Understanding of the physiological developments in a surgical patient, as well as the advancement of diagnostic tools enable a clinician to identify preoperative malnutrition or risk of malnutrition and thus to determine who needs nutritional therapy in order to prevent postoperative complications related to malnutrition. Enteral nutrition is a superior choice. In cases where more than 60% of energy needs cannot be met by enteral intake, combination with parenteral nutrition should be considered. Routine use of parenteral nutrition has not proved useful, but the use of parenteral nutrition 7-10 days before surgery improves postoperative results in patients with severe malnutrition. Inadequate oral intake in a period longer than 14 days leads to higher mortality.

Conflict of interest

The authors declare that there is no conflict of interest.

Abbreviations

ENHA — European Nutrition Health Alliance
TNF-α — Necrosis tumor factor – alpha
IL — Interleukins
ESPEN — The European Society for Clinical Nutrition and Metabolism
ASPEN — American Society of Parenteral and Enteral Nutrition
BMI — Body mass index
SGA — Subjective Global Assessment
NRS - 2000 — Nutritional risk screening – 2002
NRI — Nutritional risk index
CRP — C - Reactive protein
BMR — Basal metabolic rate
ABW — Actual body weight
AjBW — Adjusted body weight
IBW — Ideal body weight
REE — Rest energy expenditure
RQ — Respiratory quotient
V02 — Oxygen uptake
VC02 — Carbon dioxide output
FiO2 — Fraction of inspired oxygen
PEEP — Positive end – expiratory pressure
Ig A — Immunoglobuline A

Sažetak

MALNUTRICIJA KOD HIRURŠKIH BOLESNIKA

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Malnutricija je široki termin koji se koristi kada se treba opisati svaki disbalans u ishrani. U 2009. bilo je potvrđeno da je malnutricija hitni zdravstveni problem i zdravstveni problem u celoj Evropi. Razlozi zbog kojih

se malnutricija može pojaviti ili razviti su različiti. Kao posledica loše ishrane desi se gubitak na ćelijskom, fizičkom i fiziološkom nivou. Studije pokazuju da u hirurškoj praksi postoji malnutricija kod 50% pacijenata i da postoji veza između neadekvatnog prehrambenog statusa i hirurškog rezultata. Malnutricija dovodi do produženog lečenja, povećanog nivoa morbiditeta i mortaliteta, povećanih bolničkih troškova itd. Ponekad malnutricija ostaje neprepoznata, što dovodi do njenog pogoršanja i nedovoljnog lečenja. Iz tog razloga cilj ovog rada je da elaborira patofiziološke mehanizme kod hirurškog pacijenata, procenu prehrambenog statusa, kao i enteralnu i parenteralnu ishranu u cilju utvrđivanja uslova i procedura koji utiču na izgled, prepoznavanje i tretman malnutricije.

Ključne reči: malnutricija, hirurški pacijent, enteralna ishrana, parenteralna ishrana.

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Review paper

THE SUBTYPES OF PANCREATIC DUCTAL ADENOCARCINOMAS

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Abstract: Being the 4th leading cause of cancer deaths in the U.S. and with a global increase in incidence, above 80% of pancreatic cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection is the only hope for a cure, the answer is probably in early screening, proper classification and right therapy. The advancing research will likely lead to a better understanding of Pancreatic Ductal Adenocarcinoma (PDAC) as well as enhance the techniques for screening, diagnosis, accurate subtyping and enable the use of targeted therapy. Thus, instead of clubbing together various subtypes of PDAC for trials, improving the subcategorization will ensure statistical significance for the academicians, and the clinicians would avoid administration of placebo drug to a vast number of patients.

Key words: pancreatic cancer, subtypes, genetic, proteomic, phosphoproteomic.

INTRODUCTION

Pancreatic cancer is the 4th leading cause of cancer death in the USA, and is increasing globally. The cure rate, although showing improvement, is still very low, approximating at less than 7%. It is often diagnosed at a very late stage, when curative treatments are limited. Above 80% of these cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection is the only hope for a cure, the answer is probably in early screening, proper classification and right therapy (1) The advancing research technologies and easy accessibility, will hopefully lead to a better understanding of Pancreatic Ductal Adenocarcinoma (PDAC) as well as enhance the techniques for screening, diagnosis, accurate subtyping and enable the use of targeted therapy.

Though PDAC is the most common form of pancreatic cancer, its causes and risk factors are largely unknown. In spite of the emergence of various treatment modalities, very few randomized trials have shown a drastic alteration in PDAC management. This is attributed to inadequate statistical significance leading to the hypothesis that PDAC is an aggregate of many diseases. Scientifically, the fundamental differentiation in PDAC lies in its genetic mutations and variable activation of them. Sporadic mutations (p16, TP53, KRAS, BRAF, SMAD4 mutations) are much more common than inherited genetic mutations and associated syndromes (p16, TP53 mutations). The different prognosis and managements for each PDAC probably stem from these variable genetic mutations (2).

The vast genetic studies on PDAC have failed to affect the clinical decision making, thus, paving way for addition of proteomic data to these studies. Proteomics improves the functional accuracy of data while, genomics is concerned with physical information. In addition to this data, phosphorylation of proteins lets us know about the active proteins.

The challenge has been to Subtype PDAC so that we do not cluster the different types in the same group, wishing one modality will treat all of them. This would help us in designing better future clinical trials. With newer techniques, we have been able to subtype PDAC. These classification systems have not been universally accepted, thus, this field is in a stage of exponential growth and promise. The first classification was tried by Collison and group in 2011. It has been debated and restructured with newer subtyping coming out more recently. We had previously reported 3 classifications in a previous paper (2).

Subtypes

Collisson et al (3) and his team used Gene expression analysis and used 62 designated gene signatures to subtype Pancreatic Cancer tissue it into “classical”,

"quasi-mesenchymal (QM)", and "exocrine - like". The "Classical" subtyped showed favorable prognosis. The "classical" subtype had high expression of epithelial and adhesion-associated genes. The "Quasi-Mesenchymal)" subtype showed high expression of mesenchyme associated genes and the "exocrine-like" subtype similarly showed relatively high expression of exocrine enzyme genes.

Moffitt et al on genetic analysis subtyped it into two tumor subtypes on the basis of two different tissues. The micro-dissected and analyzed the tumor cells and stromal cells. On the basis of genetic analysis of the ductal cells the subtyping was classified into "classical" and "basal-like" and on the basis of the stromal cells into "normal" and "activated". The "Classical" ductal subtype again showed favorable prognosis when compared to "basal - like". Patients with "activated" stromal subtype had a worse prognosis (4).

To identify metabolomic clustering within PDAC, Daemen A. et al. (5) investigated the PDAC metabolite profile. They quantified 256 metabolites and studied 38 PDAC cell lines. They identified three subtypes that showed different profiles associated with glycolysis, lipogenesis, and redox pathways. A subtype was defined by "reduced proliferative capacity", while the other two showed distinct metabolite levels associated with glycolysis, lipogenesis, and redox pathways. These were named subtypes "glycolytic" and "lipogenic" subtypes. In PDAC clinical samples, functional relevance in disease progression was suggested by the following association: The "lipogenic" subtype is associated with the epithelial "classical" subtype of Collison, with better prognosis, whereas the "glycolytic" subtype is associated with the "Quasi-mesenchymal" subtype of Collison.

Bailey et al (6) identified genes that are consistently mutated in pancreatic cancers. On analysis of gene activity, it revealed four distinct subtypes of PDAC, Squamous, Pancreatic progenitor, Immunogenic and aberrantly differentiated endocrine exocrine-(ADEX).

The primary mutation in "Squamous tumors" was p53 and these tumors were found to have worse prognosis while "Pancreatic progenitor tumors" had abnormal expression of genes involved in early pancreatic development. "Aberrantly Differentiated Endocrine Exocrine -ADEX tumors" had aberrant activity of genes involved in KRAS activation, exocrine, and endocrine differentiation and "Immunogenic tumors" had aberrant activity in genes regulating the immune pathways.

Another study, subtyping the PDAC on the basis of selective signaling networks, provides insight into PDAC biology. Humphrey et al resolved PDAC into subtypes by global phospho-tyrosine profiling. Using immune-affinity coupled high-resolution mass spectrometry, global tyrosine phosphorylation patterns were characterized across two large panels of human PDAC cell lines: the ATCC series and TKCC series, resulting in the identification of more than 1,800 tyrosine phosphorylation sites and the consistent classification into three subtypes with distinct phosphorylation profiles (7).

The 3 subtypes characteristic of the ATCC series, were associated with changes in signaling networks associated with: "cell-cell adhesion and epithelial-mesenchyme transition, mRNA metabolism and receptor tyrosine kinase signaling. Further investigation showed that the three subtypes were conserved in the both the series. These receptor tyrosine kinase enriched cell lines exhibited enhanced sensitivity to EGFR inhibitors which may act a prognostic marker for response to therapy.

DISCUSSION

The premalignant lesions like IPMNs and MCNs are detectable with radiological and endoscopic ultrasound imaging. We are unable to predict accurately which cysts can be safely monitored, and which likely to progress to infiltrating carcinoma. A major help to the clinician was the establishment of consensus guidelines by a consortium of the international association of Pancreatology at a meeting held in Sendai, Japan, in 2006, followed by a revision of the guidelines in 2012 (8, 9). Though the original and the revised Sendai guidelines are extremely helpful, they rely on indirect measurements of risk. Studies to validate these guidelines have not been successful in confirming them. Therefore, more reliable markers are needed for the management of individual patients. Many studies correlating the grades of (Pancreatic Intra epithelial Neoplasia) PanIN lesions and genetic mutations have been done. One by Saiki et. al (10) has shown that approximately 45% of PanIN-I lesions were found to harbor KRAS mutation, thus suggesting that one of the earliest genetic mutations is activation of KRAS. After it the inactivating mutations of CDKN2A may be responsible for PanIN-II and inactivation of TP53 and SMAD4 are generally associated with PanIN-III. Similarly, Fritz et. al (11) found the expression of SPARC is lost in 50% of low and moderate grade dysplasia, while it is lost in 80% of the IPMNs with high-grade dysplasia.

CONCLUSION

In this bioinformatics driven era it would not be prudent for the academicians and clinicians to put all kinds of PDAC in the same arm of a clinical trial. For the academicians, it would only surmount to bias and achieving statistical significance would be very difficult, while for the clinicians, we would be knowingly giving a placebo drug to a vast number of patients. The

sub-classifications that emerge with the rapidly evolving novel technologies will provide an opportunity to not only better the understanding of the etiology and progress of PDAC, but will also help in targeting the therapy selectively and may give clues to early detection of this aggressive carcinoma, thereby improving the mortality and 5 year survival rates. Therefore, it's wise to follow and grow the growing field of Subtyping the Pancreatic Ductal Adenocarcinoma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Abbreviations

PDAC — Pancreatic Ductal Adenocarcinoma
USA — United States of America
TP53 — Tumor Protein p53

KRAS — V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog: It is a protein encoding Gene.

BRAF — v-Raf murine sarcoma viral oncogene homolog B: It is a protein encoding Gene.

SMAD4 — It is a protein encoding Gene that plays a role in maintaining balance between atrophy and hypertrophy: Mothers against decapentaplegic homolog 4.

QM — Quasi Mesenchymal type of Pancreatic Adenocarcinoma.

ADEX — Aberrantly Differentiated Endocrine eXocrine type of Pancreatic Adenocarcinoma.

ATCC — ATCC is a company in Washington, DC, USA.

TKCC — The Kinghorn Cancer Centre, Australia.

EGFR — Epidermal Growth Factor Receptor.

IPMN — Intraductal papillary mucinous neoplasm.

MCN — Mucinous Cystic Neoplasms.

PanIN — Pancreatic Intra epithelial Neoplasia.

SPARC — Secreted Protein Acidic & Rich in Cysteine: It is a protein encoding Gene.

Sažetak

PODTIPOVI PANKREASNOG DUKTALNOG ADENOKARCINOMA

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Karcinom pankreasa predstavlja četvrti po redu uzrok smrti od karcinoma u Sjedinjenim Američkim Državama. Porast incidence kao i činjenica da preko 80% pankreasnih karcinoma je lokalno uznapredovalo ili sa prisutnim metastatskim promenama u vreme postavljanja dijagnoze, stavlja ga u fokus istraživanja današnjice. S obzirom da je jedina nada za izlečenje hirurška resekcija, unapređenje leži u ranom skriningu, odgovarajućoj klasifikaciji, kao i ispravnoj terapiji. Uznapredovala istraživanja na ovom polju će najverovatnije dovesti do boljeg razumevanja pankreasnog duktalnog adenokarcinoma (AKPD), kao i unapređenja tehnika skrininga, dijagnostike, do ažuriranja subtipizacije i omogućavanja upotrebe ciljane terapije. S toga, umesto raportiranja o raznovrsnim subtipovima AKPD, unapređenje subkategorizacije će obezbediti statističku značajnost za akademike, a ujedno će i kliničari izbeći uvođenje placebo leka velikom broju pacijenata.

Ključne reči: karcinom pankreasa, subtipovi, genetika, proteomik, fosfoproteomik.

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Review paper

PRIMARY OPEN-ANGLE GLAUCOMA AND FARMACOECONOMICS — REVIEW

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Abstract: Primary open-angle glaucoma (POAG) is defined as a chronic and progressive disease. Date suggested that it is the second most common cause of the blindness in the world. Blindness, as global problem, is partially consequences of poor health insurance, low medical education, etc. The only modifiable risk factor for glaucoma is intraocular pressure. Cost of the antiglaucomatous treatment increased by prescribing and using wide spectrum of antiglaucomatous drugs. If an ophthalmologist is not satisfied with glaucomatous disease control, need for the laser or surgical treatment is appeared. Disease stadium also determines the cost of the treatment. The social and economic burden of glaucoma can be changed by increased life expectancy, older population age and higher per capita GDP. Unique opinion about cost effectiveness cannot be reached, due to nonconforming findings of many studies. Treatment approach must be individualized to every patient, according to the disease's stadium, availability of therapeutic modalities and approaches, life expectancy and the level of GDP. Efficacy, compliance and potential side-effects of prescribed medication also determine the proper treatment choice.

Key words: primary open-angle glaucoma, therapy, pharmacoeconomics, social burden of glaucoma.

INTRODUCTION

Primary open-angle glaucoma (POAG) is defined as a chronic and progressive disease. Also, it is a consequence of raised intraocular pressure (>21 mmHg) in at least one eye, with acquired loss of optic fibers, glaucomatous disc progression, visual field changes, and normal appearing anterior chamber angle with no underlying cause (1). It is a disease which requires life-long treatment (2). Without the adequate treatment, glaucomatous disease induces irreversible changes of the optic nerve head with consequential visual deterioration and loss. Burr et al. estimated that mild glaucomatous visual field impairment would progress to at least unilateral blindness in 23 years without the antiglaucomatous drugs (3). The minimum age limit for the occurrence of glaucoma becomes gradually decreased throughout the lifetime (38 years of age). However, glaucoma incidence raises and challenges our treatment fund (4).

Date suggested that it is the second most common cause of the blindness in the world. Quigley and Broman in their study established that in 2020, about 80 million of population will have glaucoma diagnosis in the world. Also, they calculated that 11 million of them will be blind bilaterally (5).

THERAPEUTIC APPROACHES

The only modifiable risk factor for glaucoma is intraocular pressure (6). Visual filed damages can be prevented by lowering the IOP using different therapeutically approaches: medications, laser and surgery (7).

MEDICAL ANTIGLAUCOMATOUS THERAPY

There are five different groups of medications that can be used for IOP control: beta blockers, cholinergic, carbonic anhydrase inhibitors, alpha-2 agonists and prostaglandin analogs. Ophthalmologists, specialist for glaucoma, suggested antiglaucomatous medications as the first line drugs in treatment of glaucoma (8). Using different antiglaucomatous drugs decreased the antiglaucomatous surgeries number (9). On the other hand cost of the antiglaucomatous treatment increased by prescribing and using wide spectrum of antiglaucomatous drugs. Long term using antiglaucomatous drugs can in-

crease the noncompliance rate. If an ophthalmologist is not satisfied with glaucomatous disease control, the need for the laser or surgical treatment is option (7, 8, 9).

LASER ANTIGLAUCOMATOUS THERAPY

According to the ocular finding as well as the IOP value, different laser techniques can be used for controlling IOP (10). Trabeculoplasty done with argon or diode laser, gave similar results (50% with diode laser treated eyes and 58% with argon laser treated eyes were successful after 5 years) (11). Selective trabeculoplasty can be the first choice of glaucoma treatment in some cases. Data suggested that LTP as initial treatment in 50% of patients did not demand additional medical treatment for 1-2 years (12).

SURGICAL THERAPY

Long-term use of antiglaucomatous drugs can lead to the fund insufficiency in the developing countries (13). Surgical treatment of glaucoma can help in solving this economic problem. Different surgical techniques can be used for IOP control. Basically, creating of alternative outflow of humour aqueous is the target the antiglaucomatous surgery. Trabeculectomy, as the main surgical technique, make the fistula through the sclera from anterior chamber to subconjunctival spaces. Wound healing can decrease the outcome of the surgery (14). The success rate can be improved using antimetabolites (mytomicin C, 5 fluorouracil) (15) or beta irradiation (16). If the antiglaucomatous surgery did not provide IOP control, glaucoma drainage devices are reserved (17). Also, some other surgical techniques were described for IOP control: trabecular aspiration, goniocurettage, laser trabecular ablation, angle shunting devices and transcleral cyclophotocoagulation or cryoablation (17).

NEW TREATMENT OPTION

No matter how powerful the different antiglaucomatous drugs are, the glaucoma is still the second cause of blindness in the world (17). Also, despite the fact that IOP is normal, optic nerve damage progresses. This fact proves the statement that some improvements must be made in order to gain the better control of glaucoma disease. IOP control is not enough for controlling glaucoma disease, but neuro-protection or neuro-regeneration can improve control of optic nerves damages (17).

Ganglion cells apoptosis in glaucomatous eye can be explained by different mechanisms: deprivation of neurotrophic growth factors, mechanical compression with consequential ischemia, reactive astrocytosis, oxidative stress, etc (18). Lot of clinical trials was performed in order to prove the protective effect that different substances have on optic nerves. There has not been many benefits in examined groups compared to placebo groups in Phase III clinical trials (18). Recently published data suggested for new antiglaucomatous drug-Rho kinase inhibitor (RKI). It was proved that Rho kinase inhibitor inhibits Rho-associated protein kinase (ROCK)-signaling pathway. This pathway provokes cellular contraction and transdifferentiation of fibroblasts in myofibroblasts. Thus, Rho kinase inhibitor can relax trabecular meshwork, with consequently decrease resistance in outflow pathways. Also, it was documented that Rho kinase inhibitor decrease progression of glaucomatous optic disc damages acting on its blood vessel. After antiglaucomatous surgery, Rho kinase inhibitor improves its success by inhibiting myofibroblasts transdifferentiation (19).

PHARMACOECONOMICS ASPECTS

Blindness is reserved approximately about 90% in developing countries (20). Blindness, as the global problem, is partially consequences of poor health insurance, low medical education, etc. In ophthalmological world, lots of facts are known about POAG (pathogenesis, clinical signs, therapy), in developing countries knowledge about this insidious disease is very poor (21).

As glaucoma is asymptomatic when medical treatment is recommended, in developing countries surgery gives low improvement postoperatively, because of advanced stadium of glaucoma in the moment of establishing the diagnosis (21). Also, patients from developing countries showed poor acceptance of surgery suggestions (22). Developing countries reported some data which indicated that cost of surgical treatment in advanced stadium of glaucoma disease with postoperatively prescribed anti glaucomatous drugs is more expansive for the country, than medical therapy prescribed for medical treatment only (23). On the other hand, only successful surgical treatment, with postoperative IOP control, is cheaper than medical treatment (24). Non-drug costs (direct non-medical and indirect cost) accounted for 54%–66% of the overall treatment cost (25). Direct non-medical cost includes visit transportation fee, work hours off (3-8), as well as cost-time of accompanying person when visiting ophthalmologist (26, 27).

WHO Commission of Macroeconomics and health suggested that treatment which costs less than three times per capita GDP (gross domestic product) is cost effective (28).

In developing countries, data showed that default scenario for the glaucomatous patients is 4.4 up to 6 ti-

mes per capita GDP (medical treatment and eventual laser surgery) per year. Laser surgery fee in developing counties, is enough for the fee which WHO implies in cost-effectiveness definition (29).

In the consideration of surgery cost, lots of different facts are included. Wound healing is one of them. Postoperatively, scar wound healing is not rare complication (30). It is the consequence of the great prevalence of capsular glaucoma (31). So, antimetabolites must be included in the treatment. This drug raised the cost of the treatment (30, 31, 32). On the other hand, some glaucoma surgeons preferred to use â radiation postoperatively (16). It is well known that â-radiation induces cataract, bleb's leakage, postoperatively endophthalmitis, advanced and poor prognosis hypotony. All those complications, which are not so rare, need additional follow up care and expansive treatment (additional surgery, expansive antibiotics and other drugs) (30). Despite the all used tools to prevent blindness and to control glaucoma disease, blindness has an upward trend. Patients, who need more follow up care, surgeries and drugs increase their treatment cost. In the case, of earlier bad surgical antiglaucomatous experience, they do not accept suggested new surgeries (30). This situation can decrease their work abilities.

The situation is completely different in developed countries. The medical education of the patients is on higher level. Ophthalmologist and medical scientist should give more attention whether something works, to evaluating which works better, and whether it is worth the expenditure. Researchers have more resources for the evaluating the cost-effectiveness ratio and cost of the treatment alone. It makes it difficult to compare the cost of glaucoma and the costs or cost-effectiveness between studies (31, 32).

Direct cost in ocular hypertension, normal tension glaucoma and POAG, based on drug (19 different drugs) and non-drug (inpatient/outpatient, surgical or medical procedures, and diagnostic testing) costs was analyzed in Glasgow study. Its results suggested that average yearly and life time cost of glaucoma treatment is approximately similar as surgical treatment for 8-year period (33). Today, situation is different. Lots of drugs (prostaglandin analogues) become generic, which decreases the cost and increase medical treatment rate. Economic situation is also changeable, based on normal inflationary pattern, or changeable monetary trend (26).

Disease stadium also determines the cost of the treatment. Progressive stadium of the disease is more expansive for the fund than initial. European studies indicated that US$ 613 per person in 0 stadium of the disease was used for the treatment; but 1335 US$ was used in advanced stadium of the glaucoma (34). So, it implies for the improving the prevention of glaucoma progression. Non-compliant patients also increase the treatment cost (34).

By not using the prescribed therapy, expected life quality was decreased, and the cost was increased (35). These data was mentioned in the Stein et al study (36). They compared the cost of the treatment and life lasting of the three groups: no treated, PG and LTP. The results of their study showed that the cost PG group was higher than other, but the life quality and lasting was the highest in LTP group. But, it must be added that LTP treatment effect lasts for seven years (37), and additional medical or laser treatment is indicated (38).

The best and the most useful way for the glaucoma treatment is drug treatment in developed countries. We must think of its tolerating and side effects. The main reason for not using the prescribed drugs is their costs and life-long application. The glaucomatologists suggested minimal therapy switches as the initial. This state can be compromised by surgery and low vision support. Overall medical therapies accounted for around 8%–42% of the total cost of glaucoma (38). The cost of the glaucoma treatment also increases if the outdoor patients with unsuccessfully treatment referred back to the hospital (39, 40).

Glaucoma reduces quality of life (QoL) despite the fact that there is no one gold standard. QoL is a subjective category and individual approach. The relationship between disease progression and QoL are inversely proportional. QoL labeling is an important outcome in understanding disease progression and evaluating the effectiveness of health care interventions (40). Clinical signs (IOP level, visual acuity, visual field finding, side-effects of the antiglaucomatous drugs) were used for the glaucoma medication efficacy (41). Decreased visual acuity and visual filed defects have impact on vision related of life (VRQoL). These parameters make clinicians for better understanding of patients' life quality (42).

Ocular surface disease deteriorates patient's quality of life and work's ability (42). Frequently use of antiglaucomatous drug during long term has influence on the ocular surface disease signs. Pisella et al. reported that 50% of all examined patients had at least one symptom after the using prescribed antiglaucomatous medications (43). OSD symptoms are more frequent in patients using preservative containing eye drops compared with patients using preservative-free eye drops (43). Converting the prescribed eye drops with preservative to preservative-free eye drops increase the quality of life of glaucomatous patients, or even the decreasing the number of application (44, 45). All those facts must be in mind of ophthalmologists when prescribing antiglaucomatous drugs.

Glaucoma diagnosis has the impact on the quality of life of glaucomatous patients in different ways (45). The cognition that glaucoma is presented changes patients' conscience, by producing the depressive episodes and anxiety without presented any other symptoms. Also, progression of the glaucoma, decreased vision acuity, fear of blindness aggravates the life quality. Long-term follow up decreases their mental condition as well (46).

Non-compliance of glaucomatous patients, as mentioned in Mansberg et al study, is linked with fear of blindness, forgetfulness, health literacy, difficulty with drop application, and age (47). All those facts are described in Glaucoma Treatment Compliance assessment tool, authored Mansberg. Personalized information and guidance improve the compliance. In developing countries, surgery increases the compliance if medical treatment has no positive effect on the disease progression (48).

Information about the disease, potential risks, side effects of the prescribed drugs, potential blindness and inconvenience of eye drops have the impact on the compliance as well as on the quality of glaucomatous patients (49, 50).

CONCLUSION

The social and economic burden of glaucoma can be changed in order to increase the life expectancy and higher per capita GDP. Unique opinion about cost effectiveness cannot be reached because of conflict of different findings in many studies. The level of country's development impacts on the final finding of those studies. In the developing nation, individual patient availability and affordability to treatment may vary the treatment choice. Treatment approached must be individualized to each patient according to disease's stadium, availability of therapeutic modalities, life expectancy and level of GDP. Efficacy, compliance and potential side-effects of prescribed medication also determine the proper treatment choice.

Conflict of interest

Authors confirmed that no actual or potential conflict of interest exists in relation to this article.

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Abbreviations

POAG — Primary-Open Angle Glaucoma
GDP — Global personal
IOP — intraocular pressure
LTP — laser-trabeculoplasty
RKI — Rho kinase inhibitor
ROCK — Rho-associated protein kinase
QoL — quality of life
VRQoL — vision related quality of life

Sažetak

PRIMARNI GLAUKOM OTVORENOG UGLA I FARMAKOEKONOMIJA

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Primarni glaukom otvorenog ugla (POAG) se definiše kao hronična i progresivna bolest. Glaukom predstavlja drugi najčešći uzrok slepila u svetu. Slepilo, kao globalni problem, je delimično posledica lošeg zdravstvenog osiguranja, loše medicinske edukacije, itd. Faktor rizika na koji može da se utiče je visina intraokularnog pritiska. Troškovi antiglaukomskog tretmana povećani su zbog propisivanja i korišćenja širokog spektra antiglaukomskih lekova. Ako oftalmolog nije zadovoljan kontrolom glaukomske bolesti, ukazuje se potreba za laserom i/ili hirurškim tretmanom. Razvojni stadijumi bolesti takođe određuju troškove lečenja. Socijalni i ekonomski teret glaukoma može da se promeni zbog povećanja životnog standarda, starije dobi stanovništva i većeg bruto ličnog dohotka (GDP) po glavi stanovnika. Jedinstven stav o troškovima efektivnosti ne može da se postavi zbog sukoba različitih nalaza u mnogim studijama. Terapija glaukoma ima individualni pristup za svakog pacijenta u zavisnosti od stadijuma bolesti, dostupnih terapijskih modaliteta, očekivane dužine života i nivoa BDP. Efikasnost, pridržavanje tretmana i potencijalnih sporednih efekata propisanog leka određuje potencijalnu terapiju glaukomne bolesti.

Ključne reči: primarni glaukom otvorenog ugla, terapija, farmakoekonomija, socioekonomski aspekt.

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Review paper

BLIND SERBIAN RULERS AND FAMOUS PERSONS

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Abstract: History and medicine were an integral part of life-being of blind serbian acters. One of the main actors was half-blind serbian ruler, Stefan of Decani and whose name was associated with first ophthalmologic hospital and precursor of the eye's injuries care. After, national reputation as Stefan Blind Righteous, ruler of the Serbian despot between 1458. and 1459. (member of Brankovic's dinasty), and he was blinded by eye injuries burns. The famous national was also Filip Visnjic, as blind minstrel and authentic creator of serbian folk traditions, with sequels as a child, by bilateral infective panuveitis.

Keywords: serbian's history, blind personality, medicine, Stefan Decanski, Stefan Brankovic, Filip Visnjic.

INTRODUCTION

Authors looked through domestic historical references in proposed future research and challenges and the connection between Serbian history and blindness (caused by personal injuries or diseases of the eye). Authors have analyzed the aspects of war-interest known, of blind Serbian rulers and historical figures, through the results of their injuries or diseases of the eye.

Do you, for example, believe that Serbian history has properly recognized the importance of people (rulers, poets) who were deprived of sight? Or do you think that blindness of certain people had an impact on decision-making or events important for Serbian history and medicine? These and similar questions are left to readers that they themselves have to try to find possible answers.

The significance of this work certainly has a clear meaning, given the historical and/or medical context. The most well-known facts, set of analysis and set goal of this paper is hopefully reached in part through the efforts of all authors.

The aim of this study was to draw attention to the problem of blindness in important people throughout our history and medicine. Original thought is that perhaps we are not always aware of how important people in our history and church were blind, but still performed some of their life's work at the nation's best and now deserves more attention.

STEFAN DECANSKI - SERBIAN HISTORICAL RULER

The domestic history scene and the ophthalmic pathology were presented through the first of the three epoch-making historical figures. St. King Stefan of Decani was one of the best known Saints of the Serbian Orthodox Church. He was born as the oldest son of the saintly King Stefan Uros II Milutin and his wife Elizabeta, a Hungarian princess. Living at the court of his parents, and as the heir-apparent, he received good education, exercised studying of the languages and writings of Serbian people, and so his heart strengthened by study of the Holy Scripture, and the teachings of the Orthodox Faith. Since he was the half-blind, and the first ophthalmologic hospital for the eye injuries in Serbia, maybe took his name (it is assumed). Saint King Stefan Uros III Decanski was born about 1276, and died in Zvecane 11th of November 1331. He was the King of Serbia from Nemanjic family (1331-1346), the son of King Milutin (1282-1321), and later through the history, his son Dusan, the Mighty became the king (Emperor from 1346-1355) (1).

Wearing the black blindfold after the burns of both eyes, he was faithfully learning about his own (eye injuries, burns) and the other eye problems in Constantinople, and shared his knowledge, returning to Serbia. He continued expanding Serbia on account of the Byzantine Empire and created from it, the most power-

Figure 1. *St. King Stefan of Decani; Original source: The fresco in Decani Monastery, Stefan with church model, in 14th century*

ful force in Balkan. His military force won at Velbuzd in 1330th, so Serbian Orthodox Church canonized him as a holy king. Monestary Decani, under Prokletija was the Stefan's foundation (Figure 1).

His father blinded him in 1310, because of his revolting, and then sent him to the monastery of Christ Pantocrator, which was also forerunner of the hospital for the treatment of blinds. He ruled from 1321-1331, when he was over from the throne in the civil war by his son Dusan. Foreign sources said that he had been strangled by Dusan. He was executed in the tomb, which he raised on the south side of the nave in Visoki Decani of Kosovo. After the vision of a monk's tomb was opened and found his body incorrupt and the relics placed in the casket and now it can be found in the monastery. His cult, born during his life; it was followed by blind people in that time. His title "saint emperor" was found for the first time on the one cross in 1330, and it was kept in its endowment. Bulgarians during the First World War took his body, but after that, they had to return it (2).

Archbishop Danilo II, in literary work "Lives of the Serbian kings and archbishops" wrote, that Milutin's son had offered to negotiate, and that Stefan moved by this act, he went to his father and begged him for his forgiveness. When Milutin put hands on Stefan, he had no mercy. Stefan was shackled and sent to Skopje where he was blinded, and later sent off to Constantinople. Stefan, in the fear of his father, wore the black blindfold almost for the rest of his life. He was only partially blinded, with a hot iron. He removed it many years later in his reign.

In Istanbul, former ruler of that time the Emperor Andronicus had sympathy for the young and sacrificed prince, because of death of his own young son. So, he didn't want to make his miserable fate even worse (2).

The death of Stefan, half-blind Serbian giants was linked to the legend of the curse of Dusan's descendants and later the entire Serbian state. Stefan, when they came to kill him, cursed his son and his descendants. Although, the curse did not fur field on the son, it fell on his grandson Uros, who lost all military kingdom. This legend has lasted for many centuries, and they all remembered the curse, when Emperor Lazar with his warriors felt in Kosovo and Serbia felt under the Turks (3).

Serbian medieval medicine had the characteristics as western medicine of those times in terms of practical medical science, whereas the ancillary medical branches were under Byzantine influence. Besides the compositions of Christ's miracles and paraboles were underlying part of the fresco-painting, the scenes of Christ's miraculous recoveries had an important place in the Christian iconography of the New Testament events. One of the most impressive cycles of Christ's miracles in the Serbian and Byzantine medieval art was painted in 1340, in the church dedicated to the Ascension of Lord Christ at Decani Monastery (constructed between 1327 and 1335). A considerable number of 22 frescoes of different artistic value and technique displayed the miraculous recovery of patients afflicted by various chronic ailments: handicapped - as blind, lame and deaf, and paralytics, lepers, etc (4). The King Stefan Uros Decanski III founded the hospital in the Decani Monastery, as a purely medical institution for providing treatment. This hospital was organized and modeled by the hospital in Pantocrator Monastery in Constantinople. His biographer Gregory Camblak described that this hospital took patients suffering from epilepsy and serious nervous disorders, lepers, cripples, paralytics and the eye diseases (the injuries) (4). This was supported as the certain that masters painted even some of patients from Monastery Hospital.

The scenes of Christ's miraculous recovery in the Decani Monastery were undoubtedly significant for both: the military history and the Serbian medieval medicine. This considerable cycle of the monumental painting and frescoes with medical matter, constituted the basis for research of the Serbian medicine of the Middle-Ages. Today, as the Serbian people suffer through another turbulent chapter in their history, they would do well to have on mind such exemplary character of their Martyred King Stefan Uros III (Decanski) (4, 5). He was crowned 6 January 1322 by the Archbishop of Serbia as Stefan Uros III Decanski, King of Serbia. In 1323, he defeated and killed his half-brother Konstan-

tin, retaking of Zeta (5). Having in the true Christian manner endured the grievous trials and afflictions which he met through the years, the King deserved to live out the rest of his life in peace. But, it was only fitting that he who suffered as martyr in life should be granted an opportunity to receive in death a martyr's crown. Dusan's successes on the field of battle had given him the appetite for power and glory, and encouraged by his entourage of nobles, so he decided to hasten his father's death. St. Stefan was taken to prison to a fortress in the town of Zvecan and cruelly murdered (by some data he was hung, according to another he was strangled) (6, 7, 8).

Dusan earnestly and tearfully repented of his treachery, and the next year, on the feast of the Holy Apostles, Petar and Pavle, he had his father's remains transferred from Zvecan to Decani, where they were placed in the marble tomb. In 1339 the tomb was opened, and his body was found to be incorrupt. On that day people saw many miracles of the healing: especially that the holy king proved to heal diseases and injuries of the eye, and at his relics blind people received their sight (9, 10, 11). The medical analysis of illnesses and causes of death of Serbian rulers in the Middle-Ages was difficult. King Stefan Uros II Milutin (1282-1321) died as a seventy years old man. His biographer, Archbishop of Pec, Danilo II wrote about a sudden onset of the disease. King Milutin was paralyzed and aphasic. In the terminal stage, he was unconscious and insensible (12).

The first written Serbian medical records could be found in the Middle Ages (XIII century) when the Serbian state was very well organized. St. Save was the son of Grand Prince Stefan Nemanja (1171-1196), founder of the Serbian independent state and of the powerful dynasty that ruled Serbia for two centuries. At that time, the first hospital service was established, as well as the social program which regulated the relationship between marriage and family, and the kind of therapy, under the church and state control (13). The famous Hylandar place was perhaps the first of Medical Codex as the most famous reminder of Serbian medical sciences (14). The enviable level of health culture and social care of the ill and debilitated people of the Serbian medieval state was far advanced for that time (15, 16, 17). Favorable conditions for the development of medieval medicine was linked with the arrival of the Nemanjic's dynasty to the throne of the Serbian medieval state, i.e. Stefan Nemanja, and later with the life and work of his son Prince Rastko Nemanjic - Saint Sava (18, 19). The wide field of activity of the Grand Prince Stefan Nemanja included the creation of stable and independent state with the significant and shrewd political activity, building of churches, defender of the Orthodox Christianity, foundation of the first Serbian hospital outside of borders of Serbian, state in Hylandar monastery (20, 21).

ST. STEFAN BRANKOVIC - SERBIAN DESPOT

St. Stefan Branković was righteous descendant of the glorious Serbian Prince Lazar, of the Great Kosovo. Lazar and Milica had the oldest daughter Mara, who married for Serbian nobles, Vuk Brankovic. Vuk and Mara had three sons: Grgur, Djuradj and Lazar. After the death of Lazar and Milica, their son Stefan High (from 1389 until 1427) married the Greek princess Irina (Jelena) Paleologovom of Thessaloniki. Djuradj and Jelena had many children and among them was born the Blessed Stefan (about 1417 years). In his childhood, Stefan was blessed in every good mannered: he gained a great intellect and piety, obedience to parents, so that faith, wisdom and courage of many overcame, and its natural physical beauty. But the most important features Blessed Stefan lied in his commitment to the will of God, pure life and fidelity to the Church and the Orthodox faith. When the Turks attacked the capital of Smederevo, Grgur was captured and taken to Adrianople, where they were, on the orders of the Sultan Murat, and without knowledge of sister Sultana Mara, cruel both blinded by the Turks, on Easter Sunday in 1441. The one of the main reasons for this blindness of Serbian nobles was turkey envy, for their beauty and chivalry and fear that they did not become

Figure 2. *Righteous Blind Stefan, St. Serbian Despot Branković; Original source: The fresco of the young Stefan Esfigmenske Charter, in 1429*

heirs and Serbian rulers of the country. A few years after the suffering of the innocent, blissful and much suffering Stefan sighted and blinded his brother Gregory.

Sultan Murat returned to Serbia and lived surrender father despot Giurgiu. Turks were forced to make peace and to return to live despot Giurgiu's sons, and the entire city of Smederevo and despotism. Sadly was the scene when they met the blind father and his children: children went into the arms of his father, but the old despot roared like a wounded lion and tumbled to the ground unconscious. The old father died on Christmas Eve, 24th December 1456, in ninety years of life, and soon after his death, and the death of his wife Jerina, Stefan's mother (3sr May 1457), and soon after her young despot Lazar (20th January 1458). Then, if desired Serbian people and the nobles, and the blessing of Serbian Patriarch, blessed Blind Stefan enthroned in Smederevo for the new Serbian Despot (Figure 2).

As the ruler he was awarded the wisdom and courage, because it was very difficult time and occasions managed to preserve the Serbian country and people and not to hand over the city of Smederevo (not the Turks, nor the Hungarians). Innocent righteous Blind Stefan, the last legitimate Serbian ruler would then be expelled from the homeland, and he would have the big troubles. However, in his unjust exile from the homeland, Smederevo immediately fell of the Turks (20th June 1458), and so the punishment of God came upon Serbian's land (22). Righteous Stefan and his wife Angelina stayed with their children and lived a peaceful life devoted to the Orthodox Church, although it was not easy in that time and in the middle of the Latin and Papal countries. Stephan with his family lived in Serbia in the humility and privation, sometimes receiving alms from many sides. He died on 9th October 1476, and his holy body was buried in Belgrade, on Furlandi. In 1688, the relics of St. Stefan (with relics of other Brankovic) had put away for some time in St. Andrew, but soon returned to Krusedol, when rested peacefully until Turks put into pieces, and together with the church burned of Krusedol in 1716. From that fire, stated only some and smaller parts, including the right foot, as holy and righteous Blind Stefan as martyrs and victims of many Serbians. Grgur and Stefan were blinded (the burns) by the Sultan Murat II, of 1441 in Tokat fortress by the sea and near to Istanbul, in an old mansion called "Bedevi Cardak". They were blinded with hot iron over the eyes (burns). Stefan's brother, Blind Gregory, after the conquering the city of Smederevo by Turks (20th June 1459) retreated to monastery Hylandar, where he passed away as a German monk (in late 1459). The relics of Stefan Blind based at the monastery of Krusedol, which was endowed by his son, Maxim. Stefan Blind, as New Brankovic and despot ruled only a year in the mid of XV century. His body wasn't falling apart, after which he transferred the relics to the monastery, probably 1515. Stefan Brankovic (born - 1417, died - 9th October 1476 in Belgrade, it was a fortress in present-day - Italy), also known in historiography as Stefan Blind was briefly the despot (ruler) of the Serbian Despotate, between 1458 and 1459 as a member of the Brankovic dynasty. On 11th September 1429, Djuradj made donation to Esphigmenou Monastery at Mount Athos. The charter for the document named by his wife Eirene and five children. The MaÐpard -sarelli manuscript also named by the same five children of Djuradj and Eirene. Other genealogies mentioned a sixth child - Todor Brankovic. The 1429 document mentioned him with the title of Despot. Grgur was appointed governor of territories of southern Serbia associated to House of Brankovic. He was reportedly appointed by Murat II of the Ottoman Empire in 1439. In April 1441, Grgur was accused of plotting against Murat and his governorship terminated. He was imprisoned in Amasya and blinded on 8th May 1441. The Massarelli manuscript mentioned Grgur as unwed. Later genealogies name his wife as "Jelisaveta". Vuk Grgurevic, a son of Grgur, was later a titular Serbian despot (1471–1485). Both blind brothers seem to be omitted from considerations as possible heirs to their father. They could only claim the throne in 1458, since the death of Lazar leaving them the only male representatives of the Brankovic. When Serbian Despotate had been lost to Ottomans, Stefan's son Jovan of Serbian refugees to Kingdom of Hungary. There Jovan was finally recognized as Serbian Despot, with a principality called Raitzen (23). He was venerated as Saint Stefan Blind by the Serbian Orthodox Church. He long after that his body would be published as incorrupt, and so what is the tomb began to appear a marvelous heavenly light. The brightness of the first saw some guys were thieves who came to rob his grave. When they turned then to open his tomb, his body was found incorrupt and even, together with decomposed his suit. From its many holy relics then got healing, and many blind received their sight (24). Serbian Orthodox Church today celebrates St. Stefan's (1425-1476), despot of Serbian who did not want at any price and became Turkish vassal renounced Serbianism, who died in Udine (Italy) in the greatest misery (25). Turks to Stefan blinded, thinking that this would weaken the Serbian government, and that the Serbs would have to respecting to the leader who had a disability. However, Stefan Blind was shown as "tough nut" that was willing to cooperate and only the Hungarians resisted the Turks. Stefan immediately after the entry into throne managed to preserve Smede-

revo from Turks led by Mehmed II Conqueror. After the successful defense of Smederevo, many foreign powers have intervened, but not for the sake of defending the interests of Serbia, but for fear of Ottoman Turks coming to their doorstep (26).

"Opinions about the rule of despot Stefan blind today are divided. Some believe that he never should take charge, while others think it was the last ruler who then sincerely defended Serbia from the Turks. Serbian Church has never forgotten the role of the ruler who was given the title of saint. Stefan Blind was remembered as the person, who strongly believed that Orthodoxy was the only thing that could have saved Serbians, throughout the Turkish invasion" (27).

FILIP VISNJIC - SERBIAN HISTORICAL MINSTREL

Another historical and national character, Filip Visnjic (1767-1834), was one of the most famous Serbian minstrels and authentic creator of Serbian folk songs and traditions. He was born in Majevica, at village of Gornja Trnova in Ugljevik. As he turned blind after being sick from smallpox and the sequels as a child by panuveitis (complicata), he had become a professional Serbian singer with old fiddle in hand he traveled throughout the Bosnian pashadom. At the monastery councils he sang for Serbs, and passing through the towns narrated in the courts of the Turkish rulers. Two audiences were looking for different poems, so Visnjic had two different repertoires, one for the Christian and the other for the Muslim audience (28). His poems about Saint Sava were characteristic of the monastery, hagiographic repertory of total blind singer. Filip Visnjic was the creator of new poems. Thirteen poems "Karadjordje's time" along with several other less important poems of other poets make the last and insurrectionary cycle of Serbian folk epics. The most important moment in the life of Filip Visnjic was his move to Serbia in 1809. Direct contact with the insurrectionist events was the moment of his birth as the famous Serbian and military poet. After the collapse of the First Serbian Uprising, Visnjic has moved to Srem and settled in the village Grk, now Visnjicevo. Main place occupied the Serbian rebel poems, which he sang by himself (28). In monastery Sisatovac in 1815, he met Vuk Karadzic, who had written seventeen of his songs, four old and thirteen new poems. In Sisatovac, Filip Visnjic had often been the guest at then leading Serbian poet and famous person to Lucian Musicki. To these meetings of "Serbian Homer" and "Serbian Horace" authors owed information about Visnjic's life and work. Musicki told how he had created the songs: he asked the warriors when they returned from battlefield which was in

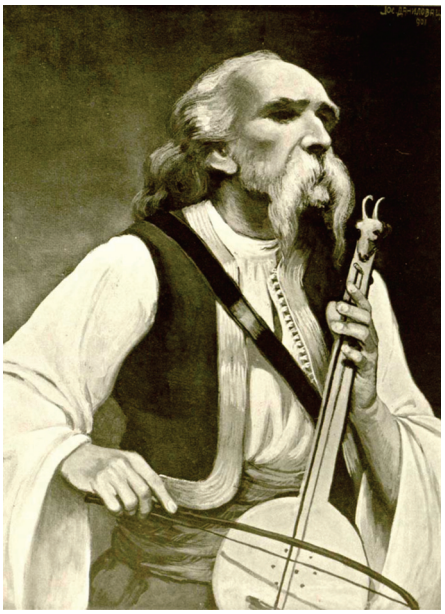

Figure 3. *Filip Visnjic as blind serbian minstrel end historical poet; Original source: The grafic portrait of Josip Danilovac of Eminent Serbs in XIX century of Zagreb, in 1901.*

head, where they were beaten, who died, against whom they were going. Songs from the first group were more artistically built, mainly "Start uprising against Dahias" and the first part of the song "The Battle of Misar", while in the second group the songs of value and importance of Ivo Knezevic. With his liberation enthusiasm Visnjic was most similar to Petar Petrovic Njegos (II), with whom he was bound trough the number of common features (29). Although he worked in the traditional framework of national epics served by standard formulas and cliches, he had largely outgrown the boxes and in the best moments of the epics made a new type of rebellion, liberation, revolutionary songs, with the strong individual and blind Serbian feature (30). With completely blind Serbian minstrel and poet, the great Serbian folk words trough heroic poems have recorded epochal Serbian history, art, culture and medicine traditions (Figure 3).

CONCLUSION

It should be noted that the Serbian historical and medical scenes from the perspective of the eye injuries and the eye diseases of the blindness, has not been fully understood by now. However, with the attitude towards the critical ophthalmic thinking, we are on the right path in shedding the light on the new discoveries.

Conflict of interest

The authors declare that there is no conflict of interest.

Sažetak

SLEPI SRPSKI VLADARI I ČUVENE LIČNOSTI

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Istorija i medicina predstavljaju sastavni deo bivstvovanja slepih srpskih aktera. Jedan od glavnih aktera je poluslepi srpski vladar, Stefan Dečanski, čije je ime povezano sa možda, prvom očnom bolnicom, kao pretečom za zbrinjavanje povreda oka, opekotina. Po nacionalnom čuvenju, Stefan Slepi Pravedni, bio je vladar Srpske despotovine između 1458. i 1459. (član Brankovićeve dinastije), a takođe oslepljen usled opekotina oba oka. Čuvena nacionalna i istorijska ličnost je bio Filip Višnjić, slepi guslar i autentičan tvorac srpskih, narodnih tradicija, sa sekvelama obostranog infektivnog panuvetisa još kao dete.

Ključne reči: srpska istorija, slepe ličnosti, medicina, Stefan Dečanski, Stefan Branković, Filip Višnjić.

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Correction

Correction: COCAINE CARDIOMYOPATHY — A CASE REPORT (2014, Vol 9, issue 3, p. 233–237.)

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In Sanamed Medical Journal, vol. 9, issue 3, in the text titled 'COCAINE CARDIOMYOPATHY — A CASE REPORT' authors made a mistake by inadequately citing parts of scientific paper, in sections Introduction and Discussion. The mistake was discovered by Center for Evaluation in Education and Science (CEON). Authors were informed from the Editorial Board of Medical Journal 'Sanamed' and the stated parts of paper were timely corrected.

Primljen/Received 01. 09. 2016. god. Prihvaćen/Accepted 01. 10. 2016. god.

Abstract: The second most commonly used drug in the world is cocaine. Its use is the most common cause of death among drug users. The use of cocaine is associated with acute and chronic complications. Mostly affected system in the human body's cardiovascular system. Cocaine cardiomyopathy may result from the use of cocaine.

This article presents a first case in Republic of Macedonia of 24-year-old male with reversible cocaine-related cardiomyopathy. Clinical presentation, laboratory, X-ray, ultrasound findings and treatment are reviewed.

Key words: cocaine, reversible cocaine cardiomyopathy, diagnosis, treatment.

INTRODUCTION

Cocaine is an alkaloid extract obtained from the leaves of the plant Erythroxylon coca. This plant usually grows in South America and has a data on its use before 5000 years. This drug and its complications are a worldwide problem. Cocaine is the most frequent cause of drug related deaths. Very useful data are obtained from a European retrospective study done on 479 ACS patients. The current study included subjects younger than 50 years admitted to a critical care unit from 2001 to 2008. From the total number of participants involved, 24 patients (5%) had admitted to recent cocaine abuse or tested positive on urine drug screening (1). In 2005 registered 2.4 million persons were actively using cocaine. Verified that the most frequent users of cocaine as a drug are young people aged 18 to 25 years and it is estimated that 11% of the population has used it at some point (2). The ratio of men to women is 2 : 1. The 2008 National Survey on Drug Use and Health reported that approximately 36.8 million Americans aged 12 years and older (14.7% of Americans in that age group) had tried cocaine at least once (3). The trade with this illicit drug in Republic of Macedonia is prosecuted by law. Yet there are people who use this drug and have complications from it.

Cocaine may be used by smoking, intravenous, gastrointestinal and nasal inhalation. It causes physiological changes highlighted, psychological effects but also addictive. Mechanism of action of cocaine is not completely understood. It is assumed that its detrimental effect is due to its direct toxicity. But also because of his mighty sympathomimetic action which is the main characteristic of cocaine. With sympathetic acting cocaine increases level of norepinephrine, dopamine and catecholamines, with the suitable effect on the systems in the body, particularly the cardiovascular system (tachycardia, arrhythmia, hypertension...). Cocaine also acts on muscarinic receptors blocking the reuptake of dopamine and serotonin which contributes to the appearance of "positive psychological effects". Cocaine carried blocking sodium ion channels on myocytes and contributing to the occurrence of cardiac arrhythmias (1, 4, 5).

Symptomatology in cocaine intoxication is associated with adrenergic redundancy that causes cocaine. The occurrence of hypertension is one of the most common symptoms. Impaired mental condition of the users on this drug manifested by the appearance of acute delirium or

mania (2). Very often cocaine users admitted to hospital with already manifested complications. Complications of cocaine can be acute or chronic. Cocaine related complications can affect any system: cardiac (coronary artery spasm, myocardial infarction, hypertension, cocaine cardiomyopathy, myocarditis, arrhythmia, possible occurrence of endocarditis, acceleration of atherosclerosis); vascular (aortic dissection and rupture, vasculitis, superficial and deep venous thrombosis, thrombophlebitis); neurological (cerebral infarction or hemorrhage, transient ischemic attack, seizures, migraine); gastrointestinal (ulcer disease, mesenteric thrombosis, perforation); pulmonary (pneumonia, pulmonary oedema, occurrence of haemoptysis); obstetric (abruptio placentae, spontaneous abortion, prematurity, growth retardation) (2-7)...

CASE REPORT

We present a case of a twenty four years old male, with a history of inhaling vaporized cocaine, and marihuana for two years. The main complaints of patient were fatigue, labored respiration, especially et night, dyspnea, anxiety, increased heart rate and lost of appetite during last 2-3 months. The patient was conscious, anxious, oriented to time, space and persons. Heart sounds were clear with systolic murmur. The ECG showed sinus tachycardia (HR > 100/min) (Figure 1) and about 0,5 mm upsloping ST segment depression in lateral leads. Blood pressure was elevated (150/105 mmHg). Laboratory analysis showed elevation of blood Urea (10.6 mmol/L), Creatinine (154 mmol/L), Na (149 mEq/L), K (4.2 mEq/L) and iron-deficiency anemia with Fe (7.1 mcg/dl). X-ray findings obtained enlarged heart silhouette (Figure 2). Echocardiographic evaluation showed left chamber dilatation with reduced global systolic function and ejection fraction (EF) 38%, designated mitral cusps with posterior cusp prolapsed, thin regurgitated flow and intraatrial septum tissue changes.

Preceding therapy Carvedilol and Aspirin was changed to heart failure – guideline-based heart failure therapy: Carvedilol, nonselective alfa/beta – adrenergic blocker (2 x 6, 25 mg per day), Perindopril, ACE inhibitor (4 mg per day), Spironolactone, mineral corticoid receptor antagonist, MRA (25 mg per day), Thiazide diuretic (25 mg per day) and Aspirin, acetylsalicylic acid (100 mg per day). Therapy for correction of anemic syndrome was recommended. Cocaine cessation was obligated.

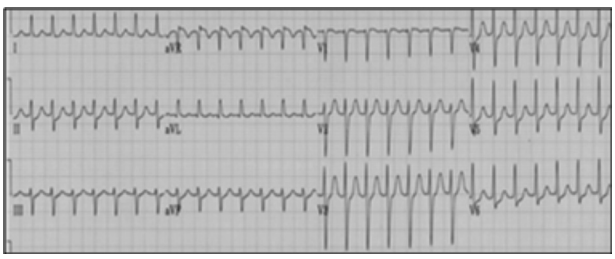

Figure 1. *ECG findings*

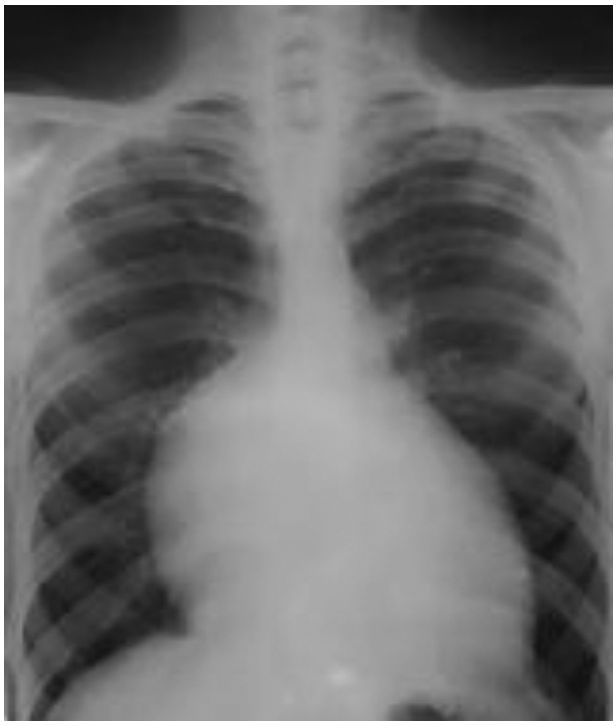

Figure 2. *X-ray findings of enlarged heart silhouette*

Two months later, after cocaine cessation and treatment in specialized hospital, the patient didn't fill the symptoms from the first examination, but he was at bad physical condition. Laboratory findings were normalized: Urea 7.6 mmol/L; Creatinin 108 mmol/L; Na 139 mEq/L; K 4.2 mEq/L and Fe 16.2 mcg/dl. EKG showed sinus rhythm with HR 65/min. Blood pressure was 120/80 mm Hg. Dimensions of left ventricle were in referent values. Left ventricle function was slightly reduced with EF 49%, mitral cusps were designated with posterior cusp prolapsed and intraatrial septum tissue changes. The patient continued with the same therapy.

The patient abstained from cocaine use and five months later he didn't fill any of the symptoms from the first examination, and he was et good physical condition. Laboratory findings were in the ranges of referent values. Left and right ventricles function and dimensions were preserved. Left ventricle EF was 62%. The patient continued with medications: Nebivolol, cardioselective â1– receptor blocker (2,5 mg per day) and Aspirin (100 mg per day).

DISCUSSION

This is the first case of cocaine reversible cardiomyopathy registered at the Clinic for Cardiology in Macedonia. Patients who are addicted to drugs are difficult for cooperation. This medical case demanded great personal and professional effort.

Among cocaine users certainly dominated symptoms of the cardiovascular system. Symptoms resulting from hypertension, angina pectoris, also these patients can be hospitalized with symptoms of myocardial infarction or dissection of the aorta. Other symptoms from the vascular origin may occur in cerebral ischemia or hemorrhage. Cocaine leads to damage of cardiac myocytes, leading to the emergence of cardiomyopathy. Often these patients are with signs of congestive heart failure. So, the first clinical symptoms in these patients may arise as a result of acute cardiac decompensation with or without pulmonary edema. Hypotension and shock make investigations and treatment in these patients very demanding. It is not uncommon for these patients their first hospitalization to finish lethal. Cocaine is the most common cause of sudden death caused by drugs (1, 4, 7, 8, 9).

In our case, which is very rare in the literature, we refer for the 24 year old boy who at first medical examination was with signs of congestive heart failure, hypertension, iron-deficiency anemia and elevated electrolyte and degradation products. First echocardiography evaluation showed reduced global systolic function with EF 38%. After five months of using the appropriate therapy and complete renunciation of the use of cocaine, on control echocardiography evaluation showed completely normalization of cardiac left ventricular function with 62% EF and the full normalization of the general condition and laboratory analysis. This represents the classical case of reversible cocaine-related cardiomyopathy.

In the absence of prospective randomized studies the literature data obtained mainly from case reports or from autopsy studies. Saurabh K. Chokshi et al. in their case report also refer for reversible cocaine-related cardiomyopathy. In their case it is a woman, 35 years old, which is also completely withdrawn clinical signs of cardiac decompensation, with normalization of the findings of all investigations. In this case endomyocardial biopsy was done and it was not found any fibrosis, necrosis or inflammatory infiltrate (10).

Virmani et al. in their study included autopsies of 40 patients, 31 of whom died cocaine-related deaths and 9 of whom were homicide victims with detectable blood cocaine levels. In this study, in 20% of respondents has been established the existence of a myocarditis proven with toxicology screen laboratory tests (11). In another autopsy study, Tazelaar et all., refers for finding of myocardial necrosis very similar to the findings in pheochromocytoma (12).

Robledo-Carmona at all. in their case report refers for severe cardiomyopathy associated to cocaine abuse. Histological findings, in this case, of the left ventricular myocardium indicate the presence of mononuclear infiltrates, degenerative changes, present necrotic changes on myocytes and also distinctly marked and severe form of fibrosis in interstitial space (13).

While most cases of cocaine-related cardiomyopathy have proved to be reversible, others have resulted in permanent cardiac dysfunction or death. Any patient with the data that used cocaine and clinical signs of congestive heart failure should make us suspicious and induce as on cocaine-related cardiomyopathy etiological basis. This especially refers to a younger patient, a smoker with signs of adrenergic excess (5, 10).

If there is doubt about cocaine cardiomyopathy first need to make laboratory investigations: urine toxicology screen for cocaine and its metabolites, also might expect electrolytes abnormalities (Na, K), anemic syndrome and a rise of renal degradation products (blood urea nitrogen and creatinine), blood tests for possible infection.

Radiographic analysis mostly shows a picture of cardiomegaly and congestive heart failure. But for most cocaine addicts radiographic analysis is often normal.

Echocardiography evaluation shows reduced global systolic function with chamber dilatation. In cocaine addicts who had myocardial infarction we can expect echocardiographic finding of impaired (hypo/akinesia) regional mobility on the wall of the chamber.

Cocaine addicts often have angina symptoms and they are indicated to make angiography. Coronary angiography is usually with normal finding on coronary arteries or with insignificant changes.

In cases of cocaine cardiomyopathy mostly have no specific ECG changes. In these patients are also possible nonspecific ST-T wave changes, ECG signs of left ventricular hypertrophy and the occurrence of arrhythmias. Unpredictable possible ECG changes especially malignant arrhythmias suggest a need for constant monitoring of these patients.

Management

Associations of cardiologists donžt have recommendations for concrete medicamentous treatment of cocaine cardiomyopathy (1). Medical treatment of these patients is similar to the recommendations for treatment of patients with other forms of dilated cardiomyopathy. Certainly in the first line beta-blockers should be included in these patients with cocaine-related heart failure. Cocaine addicts are usually in adrenergic excess and ordination of benzodiazepines for them is recommended. In the event of complications in these patients should be adequately reacting. So, in developing a shock should be given vasopressors and inotropic drugs. The occurrence of arrhythmias especially malignant nature the need to react quickly by giving antiarrhythmics is crucial. Cardioversion is used if there is no effect from drug

conversion of arrhythmias. These patients requires continuous monitoring and in case of apnea to perform endotracheal intubation by connecting the respirator (mechanical ventilation). In cases where angina symptoms are accompanied by ST segment changes on ECG, besides the right drug treatment (beta-blockers, nitrates, calcium channel blocking medicaments), coronary angiography should be performed. It is not uncommon for these patients to survive the myocardial infarction (1, 4, 14, 15). For the purposes of this, these patients need to know and to be familiar with the medical practice of cardiac magnetic resonance as a method that is quite useful for predictions of reversibility of cocaine-induced ventricular dysfunction (16).

John McMurray et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (17) recommend the following therapy:

The combination of beta blockers with ACE inhibitors used in the treatment of patients with cardiomyopathy and left ventricular EF < 40%. This combination of drugs is used to reduce the risk of heart failure hospitalization and the risk of premature death. An MRA is recommended for all patients with left ventricular EF < 35% and persisting symptoms despite medicament treatment. It is good to mention that analysis of B-type natriuretic peptide (BNP) level can help monitor the presence of congestive heart failure. Also BNP is very helpful to monitor response to treatment (17).

Most of reported cases with cocaine cardiomyopathy showed that treatment of these patients depends on stopping of drug use. Patients who stopped using drugs have registered significant improvements of the condition of cocaine-related cardiomyopathy. There are cases, as in our patient in this case report, when we have a full reversibility of cocaine cardiomyopathy and the establishment of completely normal cardiac function. But if these patients start using drugs again, the possibility reoccurrence of cocaine-related cardiomyopathy is confirmed most of the cases described in the literature (4).

Physicians usually don't consider the possibility of cocaine use of their patients. It is therefore necessary to inform and educate them. Abstinence from cocaine use and long time follow up is mandatory in these patients. The regular echocardiographic controls are necessary. The patient needs to take care of the other risk factors such as hypertension, smoking and others. In planning the treatment of these patients of great importance is ambulatory treatment of addiction. Also there is a need for hospitalization centers when it is necessary for their detoxification.

CONCLUSION

This is the first publication of cocaine-related cardiomyopathy in our country. Recognition of cocaine cardiomyopathy is crucial for optimal treatment. It requires a structured education of drug users about the consequences, risks of using cocaine and "Life benefit". It requires a multidisciplinary approach in treating these individuals and it should include the family, but also a psychiatrist, psychologist, sociologist, cardiologist and other professional disciplines.

Abbreviations

ACE — Angiotensin converting enzyme
BNP — Natriuretic peptide
BUN — Blood urea nitrogen
ECG — Electrocardiography
EF — Ejection fraction
ESC — European Society of Cardiology
HR — Heart rate
MI — Myocardial infarction
MRA — Mineral corticoid receptor antagonist
ST — ECG between the end of the S wave (the J point) and the beginning of the T wave

Sažetak

KOKAINSKA KARDIOMIOPATIJA — PRIKAZ SLUČAJA

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Kokain je druga najčešće korišćena droga u svetu. Upotreba ove droge je najčešći uzrok smrti kod korisnika droge. Upotreba kokaina daje akutne i hronične komplikacije. Najčešće afektirani sistem u ćovekovom organizmu je kardiovaskularni sistem. Kokainska kardiomiopatija može biti izazvana konzumiranjem kokaina.

Ovaj članak predstavlja slučaj dvadesetčetvorogodišnjeg muškarca s reverzibilnom kokainskom kardiomiopatijom, što predstavlja prvi takav u Republici Makedoniji. Nalazi kliničkog pregleda, laboratorijskih analiza, rendgenografije srca i pluća, ultrazvuka srca i tretman su prikazani.

Ključne reči: kokain, reverzibilna kokainska kardiomiopatija, dijagnoza, lečenje.

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Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prva tri i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad. Svaku tabelu odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slike nemaju nazive. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Treba poslati dva kompleta slika, u dva odvojena koverta, zaštićene tvrdim kartonom. Na pozadini slika treba napisati običnom olovkom prezime prvog autora, broj slike i strelicu koja pokazuje vrh slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page. The first author's last name is typed at the top right corner of each page.

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Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

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Statistical methods used, are outlined.

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Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first three are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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