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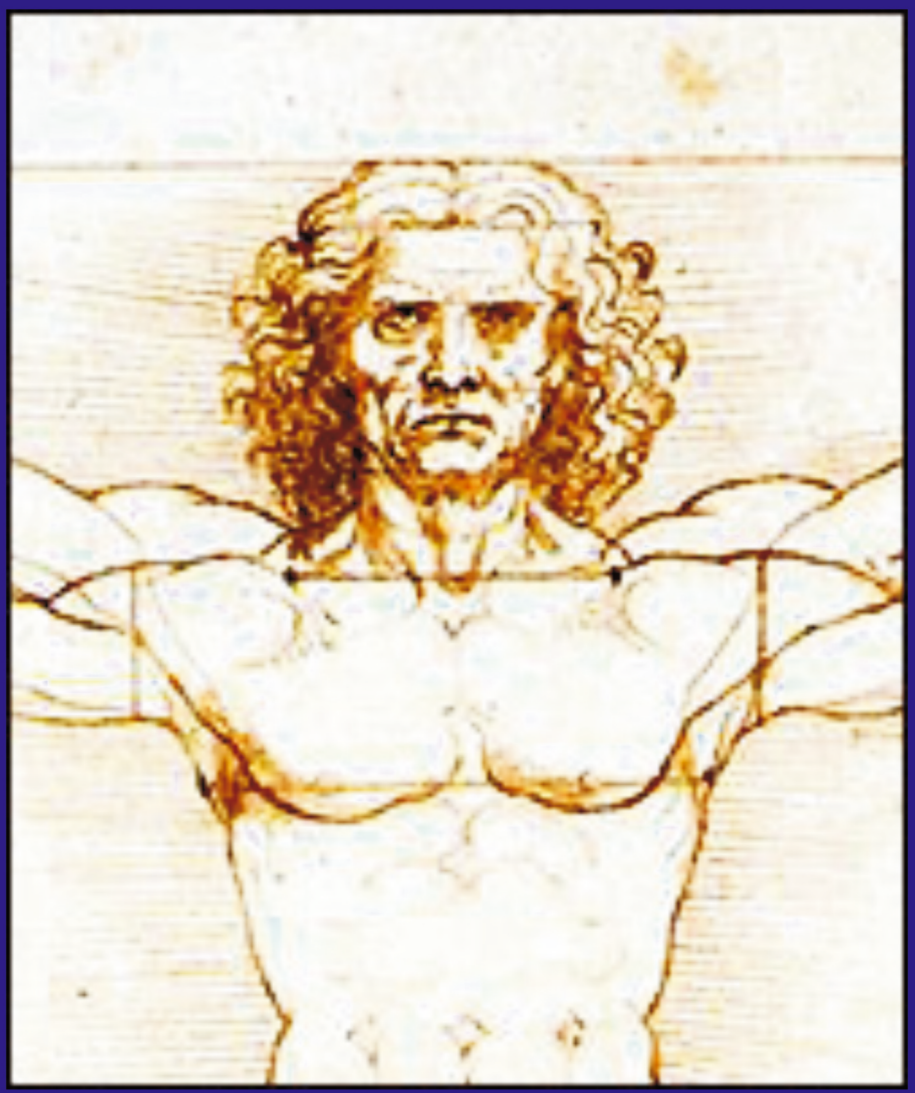

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Riječ urednika

Poštovani,

svedoci smo globalne krize koja je nastala zbog pandemije korona virusa i koja će definitivno obeležiti našu epohu. Uprkos vanrednom stanju i otežanim uslovima rada, posebno zadovoljstvo mi pričinjava nesmetan kontinuitet publikovanja časopisa „Sanamed" i zbog toga se zahvaljujem celom timu počevši od najbližih saradnika, preko naučnog odbora, recenzenata do autora zahvaljujući kojima sa punim pravom možemo reći da je „Sanamed" održao zavidan nivo po kvalitetu sadržaja.

U žiži same pandemije posebno su se istakli lekari širom svijeta, zajedno sa svim ostalim zdravstvenim radnicima, koji su se borili skoro na život i smrt sa nepoznanicom koja je zadesila svijet. Označeni su kao superheroji. U toj nesebičnoj borbi ogroman broj lekara i medicinskih sestara, izolovani od svojih porodica, posvetili su se u potpunosti pacijentima sa verom da će uspjeti da pomognu u borbi za očuvanje zdravlja. Na žalost, u toj borbi, uprkos svim mjerama zaštite i mjerama predostrožnosti, stradao je značajan broj lekara, stručnjaka, medicinskih sestara i onih drugih koji su radili u mnogim zdravstvenim ustanovama. Ovom prilikom, u ime uredništva i u svoje lično ime, želim da im svima širom svijeta izrazim svoje poštovanje, a njihovim porodicama i društvu u kojem su radili i zbog kojeg su položili svoje živote izrazim duboko saučešće i zahvalnost. Opravdano su istaknuti kao superheroji, jer samo superheroji se ne boje da smrtno stradaju radi spasa tuđeg života.

Pandemija ovog virusa je barem do sada ostala nedovoljno raščišćena pojava, ostavljajući za sobom tragičan trag za sve one koji nijesu uspjeli da joj se odupru i one koji su nedovoljno ozbiljno shvatili sve one koji su svojim savjetima i upozorenjima pokušali da im skrenu pažnju na ozbiljnost, te su opustivši se, smrtno stradali. Na svjetskoj sceni su se pojavila mnoga lica iz oblasti struke i nauke. Dok su jedni govorili da je to obična sezonska infekcija, drugi su isticali da je to manje poznati virus koji se razlikuje od dosadašnjih iz te grupe i da je dodatno opasniji za zdravlje ljudi. Bilo je i onih koji su sa naučne strane bili zbunjeni i uzdržani da ulaze u direktne procjene i analize jer nauka je tek sada pred izazovom i u iščekivanju je definitivnog zaključka. Bilo kako bilo, svjedoci smo da ono što je protutnjalo planetom i što još u mnogim zemljama hara i nosi ljudske živote je skrenulo pažnju svjetskoj sceni da tehnologija, ma koliko bila razvijena u smislu sile osvajanja i istovremeno sile otpora tehnološkim osvajačima, sejući strah među mnogima i na taj način pokazujući svoju moć i svoju snagu, odjednom može da zanemi pred jednom nevidljivom izuzetno sićušnom živom česticom koja je paralisala život na zemljinoj kugli. To mnogo govori o tome koliko je čovjek zaista slab i nemoćan kad mora da ustukne pred njom izolirajući se, a svi tokovi društvenog života staju kada se zaustavi protok ljudi i kapitala. Nebo odjednom postane prazno, a zemlja pusta.

Medicina je na ispitu. Bez obzira na sve one koji su bili najodgovorniji u svojoj zemlji i koji su dali sve od sebe, uz dužno poštovanje prema njima, lekari i medicinsko osoblje su bili jedina svijetla tačka u koju su svačije oči bile uprte. Mislim da je je ovo ujedno i opomena svima onima koji bogatstvo i moć mjere i vide u novcu i materijalnim stvarima, koji su vjerujem shvatili da im sve to malo znači ukoliko društvo nije obrazovano i potkovano znanjem i spremno da ga upotrijebi za spas života ljudi. Ovo je zbog toga pouka i poruka, da se iz tog velikog papirnog žbuna koji zovemo novac pojačaju sredstva za nauku i podrže ljudi naučnici u pokušaju da pravovremeno učine sve u njihovoj moći u iznalaženju načina za suzbijanje mogućih epidemija sličnih razmjera, avioni i tenkovi neka sačekaju. Moja vjera je uvijek bila usmjerena ka medicini, možda najviše i zbog toga što sam vjerovao u ono što sam kao lekar činio za ljude i zbog toga želim da podržim sve sjajne ljude lekarskog esnafa da razvijaju svoje znanje, razmjenjuju mišljenja putem pisanja, objavljivanja preko svih sredstva informisanja, a za dobrobit svjetske populacije.

Dragi prijatelji, sve što napisah u ovih nekoliko redova, znam, sve je poznato, ali meni je bio cilj da i ja koji sam takođe bio na udaru ove pošasti i sa žaljenjem pratio naše i svjetske slabosti, kako u organizacionom smislu tako i u kadrovskom, a posebno naučnom, istaknem da jedino dobra pamet i znanje daju najbolji odgovor. Ono se stiče čitanjem, pisanjem, obrazovanjem. Naši mladi lekari odjednom nespremni uletješe u žarište i sa onim iskusnim ovladaše situacijom ispitujući i provjeravajući svoje, kao i svjetsko znanje iz medicine. Ako bih da citiram, sada bih odabrao tuđe misli koje glase „Pametan čovjek uči od svakog i svega, prosječan iz svog iskustva, a budala sve zna". Treba se čuvati ovog trećeg, a boriti se za sve one koji žele da stvaraju i da se razvijaju za očuvanje zdravlja svog društva.

Još jednom hvala svim medicinskim radnicima na svemu onome što su učinili da savladaju nastalu pandemiju i očuvaju živote stanovništva.

Slava onima koji stradaše u toj borbi.

S poštovanjem,
prim. dr Avdo Ćeranić
glavni i odgovorni urednik

A word from the editor

Dear,

we are witnessing a global crisis caused by the coronary virus pandemic which will definitely mark our era. Despite the state of emergency and difficult working conditions, I am especially pleased with the uninterrupted continuity of publishing the "Sanamed" journal and for that I thank the whole team from the closest associates, through the scientific committee, reviewers to the authors thanks to whom we can rightly say that "Sanamed" maintained an enviable level in the quality of content.

In the focus of the pandemic itself, doctors around the world stood out, along with all other health workers, who fought almost to life and death with unknown disease that spread around the world. They are labeled as superheroes. In that selfless struggle, a huge number of doctors and nurses, isolated from their families, dedicated themselves completely to the patients with the belief that they would be able to help in the fight to preserve their health. Unfortunately, in that fight, despite all the protection and precautionary measures, a significant number of doctors, experts, nurses and all of those who have worked in many health institutions, lost their lives. On this occasion, on behalf of the editorial board and on my own behalf, I would like to express my respect to all of them and express my deep condolences and gratitude to their families and the society in which they worked and for which they laid down their lives. They are justifiably highlighted as superheroes, because only superheroes are not afraid to die in order to save someone else's life.

The pandemic of this virus has at least so far remained an insufficiently cleared phenomenon, leaving behind a tragic trace for all those who failed to resist it and those who did not take seriously all those who tried to draw their attention to its seriousness with their advices and warnings. Many people from the field of medical profession and science have appeared on the world stage. While some said that it was a common seasonal infection, others pointed out that it was a lesser-known virus that differed from the previous ones from that group and that it was additionally more dangerous for human health. There were also those who were confused and refrained from entering into direct assessments and analyzes, because science, especially now, is facing a challenge and is waiting for a definitive conclusion. In any case, we are witnessing that this pandemic has drawn the world's attention to the fact that technology, no matter how developed in terms of conquest and resistance to technological invaders, sowing fear among many and thus showing its power and strength, can suddenly be dumbfounded in front of an invisible, extremely tiny living particle that has paralyzed life on earth. This says a lot about how weak and powerless a man really is.

Medicine is on the test now. Regardless of all those who were the most responsible in their countries and who did their best, with all my respect to them, I must say that doctors and medical staff were the only bright spot on which everyone's eyes were focused.

I hope this pandemic is also a warning to all those who measure their wealth and power with money and material things, who I believe

have realized that all this means nothing if society is not educated and knowledgeable and ready to use it to save lives. This is therefore a lesson and a message that from this great paper bush we call money, funds for science will be strengthened and scientists will be supported in trying to do everything in their power to find ways to suppress possible epidemics of similar proportions. Planes and tanks can wait. My faith has always been focused on medicine, perhaps mostly because I believed in what I did as a doctor for people and because of that I want to support all the great medical professionals to develop their knowledge, exchange it through writing, publishing through all kinds of media and for the benefit of the world's population.

Dear friends, I know that everything I have written in these few lines is already known, but for me who was also under the impact of this pandemic and regretfully followed our and the world's weaknesses, both in organizational and personnel terms, and especially the scientific one, the goal was to emphasize that only good intelligence and knowledge give the best answer. It is acquired through reading, writing, education. If I have to quote, I would now choose other people's thoughts that say "Smart people learn from everything and everyone, average people from their experiences, only a fool knows everything." We should beware of this third one and fight for all those who want to create and develop themselves in order to preserve the health of their society.

Thanks again to all the medical workers for everything they have done to fight the current pandemic and save the human lives.

Glory to those who have died in that fight.

With respect,
prim. dr Avdo Ćeranić
editor in chief

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Original article

OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION WITH ACTIVE DISEASE IN ACUTE MYELOID LEUKEMIA

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Abstract: **Introduction:** Despite multiple lines of chemotherapy, some patients with acute myeloid leukemia (AML) can not achieve remission. The prognosis of these patients is quite poor and they should be evaluated for clinical trials, otherwise myeloablative conditioning regimens followed by allogeneic stem cell transplantation (Allo-SCT) should be performed to overcome the active disease which is resistant to conventional doses and as it is the only curative option.

Method: In this study, we evaluated the outcome of AML patients who underwent Allo-SCT with active disease in our center retrospectively.

Results: A total of 161 AML patients underwent Allo-SCT between December 2009 and November 2018 at our center. 130 of them underwent Allo-SCT in complete remission while 31 of 161 had to undergo Allo-SCT with active disease due to refractoriness to salvage therapies. The median overall survival (OS) was 7.9 ± 2.8 months. 6-month OS was 25% and 1-year OS was only 6%. Progression-free survival (PFS) was 3.53 ± 1.1 months. The transplant-related mortality rate was 12.8%.

Conclusion: OS and PFS are short in patients who undergo Allo-SCT with active disease so novel treatment approaches and targeted therapies should be developed to overcome active disease that are refractory to conventional chemotherapies.

Keywords**:** refractory acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, salvage therapy.

INTRODUCTION

Acute myeloid leukemia (AML) is a disease which occurs as a result of hematopoietic progenitor cells' clonal disorder that lose their skills to normally differentiate and proliferate. In spite of intensive treatment methods, AML has poor prognosis because of its aggressive nature. Better survivals have been achieved with improvements in intensive chemotherapies and supportive care. In addition to this, targeted therapies like FMS-like tyrosine kinase 3 (FLT3) inhibitors have been started to use in selected AML cases. Despite these improvements and new agents in AML treatment, the relapse rate is still high (1, 2).

AML patients are classified into risk groups according to their genetic features and treatment plan is made according to their risk groups (3). Allogeneic stem cell transplantation (Allo-SCT) is not considered for the AML patients in good risk group in first complete remission, instead Allo-SCT should be considered in intermediate and high risk groups in first complete remission. In addition to this, in patients from all risk groups who are refractory to chemotherapy or have relapsed disease, Allo-SCT should be performed because short remission durations and high rates of relapses are expected in relapsed/refractory AML patients. In this group of patients, Allo-SCT is the only potential curative treatment option (3, 4, 5, 6)

Ideally, the patients who achieve complete remission after induction chemotherapy in intermediate and high risk groups or after salvage therapy in relapse-refractory patients should be taken to Allo-SCT. This means that patients should be in remission while they are receiving conditioning regimen before Allo-SCT. However, in spite of multiple line chemotherapy regimens, there are patients who cannot achieve remission. The prognosis of these patients is quite poor and they should be encouraged to participate in clinical trials (7, 8). If these patients cannot participate in clinical trials, myeloablative conditioning regimens followed by Allo-SCT should be performed in order to overcome the

active disease which is resistance to conventional doses and as it is the only curative option.

At this point, the main question to be answered is how we can improve the outcome of patients who have to be performed Allo-SCT while the disease is still active. Is there a way to improve overall survival similar to patients who undergo Allo-SCT while the disease is in complete remission? For this purpose we evaluated the outcome of AML patients who underwent Allo-SCT with active disease in our center retrospectively.

MATERIALS AND METHOD

A total of 161 AML patients underwent Allo-SCT between December 2009 and November 2018 at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Bone Marrow Transplantation Center. 130 of them underwent Allo-SCT in complete remission while 31 of 161 had to undergo Allo-SCT with active disease due to refractoriness to salvage therapies. The data was collected from the clinical records retrospectively. The local ethical committee approval received.

Relaps-refractory AML patients who were over 18 years old, whose active diseases were verified by flow cytometry, immunohistochemistry analyzes, morphological findings of bone marrow aspirates and who did not have hepatic and renal failure were included in the study. The patients who did not meet criteria of participation were excluded from the study.

Complete response (CR) was defined as < 5% blast in bone marrow, absolute neutrophil count ≥ 1000 μL and thrombocyte count ≥ 100.000 μL in peripheral blood and having no blast in peripheral blood in addition to the absence of extramedullary AML. Partial response (PR) was defined as at least 50% decrease of the blast percentage after the induction chemotherapy as opposed to the initial blast percentage and having bone marrow blasts percentage between 5% and 25% (9). Disease status other than CR or PR after induction or salvage chemotherapies was described as active disease.

Overall survival (OS) was described as the duration between the first diagnosis (the date of relapse for the relapsed patients) and death or the last follow up for the survivors. OS after Allo-SCT was described as the duration between Allo-SCT and death or the last follow up for the survivors. Progression free survival (PFS) was described as the duration between the first diagnosis (the date of relapse for the relapsed patients) and progress in disease, death or the last follow up (9). PFS after Allo-SCT was described as the duration between Allo-SCT and progress in disease, death or the last follow up.

The first end point in the study was defined as OS, and the second end point was described as transplant related mortality (TRM) and acute and chronic graft versus host disease (GVHD) incidence. The severity of acute GVHD was graded according to the grading system of International Bone Marrow Transplantation Records (IBMTR) (10). Chronic GVHD was graded according to 2015 consensus criteria of the National Institute of Health (NIH) (11).

Statistical analyses were performed by using IBM SPSS Statistics v21 software. The rates of survival was calculated by using Kaplan-Meier survival analysis. The impacts of variables on OS and PFS were studied by means of long rank test. The calculations with Type-1 error level of under 5% were accepted as statistically significant.

RESULTS

The median age of 31 patients included in our study was 37 (range 19-63). There were 24 male and 7 female patients. The patients' age, gender and distribution according to French-American-British (FAB) classification is given in Table 1. Stem cell origin (bone marrow/peripheric blood derived), donor type (related/unrelated), human leukocyte (HLA) compability (full matched/ mismatched/ haploidentical) and conditioning regimen used were given in Table 2.

Table 1. *Clinical characteristics of the patients*

Patients Characteristics	Patient	Rate (%)
Number of Patients	31	100
Gender		
Females	7/31	22,6
Males	24/31	77,4
Age		
≤ 25	6/31	19,35
26-40	14/31	45,16
≥ 41	11/31	35,49
FAB		
M0	1/31	3,22
M1	2/31	6,44
M2	4/31	12,88
M3	0/31	0
M4	4/31	12,88
M5	4/31	12,88
M6	0/31	0
M7	0/31	0
Not evaluated	16/31	51.7%

FAB: French-American-British classification

Table 2. *The patients' stem cell origins, HLA compatibility, conditioning regimen and donor type*

	Patient	Rate (%)
Stem Cells' Origin		
Bone Marrow	3/31	9,66
Peripheric Blood	28/31	90,34
HLA compatibility		
Full Match (10/10)	26/31	83,9
Missmatch (9/10)	3/31	9,66
Haploidentical	2/31	6,44
Donor Type		
Unrelated	2/31	6,44
Related	29/31	93,56
Conditioning Regimen		
CY-BU	18/31	58,14
CLOAMSA	6/31	19,32
BU4-FU4-ATG	7/31	22,54

CY-BU (cyclophosphamide, busulfan), CLOAMSA (clorafabine, cytarabine, amsacrine, total body radiation, cyclophosphamide), BU4-FU4-ATG (busulfan, fludarabine, Antitimositantiglobulin).

The median OS after transplantation was 7.9 ± 2.8 months. 6-month OS after transplantation was 25% and 1-year OS after transplantation was only 6%. PFS after transplantation was 3.53 ± 1.1 months. The TRM rate was 12.8%.

The evaluation of post-transplant response revealed that CR was achieved in 21 of 31 patients (71%). Relapse was observed in 10 of 31 patients (32.2%) during the first 90 days after the transplantation, in 2 patients (6.44%) between the 3rd and 12th months after Allo-SCT and in 1 patient (3.22%) in the 2nd year.

Grade III-IV acute GVHD was observed in none of the patients. Grade III-IV chronic GVHD was observed in 6.4% of patients. The variables affecting post-transplant OS in the patients who underwent Allo-SCT with active disease were age, The Eastern Cooperative Oncology Group (ECOG) performance score, Karnofsky performance score and the quantitiy of infused $CD34^+$ stem cells. Variables affecting PFS were identified as age, the number of chemotherapy lines received, Sorror score, the number of $CD34^+$ stem cells given and the presence of GVHD (Table 3). No impact over OS was observed with gender, the number of chemotherapy lines received, blast percentage in bone marrow, the source of stem cells, European Society for Blood and Marrow Transplantation (EBMT) score, Sorror score, the presence of GVHD, and blood type incompatibility. We did not observe any impacts of ECOG performance score, Karnofsky performance score, gender, the source of stem cells, blast percentage in bone marrow, EBMT score, blood type incompatibility on PFS. Also we did not observe significant effect of conditioning regimen over OS and PFS (p: 0.88 and p: 0.09 respectively).

DISCUSSION

Therapy options are limited in relapsed/refractory AML patients (7). This group of patients should be performed Allo-SCT, the only curative therapy method, as soon as possible as remission is achieved. Today, there are still patients who cannot achive remission in spite of targeted therapies in addition to conventional chemotherapies (7, 8).

In our study 71% of patients achieved CR one month after Allo-SCT and the median OS after transplantation was found 7.9 ± 2.8 months. In the study conducted by Ivanoff et al., overall response rate was 38% and median OS was 9 months when refractory AML patients received 5-azasitidine maintenance followed by intensive chemotherapy. In their study, the patients who underwent Allo-SCT with active disease had higher response rate than the patients who received 5-azasitidine maintenance followed by intensive chemotherapy (66% vs 38%); however, their OS was shorter (8 months vs 9 months) (12).

In the study conducted by Mello et al., the relapse rate during the first 90 days after Allo-SCT was 56.5% in patients who underwent transplantation with active disease. TRM was 47.6% in the same study. In our study relapse was observed in 10 of 31 patients (32.2%) during the first 90 days after transplantation,

Table 3. *Factors related with OS and PFS*

OS	PFS
Age (p:0,002)*	Age (p:0,013)**
ECOG performance score (p:0.001)*	The number of chemotherapy lines (p:0,004)**
Karnofsky score (p:0.001)*	Sorror score (p:0,004)**
Number of CD34+ infused (p:0,001)*	Number of CD34+ cellsinfused (p:0,002)**
	Presence of GVHD (p:0,04)**

*Factors impacting OS, **Factors impacting PFS, ECOG: Eastern Cooperative Oncology Group, GVHD: Graft versus host disease

in 2 patients (6.44%) between the 3rd and 12th months after Allo-SCT and in 1 patient (3.22%) in the 2nd year. TRM was 12.8% in our study. Although we found lower relapse and TRM rates in the first 90 days after transplantation in our study than those of the patients in the study conducted by Mello et al., PFS and OS were found to be similar (OS 7.9 months vs 8 months and PFS 3.5 months vs 3 months) (13).

In our study, cyclosporine was used for GVHD prophylaxis and the rate of grade I-II acute GVHD was 19.32%. Grade III-IV acute GVHD was not observed. The rate of grade III-IV chronic GVHD was 6.4%. In the study conducted by Mello et al. where cyclosporine and mycophenolate mofetil were used for GVHD prophylaxis, the rate of grade II-IV acute GVHD was 42.6% and the rate of grade II-IV chronic GVHD was 64.4% in the AML patients who underwent transplantation with active disease (14).

Although there was no statistically significant difference regarding post-transplant OS between the patients who had GVHD and the ones that did not present GVHD, we found that presence of GVHD had an impact on post-transplant PFS (p:0.04). This finding is supported with the fact that similar OS rates were found in our study and the study conducted by Mello et al., although Mello et al. observed higher GVHD rates in their study. The impact of GVHD on PFS makes us consider the importance of graft versus leukemia impact (15).

Due to acquired adverse genetic features and clonal evolution, the OS durations obtained by either repeated conventional chemotherapies or Allo-SCT is very short. Until recently, no standard therapy regimen has been identified for the relapse/refractory AML patients as a salvage therapy. Reaching to the newly developed targeted therapies such as FLT-3 inhibitors, isocitrate dehydrogenase (IDH) inhibitors according to the genetic risk features prior to the transplantation will also be reflected on the results of transplantation.

In conclusion; OS and PFS are short in patients who undergo Allo-SCT with active disease so new treatment approaches and targeted therapies should be developed in order to overcome active diseases which are refractory to conventional chemotherapies. Therefore, such patients should be supported to participate in clinical trials as much as possible. There are a number of ongoing clinical trials for the development of new therapy methods (14, 16, 17). In addition to this, Allo-SCT is still a valid therapy option in relapsed/refractory patients that are unable to reach clinical trials but new therapy approaches that would reduce TRM, relapse rates and GVHD incidence in AML patients that are admitted to transplantation with active disease are required.

Abbreviations

EBMT — European Society for Blood and Marrow Transplantation
ECOG — Eastern Cooperative Oncology Group
FAB — French-American-British
GVHD — graft versus host disease
TRM — transplant related mortality
AML — acute myeloid leukemia
Allo-SCT — allogeneic stem cell transplantation
OS — overall survival
PFS — Progression-free survival
CR — Complete response
PR — Partial response

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Sažetak

ISHOD ALOGENE STEM ĆELIJSKE TRANSPLANTACIJE SA AKTIVNOM BOLEŠĆU KOD AKUTNE MIJELOIDNE LEUKEMIJE

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Uvod: Uprkos mnogim linijama hemoterapije, neki pacijenti sa akutnom mijeloidnom leukemijom (AML) ne mogu da postignu remisiju. Prognoza ovih pacijenata je izuzetno loša i trebalo bi ih istražiti u kliničkim studijama, jer se u protivnom moraju sprovesti mijeloablativni režimi kondicioniranja praćeni alogenom ćelijskom transplantacijom matičnih ćelija (Allo-SCT) da bi došlo do aktivne bolesti i koja je rezistenta na uobičajene doze i kao takva je jedina terapija izbora.

Metod: U ovoj studiji smo evaluirali ishod pacijenata sa AML koji su retrospektivno podvrgnuti Allo SCT sa aktivnom bolešću u našem centru.

Rezultati: Ukupno 161 pacijent sa AML je podvrgnut Allo-SCT između decembra 2009.te i novembra 2018.te godine u našem centru: 130 njih podrgnuto je Allo SCT u potpunoj remisiji, dok je 31 od 161 morao da se podvrgne aktivnoj bolesti Allo SCT zbog otpornosti na terapije. Medijana ukupnog preživljavanja bila je 7,9 ± 2,8 meseci. 6-mesečno preživljavanje bilo je zabeleženo kod 25% a jednogodišnje preživljanje kod samo 6%. Preživljavanje bez progresije (PFS) bilo je 3,53 ± 1,1 meseci. Transplant-related stopa mortaliteta bila je 12.8%.

Zaključak: OS i PFS su kratki kod pacijenta koji su podvrgnuti Allo SCT sa aktivnim bolestima. Takođe tebalo bi da se razviju terapije koje bi bile specifične kako bi se prevazišlo aktivno stanje bolesti, koje su refraktorne na konvencijalne hemoterapije.

Ključne reči: refraktorna akutna mijeloidna leukemija, alogena hematopoetska stem ćelijska transplantacija, terapija spasa.

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URINARY IODINE LEVELS OF PRIMARY SCHOOL CHILDREN IN ILORIN, NIGERIA

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Abstract: **Background:** Iodine deficiency is one of the commonest micronutrient deficiencies. Globally, it is the commonest cause of preventable mental retardation and also associated with impaired physical growth. The current iodine nutrition of school children in Ilorin, North-Central Nigeria is not known.

Objective: The study aimed to determine the urinary iodine levelsv(UIL) of school children in Ilorin and explored the relationship with socio-demographic variables.

Methods: This cross-sectional study was carried out among primary schools children in Ilorin, Nigeria. We recruited school children aged 6-12 years through a multi-staged sampling method. Relevant data including socio-demograhic variables were obtained with a pretested study proforma. The recruited school children had urinary iodine determined using the Sandell-Kolthoff method. Data analysis was with Statistical Package for Social Sciences version 20.0.

Results: The median with interquartile range (IQR) of urinary iodine level was 117.2 (99.6-148.6) µg/L. Of the 480 recruited children, 336 (70.0%) had normal urinary iodine levels while 144 (25%) had mild iodine deficiencyand two (0.4%) had excess urinary iodine levels. Pupils with iodine deficiency was higher among public schools than those in private schools (33.3% vs 23.6%, $\chi^2 = 150.149$, $p < 0.022$). The median UIL of the age-group 6-9 years was higher than the 10-12year age group (***p* = 0.026**). However, the median UIL values were comparable across gender, socioeconomic strata and mother's educational level.

Conclusions: This study showed that a quarter of the children still had mild iodine deficiency despite salt iodisation policy adopted by the country. Also, the iodine levels were not influenced by socio-demographics.

Key words: Urinary iodine, Primary school children, Ilorin, Nigeria.

INTRODUCTION

Malnutrition remains an important public health concern in the developing countries with micronutrient deficiency accounting for 7% of the global disease burden (1). Globally, iodine deficiency is one of the commonest micronutrient deficiencies (2). Severe iodine deficiency causes stunted physical growth and it is the commonest cause of preventable mental retardation (3, 4).

Globally, about two billion people, most of whom are domiciled in the Sub-Saharan Africa and South Asia have inadequate iodine intake (3, 5). One third of these are school-aged children; and nearly half of these children live in West Africa (3, 5). Iodine deficiency has been previously reported in different parts of Nigeria, including Ilorin, Kwara State, the present study site (6, 7, 8).

The World Health Organisation (WHO) introduced the universal salt iodisation to curb this menace, and recommends that the iodine nutrition of a population be monitored at least once every ten years using the urinary iodine levels (UIL) of school-aged children in that population as an indicator (5, 9). This is in order to evaluate the iodisation programme in that population.

Urinary iodine determination is a cheap, easy and effective way of measuring body iodine. About 90% of absorbed iodine is excreted by the kidneys; therefore its urinary level is a sensitive bio-marker of current iodine intake (5). On the other end of the spectrum is exces-

sive iodine nutrition, which may lead to iodine-induced hyperthyroidism(IIH) (4). This has been reported in some African countries including Nigeria due to consumption of excessively iodised salt (3, 6, 10, 11, 12).

The ongoing salt iodisation program in Nigeria and the WHO recommendation of frequent monitoring of the iodine nutrition of a populace makes its imperative to frequently sample school children for their iodine levels in the developing countries where iodine deficiencies are more prevalent. Furthermore, the earlier study conducted in Ilorin about two decades ago showed a high prevalence of iodine deficiency, and the current status of iodine levels in the school children is unknown. Hence, the need for the generation of more recent data on the iodine levels of school-aged children in Ilorin. This study therfore, aimed to determine the urinary iodine levels of school-aged children in Ilorin, Kwara State, Nigeria, and explore the relationship between UIL and socio-demographics.

METHODS

We carried-out a cross-sectional descriptive study between February 8th 2016 and May 13th 2016 in 16 primary schools; 3 public and 13 private schools (with proportionate representation of public and private schools) in Ilorin West Local Government Area of Ilorin, Kwara State, North-Central region of Nigeria. Ilorin West LGA has 260 registered primary schools: 55 public and 205 private primary schools Ilorin City lies in the Precambrian Basement complex of northern Nigeria and is underlain by rock of metamorphic and igneous type, therefore prone to iodine deficiency (13). The minimum sample size required for the study was estimated using the Cochran's formula; [$n = (z^T pq) / d^T 2$], and used a prevalence of iodine deficiency of 56.3% previously reported in Nigeria (14) at a tolerable margin of error of 5%.

The participants were selected through a multi-staged sampling technique using the school list obtained from the State Ministry of Education. Schools were stratified into public and private. Proportional allocation was used to select the number of public to private schools used based on the calculated ratio of public to private schools in the LGA. i.e 55:205 =1:4. Therefore, 3 public and 13 private schools were selected.

A table of random numbers was then used to select 3 public and 13 private schools sampled based on their serial numbers on the school register from the Ministry of Education. This was done separately for the public and private schools. The number of children selected in each primary school was obtained by dividing the total number of pupils to be recruited (calculated sample size = 411) by the total number of schools (16) to be sampled in Ilorin West LGA. For easy recruitment of subjects, 30 pupils were recruited from each selected primary school in Ilorin West LGA. In each selected primary school, the pupils were stratified into their classes (basics 1-6) and pupils were recruited from each class. The number of children selected from each class was calculated by dividing the total number of children to be selected from that school by 6 (representing 6 classes from basics 1 to 6). Thus, 5 children were recruited from each class in the selected primary school in Ilorin West LGA. In a situation where there was more than one arm in a class, simple random (by balloting) method was used for the selection of a single arm of the class which formed the sampling frame. In each class, using the class register, the pupils were stratified based on their sex; and the ratio of the boys to girls in the class was determined. Proportional allocation was then used to determine the number of boys and girls to be recruited in the class based on their ratio. Simple random sampling by balloting was used to select the required number of boys and girls to make a total of 5 pupils recruited in each class.

Semi-structured questionnaires were used to obtain relevant history and socio-demographic information from the parents of the participants. A total of 480 primary school pupils were recruited into the study; 90 from public and 390 from private primary schools.

Children aged 6-12 years who were apparently healthy and whose parents gave consent were included in the study, while children with cardiac arrhythmias on amiodarone, an iodine containing drug; children with hyperthyroidism on antithyroid drugs such as propylthiouracil, carbimazole and methimazole; and children whose parents / guardians did not give informed consent were excluded from the study.

Parental educational level and occupation was used to calculate the child's social class using adapted Oyedeji (15) classification into upper, middle and lower classes. Ten millilitre (10 ml) of Spot urine samples were collected from the pupils into clean universal bottles with the lid tightly screwed and transported in ice-packs to the Chemical Pathology Laboratory of the University of Ilorin Teaching Hospital (UITH) where they were kept in the refrigerator at 2-8 °C till analysis. Samples were pooled and analysed in batches.

Urinary iodine was tested using the Sandell-Koltkoff method. It is based on the Sand-ell-Kolthoff reaction which measures the rate of colour disappearance of ceric ammonium sulphate in urine that is digested with ammonium persulfate. Ceric ammonium sulfate (which is yellow) was reduced to the cerous form (which was colourless), and the reaction was catalysed by iodide. The rate of colour disappearance, as measured by a spectrophotometer determined the iodine content of urine. A standard curve plotted during the analysis was used to extrapolate the concentration of iodine in the urine samples (9, 16).

Urinary iodine level below 100 μg/L was classified as iodine deficiency, levels between 100 and 199 μg/L as sufficient iodine nutrition, those ranging between 200 and 299 μg/L as more than adequate iodine nutrition while levels above 300 μg/L as excessive iodine nutrition (5, 9).

Ethical consideration

Ethical clearance (with reference number UITH/CAT/189/19A/342) was obtained from the Ethics and Research Committee of the University of Ilorin Teachng Hospital. Approval was sought from the Kwara State Ministry of Education and Head Teachers of the selected schools. Parental consent was sought from the parents of the selected pupils and the informed consent form was signed by them. In addition, assent was sought from children 10 years and older.

Data analysis

Data collected on the study pro forma was analyzed using the IBM Statistical Package for Social Sciences (SPSS)^{Tm} version 20.0 for windows. Frequency distribution tables were generated. Urinary iodine level (UIL) was not normally distributed and was therefore represented as median with interquartile range (IQR). Mann-Whitney-U test was used to compare median values of UIL and Kruskal-Walis test was used when comparing more than two sets of median UIL. Student t-test was used to compare means of normally distributed continuous variables. Differences between proportions of categorical variables were evaluated using the Chi-square test or the Yates continuity corrected Chi square. The confidence level was set at 95% and level of significance at $p < 0.05$.

RESULTS

Socio-demographic characteristics of the study participants

A total of four hundred and eighty (480) children were enrolled from sixteen primary schools in Ilorin West LGA. The mean ± standard deviation (SD) age of the study participants was 8.6 ± 1.8 years. Two hundred and thirty-eight (49.6%) of the children were males and 242 (50.4%) were females, with a male: female (M:F) ratio of 1:1. Regarding the highest educational qualification, 76% of the subjects had mothers with at least a Senior School Certificate (SSCE); only 6.9% of the subjects had mothers with no formal education. The other socio-demographic parameters are as shown in Table 1.

Among the pupils recruited in this study, 7.9% were from households that bought salt from unpackaged and

Table 1. *Socio-demographic characteristics of the pupils*

Variable	Frequency (N = 480)	Percentage	Cumulative percent
Age group (years)			
6-9	319	66.5	66.5
10-12	161	33.5	100.0
Sex			
Male	238	49.6	49.6
Female	242	50.4	100.0
Educational Status of Father			
Post-secondary	198	41.3	41.3
Secondary	203	42.3	83.6
Primary	61	12.7	96.2
No Formal Education	18	3.7	100.0
Educational Status of Mother			
Post-secondary	130	27.0	27.0
Secondary	235	49.0	76.0
Primary	82	17.1	93.1
No Formal Education	33	6.9	100.0
Ethnicity			
Yoruba	417	86.9	86.9
Igbo	28	5.8	92.7
Hausa	4	0.8	93.5
Others	31	6.5	100.0
Social class			
High (class I & II)	269	56.0	56.0
Middle (class III)	165	34.4	90.4
Low (class IV & V)	46	9.6	100.0

Table 2. *Characteristics of salt consumed by study participants*

Variable	Frequency (N = 480)	Percentage
Salt Packaging		
Sealed Nylon	436	90.8
Loose in bowls	38	7.9
In Jute/woven sacks	6	1.3
Storage of salt		
Nylon	65	13.5
Tightly closed container	393	81.9
Open container	17	3.5
Sacks	5	1.1
Awareness about salt iodization		
Yes	358	74.6
No	122	25.4
Utilisation of iodized salt (n = 358)		
Yes	261	72.9
No	97	27.1
Look out for iodine in ingredient list		
Yes	210	43.8
No	270	56.2

Table 3. *Urinary iodine status of study participants*

Iodine level	Frequency (N = 480)	Percent
Mild deficiency	122	25.4
Normal	334	69.6
Above normal	22	4.6
Excess urinary iodine	2	0.4

Severe iodine deficiency: UIL= 0-19 µg/L, Moderate iodine deficiency: UIL = 20-49 µg/L, Mild deficiency: UIL = 50-99 µg/L, Normal iodine level: UIL = 100-199 µg/L, Above normal iodine level: UIL = 200-299 µg/L, Excess urinary iodine: UIL: >300 µg/L

Table 4. *Comparison of iodine nutrition across the public and private schools*

Variable	Total N=480	Private n = 390	Public n = 90	U or χ^2	*p* value
UIL (Fg/L)					
Median	117.2	117.2	116.8	16734.000[U]	0.392
Inter-quartile range	99.6-148.6	101.4 – 149.3	88.4 – 147.3		
UIL group					
Mild deficiency	122 (25.4)	92 (23.6)	30 (33.3)	8.244[y]	**0.041**
Normal	334 (69.6)	283 (72.6)	51 (56.7)		
Above normal	22 (4.6)	14 (3.5)	8 (8.9)		
Excess	2 (0.4)	1 (0.3)	1 (1.1)		

U: Mann Whitney U test; y: Yates corrected chi square; UIL: Urinary iodine level

Table 5. *Relationship between the median urinary iodine level of participants and their socio-demographic features*

Variable	UIL		
	Median (IQR)	**U or K**	***p* value**
Age group (years)			
6–9	117.2 (101.4–153.6)	22490.500[U]	**0.026**
10 -12	115.7 (94.2 – 138.2)		
Sex			
Male	122.0 (101.4 – 150.4)	26759.500[U]	0.180
Female	117.2 (97.9– 144.7)		
Educational Status of Father			
Post-secondary	117.2(100.9-152.7)	2.012[K]	0.570
Secondary	117.2(99.6-148.6)		
Primary	117.2(101.4-137.7)		
No formal Education	114.2(83.5.9-139.5)		
Educational Status of Mother			
Post-secondary	117.2(97.9-155.4)	0.612[K]	0.894
Secondary	117.2(102.2-138.1)		
Primary	117.2(99.6-147.3)		
No formal Education	124.2(100.5-150.5)		
Ethnicity			
Yoruba	117.2(99.6-149.3)	1.196[K]	0.754
Igbo	115.6(104.4-130.1)		
Hausa	106.9(91.6-146.7)		
Others	117.2(94.2-153.6)		
Social class			
High (class I & II)	115.7 (94.2 – 153.6)	0.591[K]	0.744
Middle (class III)	122.0 (102.2 – 141.6)		
Low (class IV&V)	123.7 (102.2 – 148.6)		

IQR: Inter-quartile range; U: Mann Whitney U test; K: Kruskal Wallis test; UIL: Urinary iodine level

loose in bowls while 1.3% bought salt in jute sacks. Three hundred and ninety-three (81.9%) pupils belonged to households that stored their salt in tightly closed containers, while 3.5% left them in open containers. Three hundred and fifty-eight (74.6%) of the participants had parents that had heard about salt iodisation, and of these, only 72.9% use iodised salt. This is as shown in Table 2.

The median (inter-quartile range) urinary iodine level of the study population was 117.2 (99.6-148.6) μg/L. Three hundred and thirty-four (69.6%) of the total population screened had normal urine iodine level (UIL) while 122 (25.4%) children had mild iodine deficiency as shown in Table 3. None of the pupils had moderate or severe iodine deficiency.

Although the median UIL of both school populations were comparable, significantly higher number of pupils in the public schools had mild iodine deficiency than those in the private schools (33.3% VS 23.6% χ^2 = 150.149, OR 1.8, 95% CI 1.088 to 3.009, ***p* = 0.022**). Other details are shown in Table 4.

Comparing the median urinary iodine level of the school children across the different age groups, there was a significant difference between age and urinary iodine level as shown in Table 5. The median UIL of the age-group 6-9 years was statistically higher than the 10-12-year age group (***p* = 0.026**). The median UIL values were comparable across the socio-economic strata, ethnicity and the different levels of father's and mother's education.

DISCUSSION

Twenty five percent of the study participants had iodine deficiency (mild -UIL between 50 and 99 μg/l). The 25.4% prevalence of iodine deficiency in this study is similar to the findings during the year 2001 national study that reported a prevalence of iodine deficiency as 28% in the State of the present study (8). This may mean that the iodine nutrition has not changed over the years in the State despite the country's iodisation policy. Also, it may be due to the fact that some of

the study participants were from households that still bought salt in loose, unpackaged forms and large porous woven sacks which are much cheaper. Iodine is very volatile and may evaporate from iodised salt especially when exposed to heat and moisture or stored in porous or open containers (9). Furthermore, the current UNICEF data on salt iodisation estimates that only 3 out 4 households in the world used iodised salt (17). The above factors may have contributed to the mild iodine deficiency seen among the children in this present study.

This study also showed the number of children with mild iodine deficiency was higher among children that attended public schools. This probably reflects the fact that the children in private schools are better nourished than those in public schools. Also, the children from public schools are more likely to come from poorer homes that consume non-iodised salt or salt sold in unpackaged loose forms.

The median UIL (of 117 μg/l) in this study was much different from the findings in Saki which recorded 285 μg/l, a value that is within the 'above normal UIL' range; but similar to the 124 μg/l recently reported in-Nsukka, South-East, Nigeria (6, 18). Furthermore, the 69.6% prevalence of adequate UIL in this study was much higher than the 8.3% and 41% previously reported by Nwaramah et al (14) in Enugu and Augustine (6) in Saki, from South-Eastern and South-Western parts of Nigeria respectively. The difference in prevalence recorded in this study may be because Ilorin, unlike Enugu and Saki, is not in the goitre belt of Nigeria (19).

This study also found that less than 1% of the children had urinary iodine level above 300 μg/l. This is suggestive of excess iodine nutrition. The prevalence of excessive iodine level in this study is very much lower than the 50% and 67% reported in South-west Nigeria (6, 12). This suggests that Ilorin populace is not presently at risk of IIH but regular monitoring the UIL of the populace is pertinent to prevent IIH. The low prevalence of excess UIL in this study may also be because Ilorin populace is not in the goitre belt of Nigeria; IIH occurs in populations which previously had chronic iodine deficiency (9).

Comparing the median UIL across the different age groups, the 6 to 9year olds had the highest median value, while the 10-12year olds had the least value. Amor et al (20) in India had earlier documented variation of UIL with age, although contrary to this study, he reported increasing UIL values with age. The possible reason for the decrease in iodine with increasing age recorded in this study may be the increased need for iodine for growth in this age-group, which marks the beginning of the adolescent years and growth spurt.

The findings in this study were consistent with the findings of Alozie et al (7) in Akwa-Ibom, South-south Nigeria and Skeaff et al (21) in New Zealand who reported no gender variation in UIL of population studied. This is however contrary to the findings from Enugu in South-east and Cross-River state in South-south Nigeria that reported more cases of iodine deficiency in boys than girls (14, 22). The reason for no gender variation with UIL reported in this study is unclear but could possibly be that households that use iodised salt for general cooking do so without prejudice to both genders in the households.

The median UIL in the present study population was comparable across the different socio-economic strata. This might be due to availability and usage of iodised salt by majority (72.9%) of households, in the community this study was carried out. This is in agreement with earlier studies by Skeaff (21) in New Zealand and Volzke (23) in Germany but contrasts Low (24) in Malaysia, who reported variations in UIL in subjects across different socioeconomic classes.

CONCLUSION

This study showed that a quarter of the children still have mild iodine deficiency despite the salt iodisation policy adopted by the country. Iodine deficiency was more marked in public schools than in private schools. Also, the urinary iodine levels were not influenced by socio-demographics.

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AUTHOR CONTRIBUTION

Y.T.O., O.O.A., R.R.O and S.K.E designed research; Y.T.O, E.D.A and S.A.B. conducted research; Y. T.O and A.O analyzed data; and Y.T.O, A.O and R.M.I. wrote the paper. Y.T.O had primary responsibility for final content. All authors read and approved the final manuscript.

Sažetak

NIVO JODA U URINU KOD DECE OSNOVNIH ŠKOLA U ILORINU, NIGERIJI

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Uvod: Deficit joda je jedna od najčešćih deficita mikronutritijenata. Ovaj deficit je najčešći uzrok preventivne mentalne retardacije, ali je takođe i povezan sa poremećajem fizičkog rasta. Zastupljenost joda u ishrani kod dece u Ilorinu, Severno-centralnoj Nigeriji do sada nije poznata.

Cilj: Studija ima za cilj da utvrdi nivo joda u urinu (UIL) kod dece školskog uzrasta u Ilorinu i ispita vezu sa socidemografskim varijablama.

Metod: Ova studija je izvedena kod učenika osnovnih škola u Ilorinu, Nigeriji. Uključena su deca uzrasta 6-12 godina, a raspoređena su pomoću multi-stage metode. Relevantni podaci koji su uključivali sociodemografske varijable bili su uzeti sa prethodno sprovedenim pretestom. Metoda Sandell-Kolthoff je korišćena za utvrđivanje nivoa joda u urinu. Analiza podataka sprovedena je koristeći Statistički paket za Društvene Nauke verzija 20.0.

Rezultati: Medijana sa interkvartalnim opsegom (IQR) urinarnog nivoa joda bila je 117.2 (99.6-148.6) μg/L. Od 480 dece uključene u studiju, 336 (70%) imalo je normalan nivo joda, dok je 144 (25%) imalo osrednju deficijenciju joda, dvoje dece (0.4%) imalo je povišene vrednosti joda u urinu. Nedostatak joda je bio učestaliji kod dece, koja su pohađala državne osnovne škole od dece koja su pohađala privatne osnovne škole (33.3% vs 23.6%, $\chi^2 = 150.149$, $p < 0.022$). Medijana UIL starosne grupe 6-9 godina je bila veća nego kod grupe od 10-12 godina (***p* = 0.026**). Bilo kako bilo, medijana UIL vrednosti je bila uporediva između polova, socioekonomskih stratuma, kao i nivoa edukacije majki dece.

Zaključak: Ova studija je pokazala da četvrtina dece i dalje ima osrednji nedostatak joda, uprkos zakonu o obogaćivanju voda i namirnica jodom. Takođe, na vrednosti nivoa joda nisu uticale sociodemografski podaci.

Ključne reči: jod u urinu, deca osnovnih škola, Ilorin, Nigerija.

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STABILITY OF THE SURGERY-ONLY ORTHOGNATHIC APPROACH IN CLASS III PATIENTS WITH MAXILLARY RETROGNATHIA

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Abstract: **Introduction:** The aim was to compare the stability of the surgery-only approach (SOA, indicating surgery without orthodontics) to the orthodontics-first approach (OFA; orthodontics followed by surgery) in patients with dentofacial deformities.

Methods: All ten patients who underwent SOA and 10 OFA were included. Cephalometric radiographs were taken before surgery (T0), and six months after SOA or OFA(T2). The actual maxillary movement was measured intraoperatively (T1). The difference between T2-T0 and T1 is accepted as relapse. Each cephalometric film was analyzed using specialized software and the stability of actual advancement was analyzed.

Results: Difference of relapse amount between SOA and OFA groups was statistically significant ($p = 0.016$).

Conclusion: Although the stability of SOA was less than OFA, the amount of advancement was higher in SOA.

Key words: orthognathic surgery, surgery only approach, orthodontics first approach.

INTRODUCTION

Skeletal disharmonies associated with severe malocclusion can be treated with orthognathic surgery. The classical treatment procedure, known as the orthodontics-first approach (OFA), has three stages: initial orthodontics, surgery, and final orthodontics. As the total duration of OFA treatment is long, patient cooperation may diminish during this time.

In the surgery-only approach (SOA), surgery is performed without orthodontics (1). At the initial examination, cast models are made and cephalometrics are recorded. Occlusion is evaluated using the cast models. In cases where the model can be occluded acceptably with single- or multi-piece surgery and the patient refuses orthodontic treatment, orthognathic surgery without orthodontics becomes an option. This procedure (SOA) is classified in the surgery-first approach (SFA) that involves no orthodontic treatment pre- or postoperatively (2). Typically, patients who undergo SFA are older, have higher numbers of missing or restored teeth, and require only minor occlusal adjustments.

While the stability of other forms of SFA has been reported previously (3), the stability of SOA is unknown. This study aimed to compare the relapse amount between SOA and OFA.

MATERIALS AND METHODS

This retrospective study was carried out between April 2014 and April 2016 at the Oral and Maxillofacial Surgery Department at Medipol University, School of Dentistry. Ethics Committee approved the protocol and participants gave informed consent. All patients who underwent SOA during this period participated and ten control (OFA) patients were also randomly selected. The criteria for SOA were as follows: skeletal malocclusion with no need for orthodontic treatment, no craniofacial syndrome, no prior maxillofacial trauma, no previous maxillary surgery, and no evident physiologic problem. Cephalometric radiographs were taken before (T0) and six months after surgery (T2) in both groups. To measure the horizontal movement of the maxilla, we drew a line passing from the Nasion perpendicular to the SN plane. The distance of ANS to this line was noted. The difference between T2 and T0

radiograph noted as maxillary advancement amount (Figure 1). Maxillary linear surgical movement was also measured intraoperatively (T1) from two opposite points marked on osteotomy sites. Following maxillary down fracture and stabilization with miniplates, the horizontal distance was measured and noted as T1.

Statistical Analysis

Power analysis was done before data collection, and it was determined that a sample size of 10 patients per group yielded a power of 83%. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, SPSS Inc., Chicago, USA). Differences between the noted measurements of the maxillary movement were evaluated between the SOA and OFA groups using Student's t-tests for independent samples. Significance was set at $p < 0.05$.

RESULTS

The SOA group comprised four men and six women of mean age 33,2 years. The OFA patients were five men and five women of mean age 30.4 years. The advancement amount of SOA group was larger than OFA group and relapse amount of OFA and SOA groups was statistically significant ($p < 0.05$) (Table 1).

In the present study, the amount of maxillary advancement in each patient was measured in the operation room. Mean value of advancement was 7.5 ± 1.6 mm for SOA group with 0.74 mm ± 0.19 relapse and 3.5 ± 0.6 mm for OFA group with 0.08 ± 0.23 relapse.

Table 1. *Comparison of maxillary movement recorded at the two timepoints in each group (values shown as mean ± SD)*

	n	Maxillary movement at T1	Maxillary movement at T2-T0	p
SOA group	10	7.5 ± 1.6	6.8 ± 1.5	0.006*
OFA group	10	3.5 ± 0.6	3.6 ± 0.5	0.730

SOA: surgery-only approach; OFA: orthodontics-first approach; T1: intraoperative; T2-T0:
* statistically significant

Table 2. *Between-group comparison of the relapse difference in maxillary movement (values shown as mean ± SD)*

	n	Relapse Difference in maxillary movement	p
SOA group	10	0.74 ± 0.19	0.016*
OFA group	10	-0.08 ± 0.23	

SOA: surgery-only approach; OFA: orthodontics-first approach
* statistically significant

There was a statistically significant relapse between the SOA and SFA (Table 2).

DISCUSSION AND CONCLUSION

Surgery first approach has been becoming popular as a new treatment concept in the correction of dentofacial deformities. SOA approach that is included in surgery first approach is carried out when the patient has skeletal malocclusion, but unwilling orthodontic treatment, when the need for dental decompensation is low and the patient has acceptable occlusion (Figure 2 and 3). The main finding of this study was that the re-

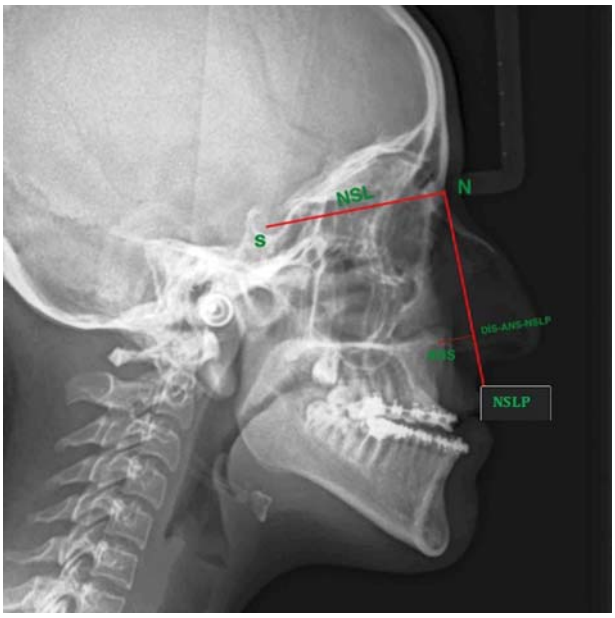

Figure 1. *Anatomical landmarks and reference lines used for the cephalometric evaluation. S: sella; N: nasion; NSL: nasion-sella line; ANS: anterior nasal spine; NSLP: nasion-sella line perpendicular; Dis-ANS-NSLP: distance from ANS to NSLP*

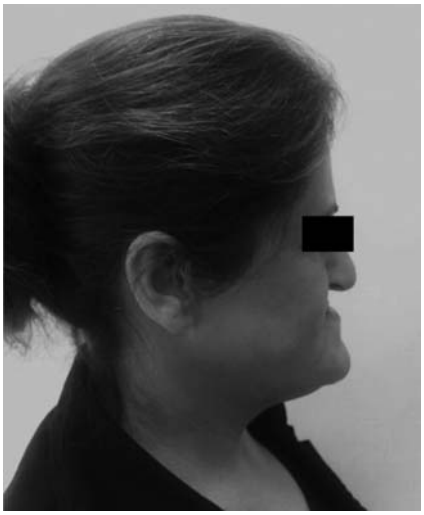

Figure 2. *Pre-operative profile picture of a patient in SOA group*

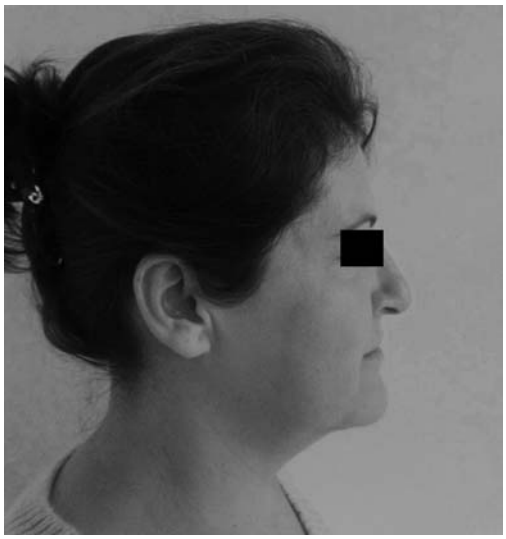

Figure 3. *Post-operative profile picture of the patient in Figure 2*

lapse amount in the SOA group was larger than the OFA group. In previous reports, acceptable postoperative relapse in the first year of Le Fort I osteotomy was reported as 'less than 2mm' (4). In our study, relapse amounts in both SOA and OFA group came accordance with previous reports.

There may be several reasons causing more relapse in the SOA group. One of them was the advancement amount in SOA is higher than OFA. Similar to our study's findings, Chen KJ. et al. (5) found a significant correlation between the amount of maxillary advancement and skeletal relapse. Another reason; intercuspation was not as good as in OFA. In the SOA group, less tubercule contact may be a potential risk for skeletal relapse. The relationship between skeletal stability and occlusal contact remains controversial in the literature. In previous studies, it was reported that occlusal contact was a risk factor for skeletal stability (6, 7). However, Lo S.H et al. (8) found no significant difference between skeletal relapse and occlusal contact.

In our study, we measured the real advancement amount of maxilla in the operating room. Because duration between removing intermaxillary fixation in operating room and the first postoperative cephalometric radiograph may affect the relapse amount of our study. Larsen et al. (9) stated that maxillary stability could be evaluated by knowing the amount of movement in orthognathic surgery operation.

SOA is the best treatment option for especially elderly patients who will undergo orthognathic surgery and unwilling to have fixed orthodontic appliances. Treatment duration in SOA only includes surgical procedure and aftercare period and minor occlusal grinding. In this study, the stability of SOA was less than OFA, but both of the groups showed sufficient stability. However, higher relapse rates should be considered in the planning of SOA and overcorrection may become an option in skeletal relapse. Within the limitation of this study, it can be concluded that in selected patients, SOA has many advantages with acceptable relapse and should be considered in treatment alternatives of orthognathic surgery patients. However, relapse should be evaluated in more extensive trials by correlating the results by the amount of movement.

Abbreviations

SOA — surgery-only approach
OFA — orthodontics-first approach

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Licensing

Sažetak

STABILNOST SAMO HIRURŠKOG ORTOGNATSKOG PRISTUPA KOD PACIJENATA SA MAKSILARNOM RETROGNACIJOM III KLASE

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Uvod: Cilj ove studije bio je da se uporedi stabilnost samo hirurškog pristupa (SOA, koja indikuje hirurgiju bez ortodoncije) i inicijalno-ortodoncijskog pristupa (OFA, ortodoncija praćena hirurškom intervencijom) kod pacijenata bez dentofacijalnih deformiteta.

Metod: Svih deset pacijenata koji su podvrgnuti SOA i 10 OFA su bili uključeni. Cefalometrijska radiografije su urađene pre hirurgije (T0) i 6 meseci nakon SOA i OFA (T2). Trenutna pokretljivost maksile je bila merena intraoperativno (T1). Razlika između T2-T0 i T1 su shvaćeni kao relapsi.

Svaki celafometrijski film je analiziran koristeći specijalizovani softver i analizirana je stabilnost aktuelnog napretka.

Rezultati: Razlika relapsa između SOA i OFA grupa su bile statistički značajne (p = 0.016).

Zaključak: Iako je stabilnost SOA manja od OFA, napredak je značajno viši kod SOA.

Ključne reči: ortognacijska hirurgija, samo hirurški pristup, prvi pristup ortodoncije.

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PHYSIOTHERAPY STUDENTS AS A PARTNER FOR THE PREVENTION OF HEALTHCARE ASSOCIATED INFECTIONS

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***Abstract*: Background:** Hand hygiene compliances of healthcare students have been examined extensively. However, there has been no study in this area for the students of the department of physiotherapy and rehabilitation. The aim was to evaluate hand hygiene compliance of the department of physiotherapy and rehabilitation students after a briefing on hand hygiene.

Methods: Before the summer practice, the students were briefed on hand hygiene. Then their hand hygiene compliance were assessed. Their sociodemographic characteristics, clinical summer practice data, and hand hygiene compliance based on the recommendations commented in the Centers for Disease Control and Prevention Guideline for Hand Hygiene in Health Care Settings were assessed with a questionnaire prepared by the researchers.

Results: Of 53 students, 52 met inclusion criteria. The average correct answer rate was 82.69%. Students had inadequacies in selecting suitable hand hygiene techniques and in complying with hand hygiene indications in some situations related to their profession. Moreover, the students suggested that there was a great need for education (n = 24; 39.34%) and improvements in physical conditions (n = 21; 34.43%).

Conclusions: As a conclusion, department of physiotherapy and rehabilitation students were aware of the importance of hand hygiene in terms of prevention of healthcare associated infections. However, for department of physiotherapy and rehabilitation students, educational programs about hand hygiene is needed in order to gain optimal competence and to be able to protect and improve health care workers and patients safety.

Key words: hand hygiene, physiotherapy education, students.

INTRODUCTION

Many studies in the literature emphasize the necessity of examining the compliance of health students with hand hygiene (HH) guidelines and the necessity to include occupation-specific programs to educational plans from the earliest period according to the needs assessed. These studies, which examine the compliance of health students with HH guidelines, frequently focus on students of medicine, nursing, and dentistry (1-16). In these studies, it is stated that the compliance rates with the HH guidelines are different according to the occupational category of the students (2, 10, 14, 15). Only in a limited number of studies, students of the department of physiotherapy and rehabilitation (DPR) have been shown to have moderate knowledge about HH and nosocomial infections (17, 18, 19). Also in these studies, DPR students' number is fewer than the other healthcare students assessed in the same studies. When the situation is examined from the DPR students' point of view, it is clear that students often have to apply a variety of assessment and treatment methods, which require them to contact directly and indirectly with the patient and the inanimate environment using their hands and some devices. However, as a result of the literature research taking HH habits into consideration, there was not any research examining the DPR students' compliance with HH in the units where they carry out the clinical practice as a partner for the prevention of

healthcare associated infections. For this reason, the aim of our study was to evaluate HH compliance of the DPR students after a briefing on HH.

MATERIAL AND METHODS

Design and participants

Our descriptive study was conducted with 52 students who had not received any education about HH and volunteered to participate in the survey. Study participants were chosen among 53 students in 2nd year who were supposed to participate for the first time in a clinical summer practice which is included in the 4 year curriculum.

Outcome measures

The first part of evaluation form included open-ended questions about the age, height, body weight, body mass index, the status of having previously worked in a health institution and the presence of health workers among first degree relatives, gender and educational status of the students. The second and third sections consisted of open-ended questions that assessed the type of unit (inpatient and/or outpatient) where the summer practice was done. The final section included closed-ended questions composed of yes/no answers about having or not received any briefing on HH, reports or warnings on complying with HH rules at the institution where the summer practice was conducted, and having or not being subjected to reports or warnings about complying with HH rules from patients. In that section, students were asked to rate the HH compliance of themselves as well as of the unit employees during the summer practice by visual analog scale (0-10; 0: poor / 10 excellent). The questions that assessed the HH compliance of the students were prepared by the researchers according to guideline (20). In this process, among the clinical activities performed by the students of the DPR during the summer practice, the most frequent ones were taken into consideration. These questions are closed-ended questions with the answers “yes, no, I do not remember” and “yes” is the correct answer for all. Finally, students were asked for their opinions about the factors that affected their compliance positively or negatively with the HH indications, and for their suggestions to improve compliance.

Firstly, having obtained approval from the local ethics committee of the Faculty of Medicine, students were informed about the research, and then the written consent of the volunteers was taken (Ethics Board Approval Number 24/06/2015/20478486-252). Secondly, the first part of the research questionnaire was applied using face-to-face interview technique. The information about the place, date and time of the briefing and evaluations to be carried out in the third and fourth steps were instructed. In the third step, two researchers briefed the students in the practice room according to guidelines (20, 21). Finally, after the students had completed their summer practice, the students were asked to complete sections 2.-4. of the questionnaire under the supervision of researchers in their own classroom environment.

Data analysis

For the analysis of the data was done using the SPSS 21.0 program. Data were presented by calculating mean and standard deviation, the number and percentage distributions. Chi-square analysis was performed to evaluate gender difference. $P < 0.05$ was accepted as significant difference.

RESULTS

Among a total of 53 students of the DPR that were apt to participate in second year summer practice. One student excluded, because previously she was a student of medical vocational highschool and participated in a course about HH practices and completed a summer practice in a clinical setting. Thirthy-eight (73.08%) of the participants were females and 14 (26.92%) were males. The mean age, body weight, height, and body mass index of the students were 20.52 ± 0.70 years, 62.54 ± 11.59 kg, 1.67 ± 0.09 m, 22.38 ± 3.41 kg/m^2 respectively. None of the participants currently or previously worked in a healthcare facility and had received any formal HH education. Eight (15.39%) of the students reported that they had a medical staff in first-degree relatives.

Within the scope of this research, 52 (100%) of the students participated their clinical summer practices in the outpatient units and 31 (59.62%) of them participated both in the outpatient and inpatient units where the physiotherapy and rehabilitation program was implemented. Thirteen (25%) stated that they got education about HH where they completed their summer practice. Thirthy-five (67.31%) of the students stated that they were informed about paying attention to HH indications, and 4 (7.69%) of the students stated that they were asked by the patients to comply with these rules.

The self-rated HH compliance scores given by the students over 10 points to themselves and to the employees of the unit they worked together were 7.98 ± 1.62 (min-max; 4-10) and 6.83 ± 2.15 (min-max; 1-10), respectively.

The correct answer rates about HH compliance of the students was 82.69% on average (Table 1A and 1B). When the gender difference was considered, only

Table 1A. *Distribution of students' compliance with hand hygiene indications*

	Questions	Answers	n (%)
1	Have you performed HH when your hands were visibly dirty or contaminated with proteinaceous material or were visibly soiled with blood or other body fluids? And have you washed your hands with either a non-antimicrobial soap and water or an antimicrobial soap and water?	No I don't remember Yes	15 (28.85) 4 (7.69) 33 (63.46)
2	When your hands were not visibly soiled, have you used an alcohol-based hand rub for routinely decontaminating hands in all other clinical situations described in items 3-8? Alternatively, have you washed your hands with an antimicrobial soap and water in all clinical situations described in items 3-8?	No I don't remember Yes	23 (44.23) 2 (3.85) 27 (51.92)
3	Have you decontaminated your hands before having direct contact with patients?	No I don't remember Yes	13 (25.0) 2 (3.85) 37 (71.15)
4	Have you decontaminated your hands after contact with a patient's intact skin (e.g., when taking a pulse or blood pressure, mobilizing and exercising the patient, etc.)?	No I don't remember Yes	2 (3.85) 1 (1.92) 49 (94.23)
5	Have you decontaminated your hands after contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings when your hands were not visibly soiled?	No I don't remember Yes	1 (1.92) - 51 (98.08)

Table 1B. *Distribution of students' compliance with hand hygiene indications*

	Questions	Answers	n (%)
6	Have you decontaminated your hands when moving from a contaminated-body site to a clean-body site during patient care?	No I don't remember Yes	- 2 (3.85) 50 (96.15)
7	Have you decontaminated your hands after contact with inanimate objects (including medical equipment, electrotherapy and exercise equipment etc.) in the immediate vicinity of the patient?	No I don'tremember Yes	15 (28.85) 3 (5.77) 34 (65.39)
8	Have you decontaminated your hands after removing gloves?	No I don't remember Yes	6 (11.54) 1 (1.92) 45 (86.54)
9	Before eating something, have you washed your hands with a non-antimicrobial soap and water or with an antimicrobial soap and water?	No I don't remember Yes	- - 52 (100)
10	After using a restroom, have you washed your hands with a non-antimicrobial soap and water or with an antimicrobial soap and water?	No I don't remember Yes	- - 52 (100)

after contact within animate objects (including medical equipment, electrotherapy and exercise devices etc.) in the immediate vicinity of the patient, women (85.29%, n = 29) were found to have more correct answer rate than men (n = 5,14.71%; $X^2 = 7.452$, p = 0.010).

The distribution of the factors that affected the students positively (80 factors in total) and negatively (75 in total) on their HH practices were presented in Table 2. The suggestions (61 in total) of the students to improve HH compliance were shown in Table 3.

Table 2. *Positive and negative factors affecting HH compliance of DPR students*

Positive Factors	**n (%)**
Self-protection	35 (43.75)
Protecting patients from diseases	22 (27.50)
Having education and information about HH	6 (7.5)
Easy access to the products needed to practice hygiene, taps, sinks, soap, water, etc.	5 (6.25)
Positive attitudes of other students and their working environment and of other employees towards hygienic habits	5 (6.25)
Individual attitudes of patients towards HH	4 (5)
Presence of personal safety & hygiene signs in the working environment	3 (3.75)
Negative Factors	
The use of gloves	20 (26.67)
Not enough time	16 (21.33)
Forget fulness	15 (20.00)
Not feeling the necessity	5 (6.67)
Lack of tap or handwashing facilities	5 (6.67)
Sinks that are not easily accessible	5 (6.67)
Lack of soap or other hand washing agents and hygienic materials	4 (5.33)
Not having enough number of sinks	3 (4.00)
Irritation and dryness of hand-skin due to hand washing agents	2 (2.67)

Table 3. *Suggestions to improve HH compliance of DPR students*

Suggestions	**n (%)**
Briefing/education	24 (39.34)
Improving water, sanitation and hygienic conditions	15 (24.59)
Usage of health&safety signs and posters for HH	12 (19.67)
Facilitating access to disinfectants for HH	6 (9.84)
Maintaining adequate nurse-to-patient ratio for the delivery of quality patient care	3 (4.92)
Conducting hygienic inspections	1 (1.64)

DISCUSSION

With this study, DPR students have been shown to be aware of the importance of HH in terms of the prevention of HCAIs, and it has been revealed that in addition to the need for improvements in the physical conditions, there was a great need and demand for education.

In our study, the rate of compliance assessed by the questionnaire following DPR students' clinical practice was 82.69%. However, the correct response rates were under average for the questions of performing HH after contact with "inanimate surfaces" and "after contact with each patient" and for the questions related to the method that should be used for HH when the hand is "visibly dirty/soiled" and "not visibly soiled". These results were higher than previous studies'. In the studies where HH compliances of students were evaluated by questionnaire, Mahmood et al. emphasized that 52% of the nursing students used alcohol-based hand rubbing technique (9). Similarly, in medical students, Graf et al. determined the compliance rate to be 52.5% (5). Ibrahim et al. stated that only 75% of the medical students had washed their hands with each patient before and after contact (7). On the otherhand, in two different studies realized by direct observation method, the average HH compliance rates in medical students were found to be 17% and 9.5% (1, 8). In addition, Herbert et al. showed that medical students' self-reported compliance of 49% was higher than the disinfection rates according to HH guidelines of 43% (6). Those results suggest that the evaluation method is a factor affecting the compliance rate and should be taken into consideration during the interpretation of the results. Another reason why the overall averages were higher than the ones figured in the

studies obtained from a literature research might be associated with the fact that, students were assessed after one month of summer practice following the HH briefing which is an important predictor of HH, and that they were in their early years of studying introductory classes in terms of physiotherapy and rehabilitation education, which is in accord with the study results of Cruz et al. They have also been emphasizing that having positive attitudes about HH practices is one of the most important predictors of compliance with HH (4). To the question "I adhere to correct HH practices at all times" which was asked to determine the students' attitudes towards HH, the nursing students' answer was 61.8% (10), 61% (12), 62.4% (2) and medical students' answer was 21.4% (10), 20.9% (2). Cruz et al. found that 59.49% of the women and (58.25%) of the men answered "I absolutely agree", and 29.11% of the women and 22.33% of the men answered "I agree" (3). In our study, the mean self-rated compliance score was 7.98 ± 1.62 (min-max; 4-10). This suggested that the DPR students' higher compliance rates should be related to the positive attitudes about HH. Furthermore, in our study, 21% of the DPR students responded correctly to all questions. While the rates of nursing students having "good" practice scores were 14% (2), 29.8% (4) and 25.24% (3) in males, 30.19% (3) in females, for medical students it was 2% (2). Our "good" practice score was close to the nursing students', but higher than the medical students' score. It is reasonable to assume that there may be professional differences at this point. In the light of these results obtained we concluded that DPR students were aware of HH, but they had inadequacies in selecting the HH technique for some situations and in complying with some of the HH indications.

Accessibility to wash basins, water, and disinfectants are among the most important factors that increase HH compliance (22, 23). In many studies it is found that students enumerated not having water and soap (2, 8, 11, 24), inadequate sinklayout (8, 11, 24), laziness (5, 16, 24), not having time (5, 8, 11, 16, 25), and forgetting (3, 5, 8, 10, 16, 24) as negative reasons. Not having time and lack of personnel are also important resource shortage (8, 22). In addition, the use of reminder tips is an other factor that increases the compliance of health care workers with guidelines (2, 22). In the context of these studies and our data, it was thought that HH compatibility could be improved positively by determining the needs proper to the type of hospital/clinic, by planning special arrangements according to the needs, by using warning signs/posters, etc., by developing physical conditions and facilitating access to products, and by planning the workflow.

"To prevent and to protect from diseases" stand among the most important factors why students and healthcare workers perform HH (8, 11, 22). In our study too, since the students singled out those two as the most important factors in complying with HH, so this was thought to be a sign of our students' awareness of performing HH to protect the health of both the patient and the healthcare worker. Also, it has been found that among the students of medicine, nursing and dentistry there was a belief in the form of "I do not have to do HH because I use gloves" (1, 10, 16, 18, 25). However, Snow et al., on the contrary, determined that students who used gloves were more likely to perform HH (13). They reported that this might have been related to the type of patient being taken. Al-Naggar et al. pointed out that among the most important barriers for medical students, the feeling that their hands are not so dirty as to cause infections was the most basic barrier (24). Martinez et al. found that some physiotherapy students had beliefs about HH recommendations such that HH should only be performed if there is a risk of infection (18). In our study, the most important negatively affecting reason was "no HH is needed if gloves are available". In addition to this, other reasons were "not enough time, forgetfulness and not feeling the necessity". All of these results have shown that the students of the DPR realized the importance of HH, and the most important need of DPR students is to get an education.

During the professional socialization process, students view other team members they work with as role models in terms of performing HH (2, 5, 7, 10, 13, 16, 19, 22, 25, 26). Moreover, the patient's individual attitudes towards HH is also important factor in terms of HH practices (8, 20, 22, 27-29). It is also an important requirement to create and maintain an organizational culture as much as the efforts of individual team members to comply with HH guidelines (22). In the light of these data and our results, it should not be forgotten that while training programs and campaigns are planned to improve the HH compliance of the students, clinical and academic supervisors as well as the patient are also part of the team. At the same time, it is necessary to give importance to organizational culture.

There are studies showing that gender has no effect on parameters such as hand washing frequency (11, 30), knowledge level (3, 19, 31), attitudes (31), awareness of theWHO's five-indications for HH (1), and compliance (1). On the other hand, there are also studies showing that women perform better self-assessment of their level of knowledge and compliance in terms of hygiene guidelines (6), had more positive attitudes and self-reported performance than men, and men had better HH practice scores than women (3). Cruz et al. pointed out male gender as the most important predictor for HH practice, too (4). In our study, it was seen that only in the case of "after contact with ina-

nimate objects in the immediate vicinity of the patient", women had a more correct response rates than men. It was thought that future studies could help in the development of educational materials that will take into account the occupational effect of gender.

One of the most important limitations of our research is that firstly, it is a cross-sectional study which examines 52 students of the DPR of one university only. This may limit the generalizability of the results. Secondly, in our study, students' compliance with HH practices has been assessed by self-report questionnaires and face-to-face interview method. This method might have caused students to have higher HH compliance rates than observed. Besides this, the Hawthorne effect which might be generated by this kind of observation method might also have been eliminated again by itself as well. Lastly, the class and experience may be a factor that may affect HH compliance was also included in the literature as an information (4, 5, 7, 13-16, 32). This point should be taken into account in future studies.

CONCLUSION

As a result, DPR students were found to be aware of the importance of practicing HH in order to prevent HCAIs. However, they had inadequacies in selecting suitable HH techniques and in complying with HH indications in some situations related to their profession. Moreover, the students suggested that there was a great need for education and improvements in physical conditions. In view of these results, it was thought that HH education which would start from the early period and would continue through out their education and that their effects on the students' HH compliances should be evaluated at frequent intervals.

Abbreviations

HH — Hand Hygiene
DPR — Department of Physiotherapy and Rehabilitation

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Sažetak

STUDENTI FIZIOTERAPIJE KAO PARTNERI U PREVENCIJI INFEKCIJA POVEZANIH SA ZDRAVSTVENOM NEGOM

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Uvod: Higijena ruku, koja je značajan faktor za prevenciju infekcija, koje se javljaju u zdravstvenom sistemu je opsežno ispitivana. Međutim, ne postoje studije u ovoj oblasti kod studenata iz odseka za fizioterapiju i rehabilitaciju. Cilj ove studije bio je da se proceni komplijansa higijene ruku kod studenata na odseku fizioterapije i rehabilitacije nakon kratke edukacije o rukama.

Metod: Pre započinjanja letnje prakse, studenti su bili ukratko edukovani o održavanju higijene ruku. Nakon toga procenjena je njihova komplijansa održavanja higijene ruku. Sociodemografske karakteristike, podaci o kliničkoj letnjoj praksi, kao i komplijansa održavanja higijene ruku zasnovana na preporukama Centra za kontrolu i prevenciju bolesti i njihovim vodičima za održavanje higijene ruku, su bili ispitivani sa upitnikom, pripremljenim od strane istraživača.

Rezultati: Od 53 studenta, 52 je ispunilo kriterijume. Prosečna vrednost tačnih odgovora bila je 82,69%. Studenti su imali poteškoća sa izborom adekvatne tehnike za održavanje higijene ruku, kao i u komplijanski sa indikacijama za održavanje higijene ruku u situacijama, koje su u korelaciji sa profesijom. Štaviše, studenti su predložili da je potrebna bolja edukacija (n = 24, 39,34%) i unapređenje fizičkih uslova (n = 21; 34.43%).

Zaključak: U zaključku se može izneti da su studenti fizioterapije sa rehabilitacijom svesni bitnosti održavanja higijene ruku u cilju prevencije infekcija,

koje se javljaju na radnom mestu i povezane su sa zdravstvenim sistemom. Kako god, za ovaj odsek, neophodni su programi za higijenu ruku u cilju održavanja optimalne kvalifikacije, kao i da bismo bili u mogućnosti da zaštitimo i unapredimo zaštitu zdravstevnih radnika, kao i pacijenata.

Ključne reči: higijena ruku, edukacija fizioterapeuta, studenti.

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Case report

FROM DERMATITIS TO CENTRAL DIABETES INSIPIDUS

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Abstract: The case report shows a seven-month-old, female infant whose malignancy initially manifested as a seemingly harmless skin condition such as dermatitis. When the patient was three months old, the first symptoms were identified such as atopic and intertriginous dermatitis and milliaria. After a few months, a tumefaction appeared on the neck, behind the left ear, which was treated as an abscess. As the prescribed antibiotic therapy showed no results, the patient underwent a surgical procedure followed by a pathohistological treatment of the lesional tissue suggestive of histiocytosis. The patient was subjected to chemotherapy for a duration of one year. However, one year after the end of the treatment, a recurrence was found, which required an additional, yet successful chemotherapy treatment. As an adverse sequelae, central diabetes insipidus was confirmed.

Key words: malignancy, dermatitis, tumefaction, chemotherapy, abscess, recurrence.

INTRODUCTION

Histiocytic disorders arise as a result of abnormal accumulation of cells of the mononuclear phagocyte system consisting of dendritic cells and macrophages. Nosology relies on the information on cell origin and biological behavior, and is based on pathological and immunohistochemical criteria (1). The classification based on biological behavior consists of: dendritic cell-related disorders i.e. Langerhans cell histiocytosis (LCH); macrophage related disorders - Primary hemophagocytic lymphohistiocytosis; monocyte-related disorders - monocytic, acute and chronic myelomonocytic leukemia (2). Langerhans cell histiocytosis is a rare disease, with a prevalence of 1.50000 and an incidence of 5-10 cases per year in one million children under the age of 15 years (3). Symptoms and signs of Langerhans cell histiocytosis vary greatly depending on which organs are infiltrated with Langerhans cells. Bones, skin, teeth, gums, ears, endocrine system, liver, lungs, pituitary gland, hypothalamus may be affected. Bones are the most commonly involved organ as for example flat bones, skull, pelvis, shoulder blades, ribs. In one third of the cases, the scalp and the skin folds are affected. The most common forms are unifocal or multifocal eosinophilic granuloma, multisystem Hand-Schüller-Christian disease may be found in young children, and the most severe clinical manifestation comes in a form of Abt-Letterer-Siwe disease (4). The diagnosis should be confirmed with biopsy and histopathological examination of the lesion, subsequently followed by a chemotherapy treatment and bone marrow transplantation. Bone lesions require a diagnostic curettage procedure which initiates the recovery process (5).

CASE REPORT

A female seven month old infant, delivered by normal vaginal birth, with body weight 3,250 g, length 49 cm, Apgar Score 9/10 and properly immunized, was admitted to the Department of Plastic Surgery for surgical treatment of a neck mass. On admission, it was reported that suggestive clinical manifestations had appeared for the first time when the patient had been three months old. The initial symptoms had included an erythematous maculopapular rash covering the trunk and back, subsequently followed by livid erythema in the perianal region.The symptoms had persisted regardless of the treatment with topical corticosteroids and antibiotics. Additionally, the patient's mother was now reporting a mass in the left retroauricular region. Upon examination, the mass was described by a radiologist as a hypoechoic, avascular, soft-tissue lesion with central calcification of 25 x 10 mm (Figure 1).

At first, the surgeon advised an observation period. However, surgical procedure was performed three months later due to the increase in lesion size. The ultrasound showed a well-vascularized, hetero-echoge-

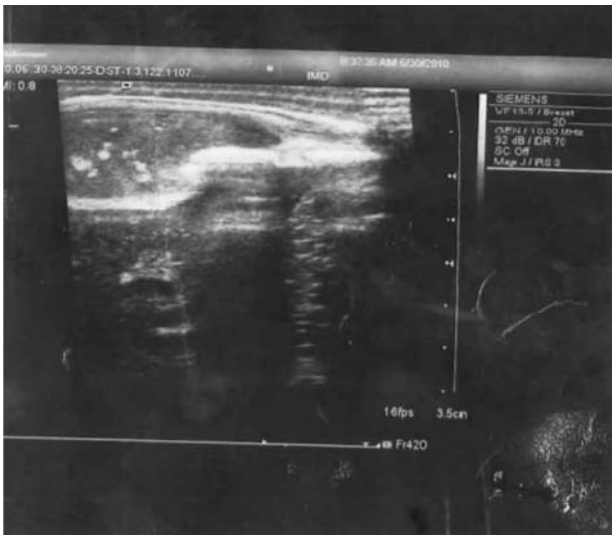

Figure 1. *Lesion in the first ultrasound image*

nic formation with predominantly echogenic characteristics and numerous punctiform hyperechogenic changes, 42 x 19 mm in diameter (Figure 2).

Blood biochemistry tests showed ESR 40 mm/hr, RBC 5.27 x 10^{12}/L, Hgb 93.9 g/l, WBC 13.3 (GR 43%, LY 47%, MO 6.35%), PLT 531, glycemia 6.8 mmol/l, BUN 3.7 mmol/l, CREA 39 mmol/l, TCO2 20 mmol/l, K 4.3 mmol/l, Na 138 mmol/l, Cl 103 mmol/l, Ca 2.33 mmol/l, Mg 0.94 mmol/l, P 1.45 mmol/l, AST 556 IU/L, ALT 317 IU/L, ALP 465 IU/L, GGT 321 IU/L, LDH 1446 IU/L, Uric Acid 166 mmol/l, Protein (total) 60 g/l, ALB 33 g/l, Plasma osmolality 283 mOsm/kg, Ferritin 83.6 ng/mL.

PA and lateral view skull radiography showed bone tissue destruction in the outer corner of the right orbit upper edge.

Computer tomography of endocranial structures detected skull bone destruction in the left temporoparietal junction caused by a large subcutaneous mass of

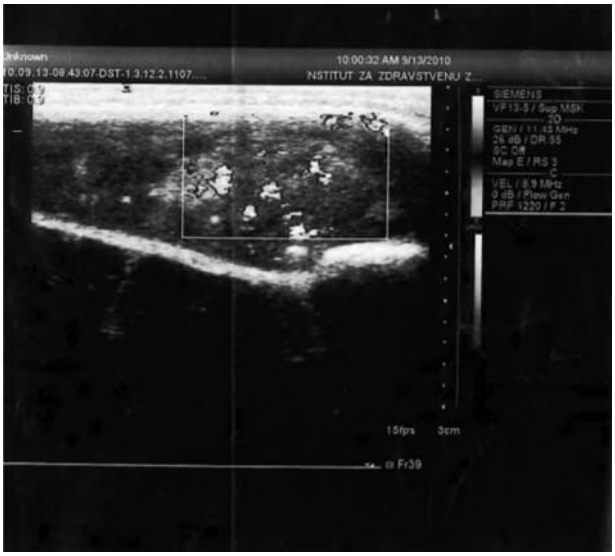

Figure 2. *Lesion in the follow-up ultrasound image*

6.8 x 5.7 x 2.5 cm and separated from the cerebral parenchyma only by envelopes. The mass was less vascularized, with a density of a lymphatic tissue. Below the right orbital roof, a mass of similar properties was detected, causing bone destruction, entering the orbit's posterior and dislocating the eyeball. The lesion size was 2.5 x 2 x 2.7 cm. This mass, unlike the previous one, was more extensively vascularized. The ethmoid sinuses were less developed with mucosal thickening in both maxillary sinuses, and the right mastoid extension was not pneumatized. Cerebral tissue was clearly recognizable with normal density and no pathological changes. The ventricular system showed normal function with normal values of cerebrospinal fluid density.

On abdominal ultrasound, the inferior vena cava and aorta were of normal position and lumen. Paravertebral and mesenteric lymph nodes were not swollen. The liver, spleen and pancreas were of normal size, preserved contours, with good parenchyma echostructure and without pathological lesions. The findings on the biliary tract, adrenal glands, and urinary tract were in order. In the abdomen and pelvis there were no pathological soft tissues or free fluids.

Chest radiograph showed on exhalation normal lung lucency and cardiac silhouette. Phrenicocostal sinuses were clear. There were no reliable signs of the pulmonary parenchyma condensation.

In the dense connective tissue, a histopathologic examination revealed numerous individual cells that were also forming cell islands or clustering in sheet-like appearance. The cells' nuclei were vesicular, indented and they were mixed with clustered Eosinophil granulocytes. The aforementioned histiocytic cells showed the following immunohistochemical profile: DC1a+, CD68+ and S 100+. It was concluded that the lesions corresponded to the eosinophilic granuloma as a part of histiocytosis.

The clinical work-up led to a conclusion that the patient had Langerhans cell histiocytosis with multifocal bone lesions and localized CNS (central nervous system) risk lesions. The patient was subjected to a one-year LCH-III Group 3 treatment protocol. One year after the treatment was completed, i.e. at the age of three, a recurrence was detected during a regular follow-up, whereby the patient was in a good general condition and with normal laboratory test values. However, the follow-up skull radiography showed three bone erosion lesions in the parietal bones and one in temporal bone. The anamnestic data provided by the patient's mother also suggested the presence of polyuria. Endocrinological examination was suggestive of the development of diabetes insipidus.

Hormone analysis showed values of Prolactin 206 mIU/L, Cortisol 167 nmol/l, TSH 1.220 mIU/L, FT4

15.26 pmol/L, Serum sodium 145 mmol/l, osmolality 345 mOsm/kg, urine osmolarity 556 mOsm/kg.

Comparing to the multiple detector computer tomography (MDCT) imaging taken two years prior, the magnetic resonance imaging (MRI) of endocranium showed multiple nodular infiltrates in calvarial bones, skull base and facial bones along with epidural infiltrates. The two lesions that had already been revealed were still present. The examination disclosed infiltration of 29 mm mastoid extending and 7 mm epidural infiltration of the right temporal bone. The skull base imaging showed infiltration of the sphenoid bone and numerous individual foci in the mandibular angulus. Lentiform infiltrates were revealed on the left parietal, next to sinus sagittalis and unilateral in temporal squama close to insula region.

Disease progression was diagnosed with detected multiple nodular infiltrates in calvary bones, skull base and facial bones and with intracranial epidural infiltrates involving the confirmed sites.

Upon examination, the patient underwent chemotherapy for a year based on an established treatment protocol for Langerhans cell histiocytosis recurrence. The diagnosis of diabetes insipidus was treated with desmopressin. It has been five years now since the chemotherapy treatment was administered. The patient visits a hematologist and endocrinologist for regular follow-ups, but currently reports no clinical symptoms.

DISCUSSION

The patient we have presented, was suffering from a very rare disease that manifests itself in a peculiar manner. As a matter of fact, a great number of infants are brought to pediatricians for examination due to the various skin manifestations. Moreover, taking into consideration the physiological characteristics of the lymphatic system as well as lymphocytosis that is considered normal at this age, cervical lymphadenopathy can often occur (6, 7). Therefore, it is more difficult to promptly set the right diagnosis and start the corresponding treatment. As a permanent sequelae of histiocytosis, diabetes insipidus occurs and in 10 % of the cases, it actually results from histiocytic infiltrations of hypothalamus and pituitary gland (8, 9). The most common cause of CDI (central diabetes insipidus) are hypothalamus and pituitary gland tumors whereas congential disorders leading to CDI are usually associated with septo-optic dysplasia (10). This scenario requires a lifelong regimen of taking prescribed medication as a synthetic analogue of the missing antidiuretic hormone. Since the therapy is administered via intranasal or peroral route and cannot reduce diuresis below the recommended levels of common fluid intake or of a standard diet, the patients run no risk of hyponatremic disorders (11, 12). However, water intoxication might ensue and for that reason both parents and children should be properly informed on how to avoid excessive fluid intake that is usually imposed by social norms.

Abbreviations

CDI — Central diabetes insipidus
CNS — Central nervous system
LCH — Langerhans cell histiocytosis
MDCT — Multiple detector computer tomography
MRI — Magnetic resonance imaging

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Sažetak

OD DERMATITISA DO CENTRALNOG DIABETESA INSIPIDUSA

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Ovim prikazom slučaja pokazaćmo 7 meseci staro odojče, ženskog pola sa malignitetom, koje se inicijalno manifestovalo kao naizgled bezopasna kožna promena, kao što je dermatitis. Kada je pacijentkinja imala 3 meseca, prvi put su identifikovani simptomi kao što su atopijski dermatitis i intertrigininozni dermatiits i miliaria. Nakon nekoliko meseci, tumefakt se pojavio na vratu, iza levog uva, koji je tretiran kao apsces. S obzirom da je propisana antibiotska terapija koja nije pokazala efekat, pacijent je podvrgnut hirurškog proceduri i histopatološkom potvrdom odstranjenog tkiva, koje je ukazivalo na histiocitozu. Pacijentkinja je podvrgnuta hemioterapiji u trajanju od godinu dana. Godinu dana po prestanku primene terapije, javio se recidiv, koja je zahtevao dodatni i uspešni hemioterapijski tretman. Kao sekvela, potvrđen je centralni diabetes insipidus.

Ključne reči: malignitet, dermatitis, tumefakcija, hemoterapija, apsces, remisija.

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Case report

PULMONARY AMEBIASIS COMPLICATED WITH MASSIVE LEFT EMPYEMA AND RESPIRATORY FAILURE: A CASE REPORT

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Abstract: **Introduction:** Amebiasis is defined as a parasitic infection with the protozoan *Entamoeba histolytica*. Amebiasis in pulmonary and pleural tissue is the second common location of extraintestinal amebias is after amoebic liver abscess. Pulmonary and pleural amebiasishappens in 2-3% of invasive amebiasis patients with mortality rate 5-16%.

Case: We report a 22-year-old man with the chief complaint of dyspnea for one week. The patient also felt pain in the left chest, had productive cough and fever. He had a history of dysentery one month ago. BGA evaluation confirmed patient had respiratory failure type 1 with PCO_2 35 and PO_2 46.1. Thoracentesis was performed, the result was brown milk (anchovy paste) color and pleural fluid analysis revealed positive *Entamoeba histolytica*. Antimicrobial therapy and drainage were given with excellent response.

Conclusion: Pulmonary and pleural amebiasis is an uncommon disease, usually occurring on the right side of the lung compared to the left side and rarely causing respiratory failure. Pulmonary amebiasis is a life-threatening, but treatable, condition. Antimicrobial therapy and drainage is an important strategy in pulmonary amebiasis management.

Keywords: Pulmonary amebiasis, massive empyema, respiratory failure.

INTRODUCTION

Entamoeba histolyticais an intestinal protozoan. Amoebic infection (amebiasis) is defined by the World Health Organization (WHO) as *Entamoeba histolytica* infection with or without clinical manifestations (1). Amebiasisis the third ranking cause of death worldwide due to parasitic infections after malaria and schistosomiasis (2). It is estimated 40,000-100,000 mortality occurs in 40-50 million amebiasis patients each year (3). Amebiasis occurs in 12% of the world's population or 50% of the population in tropical and subtropical regions. The incidence of amebiasis is quite high in developing countries such as Mexico, South and West Africa, South and Central America, Bangladesh, Thailand, India, Vietnam, and Indonesia. Fecal-oral transmission happens via fecal contamination of food and water. Lack of sanitary conditions and poor hygiene predispose to spread the disease (1, 4).

Pulmonary and pleural tissue are the second common location of extraintestinal amebiasis after amoebic liver abscess. Pleuropulmonary amebiasis occurs in 2-3% of invasive amebiasis patients with a mortality rate of 5-16% (3). Pleuropulmonary usually occurs when a right lobe liver abscess ruptures through the diaphragm and produces an empyema in the right hemithorax. We reported a rare case of pulmonary amebiasis complicated with respiratory failure and massive empyema in left hemithorax.

CASE REPORT

A 22-year-old man came to the Emergency Department with chief complaint of dyspnea for one week. The patient also felt pain in the left chest, had productive cough and fever. He had a history of dysentery dating one month ago. He denied any history of jaundice, nausea, vomiting, and abdominal pain. He went to primary healthcare and was prescribed ciprofloxacin for three days.

From the physical examination, he was compos mentis, anemic, and sweaty. Vital sign results were blood pressure 100/70 mmHg, pulse 112 bpm, respira-

tion rate 40x/min, temperature 39.2 °C, SpO_2 81%. Chest examination revealed significant decrease left side motion and tactile vocal fremitus, dullness percussion, auscultation sound was not heard, normal heart sound with no murmurs and gallops. Abdominal examination was soft and no evidence of hepatomegaly.

Laboratory report were Hb 9.6g/dl, WBC 13.83 x 10^3, platelet 350 x 10^3, neutrophil 92.2% random glucose 114 mg/dl. BGA evaluation confirmed pH 7..518, PCO_2 35, PO_2 46,1, HCO_3 29.9, and BE 5.5. Stool examination suggested *Entamoeba histolitica infection*.

Chest x-ray examination was taken which showed a left total consolidation (Figure 1). CT scan thorax showed air-fluid level with left hemithorax pleural effusion, suspect left massive empyema (Figure 2). ECG showed sinus tachycardia. USG abdomen revealed solitary abscess in left quadrant size 18mm x 17mm.

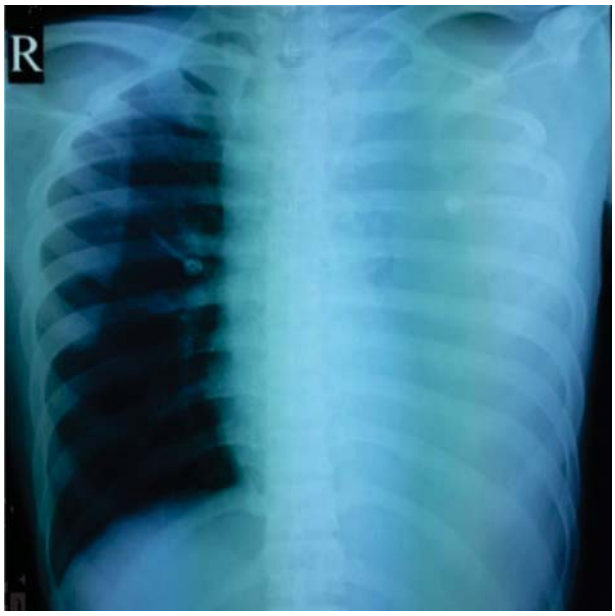

Figure 1. *Chest X-ray homogenous opacity in left hemithorax*

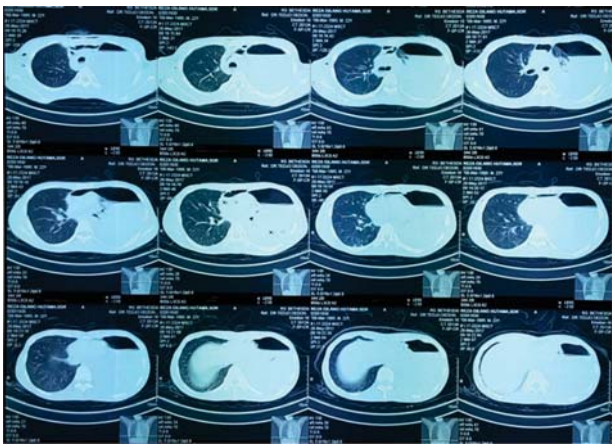

Figure 2. *CT-scan thorax*

Figure 3. *Pleural fluid anchovy paste*

Thoracocentesis was performed, the result was brown milk (anchovy paste) color (Figure 3). Hence an emergency intercostal chest drain (WSD) was placed in the left side which drained about 1250 ml. WSD was installed for fourdays and pleural fluid analysis revealed positive Entamoeba histolytica (Figure 4).

The patient was diagnosed with pulmonary amebiasis complicated with massive left empyema, respiratory failure, and anemia. Patient was hospitalized in intensive care unit (ICU), breathing with ventilator support for three days, and installation of WSD for four

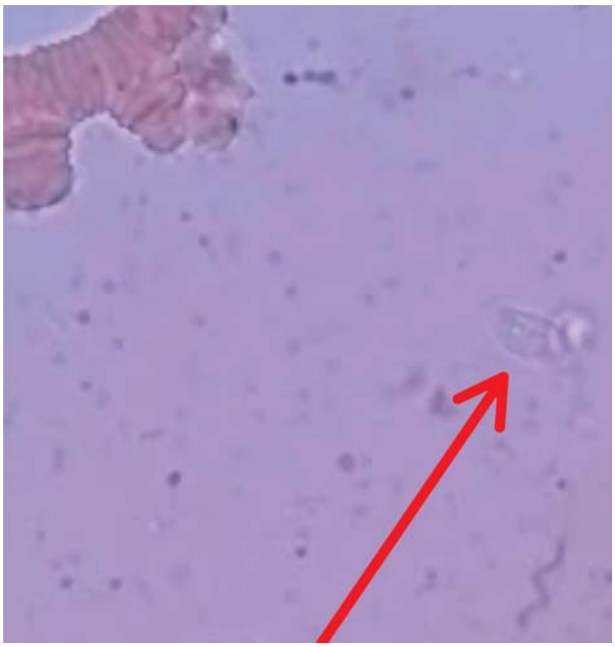

Figure 4. *Microscopic view of Entamoeba histolitica*

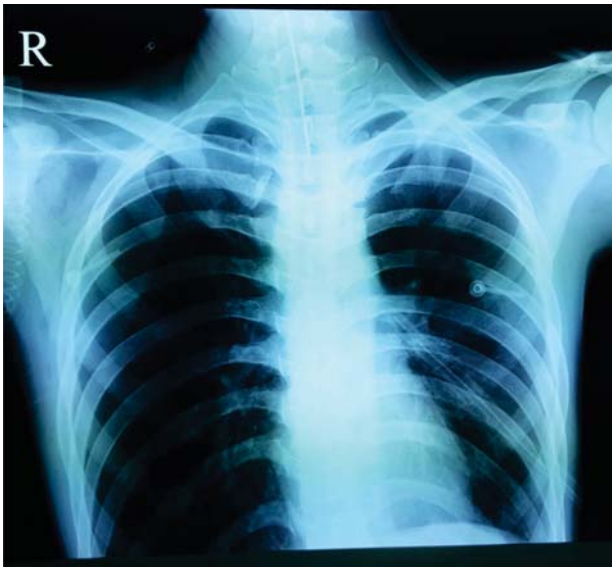

Figure 5. *Chest X-ray after WSD*

days. Evaluation of chest x-ray after WSD revealed increased bronchovascular pattern with minimal air bronchogram (Figure 5).

The patient had medication with metronidazole 3 x 500 mg intravenous for five days and continued 3 x 500 mg orally for 10 days, levofloxacin 750 mg intravenous, ambroxol 3 x 30 mg, and sulfas ferosus. The patient had good response from medical therapy.

DISCUSSION

The pathogenesis of amebiasis occurs when parasites attach to the mucus layer, without effective defense from the host immune system. In a normal host immune response, IgA can prevent pathogens from sticking and penetrating the mucus layer. Intestinal epithelial cells identify pathogens through the toll-like receptor and activate NF-êB which will produce inflammatory cytokines. Interferon gamma (IFN-γ) plays an important role in defense against infection. Macrophages and neutrophils activated by IFN- ã will go to the infection site and, thus, produce nitric oxide (NO) and reactive oxygen species (ROS), which will kill trophozoites (4).

Amebiasis generally occurs in the form of intestinal involvement. It can also present as an extra-intestinal disease. Extra-intestinal site of amoebiasis is an amoebic liver abscess (3-9% of all cases) and even more rare as pulmonary, cardiac, and brain involvement. Amoebiasis in the lung and pleural tissues is the second extra-intestinal amoebiasis. Pulmonary and pleural (pleuropulmonary) amoebiasis occur in 2-3% patients, and 6-40% of patients also have an amoebic liver abscess (3,5). Distribution of *entamoeba* infection in the chest is through: 1. independent liver abscess and hematogenous lung abscess (10.4%), 2. hematogenous spread without liver involvement (14.3%), 3. empyema extending from liver (17.6%), 4. bronchospastic fistula (19.6%), and 5. abscess extending from liver (37.2%) (2). The invasive amebiasis mortality rate was 5-16% and can increase to 80% if not treated.

Pulmonary amebiasis occurs from several mechanisms, including rupture of the right lobe liver abscess through the diaphragm causing empyema, hematogenous, and lymphogenic spread. The most common mechanism is a direct rupture of amoebic liver abscess via the diaphragm, which leads to empyema in the chest cavity. The second is through hematogenous spread from the large intestine via the hemorrhoidal vein, superior mesenteric veins, and inferior vena cava to the lung and pleura. In our patient, pulmonary amoebiasis without liver involvement occurred sporadically as a result of hematogenous spread from a primary site, the colon, which was the most probable route (3, 6).

Entamoeba infections are usually asymptomatic. The risk factors are young age, genetic susceptibility, atrial septal defect with left to right shunt, pregnancy, corticosteroid treatment, immune status, malignancy, chronic alcoholism, and malnutrition (5, 7). Pleuropulmonary amebias is sometimes mimics other illnesses. The differential diagnoses are: bacterial lung abscess, pulmonary tuberculosis, carcinoma of the lung, malaria and schistosomiasis endemic areas..

Pulmonary amebiasis diagnosis is sometimes difficult since there are various clinical manifestations. In addition to clinical manifestation, laboratory tests and imaging modalities need to be done. The exact diagnosis was established by *Entamoebahistolytica* finding in microscopic examination (7). Amebiasis clinical manifestation occurs in the form of intestinal involvement as acute or subacute colitis, with symptoms ranging from abdominal pain, mild to severe diarrhea, and bloody stools (5). Patients may initially present with fever only (1, 5). In this case, the patient had a history of dysentery which may lead to the port de entry of pulmonary amebiasis.

Blood chemistry or hematologic testis sometimes not helpful in pulmonary amebiasis diagnosis. Neutrophilic leucocytosis (> 15,000/mm^3), invariably elevation of erythrocyte sedimentation rate (ESR), and normocytic normochromic anemia are usually present. Liver function tests are sometimes within normal limit even when hepatic complication also happen with pulmonary amebiasis (2). Confirmation with laboratories testing should be pursued by stool microscopy. Trophozoites and cysts usually identify via light microscopic examination (5). Immunological tests, such as enzyme-linked immunosorbent assay (ELISA) and indirect hemagglutination assay (IHA), may detect *E. histolytica* antibodies in 85-95% of patients (5, 7).

Radiographic imaging, such as computed tomography (CT) scan, magnetic resonance imaging (MRI), chest ultrasonography (USG), and X-ray, are sometimes needed (7). From chest X-ray, we can find right lower and middle lobes cavitating lesion with homogenous opacity seen in lateral view, pleural effusion, basilar pulmonary infiltrated with focal atelectasis, and elevated right hemidiaphragm (5). Pleural effusion occurs in 62.5% of cases. When there is bronchopleural fistula, a hydropneumothorax may be seen (2). MRI and CT scan have excellent sensitivity to detect liver abscess (5, 6). USGis used to monitor extra-intestinal amebias is treatment (2).

In some studies, catheter drainage or needle aspiration are needed to diagnose pleuropulmonary amebiasis (7). The classical characteristics and colors of amebic pus are reddish-brown, thick, opaque, and resembling “chocolate sauce” or “anchovy paste”. Expectorated pus is usually “anchovy sauce” color. Aspirated pus is usually sterile and expectorated pus sometimes contains a few organisms (2).

Amoebiasis is a treatable disease, but delay in the diagnosis may lead to serious complications. This case was complicated by left side empyema and respiratory failure (respiration rate 40x/min and blood gas analysis result). In general, amoebic empyema should be aspirate (5). Drainage of pleural effusion resolves rapidly with antimicrobial therapy. Drug of choice is metronidazole (750 mg oral, three times daily for 7-10 days). Metronidazole is a nitro-imidazole derivative that can kill the trophozoites. When given orally, it is soon absorbed and immediately seeps into the tissue through the diffusion process. The drug's mechanism is activated by the reduction of the nitro group and produces radical metronidazole. Radical metronidazole will interact with proteins causing parasitic death. In this case, we gave metronidazole 500 mg, 3x daily for 15 days. Empyema requires pleural puncture, installation WSD four days and decortication is done to prevent recurrent and chronic infection. For respiratory failure, we performed ventilator support for three days. Response to treatment was good.

CONCLUSION

Pulmonary and pleural amebiasis is an uncommon disease, usually occurring on the right side of the lung compared to the left side and rarely causing respiratory failure. Pulmonary amebiasis is a life-threatening, but treatable, condition. Antimicrobial therapy and drainage is an important strategy in pulmonary amebiasis management. *Entamoeba histolytica* infection should be suspected as a possible cause in the differential diagnosis in young patients, especially in patients from endemic areas.

Abbreviations

BGA — blood gas analysis
CT — computed tomography
ECG — electrocardiography
IFN-γ — Interferon gamma
MRI — magnetic resonance imaging
NO — nitric oxide
ROS — reactive oxygen species
USG — ultrasonography
WHO — World Health Organization
WSD — water sealed drainage

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Sažetak

PLUĆNA AMEBIJAZA KOMPLIKOVANA MASIVNIM LEVOSTRANIM EMPIJEMOM I RESPIRATORNOM INSUFICIJENCIJOM: PRIKAZ SLUČAJA

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Uvod: Amebijaza se definiše kao parazitna infekcija protozoom Entamoeba histolytica. Amebijaza u plućnom ili pleuralnom tkivu je druga najčešća lokalizacija ekstraintestinalne amebijaze nakon hepatičnog apscesa izazvanog amebijazom. Plućna i pleuralna amebijaza se javlja u 2-3% invazivne amebijaze kod pacijenata, sa stopom mortaliteta od 5-16%.

Prikaz slučaja: Prikazujemo slučaj 22-ogodišnjeg mladića, koji se nedelju dana žalio na teškoće sa disanjem. Pacijent je takođe osećao bolove sa leve strane grudnog koša. Imao je produktivan kašalj i temperaturu. Navodi da je mesec dana pre pregleda imao dizenteriju. Gasne analize potvrdile su da kod pacijenta postoji respiratorna insuficijencija tip 1 sa PCO_2 35 i PO_2 46.1. Urađena je torakocenteza i dobijena tečnost braonkaste boje, a analiza pleuralne tečnosti potvrđuje Entamoeba hystolitica-u. Antimikrobna terapija i torakalna drenaža pokazale su zadovoljavajući efekat.

Zaključak: Plućna i pleuralna amebijaza nisu retke forme bolesti. Češće se javljaju sa desne strane pluća, u poređenju sa levom stranom i retko izazivaju respiratornu insuficijenciju. Plućna amebijaza je životno ugrožavajuća bolest, koja je pak izlečiva. Antimikrobna terapija i drenaža su veoma bitne u lečenju plućne amebijaze.

Ključne reči: pulmonalna amebijaza, masivni empijem, respiratorna insuficijencija.

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Case report

OCULAR ASPECTS OF USHER SYNDROME

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Abstract: **Introduction:** Usher Syndrome is a rare syndrom, which typical expressions are hearing loss, retinitis pigmentosa and in some cases impairment of balance and congenital cataract. It is inherited autosomal recessive. Nine genes whose mutation are associated with this condition have been isolated. It is diagnosed on the basis of clinical and genetic testing. The therapy is aimed at facilitating the functioning of these patients in the environment. Gene therapy is promising in treatment.

The purpose of this paper is to focus attention on the specificity and multiplicity of the disease, which would be of educational significance to ophthalmologists and otorhinolaryngologists, through the use of the case report of Usher syndrome.

Case report: We present the case of gene confirmed Usher syndrome with 85% hearing loss, retinitis pigmentosa and congenital cataract. Female at the age of 39, pregnant at 26 gestational week, second pregnancy. Genetic investigation by Macedonian Academy of Sciences and Arts (MANU) confirmed double heterozygosity for pathogenic changes c.13010C > T. p. (Thr4337Met) and c.13137delC; p. (Thr4380GinfsTer11) in the USH2A gene, a genotype that confirmed the diagnosis of autosomal recessive disease Usher syndrome type 2A (Usher syndrome 2A).

Conclusion: Detailed anamnesis is always required in patients with retinitis pigmentosa, who are referred to an ophthalmologist for hearing and vice versa for patients with hearing loss that are examined by an otorhinolaryngologist. Early diagnosis is important in terms of quality of life, i.e. timely diagnosing and undertaking measures for genetic testing in the family, in order to inform them about the type of the disease and the earlier involvement in educational programs designed for these conditions.

Key words: Usher syndrome, retinitis pigmentosa, deafness, gene therapy.

INTRODUCTION

Usher syndrome (USH) is a hereditary syndrome, usually detected before adolescence and causes hearing and vision loss. Patients with this syndrome may also have balance problems.

Gene mutations that affect the retina and cochlea are responsible for hearing loss. Several studies have shown that up to 25,000 people in the United States have some form of this syndrome. Generally, Usher syndrome is a main cause of linked deafness and blindness (1).

Nearly thirty percent of patients with retinitis pigmentosa reported hearing impairment, and almost 50 % of them are confirmed as USH (1).

Hearing loss is classified as sensory. Visual loss is due to involvement of photoreceptor cells. It first begins with peripheral scotomas in the visual field, and after a period of time it remains only a tubular vision. In some cases, the vision is further reduced due to lens clouding i.e. cataract (2).

Usher syndrome is classified into three main types: type I, II and III. While all three types involve progressive vision loss due to retinitis pigmentosa (RP), the categorization is by the genes responsible for the disease and the onset and severity of the signs and symptoms.

Type I of USH that is manifested by severe deafness, RP and absence of vestibular function is the most severe clinical presentation of the disease.

Type II of USH is less severe with moderate congenital deafness, retinitis pigmentosa without vestibular damage. Usher syndrome type III includes profound deafness, retinitis pigmentosa and varying degrees of vestibular impairment. This type typicaly occurs in the second to fourth decade of life. These patients tend to have better vision than the other two types (3, 4).

CASE REPORT

We present the case of gene confirmed Usher syndrome. Female at the age of 39, pregnant at 26 gestational week, second pregnancy.

She first came at the University Eye Clinic in Skopje in 2013, when she was diagnosed with retinitis pig-

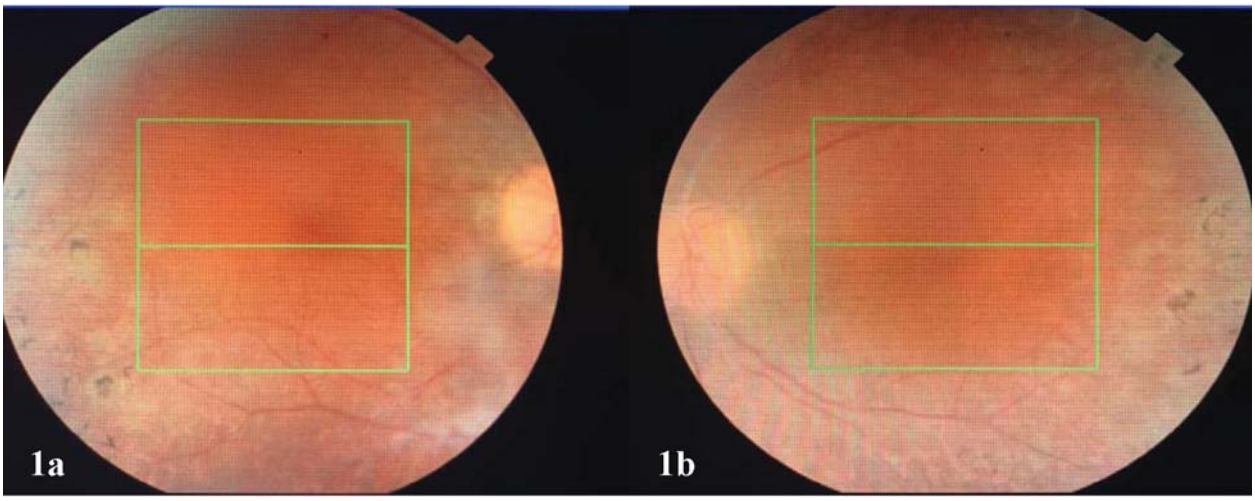

***Figure 1a and 1b**. Fundus photo, right and left eye*

mentosa (RP) and BCVA 0.1 of both eyes. Her next examinations were in 2014 and 2016, without worsening of visual acuity and no significant progression of the visual field.

After three years, at the examination in October 2019, the patient had a BCVA of 0.05 on both eyes, and a significantly narrowed visual field, i.e. tubular vision.

The biomicroscopy of the anterior segment of the eye showed a congenitally clouding of the posterior lens capsule. The fundus examination showed hyaloid membrane remnant, large opacity floating in the vitreous body of the right eye, pale papilla with narrow blood vessels, thin layers of the retina and osteoclastic changes throughout the whole medioretina and peripheral retina (Figures 1a, 1b).

Optical coherence tomography (OCT) of the posterior segment of the eye showed a posterior hyaloid membrane detachment, thinning of the retinal layers, more pronounced to the right eye, with changes in the retinal pigment epithelium (Figures 2a, 2b).

In medical history, the patient reported hearing loss, which began in childhood. Audiological tests found an 85% reduced hearing, according to the Fowler-Sabinau scale and no impairment of vestibular function.

Further genetic and intrauterine examinations of fetus were assigned to the patient.

Genetic investigation by Macedonian Academy of Sciences and Arts (MANU) confirmed double heterozygosity for pathogenic changes c.13010C > T. p.(Thr4337Met) and c.13137delC; p. (Thr4380GinfsTer11) in the USH2A gene, a genotype that confirmed the diagnosis of autosomal recessive disease Usher syndrome type 2A (Usher syndrome 2A).

While analysis for determining the presence of changes in c.13010C > T and c.13137delC in the USH2Agene in the patient's fetus has shown that the fetus is the carrier of the change c.13010C > T.

But the fact that the partner of this patient is unaffected and untested and there is a risk of being a carrier of the disease, taking into account the prevalence of Usher syndrome type 2A in the general population is 1-9/100000, the risk that the fetus will develop Usher syndrome is from 1/118 to 1/354 in this pregnancy (1, 5, 6).

DISCUSSION

Usher syndrome is a gene determinate disease, in most cases genetically heterogeneous. Nine genes have been identified whose mutations are responsible for USH. Because proteins, which are encoded by these genes, are believed to interact with each other in order

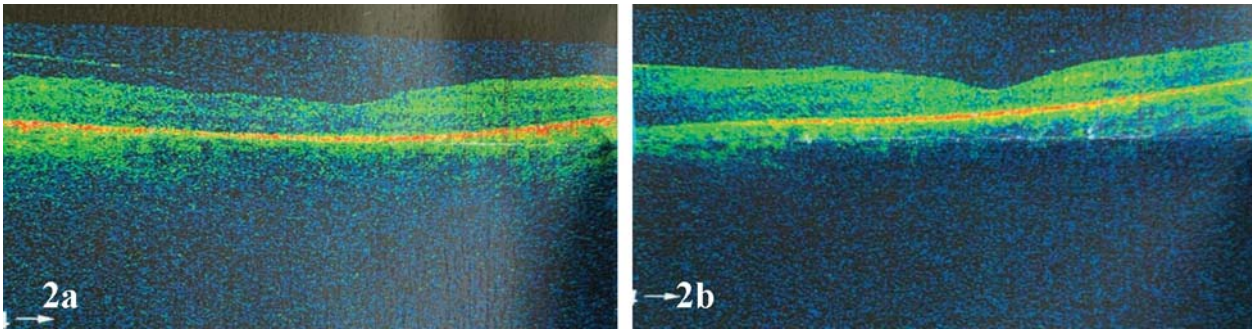

***Figure 2a and 2b.** OCT findings of the macula, right and left eye*

to form a network in the sensory cells of the inner ear and the retina (7).

Sixteen loci were found which are associated with the appearance of USH and atypical USH. Twelve of them were proven to be causative genes and one is proven to be a modification gene.

According to research on the proteins encoded by these USH genes, it seems that the USH proteins interact and operate as a multiprotein complex.

Even though their precise role remains an enigma in terms of the retina, it has been shown that these proteins are necessary for the development, maintenance, and function of hair fiber bundles, which are the main mechanosensitive structure of the inner ear fiber cells (8).

Genetic testing is necessary for the diagnosis Usher syndrome. So far, researchers have found nine genes responsible for the syndrome. Genetic testing is available for all of them: Usher type 1 syndrome: MY07A, USH1C, CDH23, PCHD15, USH1G, Usher type 2 syndrome: USH2A, GPR98, DFNB31 and Users type 3 syndrome CLRN1 (9).

USH2A gene, confirmed by our case and presented in the paper, is located on chromosome 1and it encodesa protein called usherin. This protein is a key component of the basal cell membrane, which separates and supports cells in a multitude of tissues. Usherin exists in the basal cell membranes of the inner ear and retina and plays major role in the development and maintenance of cells in the same tissues.

Pathogenic alterations in USH2A have been shown to be associated with retinitis pigmentosa type 39 and Usher syndrome type 2A, which was confirmed in our patient (1, 5, 6).

In terms of the treatment of retinitis pigmentosa, a study was performed from 1979 to 1983 with four control groups, where patients were given high doses of vitamin A, high doses of vitamin A and vitamin E, low doses of vitamin A and vitamin E, and only high doses of vitamin E, respectively.The results, measured by electroretinogram (ERG), showed a slowing of the course of the disease in the vitamin A-treated group and an acceleration of the disease in the vitamin E-treated group. The recommendation of this study is the daily use of vitamin A palmitate 15,000 IU, under medical supervision and avoiding vitamin E in high doses (10).

In another study done to examine the incidence of Usher syndrome in children with hearing loss and total deafness it was shown that the incidence was 11.3% (15/133). The prevalence is thought to be 1/6000 (1, 5). Usher syndrome is far more common than what had been observed prior to the age of genomic research. The early diagnosis of the Usher syndrome is highly beneficial for the safety of children, prior planning for their education, genetic counseling and treatment (11).

Currently, no cure is available for Usher syndrome or retinitis pigmentosa. Early diagnosis is the best advantage thus far, so that educational programs can start earlier, depending on the severity of vision loss, age and the ability of the child.

Treatment includes learning to read Braille and making use of devices and techniques intended for the visually impaired and blind. Some research suggests that the progress of certain forms of RP can be slowed down, however the high intake of vitamin A can cause deterioration of other eye conditions.

It is thought that gene therapy will take an important place in the treatment of this syndrome (9). This therapy does not compensate lost photoreceptor cells, but recent studies suggest that it slows the degeneration (12).

CONCLUSION

Usher syndrome is definitely more common than it is presumed. As many as 30% of patients with retinitis pigmentosa report hearing loss and 50% of them are diagnosed with Usher syndrome. Detailed anamnesis is always required in patients with retinitis pigmentosa, who are referred to an ophthalmologist for hearing and vice versa for patients with hearing loss that are examined by an otorhinolaryngologist.

Additional ophthalmic examinations, beside a detailed examination of fundus in mydriasis, which need to be made are perimetry and electroretinogram (ERG). Furthermore, if there is a positive history of hearing loss, a consultation with an otorhinolaryngologist and an auditory examinations are needed. Early diagnosis is important in terms of quality of life, i.e. timely diagnosing and undertaking measures for genetic testing in the family, in order to inform them about the type of the disease. Progress is also expected in the field of gene therapy in the treatment of this syndrome.

Abbreviations

MANU — Macedonian Academy of Sciences and Arts

USH — Usher syndrome

RP — retinitis pigmentosa

OCT — Optical coherence tomography

ERG — electroretinogram

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Licensing

Sažetak

OKULARNI ASPEKTI USHER-ovog SINDROMA

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Uvod: Usher sindrom je redak sindrom, koji se karakteriše gubitkom sluha, retinitis pigmentosom i u pojedinim slučajevima poremećajem ravnoteže, i kongenitalnom kataraktom. Nasleđuje se autozomno recesivno. Mutacije devet gena se mogu dovesti u vezu sa ovim stanjem. Dijagnoza se postavlja na osnovu kliničke slike i genetskog testiranja. Terapija ima za cilj da omogući funkcionisanje ovih pacijenata u okolini. Genetska terapija obećava kao terapija izbora. Cilj rada je da podseti na specifičnost ove bolesti, i da kroz prikaz slučaja Usher-ovog sindroma ima i edukativni značaj za oftalmologe i otorinolaringologe.

Prikaz slučaja: Prikazujemo pacijentkinju kod koje je genetički potvrđeno postojanje Usher-ovog sindroma, sa oštećenjem sluha, retinitis pigmentosom i kongenitalnom kataraktom. Pacijentkinja starosti 39 godina, u 26.oj gestacijskoj nedelji, kojoj je ovo druga trudnoća, genetskim ispitivanjem, Makedonsko društvo za nauku i umetnost (MANU) potvrdilo je duplu heterozigomatičnost za patogene promene c.13010C > T. p.(Thr4337Met) ic.13137delC; p. (Thr4380GinfsTer11) u genu USH2A, a genotip potvrđuje dijagnozu autozomno recesivne forme Usher-ove bolesti tip 2A.

Zaključak: Detaljna anamneza je uvek neophodna za pacijente sa retinitis pigmentosom, koji se šalju na konsultativni pregled oftalmologa zbog gubitka sluha, kao i obrnuto da se pacijenti sa oštećenjem sluha šalju kod otorinolaringologa. Rana dijagnoza je veoma bitna u smislu kvaliteta života i.e. na vreme postavljena dijagnoza i preduzimanje mera za genetsko testiranje u porodici, ima velikog smisla radi informisanja porodice o mogućoj transmisiji i naslednosti bolesti, kao i adekvatnoj terapiji i uključivanje u edukativni program, koji je dizajniran za ovu bolest.

Ključne reči: Usher-ov sindrom, retinitis pigmentosa, gluvoća, genska terapija.

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Case report

THROMBOPHLEBITIS OF PREPUBIC VEINS IN PATIENT WITH APLASIA OF THE LEFT COMMON AND LEFT EXTERNAL ILIAC VEINS — CASE REPORT

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Abstract: **Introduction:** A congenital defect of some of the large veins that drain blood from the lower extremity is a very rare occurrence and, considering the clinical consequences, it is generally diagnosed at a relatively early age - in childhood or youth. Within the complex classification of vascular malformations, a special category is comprised of large blood vessel malformations, also called truncal vascular malformations. In comparison to other anomalies, aplasia or lack of development of a certain segment in the deep venous systems, potentially has the most serious hemodynamic consequences. The appearance of varicose veins, through which the venous blood is drained distally to the obstruction into an unusual area, such as the lower part of the trunk or the anterior abdominal wall, usually spurs the patient into action in terms of conducting diagnostic procedures so that diagnosis can be reached before complications occur. Defects of large magistral deep veins, which remain unrecognized until adulthood and which are diagnosed after complications in the drainage venous network occur, are infrequent. Complications that can arise in association with this malformation are manifested not only in varicosally altered collateral veins, but also in the venous drainage area peripherally from the obstruction.

Case report: We hereby present a case of a patient admitted to hospital with a clinical picture and an ultrasound finding indicating an incarcerated inguinal hernia. During surgery, thrombophlebitis of extremely dilated prepubic veins was established. Subsequent diagnostic procedures revealed the presence of a rare vascular anomaly - aplasia of the left common andleft external iliac veins. Under the mentioned conditions, a collateral venous network developed in both groins and the prepubic region, draining blood from the left leg into the right common femoral vein.

Key words: Aplasia of the iliac vein, acute thrombophlebitis, varicosities of prepubic veins.

INTRODUCTION

Congenital vascular malformations can be defined as an embryologically formed, present at birth anomaly of vascular morphogenesis which leads to real structural disorders in the vascular system (1, 2). The classification of congenital vascular malformations was made by the International Society for the Study of Vascular Anomalies - ISSVA based on several criteria including anatomical, histological, physiological, pathological and genetic criteria (3). The last revision to the classification was made in 2018. All vascular anomalies are divided into two categories - vascular tumors and vascular malformations. Vascular malformations can be classified into four categories - simple vascular malformations, combined vascular malformations, malformations of large blood vessels (truncal vascular malformations) and vascular malformations associated with other anomalies (3).

Truncal vascular malformations in the deep venous system, which imply the absence or hypoplasia of a segment of the venous tree, are most often associated with the development of a rich collateral venous network that drains blood from the vascular area peripherally from the site of aplasia/hypoplasia towards the normal venous segment. Depending on the place of obstruction, as well as the capacity for collateral development in a certain anatomical region, this collateral network can exist only in the deep venous system, only in the superficial venous system, or in both the deep and the superficial venous system. Due to the increased blood flow and the inability to withstand the increased pressure because of their histological and anatomical features, the superficial veins included in the collateral

venous network are usually subject to varicose changes over time. The extent and extensiveness of varicose vein development that form the drainage network of the area peripherally from the obstacle is unpredictable, but it is usually not pronounced in the first decade of life (3, 4).

We will present the case of a patient whose truncal vascular malformation - aplasia of the left external and the left common iliac veins, remained unrecognized until mature adulthood. The clinical manifestation that led to the diagnosis was highly unusual - thrombophlebitis in the collateral venous network in the anterior abdominal wall.

CASE REPORT

A 48-year-old male, smoker, of typical physical constitution (Body Mass Index 25.3) presented to the surgical emergency unit of the University Hospital Medical Center "Bežanijska kosa" with clinical signs of phlegmone in the suprapubic region (redness, pain, locally increased temperature and swelling).

The difficulties started two days earlier, with increased body temperature up to 37.8 C. Based on case history data, we discovered that he had a right-sided inguinal hernia surgery in his childhood. Four years earlier, the patient had phlebothrombosis in the deep venous system of the left leg, he was treated with the oral anticoagulant drug Acenocoumarol for 6 months, until a supposed complete recanalization in the deep venous system. No antiplatelet therapy was initiated after anticoagulant therapy was discontinued. The results of the tests for congenital and acquired thrombophilia (genetic analyses, protein C, protein S, Activated protein C resistance) performed in that period were negative. Since then, the patient has had swelling in the left leg. The patient did not report in his case history any information about the occurrence of dilated veins in other parts of his body except the legs.

The patient reported in the family history that his father passed away following a cerebrovascular insult.

In addition to the documentation from previous hospitalizations for phlebothrombosis and hematological tests, the patient's medical documentation also included a finding from an abdominal ultrasound examination performed earlier that day in another healthcare facility, which describes the presence of inguinal hernias on both sides, with suspected presence of intestinal loops in them.

Clinical examination revealed the presence of redness and painful induration of the size of a male fist in the right inguinal and suprapubic region.

Soft abdomen, insensitive to pain on palpation, except in the zones of the mentioned induration. The pedal, popliteal, and femoral pulses were palpable on both sides, there were varicose veins on the left lower leg with signs of old thrombophlebitis, as well as swelling in the left lower leg - the difference in circumference between the left and right lower legs on admission was 4 cm. Early lipodermatoscleros was also present above the medial malleolus of the left leg; there was no active ulcer.

CEAP classification Left leg C2,4b,S,Ec, As,d,Pr,o
Right leg C2,4a,A, Es, As,d, Pr,o

Results of laboratory analyses on admission - Le-8.3, Er-5.51, Hg-154, Hct-0.475, Tr-184, Urea-6.0, Creatinine-83, CRP-48.0

Native abdominal radiotomography showed no hydroaeric levels or pneumoperitoneum.

Abdominal ultrasound examination– bilaterally in the inguinal region, more to the left side under the skin, there are multiple tubular structures, 3-4 cm in diameter, appearing as aperistaltic intestinal loops, the structures closer to the left groin being wider and those closer to the right groin narrower.

Due to suspected incarcerated inguinal hernia with suspected bowel perforation and phlegmon of the anterior abdominal wall, surgical treatment was indicated and preoperative preparation of the patient was carried out.

The surgery was performed under general endotracheal anesthesia with the approach for classic right-sided inguinal hernia surgery. A mass of thrombosed varicose veins with diameter ranging from 1 to 3 cm was found in the subcutaneous tissue. Thrombosed veins filled the prepubic region and the thrombosis propagated into the superficial epigastric vein to the right, which is about 3.5 cm in diameter in height of the inguinal ligament. The surgery was completed with exploration.

Postoperatively, therapeutic doses of low-molecular-weight Heparin were administered to the patient, compression bandages were placed on both legs, and the leg was elevated.

On the first postoperative day, the superficial and deep venous systems of both legs were explored by ultrasound that showed presence of thrombosis – on the left, thrombophlebitis was found in the great saphenous vein from the sapheno-femoral junction to below the knee. In the deep veins, phlebothrombosis was found in the common femoral vein and in the deep femoral vein up to about 8 cm below the inguinal ligament. The superficial femoral vein showed no signs of thrombosis. Thrombosis was present in the left popliteal vein and the posterior tibial vein with peripheral recanalization of about 25%. On the right, thrombosis was present in the popliteal vein and posterior tibial vein.

The hematologist, after examining the patient, agreed to introduce anticoagulant therapy.

Due to suspected organic obstruction to venous blood flow in the lesser pelvis, which caused the development of venous collaterals, MDCT of the abdomen and the lesser pelvis with angiography was carried out and showed that the left external and the left common iliac veins were reduced to a thin fibrous band without flow, which can be traced to the common femoral vein. The internal left iliac vein drained directly into the inferior vena cava. Complete drainage of venous blood from the left leg is carried out via the collateral, partly via subcutaneous venous collaterals formed in the left groin in the basin of the left great saphenous vein, extending through the prepubic region and ending in the right great saphenous vein, and partly via the venous collateral network in the lesser pelvis and partly ending in the right external, and partly in the right internal iliac vein, which, like the right common iliac vein, have dimensions wider than usual.

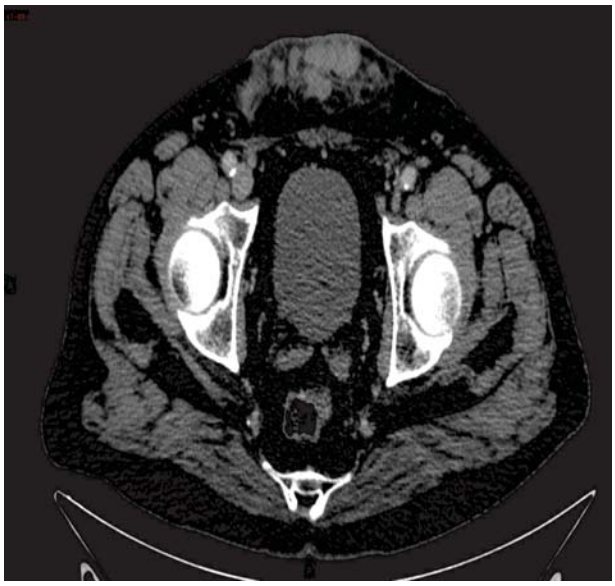

Figure 1. *MDCT shows thrombophlebitis and phlegmon in the prepubic region*

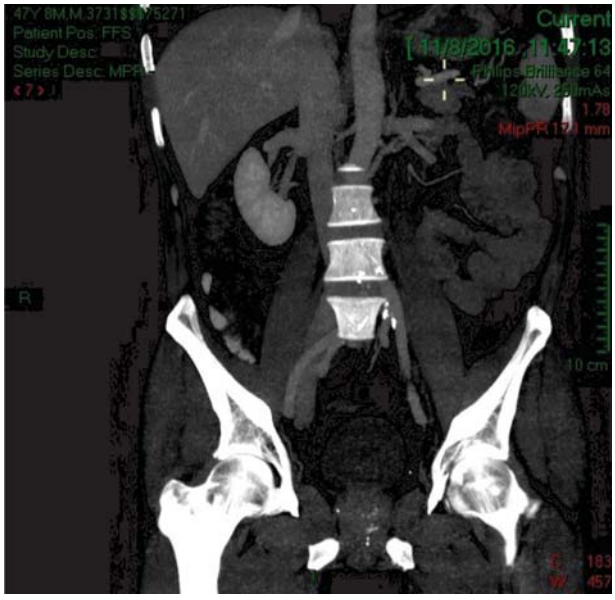

Figure 2. *MSCT venography in the frontal section shows absence of the left common and the left external iliac veins*

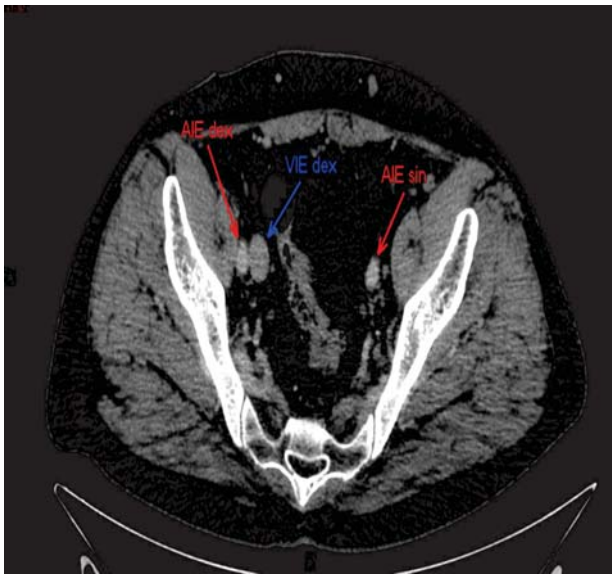

Figure 3. *MSCT cross-sectional venography shows absence of left external iliac vein*

Oral anticoagulant therapy was administered to the patient - Vitamin K antagonists and INR values were brought to a therapeutic range between 2 and 3. A two-layer bandage with compression bandages was applied to reduce leg swelling. Pads with boric acid solution were applied locally at the site of thrombophlebitis. During first 24 h after surgery, at 6-hour intervals,the arterial status on the left leg was evaluated by palpation of the pulses over the magistral arteries of the leg and foot, and the circumference of the lower and upper legs was monitored for a timely diagnosis of possible development of compartment syndrome on the left lower leg.

On the seventh day after admission to the hospital, regression of the leg swelling was verified, which continued during the following days, and the patient was mobilized. When it became clear from the improvement trend of the local status on the left leg that there was no risk of developing new complications, with INR values in the therapeutic range, the patient was discharged to further home health care.

The follow-up examination one month after the patient was discharged from the hospital revealed a partial recanalization of thrombophlebitis in the prepubic and inguinal veins with absence of redness and painful sensitivity, but still present in duration of both groins and prepubic region.

The follow-up examination after 3 months showed no redness, induration, or pain sensitivity in the groin and prepubescent region, but the mass of compressible varicose veins was palpable.

The follow-up examinations after 6 months and one year showed that with the taken therapeutic measures, there was no progression of chronic venous insufficiency, left lower leg swelling was not in progression, there was no progression of lipodermatosclerosis, there was no active ulcer. The therapeutic compression stocking, of compression grade 3, was replaced by the patient every 6 months in the previous period.

Due to the risk of new phlebothrombosis in the deep veins of the legs or thrombophlebitis in the drainage venous system, oral anticoagulant therapy was not discontinued.

DISCUSSION AND CONCLUSION

Aplasia/hypoplasia of the magistral venous segment with development of collateral venous network in the subcutaneous tissue, is a rare condition that is most commonly recognized in childhood or early youth, and depending on its extensiveness and possible hemodynamic consequences, therapy is determined in order to prevent or at least slow down the development of chronic venous insufficiency. The occurrence of extensive varicose veins in subcutaneous tissue in an unusual region in younger patients should raise clinical suspicion of a vascular anomaly. Aplasia of the magistral vein can affect only one part of the vein or the entire vein, and even multiple veins, which is actually the reason for the unpredictable course of the disease, the occurrence of complications and the rapid progression of chronic venous insufficiency. Changes in tissues and organs over time occur peripherally from the obstruction to venous blood flow. If the drainage area below the obstruction also includes the lower extremities, the edema in the lower parts of the lower leg is always the first sign of chronic venous insufficiency development. These changes are generally accompanied by varicosities occurringin the superficial venous segment of the diseased leg, which becomes a visual manifestation of malformation and a reason for diagnostic tests that can lead to the right diagnosis. It is important to be aware of the possible existence of venous vascular malformation, which is the reason for the occurrence of varicose veins in the first decades of life, since removal of these veins without insight into the condition of the deep venous network can cause worsening of venous insufficiency. For this reason, it is important to be certain that the deep venous network is complete prior to operative removal of any varicosally altered superficial venous segment.

Complications that develop in patients with truncal venous malformation can be divided into two groups, one referring to changes and complications that occur in the area distal to the obstruction and they can relate to the veins themselves beneath the obstruction, in terms of appearance of phlebothrombosis and thrombophlebitis, and development of varicose veins in that area, or they can relate to organs and tissues in the drainage area of these veins in terms of appearance of edema, stasis dermatitis, lipodermatosclerosis and active venous ulcer, all as manifestations of chronic venous insufficiency. The dynamics of the development of these complications is unpredictable and depends on other factors, such as physical activity and constitution. The second group of complications is related to varicose veins through which blood is drained from the area below the obstruction and they are indistinguishable from complications that can occur in any varicose vein. The most common complication is surely thrombophlebitis, whereas the occurrence of spontaneous vein rupture is very rare.

In this case, it was an emergency condition - the phlegmons of the anterior abdominal wall, which was preoperatively subjected to minimum diagnostic processing insufficient to make accurate diagnosis of the condition preoperatively. The existence of a serious problem in the deep venous system in the lesser pelvis with development of varicosities in the anterior abdominal wall representing the collateral drainage venous network of one extremity, was suspected during surgery by observing extremely dilated thrombosed varicosities connecting the systems of the left and right great saphenous veins via the superficial epigastric vein and venous network of the lower part of the anterior abdominal wall. The surgery itself was insufficient to determine the cause of the problem, and the differential diagnosis could be several congenital or acquired conditions that could have led to chronic obstruction of the vein flow in the lesser pelvis (aplasia or hypoplasia in the venous system; benign and malignant tumors in the pelvis).

Although the inflammatory process caused by acute thrombophlebitis manifested as extensive phlegmon of the anterior abdominal wall was the main reason for surgical treatment, the removal of thrombosed varicose veins was not taken into consideration as a treatment option. Thrombovaricectomy would damage the venous network via which the blood bypasses the obstruction in the flow, which can lead to deterioration of the condition in the extremity (ies), acutely in terms of developing venous compartment syndrome, or chronically in terms of worsening of chronic venous insufficiency. A postoperative CT scan verified the existence of aplasia of the external

and common iliac veins on the left side, thus confirming that the decision not to remove thrombosed varicose veins was the right one.

All patients diagnosed with congenital absence of a certain venous segment should be familiarize with the possible course of the disease and the occurrence of possible complications, as well as the measures that must be taken to mitigate the consequences of this rare anomaly.

The effects of adequate conservative treatment, such as maintaining optimal values of the body mass index, moderate physical activity, compression therapy in the area of potential development of chronic venous insufficiency and care of the skin exposed to edema, should not be underestimated.

Each patient for whom surgical removal of varicose veins is planned, must undergo diagnostic procedures that need to assure us of the continuity of the deep venous tree. In case thrombophlebitis in the drainage venous network occurs, it is necessary to avoid the removal of thrombosed varicose veins as this can make it difficult to derive blood from the segment peripheral from the site of aplasia/hypoplasia. The significance of maintaining the integrity of the existing venous network is indisputable, but the need to introduce anticoagulant or antiplatelet therapy should be considered for each patient individually. In case thrombophlebitis or phlebothrombosis occur, it is necessary to carry out a complete hematological examination in terms of congenital or acquired thrombophilia.

The effect of the taken conservative measures should be actively evaluated in each case, and if it is found that they are insufficient, the possibility of surgical reconstruction of the missing venous segment should be considered.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

TROMBOFLEBITIS PREPUBIČNIH VENA SA APLAZIJOM LEVE ZAJEDNIČKE I LEVE SPOLJAŠNJE ILIJAČNE VENE — PRIKAZ SLUČAJA

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Uvod: Kongenitalni defekt neke od velikih vena, koja drenira krv iz donjih ekstermiteta je veoma retka bolest, a razmatrajući kliničke posledice, moglo bi se reći da se ova bolest generalno dijagnostikuje u relativno ranom uzrastu – u dečijem uzrastu ili u adolescenciji. U okviru kompleksne klasifikacije vaskularnih malformacija, posebna kategorija je sastavljena od velikih krvnih sudova, koji se nazivaju trunkalne vaskularne malformacije. U poređenju sa ostalim anomalijama aplazija ili nedostatak razvoja pojedinih segmenata u sistemu dubokih vena, može imati značajne hemodinamske posledice. Izgled varikoznih vena, kroz koji se drenira distalno od opstrukcije u regiju u koju se obično ne drenira krv,kao što su donji delovi tela ili prednji trbšni zid, obično navodi pacijenta da «nešto nije u redu», nakon čega se javlja lekaru i započinje se sprovođenje dijagnostičkih procedura, tako da dijagnoze mogu biti postavljene pre nego što se dese komplikacije. Defekti velikih magistalnih dubokih vena, koje ostaju neprepoznate do odraslog doba i koje se dijagnostikuju nakon pojave komplikacija u okviru venske mreže, i nisu toliko česte. Komplikacije koje su povezane sa ovim malformacijama ne manifestuju se samo u varikozno izmenjenim kolateralnim sudovima, nego i u venskoj drenaži periferno od opstrukcije. Prikaz slučaja: Ovom studijom prikazujemo pacijena, koji je hospitalizovan sa kliničkom slikom inkarcerirane ingvinalne hernije, koja je potvrđena i ultrazvučnim pregledom. Tokom hirurške procedure utvrđeno je postojanje tromboflebitisa ektremno dilatiranih prepubičnih vena. Naknadno sprovedenim dijagnostičkim procedurama utvrđeno je prisustvo retke vaskularne anomalije – aplazija leve zajedničke, kao i leve spoljne ilijačne vene. Spomenutim dijagnostičkim procedurama utvrđeno je postojanje kolateralne venske mreže koja se razvila u obe prepone i prepubičnoj regiji, koje dreniraju krv iz leve noge u desnu zajedničku femoralnu venu.

Ključne reči: aplazija ilijačne vene, akutni tromboflebitis, varikoziteti prepubičnih vena.

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Case report

THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract: **Introduction:** Thrombotic thrombocytopenic purpura (TTP) is a syndrome that consists of the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal disease. Moskowitz was the first who described this syndrome in 1925, finding hyaline thrombi in many organs. The micro thrombi cause tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia. Brain involvement is common and leads to stroke, seizure, confusion, and headache. Renal injury occurs in a minority of patients and it is usually modest.

Case report: We present a 57-year old male who came to our hospital because of weakness, prostration and darkening of his urine, occurring several days before admission. On physical examination we found icteric coloring of his skin and conjunctiva, big hematoma on his right lower leg and he had neurological abnormalities presented as mild headache, disorientation and aphasia. Laboratory tests revealed anemia and thrombocytopenia and the examination of peripheral blood smear showed presence of schistocytes. Direct and indirect antiglobulin test (Coombs) was negative. Emergency treatment was started with plasmapheresis on daily basis, immunosuppressive treatment with high-dose methyl prednisolone and transfusions of red blood cells. The laboratory results and the clinical condition improved within two weeks.

Conclusion: TTP is a medical condition that can be fatal if emergency treatment with plasma pheresis is not initiated presently after suspected diagnosis.

Key words: thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), plasma exchange.

INTRODUCTION

Thrombotic microangiopathies are a group of hereditary and acquired syndromes with diverse mechanisms that lead to shared clinico-pathological features: microangiopathic hemolytic anemia, thrombocytopenia and organ injury (1). Moskowitz was the first who described this syndrome in 1925, finding hyaline thrombi in many organs (2). Classic form of this syndrome consists of the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal disease. It has been shown that these symptoms are due to decrease of the enzyme ADAMTS13 which is responsible for cleaving large VWF multimers into shorter strands and therefore platelet adhesion and aggregation is promoted (3). In some cases a genetic problem was asserted due to an irregularity in several suspect genes (4). In other cases, the disease appears without other known causes and this is called an “idiopathic” form (5). In acquired TTP, an autoantibody inactivates the ADAMTS13 protease, and there for the VWF multimers remain large and abundant. The multimers bind platelets and form aggregates in the microvasculature that induce thrombus formation. The micro thrombi cause tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia. Brain involvement is common and leads to stroke, seizure, confusion and headache. Renal injury occurs in a minority of patients, and it is usually modest. Fever may develop but it is often due to precipitating infection (6).

Since, patients rarely present with the pentad of symptoms, it is very important to start the treatment promptly. Currently, unexplained thrombocytopenia and microangiopathic hemolytic anemia are the two criteria required to establish the diagnosis. A simple blood test will show shattered red blood cells and a low platelet counts, and it is a definite sigh to initiate treatment (7). Plasma exchange is the standard of care for the initial management of acquired TTP (8) and it should be continued daily until resolution of organ dysfunction and stable normalization of the platelet count. Adjunctive therapy with glucocorticoids as immunosuppressive

treatment should also be initiated in order to decrease the production of inhibitory anti-ADAMTS13 antibodies.

CASE REPORT

We present a 57-year old male who came to our hospital because of weakness, prostration and darkening of his urine, occurring several days before admission. Laboratory tests from local laboratory revealed anemia and thrombocytopenia. He didn't have any similar symptoms in his past medical history, neither his family history was remarkable. On physical examination we found icteric coloring of his skin and conjunctiva, he had big hematoma on his right lower leg and he had neurological abnormalities presented as mild headache, disorientation and aphasia. His temperature was 36.7 °C, his blood pressure was 100/60 mm Hg and his pulse was 82 beats per minute. The physical examination of lungs was normal, his abdomen was not distended and there was not hepatosplenomegaly on palpation. There was no swelling in the legs.

Laboratory findings revealed hemolytic anemia with hemoglobin level 67 g/L; hematocrit 17.3%; reticulocyte count 7%; total bilirubin 70.7 umol/L; (indirect 54.1 umol/l). Aspartate aminotransferase (AST) was 90 U/L, alanine aminotransferase (ALT) 36 U/L, lactate dehydrogenase (LDH) 2170 U/L. There was a significant thrombocytopenia with platelet count 14 x 109/L. There were also signs of renal damage with blood urea nitrogen 17.0 mmol/l, serum creatinine 146 umol/l, total serum protein 52 g/l, albumin 31g/l. Urinalysis showed 2+ blood and 3+ protein. Examination of peripheral blood smear revealed 3-4 schistocytes in a field with no erythroblasts seen. White cells were normal with a normal granulation pattern. Direct and indirect antiglobulin test (Coombs) was negative. Blood coagulation tests (prothrombin time, activated partial thromboplastin time and thrombin time) were within normal range.

The genetic panel testing for AHUS was negative.

Emergency treatment was started with plasmapheresis on daily basis and transfusions of red blood cells. Immunosuppressive treatment consists of high-dose methyl prednisolone 2x250mg per day and Mabthera (Rituximab) 375mg/m(2) once weekly, a total of 4 doses. On hospital day 5 the hemoglobin level improved to 105g/L and the platelet count to 68 x 109/l , reticulocyte count failed to 3.4%. On the hospital day 12 the hemoglobin level was 122 g/L, the platelet count was 184 x 109/L, reticulocyte count 1.5%, and total bilirubin failed to 15.9 umol/l. As the serum glycaemia grew progressively, Insulin rapid in low doses was started. The clinical condition improved along with the improvement in laboratory results. After 64 days of hospitalization and 35 plasmaphereses performed, the patient was discharged from the hospital in a good clinical condition with Hb level 124 g/L, WBC 4.8 and Plt 75, Rtc 1.9%. Maintenance therapy with prednisolone 60 mg and Aspirin 100 mg per day was suggested.

One month after discharging from hospital the patient was still in good clinical condition with normal blood tests: hemoglobin level 139 g/L, WBC 14.8, Plt 163, reticulocyte count 3%, and indirect bilirubin in normal range. The treatment was continued with prednisolone 40 mg per day and Aspirin 100 mg per day. Two months after the last dose of Mabthera was completed, we continued a maintenance therapy with Mabthera on two-months' intervals and lower doses of prednisolone 10 mg per day. Now, seven months after the onset of the disease, the patient is still in a good condition with blood tests in normal range: Hb level 149 g/L, WBC 12.3, Plt 298, reticulocyte count below 1%, no schistocytes present in the peripheral blood smear.

DISCUSSION

Our patient presented with weakness, prostration, occurrence of dark urine and neurological abnormalities, symptoms which were initial presentation of TTP. Laboratory findings revealed hemolytic anemia and thrombocytopenia that could be associated with Evans syndrome. However, the negative antiglobulin test (Coombs) and the lack of spherocytosis in peripheral blood smear that are present in cases of Evans syndrome, excluded this diagnosis (9).

Microangiopathic hemolytic anemia warrants consideration when schistocytes are seen in a patient with hemolysis (7). Severe hypertension, disseminated intravascular coagulation, sepsis and cancer can cause microangiopathic hemolytic anemia and thrombocytopenia, but there was no evidence of these conditions in our patient. Hemolytic-uremic syndrome (HUS) is a thrombotic microangiopathy that arises when shiga toxin-secreting strains of Escerichia coli, on occasion, Shigella dysenteriae, induce endothelial damage that leads to bloody colitis and, subsequently kidney injury; these features were also not present in this case (8). Atypical hemolytic syndrome (aHUS) is considered a complement-mediated form of thrombotic microangiopathy. It is a genetic disease associated with a mutation in CFHR1 (Complement Factor H Related 1) Coding gene. AHUS genetic panel was performed in our patient and the result was negative.

There are two forms of TTP; hereditary and acquired. The hereditary form is caused by mutations of the ADAMTS13 gene. The acquired form may be idiopathic, resulting from autoantibodies against ADAMTS13

metaloprotease or secondary to other conditions such as infections, hematopoietic stem cell transplantation, certain drugs, cancers, other autoimmune diseases (10). An ADAMTS13 activity level that is less than 10% is highly suggestive for a diagnosis of TTP. Three tests are commonly performed to confirm the diagnosis of TTP: assays for ADAMMTS13 activity, ADAMTS13 inhibition, and anti-ADAMMTS13 antibodies (11). However, these tests are not available in our laboratory.

According to clinical and laboratory findings (four out of the pentad of symptoms for TTP: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, and renal disease) a prompt initiation of treatment was started in our patient with plasma exchange and high doses of glucocorticoids, with clinical and laboratory improvement within two weeks.

CONCLUSION

TTP is a medical emergency that can be fatal if not recognized on time. The most important factor in improving patient survival is initiation of treatment as soon as possible. With induction of plasma exchange, the mortality rate dropped from ninety to nearly twenty percent. Plasma exchange is essential treatment option because it depletes the circulating autoantibody to ADAMTS13 and also the very high molecular weight von Wilebrand factor multimers along with replacement of the missing protease.

Abbrevations

ADAMTS13 — a desintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
aHUS — atypical hemolytic syndrome
HUS — hemolytic uremic syndrome
TTP — thrombotic thrombocytopenic purpura
VWF — Von Wilebrand factor

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Sažetak

TROMBOTIČNA TROMBOCITOPENIJSKA PURPURA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Uvod: Trombotična trombocitopenijska purpura (TTP) je sindrom koji se sastoji od pentade: trombocitopenije, mikroangiopatske hemolitičke anemije, neuroloških ispada, povišene temperature i bubrežne bolesti. Moskowitz je bio prvi koji je opisao ovaj sindrom 1925. godine, pronašavši hijaline trombe u mnogim organima. Mikrotrombi izazivaju ishemiju tkiva, potrošnju trombocita, kao i mikroangiopatsku hemolitičku anemiju. Zahvaćenost mozga je česta, što može dovesti do infarkta, epileptičkih napada, i glavobolje. Povreda bubrega se javlja kod manjeg broja pacijenta i obično je umerena.

Prikaz slučaja: Predstavljamo 57-godišnjeg muškarca, koji je primljen u našu bolnicu zbog slabosti, prostracije i tamnog urina. Simptomi se javili nekoliko dana pre prijema u bolnicu. Na fizikalnom pregledu uočena je ikterična boja kože i konjuktiva, veliki hematom na desnoj nozi, kao i pozitivan neurološki nalaz koji se manifestovao dezorijentacijom, glavoboljom i afazijom. Urađeni laboratorijski testovi pokazali su anemiju i trombocitopeniju, a pregled razmaza periferne krvi pokazao je postojanje šistocita. Direktan i indirektan antiglobulinski test (Coombs) bili su negativni. Započeto je lečenje primenom plazmafereze svakog dana, imunosupresivnom terapijom sa visokim dozama metilprednizolona i transfuzijom eritrocitima. Laboratorijske analize i kliničko stanje pacijenta su se značajno popravile u okviru dve nedelje.

Zaključak: TTP je stanje koje bi moglo da ima fatalne posledice, ako se ne započne hitna terapija plazmaferezom nakon sumnje na ovu bolest.

Ključne reči: trombocitopenijska purpura TTP, hemolitičko uremijski sindrom HUS, izmena plazma.

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Review article

COMPLICATIONS OF TEMPOROMANDIBULAR JOINT ARTHROCENTESIS

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Abstract: Arthrocentesis is a frequently performed and accepted minimally invasive and predictable procedure in the treatment of temporomandibular joint disorders. This review aimed to evaluate arthrocentesis complications. The literature search has included PubMed, Google Scholar, and EMBASE databases by using terms "((TMJ OR TEMPOROMANDIBULAR JOINT OR TMD OR TEMPOROMANDIBULAR DISORDER) AND ARTHROCENTESIS) AND COMPLICATION". Publications up to 2019 were examined. Seven studies involving arthrocentesis complications were included. Although arthrocentesis is considered as a cost-effective and safe procedure, complications may be seen due to its proximity to important anatomical structures. Most of these complications are short-lived and can easily be managed in the outpatient clinic; however, some severe complications have rarely been reported in the literature. The practitioners who perform this procedure should be aware of these possible complications and be able to manage them in the clinic.

Key words: Arthrocentesis, Complication, Temporomandibular joint, TMJ.

INTRODUCTION

Temporomandibular joint disorders (TMD) is a term that covers many closely related conditions, which include functional changes and pathological conditions of temporomandibular joint (TMJ), maxillofacial region, and the related muscles. It is most commonly seen in young women and covers 10% of the population. In 80% of patients with TMD, internal derangement (ID) of the TMJ has been reported in the literature (1). Symptoms of TMJ ID anchored disc phenomenon, painful click and/or crepitus, disc displacement with reduction, joint erosion, joint flattening, closed lock, reduced jaw mobility, osteophytes, and free radicals and inflammatory mediators in synovial fluid (1, 2, 3).

TMD can be managed conservatively or surgically. Conservative treatment includes physiotherapy, chemotherapy (analgesics, anti-inflammatories, muscle relaxants), rest therapy, and splint therapy. Surgical treatments may include invasive (open approaches) or minimally invasive treatments. Most patients with ID can be treated successfully by conservative treatment, which can also prevent the progress of the disorder. The purpose of therapy is to eliminate predisposing factors. Open surgical procedures are the treatment methods used only when all other conservative and minimally invasive treatments have been tried and failed. This approach was developed to reduce the risk of complications (2, 3, 4).

Arthroscopy and arthrocentesis are minimally invasive surgical methods used for the treatment or diagnosis of intraarticular pathologies (5). Ohnishi performed TMJ lavage by the very first time in 1990 (6). Nitzan et al. described the TMJ arthrocentesis technique by using two needles to lavage the upper joint space, and this technique is frequently performed today (7). Arthrocentesis principles are reducing intraarticular viscosity, clearing inflammatory and pain mediators, allowing nutrient perfusion. As a result, the disc can make free sliding movement comfortable. Clinical outcomes are the reduction of pain, joint sounds, and improve mouth opening (8). Arthrocentesis has been suggested originally for the treatment of painful limited mouth opening caused by acute onset TMJ derangement. Now it is a universal procedure accepted in the treatment and diagnosis of ID, continuing pain in TMJ, unresponsive to conservative management, anterior disc displacement with and without reduction and associated osteoarthritis, and rheumatoid arthritis (9).

Although arthrocentesis is a clinically effective and minimally invasive treatment, there are reported complications. However, its complication rate remains

unclear (1-11). This study aimed to review and summarize the reported complications of arthrocentesis.

MATERIALS AND METHODS

We evaluated the search engines, PubMed and Google Scholar, and EMBASE, using the terms "(TMJ OR TEMPOROMANDIBULAR JOINT OR TMD OR TEMPOROMANDIBULAR DISORDER) AND ARTHROCENTESIS) AND COMPLICATION." These keywords were used in the same format for all databases. No time limitation applied to filtration; therefore, all the researches until 2019 December were included. Only human trials were taken into consideration.

The inclusion criteria are; English and Turkish language articles, case reports, or case series describing a clinical complication of TMJ arthrocentesis. Animal researches were excluded. Two researchers cross-checked to ensure that all relevant studies were included. The same two researchers examined the abstracts of the studies. Content relationship and degree of inclusion criteria were assessed for each reviewed publication. Full texts of the articles that fit the criteria of the research obtained. The articles included in the study were shown in Table 1.

RESULTS

As a result of our literature search, eight articles were found in PubMed, 1690 articles were found in Google Scholar, and 98 articles were found in EMBASE. As a result of the selection criteria, seven articles were included in the research. Complications and demographic data reported in the articles were shown in Table 1. One article is about Vertiginous crisis, and one is about facial nerve paralysis with lingual and inferior alveolar nerve anesthesia, one is about just lingual and inferior alveolar nerve anesthesia, one is about extradural hematoma, one is about otologic symptoms, three of are about case series which reports their complications and their

Table 1. *Summary of articles from databases included in the study*

Author/year	Type of Article	Patient/Gender	Complications
Vaira et all /2016	Case report	1 /F	*Vertigo
Efeoglu et all /2010	Case report	1 /F	*Mandibular anesthesia
Yavuz GY et all./2018	Retrospective	96(58 F ,38 M) / 102	*Temporary swelling *hemorrhage *facial paralysis *lingual anesthesia *inferior nerve anesthesia *tachycardia *syncope *dizziness *severe pain *limitation of mouth opening
Aliyev T et all /2019	Case report	1 /M	*temporary facial paralysis *lingual anesthesia *inferior nerve anesthesia *dizziness *nausea
Vaira et all /2017	Retrospective	315(252 F,63 M) /433	*Temporary swelling *external auditory canal swelling *ipsilateral temporary open bite *frontalis and orbicularis oculis paresis *preauricular hematoma *vertigo
Carrol all /1998	Case report	1/F	*Extradural haematoma
Senturk et all / 2016	Retrospective	22(18F,4M) / —-	*Postop pain *Fluid extravasation *Temporary facial paralysis *Bleeding *Irritating dizziness *Mandibular restriction

rates. The case series introduced temporary local swelling, hemorrhage, facial paralysis, lingual anesthesia, inferior mandibular nerve anesthesia, tachycardia, syncope, dizziness, severe pain, limitation of mouth opening, preauricular hematoma, external auditory canal swelling and bleeding, complications. All these articles were published between 1998-2019. The follow-up period changed from 1 day to three months.

DISCUSSION

TMJ arthrocentesis is frequently used in the treatment of internal disorders characterized by multifactorial etiology. Arthrocentesis is a minimally invasive, cost-effective, with a high success rate (91%) procedure that can easily be performed under local anesthesia in the clinical conditions. Arthrocentesis method removes catabolism products, inflammatory cells, and adhesions in the joint fluid; therefore, it reduces pain and increases interincisal distance and stops disease progression (7, 12, 13).

Prior studies have noted the safety of arthrocentesis procedure; however, like all surgical procedures, several complications have also been reported. The causes of complications may occur due to the anatomy of the joint, the physician's experience, and the arthrocentesis technique (10, 14, 15).

Complications can occur commonly secondary to mechanical damage of cannula or local anesthesia diffusion. The reported complications caused by these two main reasons affecting the middle ear are allergic reactions, facial paralysis, and vertigo, as well as dizziness and hearing difficulty (16).

In 22 TMJ arthrocentesis cases reported by @enturk et al. (12), pain (27.3%), temporary facial paralysis (21.2%), fluid extravasation (18.92%), bleeding (13.51%), mandibular restriction (13.51%) and irritating dizziness (5.41%) occurred. They concluded that these complication rates are less than arthroscopy techniques.

Vaira et al. (17) demonstrated an unusual complication a 48-year-old female suffered from independently regressing short-term vertigo attacks. The attack begins just after the local anesthesia (mepivacaine 2% and 1:200,000 epinephrine) injection before arthrocentesis. The author explained that the patient was troubling of transarticular penetration. The infiltrated anesthetic solution reached the semicircular canals near the inner ear that causes nausea, vomiting, and grade three nystagmus. When the effect of the anesthetic solution disappeared, the symptoms relieved, and the patient had no other complications.

Vaira et al. (3) in 2018 evaluated complications in 225 women and 53 male patients after 433 arthrocentesis procedures evaluated the complications. They detected temporary swelling of the periarticular tissues (95.1%) and the external auditory canal (23.5%), ipsilateral temporary open bite (68.8%), frontalis and orbicularis oculi paresis (65.1%), preauricular hematoma (0.4%), and a case of vertigo (0.2%). The stated that these complications were temporary and occurred due to anesthetic effect or soft tissue edema. All the complications were managed uneventfully on outpatient basis.

In a case reported by Efeoglu et al (18), a perforation was unintentionally created in the medial wall of the joint capsule during the placement of the cannula in the upper joint cavity. As a result of this, saline and local anesthetic agents spread to the infratemporal fossa. Anesthesia developed in the mandibular nerve adjacent to the joint. This was a rare complication od arthrocentesis and was essential to emphasize the importance of capsule integrity during this procedure.

As mentioned in the literature by Yavuz et al. (19), eighteen complications were bserved in 102 arthrocentesis procedures. Temporary swelling (0.98%), temporary intracranial bleeding (0.98%), facial paralysis (1.96%), lingual anesthesia (0.98%), inferior nerve anesthesia (0.98%), tachycardia (0.98%), syncope (2.94%), dizziness (4.9%), severe pain (0.98%), and limitation of mouth opening (1.96%) noted. The overall rate of complications regarding the literature of arthrocentesis was 17.65% in all patients.

Aliyev et al. (20) reported a complication about developed temporary facial paralysis with mandibular and lingual nerve anesthesia. The 55-year-old male patient suffered this complication just one hour after the arthrocentesis. This complication explained by mechanical damage caused by cannula, which led to anesthetic solution diffuse to the infratemporal fossa. No further complications were observed in the following period. The reported complication resolved spontaneously. No persistent complications were detected during the postoperative follow-up.

Carrol et al. (10) reported the most uncommon complication. Following the right TMJ arthrocentesis and lavage for TMJ dysfunction, a 59-year-old woman complained about drowsiness and developed left hemiparesis. Computed tomography revealed that the cannula crossed the temporomandibular joint and perforated the intracranial part of the middle meningeal artery where extradural hematoma occurred. Hematoma removed by neurosurgeon intervention. No dural perforation or cranial bone damage reported. Severe symptoms after the procedure should be monitored carefully in order not to overlook life-threating complications.

The complication rate of arthrocentesis is low. Facial nerve trauma, preauricular hematoma, superficial temporal artery trauma, arteriovenous fistula, intraarticular hemorrhage, intracranial perforation, extradural

hematoma, intraarticular needle fracture, extraarticular injection, and fluid accumulation and allergic reactions to anesthetic agents or drugs are the up to date reported complications (10, 19, 21).

In conclusion, although arthrocentesis is considered as a safe and predictable procedure, complications may be seen due to its close proximity to important anatomical structures. Most of these complications can be easily managed in the clinics although some maybe more serious.

CONCLUSION

TMJ arthrocentesis is the removal of joint fluid containing many degradation products and inflammatory mediators. This surgical procedure is performed by inserting needles or small cannulae into the TMJ to break up intraarticular adhesions. According to literature, It has a minimum number of significant complications. Compared with other surgical techniques applied to TMJ, it is easy to determine that it is a minimally invasive treatment technique. Complications of the procedure are usually temporary. The main reason for temporary complications is the extravasation of the anesthetic solution or irrigation solution to the soft tissues. TMJ and neurocranium are in a close relationship. Due to the neighboring, serious complications can occur if cannula passes on et on other side.

Although the complication rates of arthrosynthesis are quite low, surgeons should be aware of vascular and nerve damage. Upper joint space and neurocranium are separated by a thin bone lamina. The surgeon should be aware of it due to avoid intracranial complications, which leads to immediate hospitalization for the patient. Proper knowledge of the possible complications and their frequency helps the surgeon achieve the procedure successfully. TME arthrocentesis is a less complicated procedure that does not require additional equipment and is easy to perform. It is a minimally invasive method that is effective in reducing the pain of TMD and restoring function.

Abbreviations

TMJ — temporomandibular joint
TMD — temporomandibular disorder
ID — internal derangement

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Sažetak

KOMPLIKACIJE ARTROCENTEZE TEMPOROMANDIBULARNOG ZGLOBA

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Artrocenteza je procedura, koja se često koristi i prihvaćena je kao minimalno invazivna i prediktivna u lečenju oboljenja temporomandibularnog zgloba. Cilj rada je procena komplikcija artrocenteze. Pregled literature uključuje PubMed, Google Scholar i EMBASE baze podataka, koristeći termine „(TMJ ili TEMPOROMANDIBULARNI ZGLOB ILI TMB ILI OBOLJENJA TEMPOROMANDIBULARNOG ZGLOBA) I ARTROCENTEZA) I KOMPLIKACIJE“ Publikacije do 2019.te su bile uzete u razmatranje. Sedam studija koje su uključivale komplikacije artrocenteze su bile uključene. Iako je artrocenteza relativno jeftina, tj. finansijski efikasna i sigurna procedura, komplikacije mogu da se jave zbog blizine prikazanih anatomskih struktura. Najviše komplikacija je kratkog trajanja i mogu lako biti rešene u ambulatnim uslovima; iako su i neke teže komplikacije takođe bile zabeležene u literari. Lekari koji izvode ovu proceduru trebalo bi da budu svesni mogućih komplikacija ove procedure i da budu spremni da iste i adekvatno tretiraju.

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Review article

ACUTE AND CHRONIC PROSTATITIS

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Abstract: Today is very well known that prostatitis is often disease in men in the age of 50 and also it make a 1/3 of urological diseases in men over 50 year old, following benign glandular prostatic hyperplasia as well cancer of prostata.

Acute bacterial prostatitis: Disturbed disorders are: general weakness, fever, pain or feeling of discomfort between the spine and the scrotum or the end of the colon, and frequent, painful and difficult urination is observed. Acute bacterial prostatitis most commonly occurs in men between the ages of 20 and 40. Disturbed disorders are: general weakness, fever, pain, or feeling of discomfort between the anus and the scrotum or in the end of the colon. In addition to the above symptoms, frequent, painful and difficult wetting occurs, and sometimes the urinary incontinence can occur. In case of suspected acute prostatitis, a prostate examination in the finishing section of the colon should be performed. The prostate is extremely painful on the touch, warm and sometimes "wet" consistency. In some cases, manure accumulation can occur within the prostate tissue, which leads to abscess (crowding), which should be surgically opened and emptied of purulent contents.

Chronic bacterial prostatitis: Due to the presence of bacteria in the tissue of the prostate, chronic bacterial prostatitis is associated with frequent recurrent acute cystitis, or inflammation of the bladder mucous membrane. In this disease, patients are mostly free from the acute phase of worsening condition.

Key words: prostatitis, acute, chronic.

INTRODUCTION

Pathologically, prostatitis is defined as an increase in the number of inflammatory cells within the prostate. The inflammatory process may be infectious or inflammatory. The most common histological phenomenon is lymphocytic infiltration in stroma, which borders with prostate acinus. Prostatitis is a broad diagnosis that includes four clinical entities, including acute bouts of immediate attention (acute bacterial prostatitis), two chronic conditions (chronic bacterial prostatitis, chronic pelvic pain), and a random discovery of inflammation (asymptomatic prostatitis) recorded in evaluation and treatment other urological conditions. In addition, prostatitis exacerbates the state of the kidneys and urinary tract and causes inflammatory processes in them (1, 2, 3).

Urinary tract infections are a significant source of morbidity and mortality, in defiance of the wide use of antibiotics. Prostatitis is the prevailing and exhausting disease, the most common urological diagnosis in men under the age of 50, and the third most common diagnosis in men over the age of 50 years (after benign prostatic hyperplasia and prostate cancer). Researchers estimate that between 10 and 12 percent of men will suffer from symptoms similar to prostatitis. Despite the prevalence and exhaustion of health resources, our understanding of etiology, diagnostics and the treatment of prostatitis has not yet advanced to the widely accepted level. These statistics clearly emphasize the wide and far-reaching effect of prostatitis on the quality of life of the patient and the economic impact of the disease.

DISTRIBUTION OF PROSTATITIS

Prostatitis represents an increse in the number of inflammatory cells inside the prostata gland. Prostatitis is very broad process which involve four clinical issues, as are acute bacterial prostatitits, chronic bacterial prostatitis, chronic pelvic pain and asimptomatic prostatits (1, 2, 3).

The very important precipitating factor which contribute source of morbidity and mortality are urinary tract infections. Infections of urinary tract are important in morbidity and mortality in genesis of prostatitits in men under the age of 50. Researchers estimate

that between 10 and 12 percent of men suffer from symptoms similar to prostatitis.

Distribution of prostatitis

During years prostatitis has been devided in 4 clinical entitities:

1. Acute bacterial prostatitis (ABP)
2. Chronic bacterial prostatitis (CBP)
3. Neo or abacterial prostatitis
4. Prostatodinia.

Today, there is currently classification od prostatitis created by National Institute of Health (NIH):

Category 1 – acute bacterial prostatitis (acute prostatic infection). ABP is determinated as infectious disease of the lower urinary tract, caused by bacterias, mostly often by Escherichia coli;

Category 2 – chronic bacterial prostatitis (recurent infection of the urinary tract and/or chronic prostate infection). CBP is considered as a bacterial prostate infection following by complex of simptoms, ussually including the same pathogen;

Category 3 – Chronic non – baterial prostatitis / chronic pelvic pain syndrome. This is the most common type of prostatitis (90% of all cases). The diagnosis is based on examination of the prostate secretion, clinical findings and results of the culture. Based on the difference in the findings, it can be classified in two subcategories:

Category 3A – Cronic pelvic pain inflamatory syndrome (the presence of white blood cells in seminal fluid and/or cured prostate secretion);

Category 3B Non infalmmatory chronic pelvic pain syndrome (no white cells in seminal fluid and/or cured prostate secretion);

Category 4 – Asymptomatic inflammatory prostatitis with confirmation of biopsy, sperm sample and/or cured prostat secretion,without symptoms). It is often diagnosed covering results of biopsy. The biopsy is ussually done because of the classification system of the National Institute of Health (NIH) (4, 5, 6, 7).

SYMPTOMS

Symptoms of prostatitis depend on the type of disease the patient has. He may not experience any symptoms or such sudden and severe symptoms as he is forced to seek immediate medical attention. Symptoms, when present, may be any of the following: fever, trembling, urinary frequency, frequent urination at night, difficulty urinating, burning or painful urination, perineal (thinking perineum, area between the scrotum and anus) and lower back pain, joints or muscle pain, swollen or sensitive prostate, urine or painful ejaculation.

Symptoms of prostatitis resemble the symptoms of other infections, as well as other prostate diseases. Therefore, even if the symptoms disappear, prostate check should be performed. For example, benign prostatic hyperplasia (BHP), non-cancerous prostate enlargement that is common in men over 40 years, can produce symptoms in the urinary tract of the same as in prostatitis. Similarly, urethritis, inflammation of the urethra (often caused by infection), can also lead to many symptoms associated with prostatitis. Another condition that simulates the symptoms of prostatitis (when prostatitis is not present) is prostatitis (painful prostate). Patients with prostatinia have pelvic or perineum pain. Such pain can be the result of prostate problems, but pain can have a variety of causes, including muscle cramps or other musculoskeletal conditions.

The term that can also be mentioned in the consideration of prostate problems is prostatosis, an even vague word that simply means “state of the prostate”. It can be used instead of the term prostadini (8, 9, 10).

Because of the close association of urethra, bladder and prostate, and conditions that affect these organs often have similar or overlapping symptoms.

RISK FACTORS

Risk factors may be diverse, those that allow bacterial colonization and/or prostate infection by potentially pathogenic bacteria include:

- intraprostatic ductal reflux
- phimosis
- specific blood groups
- unprotected anal relationship
- multiple partners
- Urinary tract infections
- acute epididymitis
- intraurethral catheters
- transurethral surgery
- abnormal anatomy of the urinary tract (inborn defect)
- obstruction of the bladder emptying as a result of benign prostatic hyperplasia
- immunosuppressed conditions
- poor fluid intake (reduced frequency of urination)
- pelvic trauma (riding a horse, riding a bicycle)
- the risk is higher for younger than for older men (11, 12, 13, 14).

ACUTE BACTERIAL PROSTATITIS

Etiology and pathogenesis

Acute bacterial prostatitis (ABP) is a generalized prostate infection and is associated both with lower-end infections of the urinary tract and sepsis. The

main cause of bacterial prostatitis is the family Enterobacteriales-gram negative bacteria, which origin from the gastrointestinal flora. Aerobic gram-negative microorganisms are mainly caused by ABP. The frequency of infections by different species and their antibiotic sensitivity show that these are microorganisms that usually infect urine. Escherichia coli is involved in arround 75% of infections, Pseudomonas aeruginosa, Serratia, Klebsiella and Proteus species take 10-15% of total number of isolated organisms and enterococci 10-15%. Sexually active men under 35 years of age and older men entering into high-risk sexual behavior should be tested on Neisseria gonorrhoeae and Chlamidia trachomatis. Bacteria stay deep in the prostate and arrange aggregates (known as biofilms); this is a protective mechanism that allows bacteria to persist in prostate. Gram-positive bacteria are ethiological agens of infections only under special circumstances. Anaerobic infections are usually associated with other species. Most infections occur in the peripheral zone where the channels flow out horizontally into the urethra, facilitating urine reflux as well as the intradual pathway. The glands in the central prostate area are empty in the urethra, preventing easy reflux and stagnation. Invasions by rectal bacteria, either directly or via lymphoid pathway, are also believed to cause prostatitis (15, 16, 17, 18).

Clinical features

ABP is marked by fever and anger, rectal, perineal and lower back pain, rapid and frequent urination and/or dysuria. It can lead can to acute urinary retention. Arthralgia and muscular pain are also often. Digital rectal examination confirm extremely sensitive and enlarged gland that is extremely solid and hot. Urine can be with unpleasant odor due to the simultaneous infection of the urinary tract. Huge haematuria can appears occasionally. Physical examination is an important method of evaluating a patient with prostatitis, but it is usually not useful in making a definitive diagnosis or an additional classification of prostatitis. It helps to exclude other perineal, anal, neurological and pelvic diseases, as well as other prostate diseases (19, 20).

The ABP patient may have systemic problems: feverish, febrile, nausea, vomiting, tachycardia, tachypnoea, and even hypotension. The patient usually has suprapubic disorder due to urinary retention. Prostate is usually described as hot, rusty as extremely sensitive. Patients with ABP are considered that do not need prostate massage which is unnecessary and even harmful.

Diagnosis

ABP is often diagnosed by symptoms and physical examination. A full blood picture usually shows leukocytes while moving towards immature forms. Transuretral catheterization is not recommended. Urinology and other urine tests should be performed. The presence of more than 10 white blood cells per field, observed with a microscope under the magnification of high power, suggests a positive diagnosis. Other laboratory tests (eg electrolyte level, blood culture) are performed depending on the severity of the presentation. Residual urine should be examined if the patient has a tangible bladder or frequent problems of incomplete emptying. Acute urinary retention requiring drainage of the bladder should be addressed using a suprapubic catheter. Backlog urine usually shows pyuria and microscopic hematuria due to infection of the urinary tract.

Access to the disease

Empirical treatment can be implemented primary against Gram-negative bacteria and enterococci. The choice of antibiotics is conducted on the basis of in vitro assays for antimicrobial susceptibility testing (antibiogram). Flouroquinolones act very well as initial therapy, as well as trimethoprim / sulfamethoxazole. The recommended duration of antibiotic therapy is between 4 and 6 weeks to prevent complications, as are prostate abscess and chronic prostatitis. The auxiliary therapy include antipyretics, analgesics, laxant agents, rehydration and rest. Patients with severe complications, such are: sepsis, immune deficiency and acute urinary retention, require hospitalization. Transurethral catheterization or other instrumentation is contraindicated during the acute infection. Acute urinary retention should be eliminated by suprapubic drainage until the patient is able to empty the bladder independently.

Complications

In some patients may acute bacterial prostatitis can proceed to chronic bacterial prostatitis, especially if attention is not focused on bacterial eradication. Prostate abscess can develop during acute prostatitis. Immunocompromised patients, diabetics, those with urethral catheter or those on chronic dialysis are at greater risk of developing these complications.

CHRONIC BACTERIAL PROSTATITIS

Etiology and pathogenesis

Chronic bacterial prostatitis (CBP) is associated with recurrent infections of the lower parts of the urinary tract, which are a secondary consequence of uropathogenic bacteria inhabited in prostate. Gram-negative bacteria and enterococci are usually presented microorganisms in CBP. Micoplasms, ureaplasma, and chlamydia are significant pathogens in CBP, and most

of them are believed to be involved in chronic pelvic pain syndrome. Urine reflux and bacteria into the prostate are considered as a very important etiological mechanisms involved in the pathogenesis of chronic bacterial and non-bacterial inflammation of the prostate. The researchers measured a high level of urine and creatinine in EPS (exhaled prostate secretion), which is thought to be a consequence of urinary reflux in the prostate canals. In addition, carbon particles were found in macrophages in EPS, prostate acini and ductal system after surgery in patients with non-bacterial prostatitis.

Bacterial microcolonies can be adhered to ductal and acinar walls and can become resistant to antibiotics. A large number of people with CBP have more prostate calcification confirmed by transrectal ultrasound. Prostatic stones can serve as a source of bacterial persistence and recurrent urinary tract infections. It is believed that the source of pain is located on the pelvic area of the sacral (biting) bone, the rough sedular protrusion (tuber ischiadicum), the branches of the bone (pubic ram) and the pelvic (endopelvic) fascia. These areas are directly adjacent to the prostate and bladder and can be determined by finding a hyper-measurable site (a myosphalous trigger) that is painful for compression. It is assumed that this area can be associated with mechanical disturbances of the hip and lower extremities, constipation / stress in the toilet, repetitive injuries, severe sports, unusual sexual activity, recurrent infections and operations.

Clinical features

Careful examination and palpation of external genitals, groin, perineum, vagina, external anal sphincter and internal pelvic walls can highlight certain areas of pain or discomfort. A digital rectal examination should be performed after the patient has produced urine specimens before prostatic massage. The prostate may be of normal size and consistency, and can also be described as enlarged and swollen. The degree of pain caused during prostate palpation is variable, so it is not helpful to distinguish the type of prostatitis. Prostate should be carefully examined before strong prostate massage is performed.

Most patients report dysuria and as urgent, frequent and night urination. Pain or discomfort in the lower back and perineum may be present. According to the nature of the disease, history is marked by a relapse with occasional acute exacerbation, when fever, trembling and maloseness can manifest. There are no characteristic signs in the digital rectal examination. Prostate is often normal to the touch, although sensitivity is mostly presented. Epididymitis can sometimes follow the process. Haematuria, haematospermia and urethral secretions are usually rare.

Diagnosis

Test of four glasses is standard in diagnostics of prostatitis. The technician collects the first 10 ml of urine (urethral sample), then takes a sample of the mean urinary stream (bladder sample), a prostate secretion sample after prostate massage and ultimately collect the first 10 ml of urine after massage. Alternative tests are urethral swab and sperm analysis. Spermoculture is recommended only if there is a high level of suspicion of chronic bacterial infection, despite the negative urine and EPS culture (greater sensitivity than EPS to gram-negative organism is 97% versus 84%, as well as gram-positive bacteria 100% compared to 16%). If there are no cultured microorganisms and the secretion of prostate has an increased number of leukocytes (> 10 per field of counting), a diagnosis of chronic pelvic pain (inflammatory type) syndrome is done. Despite urine sterility, the pathogen often remains hidden in the prostate, as most antibiotics are poorly diffused into the prostate fluid. Prostate specific antigens (PSAs) can be elevated.

Generally, at least 3-4 months of treatment is recommended, although some studies report the effect of using fluoroquinolone for 4 weeks. Factors that improve antibiotic diffusion in the prostate include lipid solubility, poor binding to plasma proteins. Most of antibiotics are concentrated in urine, which allows lower dosage while maintaining a bactericidal effect. The most common daily treatment are nitrofurantoin (100 mg daily), trimethoprim-sulfamethoxazole (200 mg daily) and ciprofloxacin (250 mg daily). This therapy can provide relief from symptoms in most men.

Transurethral prostatectomy (TURP) is used as an alternative treatment. Surgical therapy often provides the only chance of healing in relapse cases. Studies in which patients undergo transurethral prostatectomy, in chronic bacterial prostatitis, followed by antibiotic therapy from 6 to 8 weeks appear with success (30-100%) (20).

Complications

Urinary tract infections are a major complication of chronic bacterial prostatitis, which can even ead to sterility. There are cases of successful treatment of prostatitis leading to an improvement in sperm parameters. CBP has a negative influence on the quality of life of patients.

CONCLUSION

Prostatitis certainly takes a special place in urological practice. In order to determine the etiopathogenesis of prostatitis, it is important to determine the causes that contributed to the development of the disease. Ba-

sed on this, prostate examinations can be directed to further flows that will lead to a final assessment of the patient's condition, as well as a decision on the definitive treatment of the patient.

Abbreviations

ABP — Acute bacterial prostatitis
CBP — Chronic bacterial prostatitis
BHP — benign prostatic hyperplasia
PSAs — Prostate specific antigens0

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AKUTNI I HRONIČNI PROSTATITIS

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Danas je poznato da su prostatitisi česte bolesti kod muškaraca starosti od 50 godina i takođe čine 1/3 ukupnih urooloških bolesti kod osoba preko 50 godina starosti, a pre nje po stepenu incidencije je benigna glandularna prostatička hiperplazija, kao i karcinom prostate.

Akutni bakterijski prostatitis: **Uopšteni poremećaji**: opšta slabost, temperatura, bol ili osećaj nelagode u predelu kičme i skrotuma ili u Donjim segmentima kolona. Takođe registruje se učestalo mokrenje, praćeno bolovima. Akutni bakterijski prostatitis se najčeće javlja kod osoba koje su u uzrastu između 20 i 40 godina. Najčešći simptomi su: generalizovana malaksalost i slabost, temperatura, bol kao i osećaj nelagode između čmara i skrotuma, kao i u donjim segmentima kolona. Dodatno, na navedene simptome, učestalo, bolno i otežano mokrenje se javlja, kao i povremene urinarne inkontinencije. U slučaju suspektnog akutnog prostatitisa, ispitivanje prostate se odvija u donjim partijama kolona. Prostata je ekstremno palpatorno bolno osetljiva, topla na dodir kao i ponekad „vlažne" konzistencije. U pojedinim slučajevima, akumulacija leukocita moće da se javi u tkivu prostate, koje može dovesti apscesa, koje bi trebalo hirurški tertirati, resecirati i purulentni sadržaj izdrenirati.

Hronični bakterijski prostatits: Zbog prisustva bakterija u tkivu prostate, hronični bakterijski prostatits može biti povezan sa češćim rekurentnim akutnim cistitisom, ili zapaljenjem mukozne membrane mokraćne bešike. U ovoj bolesti, pacijenti su oslobođeni akutizacije, odnosno akutnih simptoma bolesti.

Ključne reči: prostatits, akutni, hronični.

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

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Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

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 prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 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.

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Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

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

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 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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