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RESULTS OF TREATMENT OF ACROMIOCLAVICULAR JOINT INJURIES

REZULTATI LEČENJA POVREDA KLJUČNO-NATPLEĆNOG ZGLOBA

Mile BJELOBRK[1], Mirko OBRADOVIĆ[1], Milan MAJKIĆ[1], Vukadin MILANKOV[2, 3] and Srđan NINKOVIĆ[1, 3]

Summary

Introduction. Acromioclavicular joint has an important role in the shoulder function. Loss of joint function due to injury or disease affects the biomechanics of the shoulder. The aim of this study was to evaluate the results of surgical treatment of acromioclavicular joint injuries, identify risk groups within the age groups, and to indicate the most common mechanisms of injury. **Material and Methods.** A retrospective study included 20 patients with acromioclavicular injury. We analyzed the results of surgical treatment in patients with acromioclavicular injury from January 2017 to January 2019. Patients were treated using Bosworth and Phemister surgical techniques. The Constant shoulder score was used to assess the results of surgeries. We compared the results of the operated and non-operated shoulders in each patient. Statistical analysis was performed using Student's T-test and χ^2 test. **Results.** Functional assessment was done using the Constant shoulder score: 9 patients had excellent results, 7 had good results and 3 had satisfactory results; there were no patients with poor outcome. We compared the total Constant shoulder score of the operated shoulder with the results of the opposite healthy shoulder, as well as the range of motion of external rotation, and internal rotation range of motion of the operated and the opposite healthy shoulder. There was a statistically significant difference ($p < 0.05$) in all compared parameters. The total Constant shoulder score of the operated shoulder was by 14% lower in relation to the healthy shoulder. **Conclusion.** The basic precondition for positive treatment results is timely diagnosis and early surgical intervention. Shoulder function was surgically restored and 95% of patients can perform all activities of daily living.

Key words: Acromioclavicular Joint; Treatment Outcome; Shoulder Injuries; Risk Factors; Functional Status

Sažetak

Uvod. Ključno-natplećni zglob zauzima važno mesto u funkciji ramena. Gubitak funkcije usled povrede ili oboljenja narušava biomehaniku ramena. Cilj rada bio je procena rezultata operativnog lečenja povreda ključno-natplećnog zgloba, identifikacija rizičnih grupa unutar starosnih okvira i ukazivanje na najčešći mehanizam povređivanja. **Materijal i metode.** Retrospektivna studija je sprovedena na grupi od 20 pacijenata lečenih zbog povrede ključno-natplećnog zgloba. Analizirali smo rezultate hirurški lečenih pacijenata sa povredom ključno-natplećnog zgloba od januara 2017. do januara 2019. godine. Pacijenti su lečeni operativnim tehnikama po Bosvortu (*Bosworth*) i Femisteru (*Phemister*). U proceni rezultata operacija upotrebljena je Konstantova bodovna skala za rame. Poredili smo rezultate operisanog i zdravog ramena za svakog pacijenta. Statistička analiza je vršena pomoću Studentovog T-testa i χ^2 testa. **Rezultati.** Prema Konstantovoj bodovnoj skali, devet ispitanika imalo je odličan rezultat, dobar rezultat sedam, zadovoljavajući tri i nije bilo ispitanika sa lošim rezultatom. Uporedili smo zbir Konstantove bodovne skale operisanog ramena sa rezultatima suprotnog zdravog ramena, kao i obim pokreta spoljašnje rotacije i obim pokreta unutrašnje rotacije operisanog i suprotnog zdravog ramena. Utvrđena je statistički značajna razlika ($p < 0,05$) u svim upoređenim parametrima. Zbir Konstantove skale operisanog ramena je 14% manji u odnosu na zdravo rame. **Zaključak.** Osnovni preduslov pozitivnog rezultata lečenja je pravovremena dijagnostika i rana hirurška intervencija. Funkcija ramena je hirurški obnovljena tako da 95% ispitanika može da obavlja sve aktivnosti dnevnog života.

Ključne reči: akromioklavikularni zglob; ishod lečenja; povrede ramena; faktori rizika; funkcionalni status

Introduction

Acromioclavicular joint has an important role in the shoulder function. Loss of joint function due to injury or disease affects the biomechanics of the shoulder [1].

Injury of acromioclavicular joint in most cases occurs as an isolated injury, but muscles of the rotator cuff should always be checked for possible as-

Corresponding Author: Dr Mile Bjelobrk, Klinički centar Vojvodine, Klinika za ortopedsku hirurgiju i traumatologiju, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: m.bjelobrk.ns@gmail.com, vukadin.milankov@mf.uns.ac.rs

Abbreviations

SICK – scapular malposition, inferior medial border prominence, coracoid pain and abnormal movement of the scapula

sociated lesions [2]. Chilemi et al. [3] found that the incidence of these injuries is 1.8 per 10,000 inhabitants per year. Gender distribution shows almost 9 times higher incidence of these injuries in men. Injury of acromioclavicular joint is most common in patients between the ages of 20 – 39. This incidence is related to the average urban population [3].

Injury of acromioclavicular joint is usually a result of trauma. The mechanism of injury can be direct (football, rugby, hockey) and indirect (fall onto an outstretched hand) [4]. The classification system of Rockwood and Young is widely accepted for acromioclavicular joint injuries [4] **(Figure 1)**. It describes six types of injuries according to the degree of displacement of the outer part of collarbone, stretching or tearing of the acromioclavicular and coracoclavicular ligaments and integrity of the fascia that covers the deltoid and trapezoidal muscle [5]. Radiographic examination consists of three different radiographic techniques: standard radiography, weight-bearing view, and Stryker Notch [6] view. Confusion regarding anatomical variations and/or technical inconsistencies can be easily avoided by radiography of both shoulders [4]. The main goal of treatment is to restore the level of function before injury, with a pain-free, strong and mobile shoulder [7, 8]. Choosing the method of treatment depends primarily on the type of acromioclavicular joint injury, but also on the patient's profession, his expectations, medical history of the disease and the time that has elapsed between injury and diagnosis [5, 8].

Non-surgical treatment of patients with acromioclavicular joint injury is the method of choice for patients diagnosed with Type I or Type II acromioclavicular joint injury [4–6, 8]. Surgical treatment is considered with Type III, IV, V and VI injuries. Open techniques have poorer cosmetic outcome, they are technically less demanding, yet allow a direct view on the joint, while the deltotrapezial fascia injury can be repaired only by open surgery. Arthroscopic approach requires better technological equipment and the learning 'curve' of operative technique is longer, but a view of damaged tissue is better [7]. Static stabilization can be achieved by fixing the acromioclavicular joint, or by fixing the clavicle and acromion. The most commonly used are Kirschner wires, screws, non-absorbable sutures, hook plates and zuggurtung tension bands [8]. Dynamic stabilization is described by many authors [9, 10] and consists of separating the tendons of coracobrachialis muscle and short head of biceps muscle from coracoid and attaching them on the bottom surface of the clavicle. Tendons of listed muscles stabilize the joint by pulling the clavicle down [8]. Nowadays, dynamic stabilization techniques are rarely used. There are new techniques of Dog Bone stabilization and techniques using semitendinosus tendons. Dog Bone is a precontoured titanium button allowing passage of two fiber tapes. This system is set through

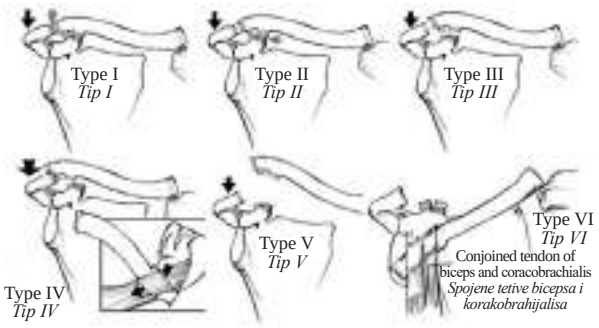


Figure 1. Rockwood classification of the acromioclavicular joint injury

Slika 1. *Rokvud klasifikacija povrede akromioklavikularnog zgloba*

tunnels on the clavicle and coracoid, enabling repositioning of the acromioclavicular joint by tightening the fiber tapes. Similarly to this technique, semitendinosus tendon is used instead of fiber tapes, which passes through the tunnels of coracoid and clavicle fixating it and thus repositioning the acromioclavicular joint [11].

The aim of this study was to evaluate the results of surgical treatment of acromioclavicular joint injuries, identify risk groups within the age groups, and to indicate the most common mechanisms of injury. It is assumed that the injured shoulder that was surgically treated can restore muscle strength and range of motion equal to the healthy shoulder.

Material and Methods

After the approval of the Ethics Committee of the Clinical Center of Vojvodina, a retrospective study was conducted including 20 patients treated for acromioclavicular injury. The results of surgically treated acromioclavicular injuries were assessed at the Department of Orthopedic Surgery and Traumatology, Clinical Center of Vojvodina in Novi Sad. Data on treatment were collected from the medical records of patients treated between January 2017 and January 2019. Measurements were taken at regular outpatient controls. Patients were treated using Bosworth [12] and Phemister [13] surgical techniques. Average follow up was 4 years (2 – 9) and all patients were operated by the same surgeon.

The Constant shoulder score was used in the evaluation of the results: pain intensity monitoring, level of daily activities, and measurement of the strength and range of motion of the operated and healthy shoulders [14]. Patients were asked about the presence and intensity of shoulder pain, limitations in daily activities and sports, and pain during the night. Measuring the strength of withdrawal is based on the number of kilograms the patient can retain in a position of abduction to 90˚ (a twenty five year old man with a healthy shoulder can withstand 12.5 kilograms without much difficulty so this value was taken as the highest with 25 points). Points for all

parameters of each shoulder (operated and healthy) provide the total point value (sum of Constant scale). The Constant scale result is the difference between the total number of points in the operated and healthy shoulders. The data of the operated and healthy shoulders for each patient and the sum of Constant shoulder score scale, as well as the range of external and internal rotation, abduction and flexion were compared. Statistical analysis was performed using Student T-test and χ^2 test.

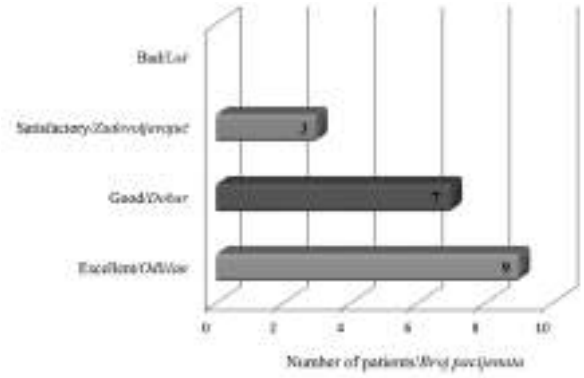
The study included 18 male (90%) and 2 female patients (10%). The average age of patients was 29 years. The oldest patient was 43 and the youngest 21 years old. Thirteen patients practiced recreational sports before injury, and all of them continued with recreation after surgery. In 6 patients the injury was the consequence of traffic accident, in 4 cases the injury occurred during sports activities, occupational injuries occurred in 3 patients, skiing-related injuries were also found in 3 patients, and 3 patients fell off the bicycle/motorcycle. The most common mechanism of injury was a fall on the shoulder in 65% of cases, 10% of patients reported a fall on the elbow, and 25% reported a blow to the shoulder. After the injury, patients were sent to a general practitioner in 85% of cases, a doctor of sports medicine in 5% of cases, and a physiatrist in 10% of cases. Magnetic resonance imaging was performed in two patients on the day of injury. All injuries were unilateral. There were 12 patients with a right side injury, while 8 patients sustained a left side injury of the acromioclavicular joint. The dominant hand was affected in 60% of patients. Type III injuries of the acromioclavicular joint were diagnosed in 15 patients, type IV in 4 subjects, and type V in 1 subject. There were no patients with type VI injury of the acromioclavicular joint.

Results

Postoperative complications occurred in three cases: superficial wound infection in two cases, which was treated conservatively, and pain syndrome in one patient who was treated with rehabilitation therapy and painkillers. Seventy-five percent of patients were regularly treated with rehabilitation therapy, 12 patients denied pain in the operated shoulder, 2 had mild pain, 6 had moderate pain, and none of the patients reported severe pain in the operated shoulder. Ninety-five percent of patients reported no pain in the opposite healthy shoulder, and 5% had mild pain. After surgery, 13 patients could perform all activities of daily living, six patients occasionally

Table 1. Comparison of the sum of Constant scoring scale, external and internal rotation range of motion of the operated and opposite healthy shoulder
Tabela 1. *Upoređivanje vrednosti zbira Konstatove skale, obima pokreta spoljašnje i unutrašnje rotacije operisanog i suprotnog zdravog ramena*

	Operated shoulder/*Operisano rame*	Opposite shoulder/*Suprotno rame*	Operated shoulder/*Operisano rame*	Opposite shoulder *Suprotno rame*	Operated shoulder/*Operisano rame*	Opposite shoulder/*Suprotno rame*
Number of patient *Broj pacijenata*	Sum of Constant scoring scale *Zbir Konstantove bodovne skale*		Internal rotation *Unutrašnja rotacija*		External rotation *Spoljašnja rotacija*	
1.	89	98	70˚	80˚	70˚	90˚
2.	94	98	75˚	85˚	80˚	80˚
3.	95	98	75˚	80˚	60˚	80˚
4.	76	96	40˚	60˚	60˚	80˚
5.	82	96	70˚	85˚	80˚	80˚
6.	71	98	75˚	85˚	55˚	80˚
7.	85	94	45˚	80˚	55˚	80˚
8.	83	98	70˚	70˚	60˚	85˚
9.	96	98	70˚	70˚	80˚	85˚
10.	92	98	65˚	60˚	80˚	80˚
11.	75	94	70˚	70˚	60˚	80˚
12.	90	100	65˚	60˚	60˚	85˚
13.	92	98	75˚	80˚	55˚	65˚
14.	76	98	60˚	70˚	50˚	80˚
15.	71	98	60˚	80˚	50˚	85˚
16.	90	98	80˚	75˚	65˚	70˚
17.	82	98	60˚	70˚	55˚	80˚
18.	76	96	60˚	75˚	40˚	70˚
19.	83	98	60˚	65˚	60˚	80˚
20.	71	96	70˚	70˚	60˚	85˚



Graph 1. Constant scoring scale results of surgically treated patients
Grafikon 1. *Rezultati pacijenata prema Konstantovoj bodovnoj skali*

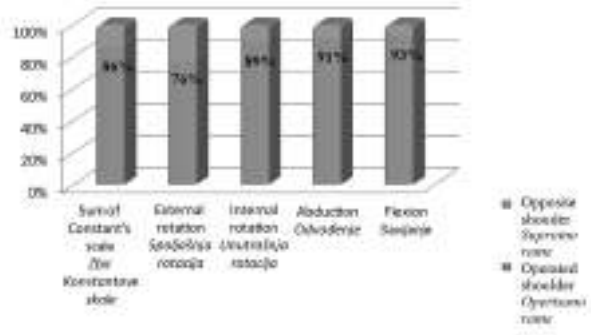
had limitations, and one patient had a permanent limitation in daily activities. Regarding the opposite healthy shoulder, patients did not have difficulties in performing activities of daily living. Ninety-five percent of patients claimed that they were satisfied with the results of surgery. According to Constant scoring scale, 9 patients had an excellent result, 7 had a good result, 3 had satisfactory, and there were no patients with poor outcome **(Graph 1)**. We compared the sum of Constant scoring scale of the operated shoulder with the results of the opposite healthy shoulder. We compared the range of motion of external rotation, and internal rotation range of motion of the operated and opposite healthy shoulder **(Table 1)**. A statistically significant difference ($p < 0.05$) was found in all compared parameters. Comparing the range of the upper arm abduction of the operated and opposite healthy shoulder, we found a statistically significant difference ($p < 0.05$). The range of flexion of the operated and healthy shoulder showed a statistically significant difference ($p < 0.05$) **(Table 2)**. The average value of the sum of Constant shoulder scoring scale for the operated shoulder was 83.45° ± 8.5°, and for the opposite healthy shoulder it was 97.3° ± 1.49°. The average value of the range of motion in external rotation for the operated shoulder was 61.75° ± 11.15°, and for the opposite healthy shoulder it was 80° ± 5.84°. The average value of internal rotation of the operated shoulder was 65.75° ± 10°, and for the opposite healthy shoulder it was 73.5° ± 8.28°. The average range of abduction for operated shoulder was 142.85 °± 16.65°, and for the opposite healthy shoulder it was 156.75° ± 13.5°. Flexion of the operated shoulder was on average 147° ± 16.62°, and for the healthy shoulder it was 158.75° ± 12.65° **(Table 3)**. Sum of Constant scale of the operated shoulder was by 14% lower than in the healthy shoulder. The range of external rotation was by 22.9% lower than in the healthy shoulder. There was a decrease of range by 10.5% of internal rotation,

Table 2. Comparison of abduction and flexion range of motion of the operated and opposite healthy shoulder
Tabela 2. *Upoređivanje vrednosti obima pokreta odmicanja i savijanja operisanog i suprotnog zdravog ramena*

	Operated shoulder *Operisano rame*	Opposite shoulder *Suprotno rame*	Operated shoulder *Operisano rame*	Opposite shoulder *Suprotno rame*
Number of patient *Broj pacijenta*	Abduction *Odmicanje*		Flexion *Savijanje*	
1.	130°	170°	137°	170°
2.	130°	170°	154°	170°
3.	155°	175°	179°	170°
4.	134°	150°	134°	165°
5.	178°	175°	167°	170°
6.	139°	145°	133°	160°
7.	121°	160°	134°	155°
8.	156°	140°	162°	135°
9.	160°	150°	140°	165°
10.	158°	160°	160°	160°
11.	131°	165°	139°	175°
12.	130°	165°	124°	170°
13.	130°	130°	137°	155°
14.	131°	135°	145°	140°
15.	140°	160°	130°	155°
16.	129°	160°	133°	165°
17.	167°	165°	173°	145°
18.	133°	170°	144°	170°
19.	170°	140°	175°	135°
20.	132°	150°	140°	145°

Table 3. Comparison of the type of movements of the operated and opposite healthy shoulder
Tabela 3. *Upoređivanje vrste pokreta operisanog i suprotnog zdravog ramena*

Types of movement/*Vrste pokreta*	Operated shoulder/*Operisano rame*	Opposite shoulder/*Suprotno rame*
External rotation/*Spoljašnja rotacija*	61.75˚ ± ˚11.15˚	80˚ ± 5.84˚
Internal rotation/*Unutrašnja rotacija*	65.75˚ ± 10˚	73.5˚ ± ± 8.28˚
Abduction/*Odmicanje*	142.85˚ ± 16.65˚	156.75˚ ± 13.5˚
Flexion/*Savijanje*	147˚ ± 16.62˚	158.75˚ ± 12.65˚



Graph 2. Percentage comparison of results of the operated and opposite healthy shoulder
Grafikon 2. *Procentno upoređivanje rezultata za operisano i suprotno zdravo rame*

by 8.85% of abduction, and by 7.4% of flexion when compared to the opposite shoulder **(Graph 2)**.

Discussion

In 1941, Bosworth [12] described a technique of fixation of the clavicle to the coracoid process using a screw. Heppenstall [15] recommends the Phemister's [13] technique. Using the shoulder arthroscopy, the next step in the treatment was made, allowing greater visibility during surgery and reducing the incidence of complications. At the present, there are various opinions on which technique provides better results, but the fact is that surgery of acromioclavicular joint shows better results in restoring the lost function of this important joint that has a huge impact on daily activities [16, 17]. In our study, Type III injury of acromioclavicular joint was present in 75% of cases, Type IV in 20%, and Type V in 5% of cases. Similar results have been found by Chilemi et al. [3] where Type III injury of acromioclavicular joint was the most common, as well as Alyas et al. [18] who reported that Type III dislocation was present in 40% of cases. Patients with Type III, IV and V acromioclavicular joint injury were treated using Phemister [13] and Bosworth [12] techniques. According to the literature, Type I and Type II injuries are treated non-operatively [19, 20] while Types IV, V and VI [21–23] are treated surgically, and there is no unique stance for Type III injuries. According to some authors [23, 24] Type III injuries should be primarily treated non-operatively, while most of them believe that surgical treatment is a better choice [24–26]. Gstettner et al. [24] compared surgically and non-surgically treated subjects with Type III acromioclavicular joint injury. The average value of the sum of Constant scoring scale in the surgically treated patients was 90.4, while in the non-surgically treated patients it was significantly lower (80.7).

In addition to these positive aspects of surgical treatment, we should mention the reduced incidence of scapular malposition, inferior medial border prominence, coracoid pain and abnormal movement of the scapula (SICK) syndrome in surgically treated patients with Type III injury [25, 26]. Gumina et al. [26] allege that non-operative treatment of Type III acromioclavicular joint injury led to the development of SICK syndrome in 58.3% of these patients. Sehmisch et al. [27] stated that the type of surgical technique does not have a great impact on the treatment outcome. The average value of the sum of Constant scoring scale in the surgically treated patients in the study of the Sehmisch was 91.8, which is better than in our study, in which the average value of Constant scoring scale for the operated shoulder with Type III, IV and V injuries was 83.45. Verdano et al. [28] examined 14 subjects, 11 men and 3 women, and evaluated the results of surgical treatment of Type III, IV and V injuries, three years after surgery, on average. The average Constant scoring scale of the operated shoulder was 92.7, which is a significantly better result than in our study. Better results in Verdan's study can be attributed to the short time that has elapsed between the injury and surgery, 3 days on average, while our patients were operated 19 days after injury on average. All patients in the Verdan's study had regular rehabilitation therapy, in contrast to our study, in which 15% of patients did not have regular rehabilitation, due to poor socio-economic conditions and the unavailability of physiatrists. In Verdan's study, just like in ours, there were no cases of re-dislocation of the acromioclavicular joint [28]. Postoperative complications in our study occurred in 15% of cases (three patients: one case of pain syndrome and two superficial wound infections) that required no reoperation. This percentage is lower than in the research of Kezunović et al. [29], which included 50 operated shoulders with 26% of postoperative complications. When comparing the age of patients and postoperative results, we found that the patients' age affects the degree of recovery (due to the reduction in the regenerative capacity of tissues and poorer functional status of the joint before injury). Older patients had a worse Constant scoring scale result compared to younger patients, which is consistent with the research of

Radovanović et al. [30]. In our study, patients had physical therapy for 6 months, but 15% of patients had no regular rehabilitation. The data of our study are consistent with other studies [20, 31] that suggest that regular rehabilitation is crucial for restoration of muscle strength and range of motion in the operated shoulder. The fact that 95% of patients can perform all activities of daily living, and that 95% of patients are satisfied with the results of surgery, indicate that the results are very good. In addition to the small sample size and the fact that it is a retrospective study, the limitation of this research is that we have not measured the range of motion of the injured shoulder preoperatively, which would provide a better insight into the outcome of operative treatment.

Conclusion

Acromioclavicular injuries Type III, IV, V and VI should be treated surgically. The basic precondition for positive treatment outcomes is timely diagnosis and early surgical intervention. The function of the shoulder is surgically restored so that 95% of patients can perform all activities of daily living and 95% of patients are satisfied with the results of surgical treatment. Injuries of acromioclavicular joint are most common in males engaging in sports, 25 – 35 years of age. The leading mechanism of injury is a direct effect of force on the shoulder, which is in most cases the consequence of traffic accidents or sports activities. The dominant hand is more often affected.

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University of Priština Seat in Kosovska Mitrovica, Faculty of Medicine, Department of Physiology, Kosovska Mitrovica, Serbia[1]
Clinical Hospital Center, Kosovska Mitrovica, Serbia[2]
Community Health Center, Department of Gynecology and Obstetrics, Rožaje, Montenegro[3]
University of Priština Seat in Kosovska Mitrovica, Faculty of Medicine, Department of Public Health, Kosovska Mitrovica, Serbia[4]

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IMPACT OF OROFACIAL PAIN ON THE QUALITY OF LIFE OF STUDENTS

UTICAJ OROFACIJALNOG BOLA NA KVALITET ŽIVOTA STUDENATA

Sonja SMILJIĆ[1], Vojkan NESTOROVIĆ[1], Nenad MILOŠEVIĆ[2], Azra LUKAČ[3], Sanja GAŠIĆ[1] and Mirjana KOSTIĆ[4]

Summary

Introduction. The aim of the study was to determine the prevalence of orofacial pain in students and the impact of pain on their quality of life and everyday professional obligations. **Material and Methods.** A cross-sectional study included 319 respondents of both genders. Two questionnaires were used in this study; one that we specifically designed to detect orofacial pain among students and the Oral Impacts on Daily Performance questionnaire. **Results.** Of the total number of examinees, 101 (32%) reported that they had previously experienced pain in the orofacial region. Using the logistic regression analysis, we found that gender was an important predictor of pain and that female students had a 1.8 times higher risk for developing pain ($p < 0.05$). The highest prevalence of pain in our subjects was in the temporal region (7%; confidence interval 4%; 9%) and the region around the eye (6%; confidence interval 4%; 9%). Namely, in 65 (64.4%) students who had pain in the orofacial region, it had an impact on the quality of life and daily activities. The most prominent was the impact of the orofacial pain on the performance of their activities at the faculty. Orofacial pain has a significant impact on the psychosocial sphere, emotional and social contacts (12.3%; 14.1%). The temporomandibular joint pain and the pain when opening the mouth showed the least impact on the quality of life ($p < 0.05$). **Conclusion.** Orofacial pain is a condition that affects daily activities of students at the faculty, as well as their emotional and social life.

Key words: Facial Pain; Quality of Life; Students; Risk Factors; Temporomandibular Joint; Toothache; Eye Pain; Surveys and Questionnaires; Pain; Sex Factors

Sažetak

Uvod. Cilj studije bio je utvrđivanje prevalencije orofacijalnog bola kod studenata i uticaj bola na kvalitet života i svakodnevne profesionalne obaveze studenata. **Materijal i metode.** Prospektivnom studijom obuhvatili smo 319 ispitanika oba pola. U ovoj studiji koristili smo dva upitnika, jedan koji smo posebno kreirali za otkrivanje orofacijalnog bola među studentima i *Oral Impacts on Daily Performance* upitnik. **Rezultati.** Od ukupnog broja, 101 ili 32% je reklo da je ranije imalo bol u orofacijalnoj regiji. Koristeći logističku regresiju otkrili smo da je pol važan prediktor bola i da studentkinje imaju 1,8 puta veći rizik za razvoj bola ($p < 0,05$). Najveća prevalencija bola kod naših ispitanika bila je u temporalnom predelu (7%; interval pouzdanosti 4%; 10%) i regionu oko oka (6%; interval pouzdanosti 4%; 9%). Naime, kod 65 (64,4%) studenata koji su imali bol u orofacijalnoj regiji, bol je imao uticaj na kvalitet života i svakodnevne aktivnosti. Najistaknutiji je uticaj orofacijalnog bola na obavljanje njihovih aktivnosti na fakultetu. Orofacijalni bol ima značajan uticaj na psihosocijalnu sferu, emocionalne i socijalne kontakte (12,3%; 14,1%). Najmanji uticaj na kvalitet života ima bol u temporomandibularnom zglobu i bolovi pri otvaranju usta ($p < 0,05$). **Zaključak.** Orofacijalni bol je patnja koja utiče na svakodnevne obaveze na fakultetu, kao i na emocionalni i socijalni život studenata.

Ključne reči: orofacijalni bol; kvalitet života; studenti; faktori rizika; temporomandibularni zglob; zubobolja; bol u predelu oka; ankete i upitnici; bol; pol

Introduction

Orofacial pain is a public health problem and therefore it is important to know its incidence and its impact on the quality of life and everyday activities. Pain in the face and mouth has a biological, emotional and psychological significance, because the orofacial region has a special role in daily life activities such as eating, drinking, speech, facial expressions and expressing emotions [1, 2].

One-quarter of adults in the United Kingdom [3] reported that they experienced pain in the orofacial region in the last 6 months, and in Germany the prevalence during one year was slightly lower, about 10% [4]. Studies conducted in Brazil [5], Indonesia [6] and Hong Kong [7] indicate that the number of patients exceeds 40%, and the respondents frequently reported toothache or tooth sensitivity. Toothache is one of the leading reasons for visiting a dentist, but there are a large number of orofacial pain conditions that require a special approach and treatment

Corresponding Author: Prof. dr Sonja Smiljić, Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici, 38220 Kosovska Mitrovica, Anri Dinana bb. E-mail: sonja.smiljic@med.pr.ac.rs

Abbreviations

OIDP – Oral Impacts on Daily Performance
CI – confidence interval
TND – temporomandibular disorder

[8, 9]. The prevalence of pain in the temporomandibular joint in respondents who experienced pain in the past month was about 5% [10, 11].

The main problem in the pain perception is that it is a subjective experience including many different, unique experiences that have different causes and are characterized by different features. The pain can interfere with many aspects of everyday life, including work, social and recreational activities, as well as sleep [12]. Also, problems with eating and drinking, the use of pain medications and sleep disorders are reported, so patients are often forced to seek help from a dentist or physician [13, 14]. The greatest impact is on the psychosocial aspect reflected through the concern for health in about 70% of the patients. From 4 to 8% of patients are absent from work, remain in bed or avoid socializing with friends or family [15]. The interviews with 32 persons with temporomandibular joint pain pointed to the long-term consequences on the quality of life, loss of job, personal possessions and social contacts. Half of the respondents indicated craniofacial pain that affects chewing, one-third indicated sleep disorders and depression, limited social functions and emotional contacts [11].

Guided by the instructions of the World Health Organization, the quality of life is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live. One of the most commonly used instruments for assessing quality of life is the Oral Impacts on Daily Performance (OIDP) questionnaire, a well-known psychometric test that evaluates the oral health-related quality of life, used internationally. The questionnaire assesses the degree to which oral health problems affect everyday activities of the respondents. The main task of the questionnaire is to collect data on the impact of oral problems associated with eating, speaking, cleaning teeth, sleeping, emotional state, laughter, learning, and social relations.

Starting from the fact that orofacial pain occurs more frequently in young people [3] and students [16], we have performed a research including second year students of higher education. The aim of the study was to determine the prevalence of orofacial pain in students and to what extent the pain was associated with the socio-demographic factors (gender, place of residence, relationship status, and mode of study). At the same time, we examined the impact of pain on the quality of life and everyday professional obligations of students and their need to seek professional medical help.

Material and Methods

A cross-sectional study included 319 respondents of both genders, second year students of the Faculty of Medicine (188) and the Faculty of Technical Sciences (133) of the University of Kosovska Mitrovica. This study was approved by the Ethics Committee of the University of Priština (No: 25.09.2015/2014).

All respondents were matched by age, 20 ± 1 years. The gender distribution in these two faculties was different. There were 71 males (38%) and 117 females (62%) among the students of the Faculty of Medicine, while among the students of the Faculty of Technical Sciences the ratio was different and there were only 30 female students (23%).

In this study we used two questionnaires; one that we have specifically created for the detection of orofacial pain among students, and the OIDP questionnaire, to assess the quality of life related to oral health, the Serbian version. The questionnaire on orofacial pain included questions about specific locations and characteristics of orofacial pain that the respondents experienced in the previous three months. Orofacial pain was considered to be present if the respondent answered positively to the question "Did you have any of the following problems in the previous three months":

a. pain in the jaw joint/joints
b. pain in front of the ear
c. pain when opening the mouth and chewing food
d. pain in or around the eyes
e. pain in the temples
f. shooting pain in the face or cheeks
g. tenderness of muscles at the side of the face
h. a prolonged burning sensation in the tongue or other parts of the mouth
i. toothache.

The students who responded positively, described the nature of pain related to the timing of the pain which occurred less or more than 3 months ago and the frequency of pain in the past three months, which facilitated classification of the orofacial pain into acute and chronic. The respondents also answered the question whether they needed to seek medical/dental help or to take pain therapy.

The impact of orofacial pain and oral health on the quality of life was assessed by the OIDP questionnaire which was completed by all respondents who indicated the pain in the past 3 months in any of the listed locations in the orofacial region. The main objective of the questionnaire was to collect data on the impact of orofacial pain and oral problems on eating, speaking, brushing teeth, sleeping, emotional state, laughter, studying, and social relations. In particular, we paid attention to the impact of pain on professional obligations and social life where the students assessed the impact of pain on everyday activities with the responses such as "I ignore the pain", "it does not affect my concentration and professional activities", "it makes it difficult to carry out my professional activities" and "it seriously disrupts all aspects of my life".

The descriptive statistics, including the numbers and percentages of categorical variables, or mean and standard deviation of numerical data, were used to characterize the study sample. Univariate association between orofacial pain and sociodemographic characteristics were evaluated using Pearson's chi-square test or Fisher's exact probability test.

Multivariate logistic regression models were used in order to determine predictors of orofacial pain as a dependent variable, with sociodemographic characteristics as independent variables. Statistical analysis was performed using Statistical Package for the Social Sciences for Windows, version 21. In all analyses, the significance level was set at 0.05.

Results

The total number of students was 319, of which 101 (32%) reported pain in the orofacial region in the previous 3 months. The study included students of two faculties: Faculty of Medicine and Faculty of Technical Sciences. All respondents were matched by age, 20 ± 1 years and they were all second-year students. During the last 3 months, 64 (34%) students of the Faculty of Medicine and 37 (28%) students of the Faculty of Technical Sciences reported orofacial pain. In both groups, orofacial pain had the same prevalence and the mode of studying was not a predictor of orofacial pain. Orofacial pain was significantly more frequent in female students. In logistic regression analysis, we found that gender was a significant predictor of pain, that is, females were at a 1.8 times higher risk of pain than males **(Table 1)**, which coincided with the majority of published papers [3, 15].

Among the socio-demographic characteristics we also examined the place of residence, since the study also included students who were not living at

Table 1. Multiple logistic regression analysis with pain as the dependent variable
Tabela 1. *Multipla logistička regresija sa bolom kao zavisnom varijablom*

	B	p	OR (95% CI)
Gender/*Pol*	0.61	0.022	1.83 (1.09 - 3.09)
Faculty/*Fakultet*	- 0.028	0.918	0.97 (0.57 - 1.67)
Place of residence/*Mesto stanovanja*	Reference	Category	
Parental home/*Kod roditelja*	- 0.11	0.713	0.89 (0.51 - 1.60)
Dormitory accommodation/*Studentski dom*	0.00	0.999	1.00 (0.55 - 1.81)
Rented apartment/*Iznajmljen stan*			
Emotional relationship/*Emotivna veza*	- 0.08	0.748	0.92 (0.56 - 1.50)

Legend/*Legenda:* B – coefficient/*koeficijent*; OR – odds ratio/*koeficijent verovatnoće*; CI – confidence interval/*interval pouzdanosti*

Table 2. Prevalence of specific pain locations
Tabela 2. *Učestalost specifičnih lokacija bola*

	n	Prevalence (%)	95% CI
Jaw joint/*Bol u viličnom zglobu*	12	4	2 – 6
Area just in front of the ear/s/*Predeo ispred uva*	14	4	2 – 7
When opening the mouth wide/*Tokom otvaranja usta*	13	4	2 – 6
Around the eye/*Oko oka*	20	6	4 – 9
Around the temples/*Predeo slepoočnica*	22	7	4 – 10
Shooting pains in the face or cheeks/*Bol u licu ili obrazima*	5	2	0–3
Tenderness of muscles at the side of the face/*Mišići jedne strane lica*	7	2	1 – 4
Burning sensation in the tongue or other parts of the mouth *Osećaj gorućeg jezika ili drugih delova usta*	0	0	
Toothache/*Zubobolja*	14	4	2 – 7
Other orofacial pain conditions/*Drugi oblici orofacijalnog bola*	101	32	27 - 37

Table 3. Orofacial pain characteristics
Tabela 3. *Karakteristike orofacijalnog bola*

	n (%)
Type of pain, n (%)/*Tip bola, br. (%)*	
Acute pain (< 3 month)/*Akutni bol (< 3 meseca)*	60 (59)
Chronic pain (> 3 month)/*Hronični bol (> 3 meseca)*	41 (41)
Medical care, n (%)/*Lekarski tretman, n (%)*	
No/*Ne*	62 (61)
Yes/*Da*	39 (39)
Pain therapy/*Terapija bola*	
No/*Ne*	39 (39)
Yes/*Da*	62 (61)

Table 4. Percentage distribution of Oral Impacts on Daily Performance items
Tabela 4. *Procentualna distribucija stavki Oralnih uticaja na dnevne performanse*

Items/*Uticaj bola*	n	%
Eating/*Uzimanje hrane*	10	15.4
Speaking/*Govor*	5	7.7
Cleaning teeth/*Pranje zuba*	9	13.8
Sleeping/relaxing/*Spavanje/odmor*	7	10.8
Smiling/*Smeh*	3	4.6
Emotional/*Emotivni život*	8	12.3
Studying/*Učenje*	21	32.3
Social contacts/*Druženje*	9	13.8

home during studying. We had three possible options for housing – the first option was living with their parents, the second was a dormitory accommodation, and the third was living in a rented apartment. The place of residence, that is, separation from family and moving to another city also did not affect the frequency of orofacial pain. Having an emotional relationship was not significant for the frequency of orofacial pain either. Students with a permanent partner reported having orofacial pain just as often as those who were single.

The highest prevalence of pain among students was in the temporal area (7%; confidence interval (CI) 4%, 10%) and the area in and around the eye (6%, CI 4%, 9%). Other painful conditions, temporomandibular joint pain and toothache had the same prevalence (4%; CI 2%, 6%). None of the students mentioned a burning sensation in the tongue in the previous 3 months **(Table 2)**.

In addition to the location, description of the orofacial pain characteristics included information on when the pain first appeared, whether it occurred more or less than 3 months ago. The pain which occurred more than 3 months ago and had a greater frequency of occurrence may be considered a chronic pain. In 59% of the respondents, pain in the orofacial region first appeared less than 3 months ago, and it was described as an acute pain, while 41 respondents indicated that they suffered from orofacial pain for a long period of time, describing it as a persistent, chronic pain.

It is interesting that the majority of students (61%), whether studying Medicine or Technical Sciences, took pain medications on their own initiative and without consulting a physician. All students of the University of Priština are provided with good health care and a simple access to a physician or dentist in a specialized institution that deals with the students' health. Nevertheless, only 39% of the respondents sought professional help from a physician or a dentist because of orofacial pain **(Table 3)**.

The data analysis showed that a great number of respondents indicated the impact of pain and oral health problems on their everyday activities and responsibilities. The prevalence of the impact of orofacial pain, measured by the OIDP index, was very high. Namely, 65 (64.4%) of students who had a pain in the orofacial region in the past 3 months reported that pain affected their quality of life and everyday activities. The most prominent was the impact of the orofacial pain conditions on the performance of their duties at the faculty [6, 24]. At the same time, the orofacial pain conditions showed a significant impact on the psychosocial sphere, emotional and social contacts (12.3%; 14.1%) **(Table 4)**.

The temporomandibular joint pain and the pain when opening the mouth had the lowest impact on the quality of life. This pain was ignored by a significant number of students ($p < 0.05$). The numbness of the muscles on one side of the face did not significantly affect concentration and professional activities. The pain in the temples, in the area around the eyes, and toothache caused the most difficulties in performing professional activities with a serious impact on all aspects of life ($p < 0.05$).

Discussion

Pain in the orofacial region is a health problem with repercussions on the general state of health and the quality of life. Most studies report that about a quarter of the population has orofacial pain at least once in six months or even more often [3, 4, 7]. The prevalence and the characteristics of pain are determined by demographic, economic and psychosocial factors (current stress level, sensitivity, mood, fear, psycho-physical, and mental state).

In order to determine the prevalence of orofacial pain in students, the importance of socio-demographic impact on the prevalence and the impact on the quality of life and everyday activities, our study included students of the Faculty of Medicine and the Faculty of Technical Sciences. These students were matched by the year of study and therefore, for the purpose of the study, the second year students were selected. Thereby, another condition was fulfilled at the same time - we got a uniform group, with a mean age 20 ± 1 years. A significant difference between the two groups was gender distribution. At the Faculty of Medicine, the second year was attended by more female students, as compared to the Faculty of Technical Sciences, where there were more male students ($p < 0.05$).

The students filled out a questionnaire and they were supposed to answer whether they had pain in the orofacial region in the last 3 months. Out of the total number of respondents (319), 101 respondents had orofacial pain. Thirty-four percent of students of Medicine reported pain, while the percentage of students of Technical Sciences was 28%. Orofacial pain is more common in young population and has the lowest prevalence in persons older than 60 years [3, 18, 19]. It is a bell-shaped age distribution showing an increase in the number of patients with age and invariability of the number after the middle age. Regarding the prevalence of orofacial pain and the professions, the risk groups are students, housewives and persons with occasional employment [20].

After enrolling in the Faculty of Medicine or Technical Sciences, a certain number of students remain at home, without changing the place of residence and life habits. Some students move to a new environment to study and during that time live in the campus in dormitories or rent an apartment. Socioeconomic status of students from both faculties was matched and therefore the economic status cannot be observed as a factor in the occurrence of orofacial pain. At the same time, separation from family, moving to a new environment and different obligations did not affect the prevalence of orofacial pain and there is no significant difference in relation to place of residence. Other studies have shown that lower socioeconomic status causes greater prevalence of orofacial pain [21].

Pain in the face and mouth has a special biological, emotional and psychological significance because the orofacial region has a special role in everyday life activities such as eating, drinking, talking, facial expressions, and expressing emotions. The status of emotional relationship may have an impact on the prevalence of orofacial pain, however, the data we obtained show that emotional relationships did not significantly affect the prevalence of pain, which differs from other studies [22]. Among the students of both faculties, orofacial pain was significantly more frequent in female students and it was reported by 56% ($p < 0.05$).

Regardless of the mode of study, among young adults beginning their studies, orofacial pain is more common in female students. Higher prevalence of pain in women may be due to a higher biological sensitivity to stimuli because women can detect signals that men might not notice. At a cognitive level, the threshold for classifying stimuli as painful may be lower in women than in men. Another factor is the social difference in the upbringing of boys and girls, which makes it more acceptable for women to talk about their pain experiences [4]. It is possible that these factors, biological, psychological and social act in synergy. The correlation of gender with pain and analgesia has become a topic of great scientific and clinical importance in the last 15 years. Numerous data from epidemiological studies clearly show that women are at higher risk for a number of painful conditions, hence it is considered that postoperative and procedural pain can be more severe in women than in men. In women, there is a higher sensitivity to pain for most painful modalities, which was confirmed by the laboratory measurements on the impact of gender on pain modulation. Responses to pharmacological and non-pharmacological agents for pain treatment also differ by gender. There are significant differences both in the sense of pain and in the therapeutic approach in the pain treatment between men and women. This may have a clinical significance in the pain therapy [23, 24].

The most frequently reported pain was in the temple area (22%) and in the eye area (20%), which they additionally described in the questionnaire as a headache. Pain in the temples is more frequent in female students of Medicine (24%). The data are compatible with the research in England [3], although the research in Australia [25] shows a lower number, as well as in Indonesia, where the highest number of patients complained of toothache [6]. Temporomandibular disorders (TMDs) represent a separate entity within the orofacial pain. The majority of TMD data were obtained after the Orofacial Pain: Prospective Evaluation and Risk Assessment study which included over 3000 respondents. Pain in the temporomandibular joint, when opening the mouth or chewing, is equally common in students of both faculties. There is no significant difference in the occurrence of pain in TMD in the male and female students. However, other studies claim that female gender is the risk factor for the pain in the jaw joint [11, 24].

The published cross-sectional studies have indicated that a pain in the temporomandibular joint in women is twice more common than in men. The research on socio-demographic characteristics of TMDs and pain in the temporomandibular joint indicates that pain is more common in women and younger population [12]. The minimum number of our respondents reported a shooting pain in the face (5%), while none of them reported symptoms of burning sensation in the tongue syndrome. Researches that included more age groups and respondents older than 50 years indicate that the burning sensation of tongue syndrome has a higher prevalence and is accompanied by serious quality of life disorders [26].

Of the total number of respondents, 14 students (4%; 95% CI 2%, 7%) have reported toothache. The data we obtained are not in line with the data of other studies [5, 6, 27], Most studies report that the dental pain is the most common type of orofacial pain [5, 19, 21, 28]. Toothache is the major reason to seek urgent help from a dentist. Studies which investigated urgent dental visits because of orofacial pain or toothache indicated that rural population seeks help more often than the urban population [27]. This is most likely because the urban population has a habit of regular control visits and thus they are rarely exposed to acute dental pain. Low prevalence of toothache in students is likely the result of effective prevention of dental diseases and high health education of students. By comparing the oral health of students in Japan and Taiwan, it was concluded that it is worse in students from Taiwan, and the reasons are infrequent visits to the dentist and different policies of public health care in the prevention strategy in the early stages of the life of children [29].

Pain in the orofacial region first appeared more than 3 months ago in 41% of the respondents, or about 39% of students of Medicine and 43% of Technical Sciences students. The respondents described pain as having more episodes of pain and appeared more frequently in the previous period, which, according to the quality, classifies it as a chronic pain. Studies with larger numbers of respondents of different age groups report that approximately 26% of the respondents have orofacial pain which occurred more than 3 months ago [3].

Thirty nine percent of the respondents sought help from a physician or a dentist. However, pain medication was taken by 61% of students, either with the professional advice or on their own initiative. That is a higher number of those who sought medical advice than it is reported in the studies conducted in other areas [9, 24]. Younger people (18 – 24 years) seek medical help significantly less than the other age groups [3]. The number of those who seek professional help varies and depends on the type of orofacial pain [29, 30]. Persons with chronic orofacial pain seek help from the physician more frequently [31].

The assessment of the impact of orofacial pain on everyday activities and professional obligations of students was made by the OIDP questionnaire. According to our respondents, orofacial pain had the greatest impact on their duties at the faculty and social contacts. Also, other studies showed that orofacial pain and oral diseases have an impact on academic performance [32–34]. Discomfort during meals and food intake was significant in our respondents. The studies with elderly respondents emphasized the difficulties during eating [33–35]. Also, the middle aged respondents suffering from dental caries reported problems during eating [36].

The questionnaire has a certain degree of subjectivity; the questions in the questionnaire related to the dental treatment or a visit to the physician due to orofacial pain had insufficient individual information and we could not be sure if the students visited a physician/dentist due to urgency during the same day or at a later time.

Conclusion

Orofacial pain conditions represent an important and extensive group of diseases with different prevalence and with various adverse impacts on the quality of life in the majority of patients. The examined socio-demographic factors, method of study, place of residence or the students' emotional status had no significant impact on the occurrence of orofacial pain. The prevalence of pain was significantly higher among the female students. The most common location of orofacial pain was in the temporal region and the area around the eye. Other forms of pain (like toothache) that can be prevented with regular dental visits had lower prevalence and occurred in a smaller number of students.

There were no significant differences in the distribution of acute and chronic pain in the examined group of students. A higher number of students reported that their pain disrupted the quality of life and affected everyday activities. The most negative impact was on the performance of daily duties at the faculty and social life. Pain in the temples, in the area around the eye and toothache had the greatest impact on the quality of life.

The data of our study related to the prevalence and characteristics of the orofacial pain in students are very important. Orofacial pain affects daily duties at the faculty, as well as the students' emotional and social lives. Therefore, a proper approach to diagnosis and treatment of orofacial pain conditions and appropriate health strategy for the prevention of orofacial pain is essential.

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CONTACT SENSITIZATION AND ALLERGENS IN THE COMPOSITION OF COSMETIC PRODUCTS – CURRENT KNOWLEDGE

KONTAKTNA SENZIBILIZACIJA I ALERGENI U SASTAVU KOZMETIČKIH PROIZVODA − POSTOJEĆA SAZNANJA

Marina JOVANOVIĆ

Summary

Contact sensitivity is a latent state that lasts a lifetime with a clinically manifesting response in the form of allergic contact dermatitis that often has an unfavorable prognosis. In contact urticaria syndrome, can cause anaphylactic reactions. Exposure to irritants or sensitizing factors represents a major risk. Age and gender are not risk factors for contact sensitivity in themselves. A recent meta-analysis has shown that the prevalence of contact sensitivity in the general population is 20.1% and that 4 allergens from cosmetic products are among the top 6 allergens that cause contact sensitivity in the general population. **Cosmetics products** are responsible for more than half of all allergic contact dermatitis which mainly affects adults of middle and older age, who generally do not have atopy and whose occupations have low academic requirements. It is possible for a cosmetic allergy to develop even after years of using a cosmetic product without previous problems. **Beauty products to watch for.** Just because a label says that something is "dermatologist tested", that is no guarantee that the product will be kind to your skin. There are no rules about these terms and criteria how to use them on a label. **Ingredients that may cause allergy.** Preservatives and fragrances are the most frequently detected allergens in those with an allergy to a cosmetic product. **The future of allergen labeling.** Allergens identified by the Scientific Committee on Consumer Safety need to be present on a label. Every cosmetic product placed on the European Union market must have a compliant product information and an International Fragrance Association certificate if contains fragrances. **Conclusion.** Because so-called "hypoallergenic" products are not necessarily less sensitizing, allergy departments should distribute lists of cosmetic products not containing the respective allergen(s) that consumers can use as safe alternatives.

Key words: Cosmetics; Dermatitis, Contact; Allergens; Risk Factors; Preservatives, Pharmaceutical; Odorants; Consumer Product Safety; Health Knowledge, Attitudes, Practice

Sažetak

Kontaktna senzibilizacija predstavlja latentno stanje koje traje doživotno. Najčešće se manifestuje u vidu alergijskog kontaktnog dermatitisa, koji neretko ima nepovoljnu prognozu. Ukoliko se manifestuje sindromom kontaktne urtikarije, može izazvati anafilaksiju. Izloženost iritansima i/ili alergenima predstavlja veliki rizik. Starost i pol, sami po sebi, nisu faktori rizika. Nedavna metaanaliza je pokazala da prevalencija kontaktne senzibilizacije u opštoj populaciji iznosi 20,1% i da se četiri alergena u sastavu kozmetičkih proizvoda nalaze na listi prvih šest alergena, najčešćih izazivača. **Kozmetički proizvodi** su odgovorni za više od polovine svih slučajeva alergijskog kontaktnog dermatitisa, koji najčešće tada pogađa osobe srednjeg i starijeg životnog doba, koje uglavnom nemaju atopiju i čija zanimanja imaju niske akademske zahteve. Moguće je da se razvije i nakon prethodne višegodišnje bezbedne upotrebe kozmetičkog proizvoda. **Kozmetički proizvodi na koje treba obratiti pažnju**. Samo zato što na etiketi proizvoda piše da je nešto „dermatološki testirano", to nije garancija da je bezbedno za primenu na svačijoj koži. Ne postoje regulativna pravila kako i kada ovaj termin staviti na etiketu. **Sastojci koji mogu izazvati alergiju.** Konzervansi i mirisi su najčešće dokazane klase alergena kod osoba koje su razvile preosetljivost na kozmetičke proizvode. **Budućnost označavanja alergena.** Sve supstancije koje je Naučni komitet za bezbednost potrošača u Evropskoj uniji označio kao alergene, moraju biti prisutni na etiketi. Svaki kozmetički proizvod koji se plasira na tržište Evropske unije mora imati dostupnu datoteku a u slučaju da sadrži mirise, neophodan je i sertifikat Međunarodnog udruženja za mirise koji potvrđuje da je proizvod bezbedan za upotrebu. **Zaključak.** Pošto takozvani „hipoalergogeni" proizvodi nisu za sve osobe jednako bezbedni, odeljenja koja se bave dijagnostikom kontaktne senzibilizacije treba da distribuiraju liste onih kozmetičkih proizvoda koji ne sadrže odgovarajući alergen(e), tako da preosetljive osobe mogu da ih koriste kao bezbedne alternative.

Ključne reči: kozmetologija; kontaktni dermatitis; alergeni; faktori rizika; farmaceutski konzervansi; mirisi; bezbednost konzumerskih proizvoda; znanje o zdravlju, stavovi, praksa

Corresponding Author: Prof. dr Marina Jovanović, Poliklinika Nada Diva, 21000 Novi Sad, Vase Stajića 25, E-mail: prof.drMarina@gmail.com

Abbreviations

CS – contact sensitivity
LC – Langerhans cells
DC – dendritic cells
ACD – allergic contact dermatitis
PT – patch test
IgE – immunoglobulin E
FM – fragrance mix
PB – Peru balsam
MCI/MI – methylchloroisothiazolinone/methylisothiazolinone
PPD – para-phenylenediamine
EU – European Union
PIF – product information file
IVDK – Information Network of Departments of Dermatology
FRP – formaldehyde releasing preservative
NFRP – non-formaldehyde-releasing preservative
MDBGN – methyldibromoglutaronitrile
SCCS – Scientific Committee on Consumer Safety
CR – clinical relevance

Contact sensitivity

Contact sensitivity (CS) is a latent state of specifically altered reactivity of the immune system that lasts a lifetime, caused by contact of the skin or visible mucous membranes with substances from the external environment, the so-called contact allergens. In most cases, CS is of the eczema type, and represents a late-cellular immune response in the skin. After the first contact with the antigen, in its first, induction phase, CS results in the formation of specifically preformed effector T-lymphocytes. After 10 refractory days on average, in the second elimination phase of CS, during the first reexposure, these cells recognize the allergen and within 48 hours respond with a specific immune inflammatory response. In both phases, epidermal dendritic Langerhans cells (LC) and dermal dendritic cells (DC) play a key role in antigen processing and presentation, by interaction with neighboring keratinocytes, migration to the local draining lymph nodes, and by priming of naive T-cells. During the process of migration, pinocytosis and the so-called internalization, DC translates the antigen protein into a peptide chain and binds it within itself to the molecules of the major histiocompatibility class II molecules. The antigen in the complex thus formed is ready to bind to the receptors on the T-lymphocyte in the lymph node by stimulatory and costimulatory connections. These connections exist through inflammatory cytokines, chemokines and adhesion molecules. Antigen specific effector T-cells migrate into the skin upon contact with the same hapten, during reexposure (elicitation phase), primarily at the site of contact with the antigen. After activation by antigen-presenting skin cells, including LCs, DCs, keratinocytes, and macrophages, in the Th-1 cytokine milieu, they reach an inflammatory, clinically manifesting response in the form of allergic contact dermatitis (ACD) [1]. The ACD significantly reduces the quality of life of the affected persons, particularly in situations where exposure to an allergen is on daily basis and patients can hardly avoid it. For this reason, ACD often has an unfavorable prognosis and a high tendency of recurrence and chronicity. In each case of recurrent dermatitis, ACD should be included in the differential diagnosis [2]. The existence of CS is diagnosed by a positive epicutaneous patch test (PT), and in order to diagnose ACD, in addition to a positive PT, medical history data on exposure to the incriminated allergen is required. Epicutaneous testing is a standardized procedure and if performed technically correctly, a positive PT has medico-legal significance [3]. Contact allergens are chemically reactive substances of low molecular weight (≤ 1000 daltons (Da)) and as haptens react with larger protein biomolecules in the skin to form immunogenic complexes. The ability of haptens to bind to proteins is the main predictor of its allergenic potential, while differences in the location and mode of protein binding are predictors of the type of allergic response, early or late [4]. In rare cases CS can result in the production of specific immunoglobulin E (IgE), whereas in contact urticaria syndrome it can cause signs and symptoms of severe anaphylaxis. The role of genetic predisposition for CS refers to the existence of polymorphisms for genes that encode the synthesis of enzymes necessary for metabolic transformation in the skin of contactors, the so-called prehaptens into haptens. The number of these allergens is small [5, 6].

Surveillance of contact sensitivity

Clinical data, based on patient consultation and PT results, one can never directly interpret as estimates of disease incidence at the general population level. However, since relative changes we interpret, given that the selection process into the "clinical sample" is stable, surveillance of CS trends is validly possible. Thus, clinical surveillance provided the first data on the newly emerging methylisothiazolinone-induced epidemic of ACD and then on the reduction in disease incidence after preventive measures [7]. In this sense, population and clinical epidemiology complement each other [8, 9]. In order to examine e.g. the trend of CS by comparing the prevalence of sensitization over time, with the variable age and sex distribution of the tested patients and in combination with a negligible age gradient of sensitization risk, we should apply separate analyses for age and sex groups, e.g. population-adjusted frequency of sensitization (PAFS) method [10]. At the same time, the MOAHLFA index (M - male; O - occupational; A - atopic dermatitis present or past; H - hand; L - leg; F - face; A - age of 40 years and above), indicates the presence of demographic characteristics in the examined population that can significantly affect the incidence of CS. By including these variables in a multifactorial analysis, it provides comparison of the results obtained from different sources and in different periods. The first, and according to the available literature, the only tests of CS and ACD in Serbia, in which these principles are used, came from our institution from Department of Allergy and Clinical Immunology at the Clinic of Dermatovenerology Diseases in Novi Sad [11–14]. It is difficult to interpret the distribution of occupations, age or gender, in a patient population without knowing the distribution of these characteristics in general population. The world scien-

tific literature, considering the results of multicenter studies on ACD and CS, originates from Information Network of Departments of Dermatology (IVDK) (https://ivdk.org), which is the most relevant for studying clinical epidemiology and its comparison with the results of population epidemiological studies. The IVDK represents a unique information database which gathers results from all dermatological centers in Germany and applies the principles of good epidemiological practice [2, 10, 15, 16]. However, the incidence of CS and ACD in the general population can be determined in cross-sectional studies conducted in recent years. The data indicate that female gender, young age, and ear piercing (before 1990), are the main risk factors for the development of CS to nickel, while the relative risk for the development of CS to fragrances that are the most important allergens in cosmetics, more than doubles in older groups, compared to younger ones. Fragrance allergy is the second most frequent cause of CS after nickel and it affects every 10th patient examined for CS [5]. Age-dependent immune reactivity seems to be less significant than differences in the degree and type of complexity that exist between age groups and between the sexes [17]. The prevalence studies strongly suggest that age and gender are not risk factors for CS in themselves, but that these characteristics are associated with exposure to occupational and everyday activities [2]. Exposure to irritants or sensitizing factors represents a major risk for the development of irritant CD (ICD) and ACD.

The CD is a common cause of morbidity with a lifetime prevalence of 15% and an incidence greater than 7.9 per 1,000 inhabitants [18]. A meta-analysis of relevant population epidemiological studies [19] has shown that the combined prevalence of CS in the general population is 20.1%, in children and adolescents (under 18 years) 16.5% and that it is significantly higher in females (27.9%) than in males (13.2%). The most common incriminated allergens were nickel (11.4%), fragrance mix (FM) (3.5%), cobalt (2.7%), Peru balsam (PB) (1.8%), chromium (1.8%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (1.5%) and para-phenylenediamine (PPD) (1.5%) [19]. It has also shown that 4 allergens from the composition of cosmetic products (FM, PB, MCI/MC, and PPD) are among the first 6 allergens that cause CS in the general population [18–20].

Cosmetic products

There is an increasing use of cosmetic products in the general population, since there are over 8,000 registered substances, available for incorporation into cosmetic products [21]. Through the relevant legislation, several countries and regions of Europe have adopted Article 2 of the European Union (EU) Cosmetics Regulation (No. 1223/2009). The Article 2 defines a cosmetic product as follows: "any substance or mixture intended to come into contact with various external parts of the human body (e.g. epidermis, hair system, nails, lips and external genitalia) or with the teeth and mucous membranes of the oral cavity, with the aim of exclusively or mainly cleaning them, making them fragrant, changing their appearance and/or correcting body odors" [22]. Similarly, the United States Federal Food, Drug and Cosmetics Act defines cosmetic products as: "articles that are rubbed, poured, sprinkled, or sprayed, or otherwise applied to the human body to clean, beautify, promote attractiveness, or change in appearance" [23].

Explanation of research needs

Cosmetic products are among the most important products on the world market and their growth and diversification has become unstoppable [24, 25]. There is little data on the actual incidence of adverse reactions to cosmetics. The prevalence of 12% in the general population, reached 47% in patients referred for allergy testing. The ACD is of particular interest because of the severity of symptoms it produces, the need to identify the allergen and the risk of cross-reactions. Traditionally, ACD to cosmetic products and their ingredients in patients referred for epicutaneous testing was 2 – 4%, but recent studies indicate a progressive increase and a prevalence of 19 – 25% [24, 25]. About 16% of patients with eczema in Europe have sensitivity to odor components [26]. It is estimated that women on average use at least 9 – 15 cosmetic products every day, which contain 168 unique ingredients, while an average man uses 6 products every day for personal care with 85 unique ingredients [18]. Recent studies have shown that up to 10% of the population has some kind of reaction to cosmetics during their lifetime [27]. Today, cosmetic products are responsible for more than half of all cases of ACD. Female sex represents a risk factor. The ACD to cosmetics mainly affects adults of middle and older age (≥ 40 years), who generally do not have atopy and whose occupations have low academic requirements. Preservatives, fragrances and PPD are responsible for up to 80% of all CS to cosmetics, and this trend has remained stable over the last few decades [24–27]. The results of population epidemiological studies have shown the prevalence of CS to cosmetic products and their ingredients to be 1 – 3%. The prevalence of CS to fragrant ingredients is 1% and to all other substances 2 – 3% [18]. Recent clinical epidemiological studies showed that the ingredients of cosmetic products are responsible for 25 – 50% of all cases of ACD. Interestingly, the prevalence of CS caused by cosmetic products has become higher compared to topical pharmaceutical products, even though they are applied to diseased skin [24, 25]. A significant correlation exists between cosmetic ACD and female gender, but not atopy.

A review of the prevailing attitudes and understandings in the literature

In the United Kingdom, 51.4% of women and 38.2% of men believe they have sensitive skin. The Pons-Guiraud classification includes several entities, with a global prevalence of 38.4% of sensitive skin in the population. "Very sensitive" skin is reactive to a wide variety of endogenous and/or exogenous factors with both acute and chronic symptoms and a strong psychological component. "Environmentally sensitive" skin is clear, dry and thin skin with a tendency to blush or flush

and it is reactive to primarily environmental factors. "Cosmetically sensitive" skin is transiently reactive to specific and definable cosmetic products [18]. Muizzuddin classification includes "delicate" skin characterized by easily disrupted barrier function not accompanied by a rapid or intense inflammatory response and "reactive" skin with a strong inflammatory response without a significant increase in permeability, while "stingers" skin has heightened neurosensory perception to minor cutaneous stimulation [18]. There is a subset of patients with a condition referred to as "status cosmetics", since every cosmetic product or soap applied to the face produces itching, burning, or stinging sensation. These patients appear to have normal looking skin or a very faint erythema. They may end up having to avoid any facial cosmetics for 6 – 12 months and then slowly reintroduce some emollients [18]. The PT and repeat open application or use tests are in these cases mostly negative, although they can become positive after prolonged use due to irritancy or low-grade sensitization. It is possible for a cosmetic allergy to develop even after years of using a cosmetic product without previous problems [20].

Beauty products to watch for

The beauty products most likely to cause skin reactions are bath soaps, detergents, antiperspirants, eye makeup, moisturizers, shampoos, long-wearing lip stains, nail polish (especially those that have formaldehyde), fingernail glue with methacrylate, as well as hair products containing p-phenylenediamine or ammonium persulfate used to lighten hair. Just because a label says something is "hypoallergenic", "dermatologist tested", "sensitivity tested", or "non-irritating" that is no guarantee that the products will be kind to your skin. Some companies do the testing, others do not. There are no rules about these terms and criteria how to use them on a label [28].

Ingredients that may cause allergy

There are several categories of cosmetic ingredients: fragrances, preservatives (including antimicrobials and antioxidants), ultraviolet absorbers, excipients (vehicles), emollients, surfactants (including detergents and emulsifiers), hair styling products and dyes, nail products, and acrylates. Preservatives and fragrances are the most frequently detected classes of allergens in those with an allergy to a cosmetic product. Other important allergens include hair color p-phenylenediamine, nail polish resin (tosylamide formaldehyde resin), ultraviolet filters, and lanolin. The mixture of preservatives MCI and MI, FM and PPD are the most common causes of ACD, while acrylates are new allergens. In our Allergy Department at the Clinic of Demarovenerology Diseases in Novi Sad, we came to almost the same results after inclusion of the standard cosmetic series of contact allergens (preliminary results).

Fragrance represents a category rather than an individual ingredient. There are more than 5,000 different fragrances used in cosmetics and skincare products [20]. Patients may develop reactions to the whole host of products, which contain fragrance as a constituent. Thus, a new fragrance-related allergen C12–15 alkyl benzoate, present in sunscreen products, skincare creams, anti-aging and depigmentation products, deodorants as well as cleansing products causing ACD, appeared in the literature. It is unclear whether the reactions to benzyl benzoate and salicylate represent cross-reactivity with alkyl benzoate or concomitant reactivity [18]. Product labeling can be incomplete or misleading, thus many essential oils are not labeled as fragrances. The EU Cosmetic Directive states that cosmetics sold in Europe containing the 26 specific fragrance ingredients known to cause ACD, must be declared on the ingredient lists of cosmetic products, if present at more than 10 ppm in leave-on products or more than 100 ppm in rinse-off products. The Cosmetic Directive also states that if a product contains other fragrances, this must also appear on the label as aroma, fragrance, or perfume (with individual e-labeling rather than labeling on the package) [18].

Preservatives are the second most common cosmetic contact allergens and belong to various groups such as antimicrobials that include formaldehyde, formaldehyde releasing preservatives (FRPs), non-formaldehyde-releasing preservatives (NFRPs) and antioxidants. The latter include phenolic antioxidants, vitamins E, K, B5 and gallates. Phenolic antioxidants (e.g. butylated hydroxyanisole) that are ubiquitous food additives also present in foods containing fats or oils, as well as in cosmetics particularly in lipsticks and hair dyes, cause contact allergy. The EU Cosmetic Directive banned vitamin K in cosmetic products in the EU in 2009, although the still permitted oxidized form (phytonadione epoxide) can cause allergy when applied to treat bruising after laser therapy or in make-up for dark circles around the eyes. Gallates, esters of gallic acid (dodecyl, octyl, propyl), are antioxidant chemicals that are commonly used as preservatives in food products and cosmetics, but also in antibiotic creams, lipsticks, moisturizes, topical steroids, and eye cosmetics [18].

In the EU, the maximum formaldehyde concentration is limited to 0.2% (0.1% in oral hygiene products) whereas in the United States there are no specific regulations. Individuals allergic to formaldehyde may also react to products containing any of the FRPs. Between 30% and 50% of the cosmetic products released formaldehyde despite lacking a declaration of formaldehyde or formaldehyde releasers in the list of ingredients [18].

The NFRPs are also an important cause of contact allergy, including parabens, isothiazolinone (in cosmetics specifically MCI and MI)), methyldibromoglutaronitrile (MDBGN) and sodium metabisulphite among others. The EU Cosmetic Directive banned MDBGN in cosmetics since it first appeared in the mid-1980s. However, MDBGN is still present on the market, recently causing relevant contact allergy reported in the literature [18].

Methylisothiazolinone (MI) is a biocide used in cosmetics (e.g. hair care and personal hygiene products and facial cleansers, industrial and household products), either alone or in combination with MCI. In 2005, the

EU Cosmetic Directive banned MCI and approved MI use only as a stand-alone preservative in cosmetic products at a maximum concentration of 100 ppm, that is, considerably higher than the concentration allowed when it is in mixture with MCI (max. 15 ppm). This resulted in an epidemic of contact allergy. Initially, most cases were due to the use of wet wipes (moist toilet paper) for intimate hygiene (also for babies, causing hand dermatitis in their parents) but, later on, facial skin-care products, body lotions, deodorants, and even rinse-off products, such as shampoos and liquid soaps turned out to be important sensitization sources. Later on, there was a decline of contact allergy since its removal from leave-on cosmetic products in the EU in February 2017 and limitation to 15 ppm in rinse-off products [18]. However, it has not completely gone. The explanation lies in the fact that rinse-off products that contain MI/MCI concentrations of 15 ppm and leave-on products with concentrations of 7.5 ppm are unlikely to result in allergic contact dermatitis. Even in patients who are sensitive to MI/MCI, rinse-off products that contain MI/MCI concentrations of 15 ppm are unlikely to cause a reaction. The maximum concentration allowed in Europe was set to 15 ppm in both rinse-off and leave-on cosmetics (in the United States, the concentrations allowed are 15 ppm in rinse-off products and 7.5 ppm in leave-on cosmetics). Despite this change in legislation, there is an increase in the prevalence of sensitization to this preservative. The increased use of MI without MCI as a preservative has led to greater sensitization to MI and because of cross-reactivity, to an increase in positive reactions to MCI/MI. It remains an important allergen to look out for, especially in shampoos/conditioners, lotions and creams, wet wipes, and skin cleansers [18]. The MI is sometimes responsible for severe skin lesions and atypical clinical symptoms, leading to a delay in the correct diagnosis since respiratory problems may occur as well. Patients with suspected reactions to MI/MC, must avoid this potential allergen. If sensitization to isothiazolinones is suspected, both the MCI/MI mixture and MI alone should be included in the patch test, because if only MCI/MI is included, approximately 40% of allergies to MI will not be diagnosed. This is because the concentration of MI in the MI/MCI patch (25 ppm) is much lower than in the patch with the preservative by itself (75 ppm). Our preliminary results at the Clinic of Demarovenerology Diseases in Novi Sad have shown MDBGN, MI and MI/MCI as the top three preservatives causing positive PTs in cosmetic series® (Chemotechnique Diagnostics, Vellinge, Sweden). Although the cosmetic industry advised its members to phase out the use of MI from leave-on products, there are still such products on the market and European authorities have urgency to bring up appropriate regulations [24]. It is also worth mentioning Triclosan used as an antiseptic in cosmetics, known to have low sensitizing potential but causes contact allergy in soaps [18].

A new generation of *UV filters* has appeared, thus octocrylene (a cinnamate) replaced para-aminobenzoic acid and became the most common cause of photocontact allergies [25]. Propylene glycol as a *vehicle (exipient)* of choice, despite being cause of allergy or irritation, tends to be favored over glycerin, which is a rare sensitizer and does not irritate the skin. Moreover, propylene glycol is also cheaper, more lipid-soluble, and is widely used vehicle for topical therapeutics and cosmetics including deodorants. The amount may be as high as 70% [18].

Although emollients rarely cause allergy, the prevalence of lanolin contact allergy has increased over a 12-year period. This raises the question of which lanolin products (e.g., acetylated lanolin, hydrogenated lanolin, or ointments such as eucerin), may also be patch test preparations. Inclusion of Amerchol™ L-101, which is a mixture of 10% lanolin alcohols and mineral oil, will increase the chance of detecting lanolin contact allergy.

Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. Emulsifiers rarely cause positive PTs, probably due to lack of commercial allergens and difficulties in finding these molecules. Since the 1990s, glucosides are present in both rinse-off products, but also in certain baby products such as wipes and cleansers. Although alkyl glucosides have low irritancy and sensitizing potency, recent studies showed that the prevalence of alkyl glucoside-induced ACD is relatively high. There are frequent concomitant reactions between different alkyl glucosides necessitating its inclusion in patch test cosmetic series. Octoxyglycerin, another widely used ingredient that also has antimicrobial properties (hence its use in preservative-free cosmetics), has been reported recently concerning its presence in sunscreens [24].

Regarding *hair styling products and dyes,* glyceryl monothioglycolate persists on permed hair for months and therefore re-exposes particularly the hairdresser to the allergen. It can penetrate rubber gloves. The older perms contain thioglycolic acid combined with ammonia and rarely cause contact allergy. Various follow-up chemicals for hair care often involve application of oils and moisturizers, which may contain fragrance, preservatives, and propylene glycol.

Regarding *nail products* and *acrylates*, tosylamide formaldehyde resin has been historically responsible for almost all the allergic reactions, accounting for around 10% of reactions and stands only behind preservatives, fragrances, and emulsifiers.

The ACD caused by *nail acrylates* has become an increasing concern nearly rising to epidemic proportions [28]. Today, the main techniques are based either on acrylates that need UV curing (sculptured gel nails and long-lasting acrylate-based nail varnish), or on cyanoacrylate (glued nail tips or dipping nails). The main agents responsible for ACD caused by these products are in particular, 3-metacrylates, ethylene glycol dimethacrylate, 2-hydroxyethyl methacrylate, and 2-hydroxypropyl methacrylate.

Natural substances, such as plant extracts, have become very popular, many of which have induced CD such as glycyrrhetinic acid and castor oil, propolis, which cross-reacts with bisabolol, and Myroxylon pereirae in Compositae plants [29, 30]. Sometimes they are present because of other properties than being fragrances, and as such even in "non-scented" products.

Besides delayed-type reactions, plant extracts and hydrolyzed proteins can also cause IgE-mediated anaphylactic reactions, such as oatmeal extract and hydrolyzed wheat proteins. High molecular weight wheat hydrolysates are more allergenic than the lower ones. Subjects may become sensitized through topical agents and subsequently, develop food allergies [24].

Cosmetics regulations

Many countries around the world have regulatory standards that ensure cosmetic products to be safe for the workers handling them, the environment, and for consumers. Thus, the United States have the Federal Food, Drug and Cosmetic Act, while Europe has the Cosmetics Directive at the European Commission for Consumer Affairs. In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency, the European Centre for Disease prevention and Control, and the European Chemicals Agency. However, despite being subject to strict legislation (Directive 2003/15/EC of the European Parliament and Council of 27 February 2003, amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products - Off J Euro Union, 2003; L66:26-35), cosmetics are not free from adverse reactions [25]. All cosmetic products in the EU must comply with European Commission Regulation No. 1223/2009. Paragraph 49 of the Regulation restricts the use of any potential cosmetic allergens identified by the Scientific Committee on Consumer Safety (SCCS) [26]. They must be present on the product label. The Regulation also proposes a ban or restriction on concentrations and substances that are likely to cause allergies in a large number of people [26].

The declaration of all ingredients in cosmetic products has been mandatory for more than 35 years in the United States. However, only since 1997 the declaration of all ingredients in cosmetic products has been mandatory in Europe, while the nomenclature used in the EU, namely the International Nomenclature of Cosmetic Ingredients, is based on the American Nomenclature of Toiletries and Fragrances [18]. All cosmetic products are constituents of several categories. Thus, personal care products include shower gels, shampoos, soaps and toothpastes. Non-rinsing products include moisturizers, sunscreens and skin lightening creams. Scented products include perfumes, shavers and deodorants. Decorative products (make-up) include foundations, eye shadows and lipsticks. Products for hair care include dyes and styling agents, such as gels, waxes, sprays, shaving and hair removal creams. Nail care products include nail polishes, paint removers and acrylic nails. The Food and Drug Agency in the US has categorized the most common cosmetic allergens into fragrances, preservatives, dyes, rubber, and metals [20].

Prevention of cosmetic allergy

The best way to prevent allergic reactions is to know what you are sensitive to and how to avoid it [27]. Look for products that are hypoallergenic, fragrance-free and non-comedogenic. However, one must be aware that these may still cause reactions [27]. Almost any product that contains water must have some preservatives [28]. One way to accomplish this is by carefully reading the product ingredient panel. It is not enough to check for terms like "hypoallergenic", "fragrance-free" or "for sensitive skin," as there is no federal standard or definition to govern the use of these terms. Even products that say they are "unscented" can have a fragrance to cover up chemical scents [28]. To be sure, there is no perfume, look for products marked "fragrance-free" or "without perfume".

The present request for SCCS is to recognize fragrance allergens the consumer needs to know, to indicate thresholds for their safe use and to consider possible modification of allergens by metabolism and autoxidation. The International Fragrance Association (IFRA), as a representative of the fragrance industry, provided relevant unpublished scientific data on fragrance ingredients and together with the up-to-date published scientific literature, critically prepared an opinion for the SCCS [5]. For a long time, there were insufficient scientific data for the determination of dose-response relationships and/or thresholds for these allergens. The limits of 0.01 and 0.001% were set, for rinse-off and leave-on products respectively [5]. Special fragrance database lists more than 2,587 fragrance ingredients used for perfuming. Fragrances are volatile and therefore it is known that they may exacerbate pre-existing asthma.

Contact allergy to fragrance ingredients is a common disease. In Europe, it affects about 1 to 3% of the general population and about 16% of eczema patients [18]. The ACD can significantly impair the quality of life. Thus, prevention of contact sensitization to fragrances, both in terms of primary prevention (limiting or eliminating exposure to allergens in the population) and secondary prevention (avoiding re-exposure to specific sensitizer in clinically diagnosed individuals), is an important objective of public health risk management measures. Primary prevention includes prohibition by regulatory measures; restriction of the maximum permissible concentration; substitution of the allergen; reformulation of the fragrance or fragranced product; deliberate avoidance of fragrances where they are not essential; providing information, e.g. labeling. In this context, the valid diagnostics of sensitization by PT with ingredient labeling represents secondary prevention. In the case of prehaptens, it is possible to prevent activation outside the body. In the case of prohaptens, the possibility of activation is inherent to the molecule and extrinsic measures cannot prevent activation. A prohapten is a chemical that by itself is non-or low-sensitizing, but may become a more potent hapten in the skin by transformation ('bioactivation') usually via enzyme catalysis. It is not always possible to know whether the chemical is a prohapten. Activation can thus increase the risk of sensitization. Limonene, linalool and linalyl acetate are prehaptens and form sensitizing compounds by air oxidation. For these substances, the presence of the oxidized fraction represented by the peroxide content should not be higher than 10 ppm. The prevention of autoxidation using antioxidants

needs thorough investigation, because after their own oxidation, instead of the compound that they protect, antioxidants become skin-sensitizing derivatives. Cinnamyl alcohol, eugenol, isoeugenol and isoeugenyl acetate are prohaptens and form sensitizing compounds by metabolic transformation. Geraniol and alpha-terpinene are both prehaptens and prohaptens. Geranial (an isomer of citral) is a sensitizer without activation, but forms more potent sensitizing compounds by air oxidation and by metabolic transformation as well. Cross-reactivity exists between alcohols, esters and their corresponding aldehydes, and their parent alcohols [5].

Fragrance allergen labeling requirements

There are more than 2,587 fragrance ingredients used for perfuming. Based on available data, in 1999, the SCCS updated the list of the Scientific Committee on Cosmetic Products and Non-Food Products on fragrance substances. The substances are constituents of several categories namely category of established contact allergens in humans (82 substances) or animals (19 substances) with recommended labeling, than likely contact allergens (26 substances) with recommended labeling, and the category of possible contact allergens (48 substances) without recommended labeling. It is worth to know that if human evidence is negative, there is still a potential sensitization risk, as the number of (consecutive) patients tested was low [5].

The property of a chemical to react with and bind to proteins in the skin, either directly or after activation, determines the chemicals' potential to be a skin sensitizer [4]. The relationship between molecular structure and protein reactivity is based on principles of mechanic organic chemistry. This provides the basis for identifying structural alerts of existing structure activity relationship by computer modeling, but the computer-based methodology alone is not sufficient for the identification of skin allergens, thus structure activity relationship works in combination with human and animal data, if human and animal data are limited or missing. Up to now, based on elicitation levels in sensitized individuals, the SCCS could not establish thresholds of safe use for individual fragrance allergens but proposed a general level of exposure up to 0.8 μg/cm^2 (0.01%) to be tolerated by most consumers both the sensitized, as well as most of the non-sensitized consumers, protecting the later of developing contact allergy. However, some strong and extreme sensitizers may require lower individual thresholds. For very weak sensitizers, this generic threshold may be too conservative. The model providing a general threshold of 100 ppm includes single substances only. Dose-response studies have been performed with only 4 of these fragrance substances (hydroxyisohexyl 3-cyclohexene carboxaldehyde, isoeugenol, cinnamal and hydroxycitronellal). This general threshold does not preclude that the most sensitive part of the population may react upon exposure to these levels. Hence, it does not remove the necessity for providing information to the consumer concerning the presence of the fragrance substance in cosmetics. In cases where specific data on threshold levels for a specific allergen are available, these data can help to set an individual safe threshold. However, when such quality data are not available and a substance poses a high risk of sensitization to the consumer, a general threshold limit is operating. As data from human dose elicitation experiments are very limited, no levels that could be considered safe for the majority of allergic consumers could be established for individual substances. However, safe use concentrations of these 26 fragrances in cosmetic products had not yet been determined [5].

Clinical relevance (CR) is a concept used to describe the significance of a positive PT for an individual patient. It covers current and/or past relevance based on: 1) medical history; 2) results of PT and/or other tests; 3) ingredient labeling; or 4) chemical analysis. If the patient is weakly sensitized (e.g. by a low induction dose), and CR is "unknown", the occlusive exposure during PT may have been the only exposure above the individual elicitation threshold capable of eliciting an unequivocal allergic contact reaction. That is why a lack of or unknown CR does not make future allergen avoidance unnecessary [5].

The future of allergen labeling

Cosmetic products in the EU have to comply with European Commission Regulation No 1223/2009, thus, the allergens identified by the SCCS have to be present on a label. Every cosmetic product placed on the EU market needs a compliant product information file (PIF). However, the labeling with "contains fragrances" or "fragrance-free", does not provide sufficient information, leading to unnecessary avoidance of other fragrance substances and exposure to incriminated fragrance used for other purposes, e.g. as preservatives, respectively. In case when a cosmetic product contains fragrances, it is necessary for the PIF to include also the list of allergens and an IFRA certificate that conforms that the product is safe to use. In light of the SCCS opinion on fragrance allergens, in 2014 the European Commission proposed to amend Annex III to Regulation No 1223/2009, and added another 62 to the list of 26 allergens that need to be labeled individually and evoked a strong reaction from the industry. Due to space and readability of ingredient lists, e-labeling has been proposed, which requires access to the internet at the time of shopping. However, in terms of other ingredients labeling, when other uses are less problematic, as each ingredient is not used as a fragrance but e.g. as a preservative, they must be on the label [26].

Conclusion

Considering that so-called "hypoallergenic" products are not necessarily less sensitizing, allergy departments should distribute lists of cosmetic products not containing the respective allergen(s) that consumers can use as safe alternatives.

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University of Novi Sad, Novi Sad
Faculty of Sports and Physical Education[1]

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EFFECTS OF CORRECTIVE EXERCISES ON KYPHOTIC ANGLE REDUCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

EFEKTI KOREKTIVNIH VEŽBI NA SMANJENJE UGLA KIFOZE: PREGLED LITERATURE I METAANALIZA

Vanja DIMITRIJEVIĆ[1], Branka PROTIĆ GAVA[1], Tatjana VINAJI[1] and Nela POPOVIĆ[1]

Summary

Introduction. Kyphosis is a deformity of the spine characterized by excessive backward curvature of the thoracic spine. The normal range of thoracic kyphosis in teenagers is 20 – 40 degrees, and the diagnosis of hyper-kyphosis is beyond 45 degrees. The aim of this review was to assess the magnitude of the effects of various corrective exercises on kyphotic angle reduction. **Material and Methods.** The Web of Science and PubMed were searched to retrieve relevant literature. Ten studies were included in our systematic review and meta-analysis. **Results.** The magnitude of the effects of corrective exercises on the kyphotic angle correction was estimated and the results showed a statistical significance in standardized mean difference (-0.504, P < 0.001). The analysis of the subgroups regarding the age showed a heterogeneity that was not statistically significant and the magnitude of the effects in different age groups. **Conclusion.** The results of our meta-analysis may be useful to many physiotherapists and clinicians in solving problems in patients with kyphosis and hyper-kyphosis.

Key words: Exercise; Exercise Therapy; Kyphosis; Scheuermann Disease; Treatment Outcome; Posture

Sažetak

Uvod. Kifoza je deformitet koji karakteriše povećanje fiziološke krivine grudnog dela kičme prema natrag. Normalni opseg torakalne kifoze kod tinejdžera je 20–40°, a dijagnoza hiperkifoze se smatra većom od 45°. Cilj ove studije bio je da proceni veličinu efekta različitih korektivnih vežbi na smanjenje ugla kifoze. Deset studija uključeno je u našu metaanalizu. **Materijal i metode.** Pretraživali smo *Web of Science* i *PubMed* radi pronalaženja relevantne literature. Deset studija uključeno je u našu metaanalizu. **Rezultati.** Veličinu efekta korektivnih vežbi procenjivali smo na ishodu *kyphotic angle* i rezultati pokazuju statističku značajnost za srednje standardizovano odstupanje (-0,504, p < 0,001). Analizom podgrupe za faktor godine pronađen je i izvor zanemarljive heterogenosti i prikazana veličina efekta prema različitim starosnim grupama. **Zaključak.** Rezultati naše metaanalize mogu biti korisni mnogim fizioterapeutima i kliničarima u rešavanju problema kod pacijenata sa kifozom i hiperkifozom.

Ključne reči: vežbe; korektivna vežbe; kifoza; hiperkifoza; ishod lečenja; postura

Introduction

Kyphosis is a spinal deformity characterized by excessive backward curvature of the thoracic spine [1]. The normal range of thoracic kyphosis in teenagers is 20 – 40 degrees, while diagnosis of hyper-kyphosis is beyond 45 degrees [2, 3]. The kyphotic angle determines the magnitude of the kyphotic curve of the spine. This deformity is diagnosed by motion analysis camera system [4], spinal radiography [5] or by flexicurve ruler [3, 6, 7]. Postural hyper-kyphosis is a common spinal curvature disorder [8, 9] caused by large external loads applied to the spine of individuals with poor overall muscle strength [10]. Hyper-kyphosis is associated with rapid degeneration of the spine as well as disorders of the thoracic and cervical vertebrae [11] including cervical lordosis. Hyper-kyphosis is one of the spinal abnormalities that can develop during adolescence. In fast-growing teenagers, abnormal bending of the spine prevents normal organ development and excessive thoracic kyphosis is associated with altered respiratory function [12]. People with excessive kyphosis often have deformities in the sagittal plane [13] and such mismatch can occur due to prolonged sitting, poor posture during sitting and standing [14]. Hyperkyphosis may impair lung function, daily life activities, and reduce the quality of life [15, 16]. The underlying causes of increased thoracic kyphosis associated with aging are unknown; however, a growing body of evidence suggests that vertebral degeneration, such as wedge-shaped changes in the spinal body and dehydration of the intervertebral discs, are the primary

Corresponding Author: Vanja Dimitrijević, Univerzitet u Novom Sadu, Fakultet sporta i fizičkog vaspitanja, 21000 Novi Sad, Lovćenska 16, E-mail: dimitrijevicvanja@gmail.com, brankaproticgava@uns.ac.rs

Abbreviations

PRISMA	– Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SMD	– standardized mean difference
RCT	– randomization control trial
LCEP	– local and comprehensive corrective exercise programs
CCEP	– comprehensive corrective exercise programs
CI	– confidence interval

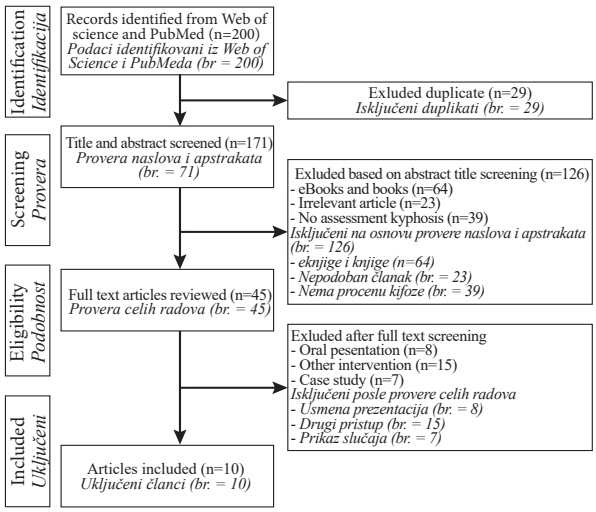
factors [17]. The incidence of this deformity in children aged 11 years is 15% and in adults aged 20 to 50 years it is 38% [6]. Various conservative treatments have been recommended for hyper-kyphosis, including exercise therapy, adhesive taping, spinal orthoses, and manual therapy [10]. In addition, exercise therapy is one of the most commonly used methods in treating hyper-kyphosis [3], while alternative treatments for kyphosis may include manual therapy [10]. Like with exercise therapy, restrictions in spinal range of movement were approached by manual mobilization performed by a physiotherapist [18]. Corrective exercise programs for hyper-kyphosis in adults have also been designed according to Kendall's theory, which includes stretching and strengthening muscles in the affected area [19]. Exercise allows people with hyper-kyphosis to take an active role in their own health care and, if performed safely, can provide many health benefits [20]. In particular, exercises aimed at increasing back extensor muscle strength and spinal flexibility can reduce kyphosis and, if combined with postural training, can enable older adults to maintain an upright posture [21]. The focus of most therapeutic exercise protocols is to facilitate functional adaptation in dysfunctional muscle groups and to improve muscle strength, flexibility, endurance, and coordination [22]. Given the expected increased prevalence and incidence of hyper-kyphosis in the aging population, effective preventive and therapeutic interventions are needed [5]. It is useful to strengthen the extensors of the thoracic spine and correct excessive thoracic kyphosis in order to reduce or prevent painful spinal disorders and other complications [23]. Increased thoracic kyphosis is associated with decreased physical performance, disturbed balance, slower walking and climbing stairs, shorter functional range [24]. The thoracic spine region can be the source of pain and disorders during the life of many people [6]. The aim of this study was to assess the magnitude of the effects of various corrective exercises on kyphotic angle reduction in subjects with kyphosis and hyper-kyphosis.

Material and Methods

This paper was done in the line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

Search strategy

A search strategy was developed to identify all relevant studies evaluating the effect of corrective exercises in the treatment of kyphosis and hyper-kyphosis. Our systematic search included Web of Science and PubMed databases and the following key words were used: kyphosis, hyper-kyphosis, corrective exercises, and kyphotic angle. The search strategy is shown in **Graph 1**.



Graph 1. Flow diagram of the process of study selection for the meta-analysis

Grafikon 1. *Dijagram toka procesa odabira studija za metaanalizu*

Eligibility criteria

To be included in our analysis, original articles had to meet the following criteria: 1) to deal with kyphosis or hyper-kyphosis; 2) different types of corrective exercises could be used as treatment; 3) studies that used the kyphotic angle as the outcome measure. Our analysis included only articles written in English language. A systematic search of two electronic databases (Web of Science and PubMed) was conducted in March 2021. All the studies listed in this review were published in the period from 2007 to 2020. The inclusion/exclusion of studies was done by two investigators by consultation and consensus.

Data extraction and quality assessment

After the selection of studies based on inclusion and exclusion criteria, two investigators jointly conducted data extraction. They independently assessed the quality of studies. The risk of bias was assessed for each study using the Cochrane risk of bias tool [26], which assesses seven domains of bias, including randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other potential biases. Each study was examined based on the above seven aspects and subsequently rated as studies with low risk, high risk or unclear risk of bias.

Data synthesis and analysis

Meta-analysis and statistical analysis were performed using Meta Analyst (Brown University) and Cochrane Review Manager (RevMan 5.4) software

(Cochrane). The magnitude of the effects was estimated for the outcome of the kyphotic angle. For each study, a random effects model was used for standardized mean difference (SMD), 95% confidence intervals (CI), and continuous outcomes. According to the Cohen guide, values of 0.2, 0.5, and 0.8 showed small, medium, and large effect size, respectively. After that, the analysis of the subgroup related to the age was performed in order to assess the size of the effects separately and in case of increased heterogeneity to solve this problem. The $P < 0.05$ was considered statistically significant. Heterogeneity between studies was assessed using the Higgins I^2 test and P values. The guide for interpreting heterogeneity in the meta-analysis of randomized trials is as follows: 0% to 40% - may not be important; 30% to 60% - may represent moderate heterogeneity; 50% to 90% - may represent substantial heterogeneity; 75% to 100% - considerable heterogeneity.

Table 1. Description of intervention
Tabela 1. *Opis intervencije*

Study *Studija*	N/*B*	Program type *Tip programa*	Outcome *Ishod*	Kyphotic angle/*Ugao kifoze*	Age *Godine*	Exercise per week/*Nedeljno vežbanje*	Duration *Trajanje*	RCT *RKT*
Ahmadnezhad (2015) [27]	30	Corrective games *Korektivne igre*	Kyphotic angle *Ugao kifoze*	> 40°	12 - 15	(3 x week) (*3 x nedeljno*)	8 weeks *8 nedelja*	Yes *Da*
		Control group (no treatment) *Kontrolna grupa (bez tretmana)*						
Bautmans (2010) [18]	48	Manuel mobilization + exercises *Manuelna mobilizacija + vežbe*	Kyphotic angle *Ugao kifoze*	> 50°	69 - 83	18 sessions *18 sesija*	3 months *3 meseca*	Yes *Da*
		Control group (no treatment) *Kontrolna grupa (bez tretmana)*						
Bezalel (2019) [28]	50	Schroth method *Šrotova metoda*	Kyphotic angle *Ugao kifoze*	> 40°	10 - 17	daily/*dnevno*	12 months *12 meseci*	Yes *Da*
		Anti - gravitation exercises *Antigravitacione vežbe*						
Elgendy (2020) [29]	40	Manipulative therapy+ correction exercise/*Manipulativna terapija+ Vežbe korekcije*	Kyphotic angle *Ugao kifoze*	≥ 40°	18 - 28	(3 x week) *(3 x nedeljno)*	4 weeks *4 nedelje*	Yes *Da*
		Correction exercises *Vežbe korekcije*						
Feng (2017) [30]	164	Corrective funktional exercises *Korektivne funkcionalne vežbe*	Kyphotic angle *Ugao kifoze*	> 40°	13 - 16	(2 x week) *(2 x nedeljno)*	8 weeks *8 nedelja*	Yes *Da*
		Exercise program/*Program vežbi*						
Jang (2017) [22]	50	Corrective exercises *Korektivne vežbe*	Kyphotic angle *Ugao kifoze*	> 40°	> 65	(2 x week) *(2 x nedeljno)*	8 weeks *8 nedelja*	Yes *Da*
		Control group (education) *Kontrolna grupa (edukacija*)						
Kamali (2016) [14]	39	Corrective exercise therapy *Terapija korektivnim vežbama*	Kyphotic angle *Ugao kifoze*	> 45°	18 - 30	(3 x week) (*3 x nedeljno*)	5 weeks *5 nedelja*	Yes *Da*
		Manuel therapy/*Manuelna terapija*						
Naderi (2019) [31]	24	Corrective exercises *Korektivne vežbe*	Kyphotic angle *Ugao kifoze*	> 50°	65 - 74	(3 x week) (*3 x nedeljno*)	12 weeks *12 nedelja*	Yes *Da*
		Control group (no treatment) *Kontrolna grupa (bez tretmana)*						
Seidi (2014) [6]	37	Comprehensive corrective exercises/*Sveobuhvatne korektivne vežbe*	Kyphotic angle *Ugao kifoze*	≥ 42°	18 - 25	(3 x week) *(3 x nedeljno)*	12 weeks *12 nedelja*	Yes *Da*
		Control group (no treatment) *Kontrolna grupa (bez tretmana)*						
Vaughn (2007) [3]	71	Home based exercises *Vežbe kod kuće*	Kyphotic angle *Ugao kifoze*	23° - 80°	21 - 63	(4 x week) *(4 x nedeljno*)	13 weeks *13 nedelja*	Yes *Da*
		Control group (no treatment) *Kontrolna grupa (bez tretmana)*						

Legend/*Legenda*: N - number of subjects in the groups/*B – broj ispitanika u grupama*; RCT - randomization control trial/*RKT - nasumično kontrolno ispitivanje*

Results

Study selection and characteristics

Based on the search strategy, 200 studies were selected for review from the initial database search. Of that number, 29 studies were excluded due to duplication; therefore, 171 studies were selected for further analysis. After the abstracts and titles were read, 126 studies were excluded because they did not meet the inclusion criteria. The remaining 45 studies were thoroughly reviewed. After reviewing the full-text articles, 35 studies were excluded. The remaining 10 studies were included in this review article and meta-analysis. The eligible studies were randomized controlled trials (RCTs). The flow diagram of the study selection process is shown in **Graph 1**.

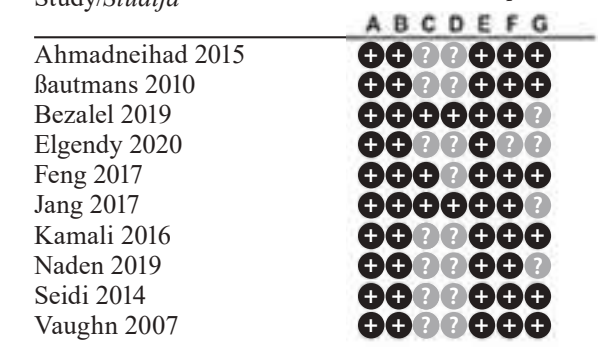
Table 1 shows the main characteristics of the included studies. The studies included 556 respondents who participated in ten studies, and the sample size of the included studies ranged from 24 to 164. The age of the respondents ranged between 10 and 83 years. The total length of treatment ranged from 4 weeks to 12 months. The study of Seidi et al. [6] included two experimental groups treated by local (LCEP) and comprehensive corrective exercise program (CCEP) and one control group. In our meta-analysis, we used results of CCEP that were better than LCEP.

Risk of bias

Graph 2 presents the summary of the risk of bias scores for each included study. Randomization was used in all 10 studies for the item of "random sequence generation". Allocation concealment showed a low risk of bias in all 10 studies. For outcome blinding, one study adopted a single-blind method to evaluate the intervention measures, and two studies used a double blind method. Because of objective outcome measures, outcome data were considered low risk in 10 studies.

Meta-analysis

The only outcome assessed in our study was kyphotic angle correction. Kyphotic angle is the most commonly used value for quantifying kyphotic spinal deformity [5, 6, 14]. All ten studies included in our meta-analysis used kyphotic angle as the outcome measure. After data pooling, SMD between post and pre-intervention in the experimental and control group showed a statistically significant difference (SMD = -0.756; 95% CI = -1.175, -0.338, $p < 0.001$), and heterogeneity ($I^2 = 80.35\%$, $p < 0.001$) (supplementary materials). Due to high heterogeneity ($I^2 = 80.35\%$),



Graph 2. Risk of bias for each study: grey - unclear risk, black - low risk

Grafikon 2. *Procena pristrasnosti za svaku studiju: sivo - nejasan rizik, crno - mali rizik*

Legend/*Legenda*:

(A) Random sequence generation (selection bias)/*Slučajni odabir uzorka (pristrasnost odabira)*

(B) Allocation concealment (selection bias)/*Prikrivanje alokacije (pristrasnost odabira)*

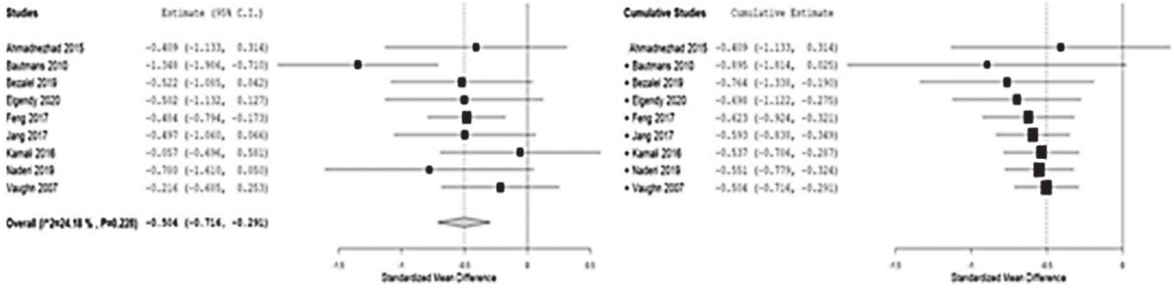
(C) Binding of participants and personnel (performance bias)/*Informativno zaslepljivanje ispitanika i osoblja (pristrasnost performanci)*

(D) Blinding of outcome assessment (detection bias)/*Informativno zaslepljivanje procene ishoda (pristrasnost detekcije)*

(E) Incomplete outcome data (attrition bias)/*Nepotpuni podaci o ishodu (pristrasnost usled osipanja uzorka)*

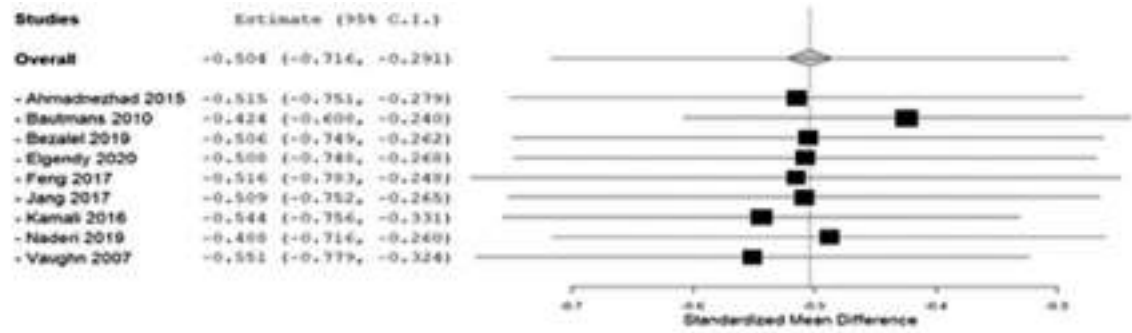
(F) Selective reportng (reporting bias)/*Selektivno izveštavanje (pristrasnost zbog nepotpunih podataka)*

(G) Other bias/*Ostale vrste pristrasnosti*

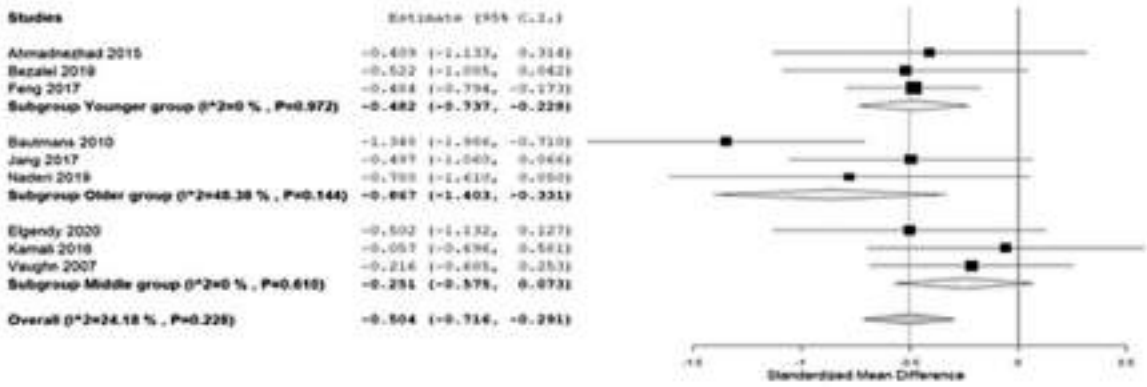


Graph 3. Standardized mean difference (SMD) between post and pre-intervention in experimental and control groups, without the study of Seidi et al. (2014), Outcome of the kyphotic angle: Squeres represent the SMD for each trial. Diamonds represent the pooled SMD across trials; Cumulative analysis is on the right side

Grafikon 3. *Standardizovana razlika aritmetičke sredine (SRA) između rezultata pre i posle intervencije u ispitivanoj i kontrolnoj grupi, bez studije Seidi i ostali (2014), ishod: Ugao kifoze. Kvadrati predstavljaju SRA za svaku studiju. Dijamanti predstavljaju udruženu SRA za sve studije; Desno je Kumulativna analiza*



Graph. 4. Leave-one-out meta-analysis; Outcome: kyphotic angle
Grafikon 4. *Izostavljanje jedne (studije), metaanaliza, ishod: Ugao kifoze*



Graph 5. Standardized mean difference (SMD) outcome: kyphotic angle, subgroup analysis: squeres represent the SMD for each trial, diamonds represent the pooled SMD across trials
Grafikon 5. *Standardizovana razlika aritmetičke sredine (SRA), ishod: Ugao kifoze, Analiza podgrupe. Kvadrati predstavljaju SRA za svaku studiju. Dijamanti predstavljaju udruženu SRA za sve studije*

by consensus of two researchers, it was decided to exclude the study of Seidi et al. [6] from further analysis under the assumption that it leads to great heterogeneity (supplementary materials). After this decision, the following results were obtained: SMD = -0.504; 95% CI = -0.716, -0.291, $p < 0.001$; heterogeneity - $I^2 = 24.18\%$, $p = 0.228$ **(Graph 3)**. **Graph 4** shows the leave-one-out meta-analysis for the kyphotic angle outcome. After this, the analysis of the subgroups regarding the age of the participants was performed. The following results were obtained: young age subgroup, SMD = -0.482; 95% CI = -0.737, -0.228, $p < 0.001$, heterogeneity $I^2 = 0\%$, $p = 0.972$; middle age subgroup, SMD = -0.251; 95% CI = -0.575, 0.073, $p = 0.129$, heterogeneity $I^2 = 0\%$, $p = 0.610$; older age subgroup, SMD = -0.867; 95% CI = -1.403, -0.331, $p = 0.002$, heterogeneity $I^2 = 48.38\%$, $p = 0.144$ **(Graph 5)**.

Discussion

In this systematic review, we combined the results of 10 studies, in order to calculate the magnitude of the effects of corrective exercises in 556 subjects with kyphosis and hyper-kyphosis. Reduction and prevention of kyphotic deformities is the main goal of therapists who work with subjects with kyphosis. Different approaches are used to achieve better results in working with these respondents, and we tried to combine these approaches in our study. The only outcome for which we examined the magnitude of the effects of corrective exercises was the kyphosis angle. For this outcome, an analysis of subgroups regarding the age of respondents was performed. Due to the large range of age in some studies, it was difficult to create categories into which each study would fit, and three subgroups were created: young age group, middle age group, and older age group.

In subjects with kyphosis or hyper-kyphosis, the kyphosis angle is used as a guideline for physiotherapists to set goals and plans for further interventions. By applying different corrective exercises shown in **Table 1,** the kyphosis angle was statistically significantly reduced. In our meta-analysis of the magnitude of effects of corrective exercises on the kyphotic angle correction, we presented pre and post intervention results in the experimental and control groups. By analyzing the outcome of kyphotic angle for the total effect size of corrective exercises, statistical significance was found (SMD = -0.504, $p < 0.001$, according to the Cohen guide moderate effect size) **(Graph 3)**. Previously, the study of Seidi et al. [6] was excluded from further analysis because it contributed to great

heterogeneity (supplementary materials). After that, the heterogeneity was negligible ($I^2 = 24.18\%$) **(Graph 3)**. The analysis of age subgroups showed that heterogeneity occurs in the older group ($I^2 = 48.38\%$). In **Graph 5** we can see how corrective exercises had different magnitude effects on subjects of different ages (young subgroup: SMD = -0.482; middle age subgroup: SMD = - 0.251; older subgroup: SMD = -0.867). **Graph 3** also shows cumulative meta-analysis of the kyphosis angle in the overall estimate changes as each study is added to the database. **Graph 4** shows leave-one-out meta-analysis that involves performing a meta-analysis in each subset of studies obtained by omitting exactly one study. This shows how each individual study affects the overall outcome of other studies.

Our meta-analysis is the only one that has addressed this issue. The meta-analysis [32] examined the effects of exercise programs on kyphosis and lordosis angle, and seven studies measured the angle of kyphosis. The problem of heterogeneity was not solved in this meta-analysis, (SMD = -0.49; $I^2 = 67\%$; results of the study of Seidi et al. [6] were excluded as in our case) and the magnitude of the effects must be taken with caution. Systematic review [21] also dealt with the problems of hyper-kyphosis and it shows the presented results of the included studies.

Nine studies included in our meta-analysis had subjects with hyper-kyphosis while the study of Vaughn, D. W. Et al. [3] had subjects who did not have hyper-kyphosis (23˚ – 80˚). All studies included were RCTs. Given the diversity of corrective programs applied in the included studies **(Table 1)**, the results obtained are representative because they show the homogeneity of the included studies. The mentioned problems that come with hyper-kyphosis [15, 16, 33, 34] point to recommendation of corrective exercises in the treatment of the deformity itself, because in addition to the positive effects, such activities bring many more benefits [20]. Through the meta-analysis of the subgroups, we showed how corrective exercises affect subjects of different ages **(Graph 5)**.

Conclusion

This study addressed the effects of different corrective exercises on kyphosis angle correction in subjects with kyphosis and hyper-kyphosis. The current meta-analysis indicates that corrective exercises have moderately positive effect on reducing kyphotic angle in kyphotic and hyper-kyphotic subjects. The results of the size of the effect are representative, because they show negligible heterogeneity. To obtain such a result, however, we had to exclude one study, which created great heterogeneity. We believe that our meta-analysis can be useful to many physiotherapists and clinicians in solving problems in patients with kyphosis and hyper-kyphosis and provide an incentive for further research.

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University of Novi Sad, Faculty of Medicine Novi Sad
Department of Psychiatry and Psychological Medicine

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BINGE EATING DISORDER IN RELATION TO OBSESSIVE-COMPULSIVE DISORDER AND FOOD ADDICTION

OPSESIVNO PREJEDANJE U VEZI SA OPSESIVNO – KOMPULSIVNIM POREMEĆAJEM I ZAVISNOŠĆU OD HRANE

Elsa FEDRIGOLLI and Dragana RATKOVIĆ

Summary

Introduction. Binge eating disorder, as a fairly new disorder, has recently been added to the Diagnostic and Statistical Manual of Mental Disorders 5, and it is characterized by recurrent and frequent episodes of eating large quantities of food in a short time frame. The aim of this study was to associate binge eating disorder with obsessive-compulsive disorder and food addiction, which is crucial for understanding and appropriate treatment of patients. **Material and Methods.** We reviewed the literature from PubMED database from January 2000 to May 2021 using the keywords: binge eating disorder, binge eating disorder and obsessive-compulsive disorder, binge eating disorder and food addiction, and food addiction, in both English and German language. **Results.** Binge eating disorder, as part of the cycle of obsessive-compulsive disorder, may be considered obsessive thinking about weight, appearance or bad mood, where hunger and satiation is replaced by compulsion and loss of control, ritual eating, and secret eating. Furthermore, binge eating disorder may cause food addiction and this paper shows that addiction to high sugar and high fat products can lead to addiction behavior by habituation of certain points in the dorsal nucleus. This division is of major importance to establish proper treatment protocols. **Conclusion.** Binge eating disorder is closely related to obsessive-compulsive disorder and addiction to behavior and substances. Further research should focus on identifying the largest subtypes and classifications of binge eating disorder.

Keywords: Binge-Eating Disorder; Obsessive-Compulsive Disorder; Food Addiction; Substance-Related Disorders; Behavior, Addictive; Classification

Sažetak

Uvod. Opsesivno prejedanje, kao relativno nova bolest, nedavno je uvršćeno u *Diagnostic and Statistical Manual of Mental Disorders 5* i može biti definisano kao unošenje velikih količina hrane u malim vremenskim periodima. Cilj ovog rada bio je da dovedemo opsesivno prejedanje u vezu sa opsesivno-kompulsivnim poremećajem i zavisnošću od hrane, što je ključno za razumevanje i adekvatan tretman pacijenata. **Materijal i metode.** Pregledane su studije, literatura na engleskom i nemačkom jeziku, uz pomoć baze PubMED (januar 2000–maj 2021) sa ključnim rečima: *Poremećaj opsesivnog prejedanja, Opsesivno prejedanje i opsesivno-kompulsivni poremećaj, Opsesivno prejedanje i zavisnost od hrane* i *Zavisnost od hrane*. **Rezultati.** Opsesivno prejedanje kao deo ciklusa opsesivno-kompulsivnog poremećaja može se posmatrati kao opsesija u formi preteranog razmišljanja o težini, izgledu ili lošem raspoloženju i kompulsivnim zamenjivanjem i gubitkom kontrole, ritualizmom i tajnim jedenjem. Osim toga, opsesivno prejedanje može izazvati zavisnost od hrane i u ovom radu je iskazano da zavisnost od supstancija sa visokim dozama šećera i masti mogu dovesti do zavisnosti ponašanja habituacijom određenih tačaka u dorzalnom nukleusu. Ova podela je izuzetno važna da bi se utvrdili adekvatni protokoli tretmana. **Zaključak.** Opsesivno prejedanje usko je povezano sa opsesivno-kompulsivnim poremećajem, zavisnošću od ponašanja i supstancija i dalje istraživanje bi trebalo da se usmeri ka utvrđivanju najvećih podtipova i klasifikacija poremećaja opsesivnog prejedanja.

Ključne reči: opsesivno prejedanje; opsesivno kompulsivni poremećaj; zavisnost od hrane; bolesti zavisnosti; zavisničko ponašanje; klasifikacija

Introduction

Binge eating disorder (BED), as a fairly new addition to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), is an eating disorder that includes recurrent episodes of binge attacks (eating a huge amount of food in a short period of time that can be considered abnormal from a point of view of a bystander), eating either more rapidly/until uncomfortably full/when not hungry in the first place/with embarrassment about the quantity or with feelings of disgust/shame and guilt after the incident, as well as a marked level of distress when eating and, unlike bulimia nervosa (BN) patients, there is an absence of compensatory behavior such as fasting, over-exercising, using laxatives or purging. These attacks need to occur at least once a week for three months in order to make a valid diagnosis of BED [1].

Although it has been added to the DSM-5, BED is unfortunately still unrecognized by health professionals and the public alike as a distinct mental dis-

Corresponding Author: Elsa Fedrigolli, Univerzitet u Novom Sadu, Medicinski fakultet, Katedra za Psihijatriju i psihološku medicinu, 21000 Novi Sad, Hajduk Veljkova 3, E-mail: el-fe@live.at, dragana.ratkovic@mf.uns.ac.rs

Abbreviations

BED – binge eating disorder
BN – bulimia nervosa
DA – dopamine
DS – dorsal striatum
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders 5
FA – food addiction
OCD – obsessive-compulsive disorder

ease and it is commonly attributed to lack of self-discipline ("they should just pull themselves together"), poor willpower, blameworthiness ("they have only themselves to blame"), low perceived control and low self-esteem in general. This is, of course, only more so the case in obese patients with BED, since even professionals, such as Dr. Allen Francis (former chair of DSM-4) claimed that BED was a fake disorder representing no more than "gluttony" [2]. It is needless to say that since then, numerous studies have in fact proven the severity of this particular eating disorder [3, 4].

In 2001, Stice et al. were among the first ones to propose two distinct subtypes of BED: dietary and dietary/depressive subtype [5].

Even though it is true that BED patients show no compensatory behaviors (cleaning or restriction) such as fasting, excessive exercise, use of laxatives or restrictive eating like BN patients, BED patients may still have intrusive thoughts about weight and body shape. These body image issues are more common in BED patients compared to non-BED controls and they are found in both obese and non-obese BED patients of the dietary subtype and include body dissatisfaction (ones actual and ones ideal body shape), overconcern with weight and shape, body checking behaviors (body fat pinching, weighing, body circumference measurements, etc.), avoidance behavior (wearing loose clothing, avoiding swimming pools, etc.), idealization of thin body shape and perfectionism [5–7]. It should also be mentioned at this point that normal weight BED patients did use compensatory mechanisms like dieting more frequently than obese BED patients, but that chronic over-dieting just resulted in more BED attacks [7, 8]. When tested for their body size, BED patients are capable of placing and perceiving their bodies quite accurately, but express the desire for a slimmer figure. On top of that, BED patients show considerable cognitive bias that contributes to a distorted body image perception through attentional bias (where focus is placed on unattractive rather than attractive body parts), memory bias (where focus in speech is placed on weight and shape over neutral information), and interpretation bias, where negative information processing is present in relation to the disorder [9].

Additionally, there is also a dietary/depressive subtype characterized by an increased rate of Axis I (depression, dysthymia, panic disorders, etc.) and Axis II disorders (avoidant, self-defeating, paranoid, etc.), as well as increased interpersonal sensitivity, higher levels of negative urgency, greater negative affect regulation, decreased or maladaptive emotional regulation strategies, alexithymia, impaired interoceptive awareness, decreased cognitive reappraisal, and decreased executive functioning [5, 7, 10–12]. The depressive symptoms in this BED subgroup can further be linked with the feeling of loss of control which is a diagnostic criterion in DSM-5 and with the interpersonal profile that BED individuals often exhibit, a friendly-submissive one that can, because of its nonassertive and exploitable nature, often lead to social withdrawal [13, 14]. Peterson et al. reported in their study that depression and anxiety symptoms are the predicting factors for a binge and increased caloric intake, rather than the BED symptoms itself [15].

Even though these classifications are still the same, they are helpful in the treatment, prognosis, and mapping of our patients; however, it seems that they are missing the most important links with BED, the link with obsessive-compulsive disorder (OCD) and food addiction (FA). The aim of this study was to associate BED with OCD and FA, in order to help healthcare professionals make the diagnosis and treatment of patients with BED. The study was performed by a systemic literature review that included studies on the neuropathology of BED, FA, OCD and affect regulation. Major studies on the treatment options of BED, as well as epidemiology and diagnostic criteria were mostly left aside. It is our wish to further deepen the understanding of BED cycle. Also, our intention was to additionally subdivide and classify the new BED relating it with OCD and FA.

Material and Methods

This paper has focused on BED in relation to OCD and FA by a systematic literature review. The PubMED was searched in May 2021, using the following key words: BED, BED and OCD, BED and FA, and FA in English and German language. Over 100 papers were selected, out of which 55 were considered most acceptable based on topic-specificity, credibility, reputation, and non-bias criteria. The majority of selected studies are literature reviews, with only a small part being experimental studies. The conclusions of these studies are presented in a reprehensible way in the result section below.

Results

BED and OCD

As mentioned in the introduction, BED has two subtypes: dietary and dietary/depressive subtype. The dietary subtype is hyper-focused on weight and body shape, while the dietary/depressive subtype is stuck in a depressive mindset and weight concerns. It has been shown that the dietary subtype is responding to treatment somewhat better than the dietary/depressive subtype [5].

Although these two subtypes help us in mapping the disorder and finding appropriate treatment op-

tions for individual persons, it does not show the whole picture, meaning that these subtypes are part of an obsessive-compulsive BED cycle. The fact that BED can be included in the OCD spectrum is nothing new, since the obsessive-compulsive trait has been linked to BED before, and the Yale-Brown Obsessive-Compulsive Scale has been recently integrated for validation and assessment of severity of BED symptoms by focusing on the obsessive/compulsive, restraint, and control domains [16, 17].

The OCD, a widely represented disorder in the mainstream media, is characterized by two distinct parts: obsession and compulsion. The obsessive part is hereby classified by recurrent and persistent thoughts or urges which are unwanted and create anxiety, as well as the need to fulfill those thoughts and urges in order to achieve a state of peace of mind. Compulsions are repetitive behavior actions (hand washing, knocking, etc.) or mental acts (praying, counting, etc.) with a strict set of predefined rules with the patients knowing of their excessive and time consuming nature. It is also important to clarify that no other mental disorder better explains the behavioral pattern of OCD than the generalized anxiety disorder [18].

One of the most pressing factors for BED to be placed among the OCD spectrum is that especially brooding rumination takes place in BED patients in an exaggerated manner. Brooding rumination is a passive comparison of one's current situation with some unachieved standard in a pessimistic fashion. This can be distinguished from reflective rumination where the current state is observed in order to find a solution. Brooding rumination is more commonly observed in BED patients, especially when it comes to weight and body shape concerns. It should be pointed out that this type of rumination increases bad mood, even more so if forcefully suppressed. This rumination and suppression phase can be considered the obsessive part of the BED cycle and as it is repressed, the bad mood itself or the unfulfilled "ideal body" can be the trigger for the following binge attack. The escape theory explains that a BED patient binges in order to escape the "flopped" body standard, specific stressors or simply to improve the mood [19–21].

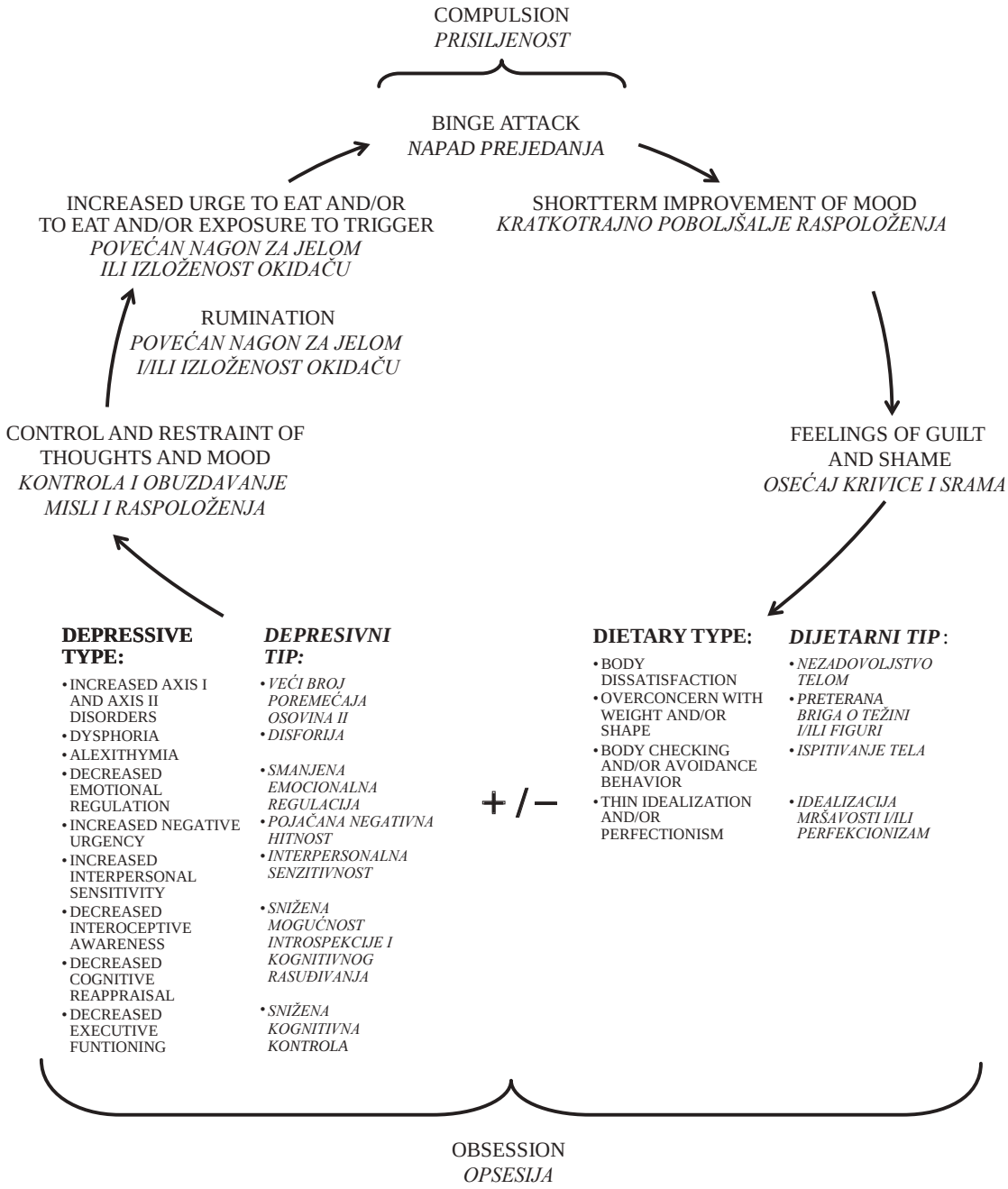
During the compulsive part of the BED cycle (the actual binge attack) patients often report a loss of control, which is similar to OCD, where patients report the feeling of having to go through with a certain action even though it does not make sense. It can be said that this is of course only a short term solution, improving the mood temporarily, while soon being replaced by feelings of guilt and shame and falling back into the trap of rumination. It is easy to see how this can create a state of helplessness. Interestingly enough, during the compulsive phase, BED patients have reported undergoing certain rituals over and over again and eating in secrecy [1, 5, 18, 22].

Just like in OCD, traumatic childhood events have also been found in BED as a predisposing risk factor, may they be of a sexual, emotional or physical nature. Weight teasing and thinness concerns in families have shown to be risk factors in adolescent BED patients, whereas sexual abuse, physical abuse or physical neglect have been proven to be more common in BED patients in general [23–26].

BED and its link to FA

Addiction as a broad popular term was defined by Dr. Gabor Mate as "any behavior or substance that gives relief in the short term, but leads to negative consequences in the long term" [27]. In the DSM-5, there is a difference between substance (alcohol, amphetamines, etc.) and non-substance-related (gambling disorder, internet gaming, etc.) addictions. Substance addiction is defined as hazardous use of substances, social problems related to substance use, withdrawal symptoms, tolerance to substance, repeated attempts to quit, giving up activities to use a substance, failure to fulfill one's roles, physical and psychological changes due to the abuse, etc. Non-substance-related disorders, such as gambling, show a similar set of symptoms such as mental preoccupation with the action, need to increase the amount spent, unsuccessful attempts to cut down, irritation when not being able to go through with the action, loss of social connections due to the behavior, etc. [28–30].

The FA, even though still a controversial topic, has been recently linked to substance use disorders with similar symptoms such as overconsumption, a persistent wish but failure to cut down, increasing amount of time spent seeking the substance, strong cravings with withdrawal symptoms, tolerance, social retreat, etc., and it is generally measured by the Yale Food Addiction Scale (YFAS) [31–33]. A major problem of FA still remains to this day: which substance exactly is the person addicted to? It is hard to pinpoint exactly what the underlying culprit is with a hyper-palatable diet of high fat and high sugar being the "dangerous" combination as it has a high glycemic load and a high fat content. When looking for a specific single ingredient, sugar seems the most likely and will be used in this article when talking about FA as a substance addiction even though fat has also been shown to have some addictive potential [34–37]. It is important to differentiate FA as a substance and FA as a behavioral addiction [31, 35, 37]. As mentioned by Dr. Bak-Sosnowska in her paper "Differential criteria for binge eating disorder and food addiction in the context of causes and treatment of obesity", a lot of obese patients will be addicted to the act of eating itself (quantity), rather than the specific food [31]. This is an important differentiation that has also been observed in animal studies and shall be further observed in detail under 2a) FA as a substance addiction, and 2b) FA as a behavioral addiction. It can also be hypothesized that food (substance) addiction may turn into a behavioral FA and that a behavioral FA may lead to a substance FA, since eating large amounts of food always carries the risk of "hidden" substance such as sugar.



Graph 1. Binge eating disorder as an obsessive-compulsive cycle
Grafikon 1. *Bolest prejedanja prikazana kao opsesivno-kompulsivni ciklus*

So why is the study of FA so crucial for understanding BED itself? In clinical practice, sometimes it is hard to differentiate these two disorders as they share common symptoms, such as overeating past the point of fullness, lack of hunger in the first place, short-term relief of feelings, unpleasant feeling of fullness, intense cravings, trying to quit but failing with physical, psychological and social consequences, emotional dysregulation and increased levels of impulsivity among many others. It is therefore especially important for a physician to identify if the underlying reason for eating is a dietary restraint (obsession). Is there a repetitive substance seeking (hedonistic satisfaction), or is the quantity of utmost importance (eating behavior)? This is even more important when choosing treatment options. The differences between BED and FA relate to the function of food, because food is used to release mental tension in BED, but it is used for hedonistic purposes in FA; the function of taste (quantity over quality in BED or important selection of spe-

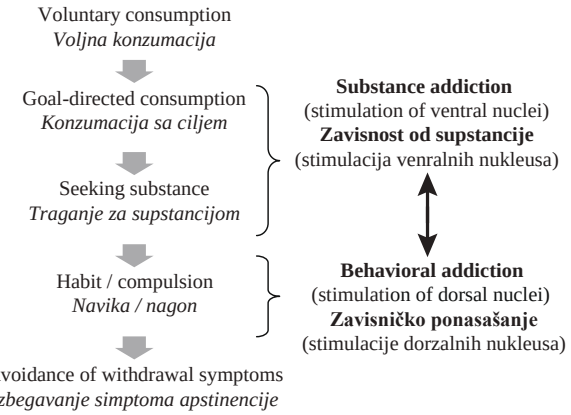
cific foods in FA), body shape concern (present in BED, absent in FA), symptoms of addiction (tolerance, withdrawal) which are absent in BED, as well as the common criterion of guilt and shame after the episode in BED which is absent in FA as the system of delusions is active. Another important factor is that BED patients will most commonly overeat in solitude in their free time, whereas for FA patients the presence of other people is of no importance [31].

The following two subsections will take a deeper look into what is behind FA as a substance and FA as a behavioral addiction:

a. FA as a substance addiction

As human studies on sugar addiction are still scarce, a look into animal studies can help in understanding FA as a substance addiction. Firstly, it should be mentioned that animals that had the choice between sucrose (sugar) and sucralose (no-calorie sweetener) generally chose sucrose due to its elevated striatal dopamine (DA) release [38]. In another study, sucralose was administered orally, while glucose was administered via the intra-gastric pathway. This study showed that sucralose enhanced DA efflux in the ventral striatum (VS), while glucose elicited DA release in the dorsal striatum (DS). This indicates that there is a different role of both the dorsal and ventral striatum when it comes to hedonic factor (sweetness) versus caloric factor (nutrients) [39]. It was hypothesized at this point that the voluntary ingestion of sugar will increase DA release from the mesolimbic system, which will further drive goal-directed seeking of sugar. At some point, a switch from ventral (cue driven) to dorsal striatal (outcome-driven) control would be responsible for formation of habits when it comes to compulsive drug seeking, as could be tested by DA D2 receptor levels as a vulnerability marker [37, 40].

Another study on sugar bingeing patterns in rodents implemented an intermittent access to it. Rodents were deprived of food for 12 hours and then left with chow and glucose solution. During the actual feeding phase, animals showed addiction-like behaviors, but prevented weight gain by reducing chow intake [41–43] (this should not exclude FA, as lean individuals can also have FA). The sugar binge elicited an endogenous opioid response during the binge with a hedonistic effect [37, 43]. It is believed by Tellez et al. that it is the sweetness, rather than the nutrient profile in the case of intermittent access that causes binge eating development [39]. Interestingly enough, sweet preference seems to be a predisposing factor in binge eating as well [44]. Furthermore, the administration of naloxone (a competitive opioid antagonist) causes withdrawal symptoms such as anxiety, teeth chattering, forepaw tremor and head shaking in the sugar-bingeing animals that resembles opiate withdrawal [43]. Moreover, the animals had decreased DA levels, increased acetylcholine levels in the nucleus accumbens and reduced D2 DA receptor binding levels in the DS [43, 45].



Graph 2. Development of substance and behavioral addiction
Grafikon 2. *Razvoj zavisnosti i zavisničkog ponašanja*

One of the well known studies concerning sugar as an addictive substance was published by Lenoir et al., where some animals picked saccharin over cocaine all the while undergoing different reinforcement schedules [46].

When comparing sugar to other addictive substances (drug abuse) it is evident that bingeing (higher food intake in the eating episodes), withdrawal (anxiety, depression), craving (increased response after period of abstinence) and sensitization mechanisms (increased locomotor response to psychostimulants during abstinence) take place when looking at those two. Similarly, we have the stimulation of the same neural brain regions with DA being released to reinforce a certain behavior (anticipatory reward) and opioids released due to successful ingestion (actual reward) with withdrawal symptoms when this opioid release does not take place. Food that causes surge of DA includes lab chow, sugar, saccharin, and corn oil. Sugar, just like drugs of abuse, alters DA (D1 and D2) and opioid binding, as well as enkephalin messenger-ribonucleic acid expression [35, 37].

b. FA as a behavioral addiction

In her paper "Differential criteria for binge eating disorder and food addiction in the context of causes and treatment of obesity", Bak-Sosnowska mentions that in her clinical practice she observed patients that were not addicted to a substance but rather "the act of eating itself" [31]. Eating activates the reward centers in the brain and causes a release of DA, regardless whether the food is hyperpalatable or not. The reward deficiency theory claims that people "medicate" themselves by overindulgence and excess consumption of subjectively palatable food. In the reward deficiency theory, there is a decreased amount of dopamine DR2 receptors in the striatum which will be "made up for" by eating. It is important to emphasize the subjective perception of taste, as for instance mice that lack the glucagon-like peptide 1 receptor show decreased sensitivity to sweetness but higher sensitivity for umami. Furthermore, it can be theo-

rized that the release of endogenous opiods after food intake is due to reinforcement of already present hedonic hotspots, whereas DA release projects an anticipatory reward. The pleasure of opioid release is of course most commonly seen with palatable foods, but it comes down to individual preference. Such an interpersonal variance may lead to difference in food choice (and not the choice for hyperpalatable foods, for instance) [37, 47].

It has long been known that transgenic mice that lack DA signaling die of starvation as they lose the motivation to seek food. It has been hypothesized that the DA neuron circuits in the ventral tegmental areas are strengthened when an expected reward is met with an expected outcome and thus creating a habit the more often it is strengthened. This is more so in "cue-reactive" individuals who will have a higher motivation to go after certain rewards and use the reward itself as a reinforcer. This habituation process leads to dopaminergic activity "switching" from the ventral striatum (outcome-driven) to the dorsal striatum (cue-driven) over time and can be a potential underlying reason for behavioral addiction [47].

One of the well known disorders among the non-substance addiction disorders is gambling disorder. This disorder is characterized by persistent and recurrent problematic behavior which leads to impairment and distress, mental preoccupation with the behavior, increasing the amount spent, unsuccessful attempts to quit, etc. [48]. Findings on gambling disorder show a decreased striatal DA activity which is compensated during the behavioral phase (playing on a slot machine) with a DA surge. This is especially of importance because an amphetamine-induced DA surge was increased in the gambling group over the control group in the dorsal striatum, once more establishing the dorsal striatum as a hotspot for behavioral addictions. Parkinson patients treated with DA agonist therapy showed, in a small subgroup, to develop pathological gambling and compulsive eating, thereby once more proving that DA dysfunction can be behind those behaviors. Moreover, gambling disorder and FA have several "risk factors" in common, such as increased impulsivity and changes in reward circuitry, and are often found together [49–51].

Discussion

The objective of this study was to highlight the association between BED and OCD and BED and FA, respectively.

The OCD is a mental disorder characterized by two distinct phases: obsession and compulsion; thus, it can be linked to BED. The patients with BED exhibit a high degree of obsessive-compulsive symptoms with brooding rumination taking place during the obsessive phase. The rumination can fixate on body related image issues or on mood with a combination of the two being the most common finding. This pressing rumination can pent up until the "ritual" of eating is fulfilled, which characterizes the second phase of compulsion [5, 19, 20].

On the other hand, FA should be divided into substance addiction and behavioral addiction. Substance addiction suggests seeking a specific substance, whereas behavioral addiction means seeking a specific behavior. It can be hypothesized that the switch of DA release from the ventral striatum in an outcome-driven fashion to the dorsal striatum in a cue-driven way is responsible for habituation and transition of a substance disorder into a behavioral disorder. The main substance in FA represents sugar in the form of a highly palatable high fat/high sugar diet, whereas the behavioral addiction is about eating large amounts of food, regardless of seeking a specific ingredient (although this may be hard to pinpoint, since sugar is hidden in a large variety of foods). It can also be hypothesized that behavioral addiction may turn into a substance addiction because of the aforementioned point [31, 37].

In diagnosis, it is crucial to differentiate the underlying cause and associations with a diagnosis of BED; the presence of dietary or dietary/depressive symptoms relates to obsessive and compulsive thoughts, the seeking of a specific substance is associated with substance addiction or intake of large quantities of food is connected with a behavioral addiction. As mentioned for substance and behavioral addictions, we need to further investigate which one was the first, because one is likely to lead to the other. This is not only important for understanding the patient, but even more so for selecting appropriate treatment options.

The fact that screening for underlying eating disorder is of importance can be best seen in patients that underwent bariatric surgery. Bariatric surgery is "marketed" as one of the best tools for effective weight loss. In reality, however, it is commonly seen that a good portion of patients will not keep the lost weight off in the long term, as loss-of-control-eating and a form of "bariatric BED" (BED just with a smaller quantity of food, but with feeling of fullness and unpleasantness, guilt/shame, etc.) can be observed. It is most likely that these patients had BED before the gastric bypass, which was not corrected by adequate means beforehand and therefore they got it after the surgery as well. It is important to address this issue and find out the exact etiology before undergoing treatment [52].

As mentioned in the introduction of this paper, patients of the dietary subtype that were chronically over-dieting ended up having more BED attacks than patients who were not over-concerned with restricting diets [7, 8]. Hutson et al. brought up an important point that reducing the intake of food by suppressing appetite without improving the underlying pathophysiology of increased compulsivity and impulsivity in BED is unlikely to be of lasting therapeutic benefit [55]. This indicates that this subtype of patients does not benefit from diet restriction, but is helped greatly with Cognitive Behavioral Therapy (CBT) concerning their body image issues such as acceptance-based mirror exposure and non-directive body image therapy [9].

Moreover, it seems logical that patients with a food (substance) addiction, just like in all substance (drug) addictions, will need to cut out the substance from their

diet because even a small amount may lead to a binge. This is a tricky point, since the most plausible substance is sugar, which has not only hedonistic value but also a caloric value, and it is found in a great variety of foods in a "hidden" form. It furthermore seems that the combination of high fat and high sugar diet has a great attraction and may have to be cut out in the treatment process. What further complicates this process is that a patient may have started with a behavioral addiction to large quantities of food, but because of the addition to sugar and fat developed a substance addiction. When visiting a doctor, this patient will be placed among patients with substance addiction, but in fact he has an underlying behavioral addiction. This is why it is of utmost importance to ask detailed questions on the first visit. It is of course necessary to refer somebody with a behavioral addiction to a cognitive behavioral therapist as well, whereas this may be unnecessary for somebody with a sheer substance addiction, to sugar for instance. Pharmacotherapy, for instance with lisdexamfetamine, may be appropriate in case of BED, with the patient's consent [21].

This study has potential limitations. There is a lack of previous research on this specific topic, as this disorder and its implications have not been investigated before. It is possible that papers chosen showed some selection bias with selection criteria varying in different papers. Furthermore, there may have been a confirmation bias by correlating BED to OCD and FA. Even though possible, it seems to the author that the "evidence" makes these links more than plausible, even though no papers have explicitly linked those disorders together yet. It seems that this interpretation and analysis was fair even though this topic of study had not been explored before. As such, a list of the excluded studies has not been provided and publication bias has not been explored in the studies used. Future research is needed on the topics discussed in this study.

Conclusion

In conclusion, it can be said that subtypes of binge eating disorder exist and that they can be classified among the obsessive-compulsive disorder and food addiction disorder, respectively. When talking about food addiciton, a differentiation between substance and behavioral addiction should be made. These classifications are of great importance when deciding on the treatment options. Physicians and health care professionals alike should therefore be educated on the importance of these divisions. It is our wish that further research into this topic will lead to better understanding of the association between these disorders in order to clearly define and delineate the borders and their differences for better treatment outcomes.

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CASE REPORTS
PRIKAZI SLUČAJEVA

Institute of Child and Youth Health Care of Vojvodina, Novi Sad
Pediatric Clinic, Department of Nephrology[1]
Clinical Center of Vojvodina, Novi Sad, Clinic of Gynecology and Obstetrics[2]
Mother and Child Health Care Institute of Serbia "Dr. Vukan Čupić", Belgrade
Department of Nephrology[3]
University of Belgrade, School of Medicine, Belgrade[4]
University of Novi Sad, Faculty of Medicine Novi Sad[5]

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TUBULOINTERSTITIAL NEPHRITIS AND UVEITIS SYNDROME – A CASE REPORT

TUBULOINTERSTICIJALNI NEFRITIS I UVEITIS SINDROM – PRIKAZ SLUČAJA

Nataša KOVAČ[1], Maja KOVAČ[2], Maja SAMARDŽIĆ LUKIĆ[1], Nataša STAJIĆ[3, 4] and Biljana MILOŠEVIĆ[1, 5]

Summary

Introduction. Tubulointerstitial nephritis and uveitis syndrome is a rare oculo-renal disease characterized by the presence of bilateral, anterior uveitis and tubulointerstitial nephritis. The pathogenesis of this disease is still not completely clear. It is associated with prior drug use, infections and autoimmune diseases. The involvement of the cellular and humoral immune responses and genetic predisposition to the development of this syndrome are frequently mentioned in the literature. In a certain number of cases, despite extensive diagnostics, the cause remains unknown (idiopathic tubulointerstitial nephritis and uveitis syndrome). **Case Report**. A fifteen-year-old female patient was admitted to the Department of Nephrology due to complaints of headache in the temples that occasionally occurred in the previous months. Three days before admission, the patient presented with symptoms of upper respiratory tract infection and subfebrile temperature (to 37.8º C). Laboratory test results revealed the development of acute tubulointerstitial nephritis, and in the fifth week of the disease, bilateral anterior uveitis was detected. The diagnosis was confirmed by percutaneous kidney biopsy. Systemic and local corticosteroid therapy was introduced, and after a month it resulted in gradual normalization of kidney function, proteinuria reduction and withdrawal of the ophthalmic symptoms. **Conclusion.** Due to the fact that kidney damage is often self-limited and that uveitis tends to be recurrent, there is a high probability of untimely diagnosis. Early recognition, detection of potential causes and initiation of treatment, are crucial in the prevention of disease progression and development of chronic sequelae such as chronic renal failure and chronic uveitis.

Key words: Nephritis, Interstitial; Uveitis; Early Diagnosis; Signs and Symptoms; Biopsy; Prednisolone; Kidney Function Tests; Eye Diseases

Sažetak

Uvod. Tubulointersticijalni nefritis i uveitis sindrom je retko okulo-renalno oboljenje koje karakteriše prisustvo obostranog, prednjeg uveitisa i tubulointersticijalnog nefritisa. Patogeneza oboljenja nije još uvek sasvim jasna. Povezuje sa sa prethodnim korištenjem lekova, infekcijom i autoimunim bolestima. Sve više se govori i o učestvovanju celularnog i humoralnog imunoodgovora i genetskoj predispoziciji za razvoj ovog sindroma. Određen broj slučajeva i pored opsežne dijagnostike ostaje bez poznatog uzroka (idiopatski tubulointesticijalni nefritis i uveitis sindrom). **Prikaz slučaja.** Pacijentkinja uzrasta 15 godina, primljena je na Odeljenje nefrologije sa podacima o glavobolji u slepoočnom predelu koja je povremeno bila prisutna prethodnih nekoliko meseci. Tri dana pre prijema u bolnicu, javili su se simptomi infekcije gornjih disajnih puteva i supfebrilnost do 37,8° C. Urađeni laboratorijski nalazi su ukazivali na razvoj akutnog tubulointersticijalnog nefritisa, a pete nedelje bolesti potvrđeno je prisustvo obostranog prednjeg uveitisa. Dijagnoza je potvrđena perkutanom biopsijom bubrega. Uvedena je terapija sistemskim i lokalnim kortikosteroidima, na čiju primenu već u prvom mesecu dolazi do postepene normalizacije bubrežne funkcije, negativizacije proteinurije i povlačenja oftalmoloških simptoma. **Zaključa**k. S obzirom da je bubrežno oštećenje često samoograničavajuće i da uveitisi imaju tendenciju povlačenja i ponovnog javljanja, postoji velika mogućnost nepravovremene dijagnoze. Rano prepoznavanje, otkrivanje potencijalnih uzroka i započinjanje lečenja je ključno u prevenciji progresije bolesti i nastanka hroničnih sekvela kao što su razvoj hronične bubrežne insuficijencije i hroničnog uveitisa.

Ključne reči: intersticijalni nefritis; uveitis; rana dijagnoza; znaci i simptomi; biopsija, prednizon; testovi bubrežne funkcije; bolesti oka

Corresponding Author: Dr Nataša Kovač, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, Klinika za pedijatriju, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: n.kovac.89@gmail.com, biljana.milosevic@mf.uns.ac.rs

Abbreviations

TIN – tubulointerstitial nephritis
TINU – tubulointerstitial nephritis and uveitis
IgM – immunoglobulin M
IgG – immunoglobulin G
HLA – human leukocyte antigens

Introduction

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare oculo-renal disease characterized by the presence of bilateral anterior uveitis and tubulointerstitial nephritis (TIN). Most commonly it occurs in adolescent and young females aged fifteen years on average. The real incidence of the disease is unknown, since most of the cases remain undiagnosed. On average, 65% of patients with TIN, actually have undiagnosed TINU syndrome. TIN presents with renal function disorders (elevated serum creatinine level, decreased creatinine clearance level), pathological findings of urine (presence of low molecular weight proteins, eosinophils, and leukocytes), and systemic signs of infection (fever, rash, muscle and joint pain, etc.). Uveitis is most commonly anterior, bilateral, and manifests with photophobia, eye pain, redness, and decreased vision. A certain number of patients remain asymptomatic. Typically, uveitis appears 2 months before or 12 months after the onset of TIN. While kidney damage is mostly acute and often self-limited, patients can have relapses of uveitis which leads to chronic uveitis, while patients under the age of 20 years are especially susceptible. The pathogenesis of this disease is not completely clear. It is attributed to prior use of drugs, infections and autoimmune diseases. The involvement of the cellular and humoral immune responses and genetic predisposition to the development of this syndrome are frequently mentioned in the literature. Despite extensive diagnostics, the cause remains unknown in a certain number of cases (idiopathic TINU syndrome). The treatment consists of systemic and topical corticosteroids, while sometimes non-corticosteroid immunosuppressive medications are also necessary.

Due to the diversity of clinical presentations and possible outcomes, in every patient with TIN and/or uveitis, it is of utmost importance to consider the possible association of these two diseases. This is especially important in patients who do not show any clear clinical signs at the time of making the diagnosis [1–3].

Case Report

A fifteen-year-old female patient presented with symptoms of upper respiratory tract infection and temperature up to 37.8° C three days before admission to the hospital. The patient complained about severe headache in the temple area, occasionally occurring in the previous months, most commonly in the evening hours, but it disappeared after having some rest. The patient did not have any problems while urinating, there were no changes in urine color, but urination was less frequent. The blood pressure was not measured. There were no swollen body parts. The patient did not complain about vision impairment. Laboratory test results showed elevated creatinine level (120 umol/l), measured creatinine clearance (66.7 ml/min/1.73 m^2), elevated erythrocyte sedimentation rate (75 mm/1/h) and anemia (hemoglobin 116 g/L). The levels of total protein, albumins, transaminases, and bilirubin were normal. Elevated protein levels in 24 hour urine were repeatedly detected (24 h proteinuria 0.32 g/950 ml, 24 h microalbuminuria 79.7 mg/l). Initially, urine sediment findings were cytologically normal, while sterile pyuria developed later. Urine culture was negative. Ultrasonography of the urinary tract was normal. On the third day of hospitalization, the patient complained about photophobia, eye pain, and redness in the right eye. An ophthalmic examination was made and dexamethasone tobramycin eye drops and artificial tears were recommended for the following four days. During the examination, no signs of uveitis were detected. In the following period the patient showed no ailments and local findings were improving. Due to elevated levels of the acute phase reactants, parenteral antibiotic therapy with ceftriaxone was introduced during the following two days and after that it was changed into oral treatment with cefixime. Due to proteinuria, angiotensin-converting enzyme inhibitor - enalapril was introduced. Since elevated levels of creatinine and 24 h proteinuria persisted, with the presence of sterile pyuria, additional diagnostic procedures were done. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-citrullinated peptide antibodies, anticardiolipin antibodies, anti-beta-2-glycoprotein, and serum angiotensin-converting enzyme findings were normal. Lupus-anticoagulant was negative. Quantiferon test was negative. Immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody titers to adenovirus were strongly positive. IgM antibodies to Epstein Barr, Cytomegalovirus, Parvo B19, Coxsackie virus, and Hantavirus were negative. Antistreptolysin O titer was normal and the nasal swab was negative. Candida spp. was isolated from the pharyngeal swab. The coproculture was negative. Taking into account the medical history, clinical course of the disease and laboratory findings, acute kidney damage was confirmed most probably as a consequence of TIN. In the fifth week of the disease, ocular symptoms reappeared: photophobia, eye pain, and redness in the right eye area. Bilateral anterior uveitis was verified during the ophthalmic examination. Due to the ophthalmic findings and clinical-laboratory parameters of acute TIN, the diagnosis of TINU syndrome was made. It was most probably caused by adenovirus infection. The diagnosis was confirmed by percutaneous kidney biopsy. Systemic corticosteroid therapy was introduced for the first three days with bolus methylprednisolone while continuing oral administration of prednisone 1 mg/kg/day, with gradual dosage decrease until discontinuation. The uveitis was treated with local corticosteroids. This therapy lasted for a month and resulted in gradual normalization of kidney function, disappearance of proteinuria and withdrawal of ophthalmic symptoms.

Discussion

The first case of TINU syndrome was described in 1975 by Dobrin et al. [4]. Since then, over 300 cases have been described, 60% of them in pediatric clinical studies. Bacterial infections (group A streptococcus, Mycoplasma pneumoniae, Mycobacterium tuberculosis, Toxoplasma gondii), viruses (Adenovirus, Epstein Barr, Varicella zoster, Hantavirus), fungi (histoplasmosis), and parasites (malaria) are specified as possible triggers. Other possible triggers are antibiotics and nonsteroidal anti-inflammatory drugs, systemic and autoimmune diseases (sarcoidosis, systemic lupus, IgA nephropathy, postinfectious glomerulonephritis, membrane nephropathy, juvenile idiopathic arthritis, Sjogren's syndrome, and Behcet's disease). The TINU syndrome commonly occurs in some families, which may indicate the importance of genetic factors in disease onset. Certain haplotypes, such as human leukocyte antigens (HLA)-A2, HLA-A24, HLA-DR4, DQA1, DQB1, DRB1, were proven to be linked to this syndrome [1–3]. Regardless of the diagnostics, a certain number of cases remain without a known cause (idiopathic TINU syndrome). Even though the exact pathophysiology is still unknown, a possible mediation of cellular and humoral immune response against different pathogens is frequently mentioned. As the tubular epithelium and ciliary body of the eye participate in the transfer of electrolytes sensitive to effects of carbohydrate inhibitors, it is assumed that they may also share cross-reactive autoantibodies [5–9]. Yin Tang et al. were the first to prove the presence of high titer of modified C-reactive protein antibodies in patients with TINU syndrome, which could be a major target autoantigen of tubular cells and ciliary body [6]. In our patient, the presence of adenovirus infection was confirmed, possibly triggering an immune response and disease onset. Systemic and autoimmune diseases were ruled out. Anamnestic data excluded prior usage of drugs that could trigger the disease.

The clinical picture of typical TINU syndrome is characterized by systemic signs of the disease such as fever, weight loss, stomach ache, weakness, malaise, muscle and joint pain, and skin rash. Ocular symptoms like pain, photophobia, redness and dryness of eyes, and impaired vision, typically appear 2 months prior or 12 months after the diagnosis of TIN, which was also the case in our patient whose ocular symptoms appeared before systemic signs of infection and TIN onset. The laboratory findings of TIN indicate a renal function disorder (elevated values of creatinine). However, systemic signs such as elevated sedimentation rate, anemia, and elevated transaminase values, may also appear. Low molecular weight protein (especially beta-2-microglobulin), eosinophils, and leukocytes (sterile pyuria) in urinalysis indicate the presence of TIN. A definitive diagnosis is made by kidney biopsy. A kidney biopsy is especially indicated in uncertain cases, such as patients with bilateral uveitis and normal kidney function and/or normal urine findings, since kidney damage is often self-limited and may remain unnoticed [2]. In this case, the diagnosis fulfilled criteria for acute TIN, but the final diagnosis was confirmed by kidney biopsy.

In cases with biopsy-proven TIN, it is necessary to perform an ophthalmic examination, since a certain number of patients with uveitis remain asymptomatic. In a large number of cases, patients suffer from bilateral anterior uveitis (80%), while some have an involvement of the posterior part. Granulomatous uveitis is also described as part of the TINU syndrome, and then sarcoidosis needs to be ruled out. Moreover, other diseases like tuberculosis, systemic lupus, Sjogren's syndrome, infectious mononucleosis caused by Epstein Barr virus, brucellosis, histoplasmosis, and others may be the cause of uveitis and TIN. Some of these diseases have typical ocular signs which are not detected in patients with TINU syndrome. While kidney damage is usually acute, relapses of uveitis appear in approximately 40% of cases, in some cases leading to chronic uveitis even 10 years after the first onset [1–3, 10, 11]. Initially, uveitis was not confirmed by the ophthalmic examination of the patient, even though clinical symptoms and a good response to local corticosteroid therapy indicated its development. The reappearance of ocular symptoms and ophthalmolog reexamination confirmed the presence of acute bilateral anterior uveitis.

In order to confirm the diagnosis, criteria proposed by Mandeville et al. in 2001 are used [11]. According to mentioned criteria, our patient met all the diagnostic criteria for TINU syndrome.

Therapy for acute interstitial nephritis is usually not necessary; the disease has a self-limited character and thus exclusion of medications that could be a potential cause/therapy of the infection, usually has a beneficial effect. Corticosteroid therapy (prednisone 1mg/kg/per day during 2 – 3 weeks with a gradual dosage decrease) is recommended in cases with progressive or prolonged kidney damage. Application of topical corticosteroids and cycloplegic agents is recommended initially in the treatment of uveitis. In patients nonresponsive to this type of treatment, application of systemic corticosteroids or immunomodulatory agents such as azathioprine, methotrexate, cyclosporine A, and mycophenolate-mofetil is recommended [2, 3, 11]. Our patient was treated with systemic corticosteroids due to a prolonged elevated creatinine level during a few weeks and relapse of ocular symptoms. The response to therapy was satisfactory – normal renal function and disappearance of proteinuria, as well as withdrawal of ophthalmic symptoms within the first month of the treatment.

Conclusion

In every patient who shows signs of tubulointerstitial nephritis and/or bilateral uveitis, tubulointerstitial nephritis and uveitis syndrome should be considered due to its potential atypical presentations. Early recognition and detection of potential causes, as well as initiation of treatment are crucial in the prevention of disease progression and onset of chronic sequelae, such as chronic kidney insufficiency and development of chronic uveitis.

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University of Novi Sad, Faculty of Medicine Novi Sad[1]
Dentistry Clinic of Vojvodina, Novi Sad[2]

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ORAL MANIFESTATIONS OF COVID-19 INFECTION IN CHILDREN – A CASE REPORT

ORALNE MANIFESTACIJE COVID-19 INFEKCIJE KOD DECE – PRIKAZ SLUČAJA

Isidora NEŠKOVIĆ[1, 2], Sanja VUJKOV[1, 2], Marija BRADIĆ VASIĆ[1], Duška BLAGOJEVIĆ[1, 2] and Jelena KOMŠIĆ[1, 2]

Summary

Introduction. The global coronavirus disease 2019 pandemic, caused by a new coronavirus, has undeniably marked the previous year. A clear link between the changes in the oral mucosa and the severe acute respiratory syndrome coronavirus 2 has not yet been precisely defined. Oral manifestations in patients with severe acute respiratory syndrome coronavirus 2 infection are mostly ulcerations, aphthous ulcers, macules and desquamative gingivitis. **Case Report.** A case of a 2-year-old child with oral leasions during severe acute respiratory syndrome coronavirus 2 is presented. The purpose of this paper was to present a case with atypical clinical manifestations of severe acute respiratory syndrome coronavirus 2, including fever, vomiting and oral lesions, without respiratory simptoms. **Conclusion.** Early reaction and response to all changes within the oral cavity is crucial, because even the earliest stages of oral manifestations may be a symptom of severe acute respiratory syndrome coronavirus 2.

Key words: COVID-19; Oral Manifestations; Mouth Diseases; Child; Oral Ulcer; Stomatitis, Aphthous; Gingivitis; Early Diagnosis; Signs and Symptoms; Telemedicine

Sažetak

Uvod. Pandemija COVID-19 na globalnom nivou, izazvana novim korona virusom, nesumnjivo je obeležila prethodnu godinu. Jasna veza između promena na oralnoj sluzokoži i virusa SARS-CoV-2 još nije tačno definisana. Oralne promene kod pacijenata sa SARS-CoV-2 infekcijom najčešće su ulceracije, aftozne promene, makule i deskvamativni gingivitis. **Prikaz slučaja.** Prikazan je slučaj dvogodišnjeg deteta sa oralnim lezijama u toku infekcije SARS-CoV-2 virusom. Cilj ovog rada bio je prikazati slučaj sa atipičnim kliničkim manifestacijama SARS-CoV-2, uključujući groznicu, povraćanje i oralne lezije, bez respiratirnih simptoma. **Zaključak.** Rana reakcija i reagovanje na sve promene u usnoj duplji presudni su jer čak i najranije faze oralnih manifestacija mogu biti simptom prisutnosti SARS-CoV-2 virusa.

Ključne reči: COVID-19 infekcija; oralne manifestacije; bolesti usta; dete; oralne ulceracije; afte; gingivitis; rana dijagnoza; znaci i simptomi; telemedicina

Introduction

The global coronavirus disease 2019 (COVID-19) pandemic, caused by a novel coronavirus, has undeniably marked the previous year. Based on the official data issued by the World Health Organization, the virus has been detected in 223 countries and infected more than a hundred million people.

Various coronaviruses are categorized as ribonucleic acid viruses. The virus in focus, the one causing COVID-19 disease, is a beta-coronavirus belonging to the severe acute respiratory syndrome (SARS) virus group, since it leads to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Additionally, its phylogenic properties are alike to those of SARS-associated coronavirus (SARS-CoV) [1, 2].

The new type of coronavirus is a respiratory virus, transmitted through air in small liquid particles, from person to person, with the most common point of primary infection being the nasopharynx [3].

Both adults and children can get infected by the virus, however, it has been observed and registered that children with COVID-19 may be completely asymptomatic or have mild to moderate symptoms [4].

On the one hand, the characteristics of the virus are well-known, but on the other, its clinical manifestations vary greatly, with the data still being collected at this very moment. The already established clinical features of COVID-19 are high temperature, dry cough, breathing/respiratory issues, fatigue, and the loss of taste and smell [3–5]. Furthermore, certain skin changes have been noted, namely, urtricaria, vesicular and petechial exanthems, as well as the chilblains, viral skin conditions affecting palms and feet, which have been registered in SARS-CoV-2 positive children, but they are also noticed in many other viral conditions in the pediatric population [6, 7].

It is a known fact that various viral infections manifest with characteristic changes in the oral mucosa, which points to the presence of virus and contributes to reaching a differential diagnosis. Al-

Corresponding Author: Asist. dr Isidora Nešković, Univerzitet u Novom Sadu, Medicinski fakultet, Klinika za stomatologiju Vojvodine, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: isidora.neskovic@mf.uns.ac.rs

Abbreviations

COVID-19	– coronavirus disease 2019
SARS	– severe acute respiratory syndrome
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
SARS-CoV	– SARS-associated coronavirus
CRP	– C-reactive protein

though a clear link between the changes in the oral mucosa and the SARS-CoV-2 has not yet been precisely defined, numerous patients worldwide have been affected in the previously described manner. Oral conditions recognized in SARS-CoV-2 patients are mostly ulcerations, aphthous ulcers, macules and desquamative gingivitis. The oral cavity areas most commonly affected are tongue surface areas, the lips and hard palate [8, 9].

The definite cause of oral tissue lesions in the course of SARS-CoV-2 infection remains unclear. Therefore, the oral conditions arising are thought to be related to the presence of the virus in the body, the weakened immune system, as well as the use of medications [10].

The oral conditions triggered by the SARS-CoV-2 infection in children aged 1 to 3 years have not been described or dealt with in any scientific studies available to us. Taking this into account, we felt encouraged to share the collected data on a particular case of ours, so that our research and case study could be a guide in detecting and following the stages of SARS-CoV-2 infection in the population of young children.

Case Report

In November 2020, the family of a two-year-old girl contacted the Dentistry Clinic of Vojvodina, about the changes in the girl's oral mucosa. A day prior to contacting the clinic, the girl's temperature was high, reaching 38.5° C, and she felt nauseous, vomiting several times during the day. Simultaneously, on the same day, the patient developed a localized inflammatory gingivitis, affecting gingival mucosa in the region of the upper right maxillary incisor and maxillary canine. Her condition, as shown in **Figure 1**, was not painful and there was no bleeding. Shortly after contacting the clinic via phone, the patient's parents both tested positive for SARS-CoV-2. Due to the mandatory home isolation, the patient could not keep her dental appointment. Prior to reporting the patient's case to the Dental Clinic of Vojvodina, the girl had received blood test results showing a decrease in the leukocyte count 4,3 x 10^9/L, optimal erythrocyte count 4,29 x 10^9/L, neutrophil ratio 56.1%, lymphocyte ratio 29.7%, and C-reactive protein (CRP) less than 5 mg/L. The throat swab culture, together with the nasal swab and buccal swab taken from the girl, did not show the presence of any pathogenic bacteria or pathogenic fungi.

A week later, several changes appeared in the patient's oral cavity, on the inner lower lip and the frenulum of the upper lip. Whitish discolorations, presented in **Figure 2** and **Figure 3**, were located on the patient's upper and lower lip mucosa on the non-inflamed surface with desquamation of the epithelial tissue. The remaining oral cavity areas were unaffected. The patient's condition was treated using the diluted panthenol solution three times a day. After several days from the beginning of the treatment, the previously described oral efflorescence had subsided.

Figure 1. Localized inflammatory gingivitis affecting gingival mucosa in the region of the upper right maxillary incisor and maxillary canine at the beginning of SARS-CoV-2 infection in a 2-year-old patient
Slika 1. *Lokalizovan inflamatorni gingivitis na gingivalnoj mukozi u regiji gornjeg maksilarnog sekutića i očnjaka na početku infekcije SARS-CoV-2 virusom kod dvogodišnje pacijentkinje*

Figure 2. Whitish discolorations located on the non-inflamed upper lip mucosa with desquamation of epithelial tissue
Slika 2. *Beličaste promene lokalizovane na neinflamiranoj mukozi gornje usne sa deskvamacijom epitelnog tkiva*

At an early stage of the patient's condition, after noticing the oral changes, the girl's pediatrician prescribed antibiotics, namely Azithromycin oral suspen-

Figure 3. Whitish discolorations located on the non-inflamed lower lip mucosa with desquamation of epithelial tissue
Slika 3. *Beličaste promene lokalizovane na neinflmiranoj mukozi donje usne sa deskvamacijom epitelnog tkiva*

sion (the specific dosage is unknown). Following the retraction of the oral cavity changes, as well as the completion of the antibiotic therapy, an additional blood test was done. This time, the results showed increase in the leukocyte count 5,20 x 10^9/L, which were still below the reference value, average erythrocyte count 4,44 x 10^9, and the lymphocyte count increased by 71.5%. A month and a half after the acute stage of the girl's illness, her SARS-CoV-2 immunoglobulin G was 24.29.

Discussion

The COVID-19 pandemic is ongoing, and medical institutions worldwide strive to efficiently treat the disease and develop prevention programs that would either inhibit or stop any further spreading of the virus. Currently, the number of the studies focusing on the pedriatic population is rather small. Nonetheless, the existing studies clearly show that the children's clinical manifestations are less severe than those in adult patients [11]. The blood analysis of SARS-CoV-2 patients of all ages shows a decrease in the white blood cell count, a decrease in the overall lymphocyte count, but also a normal CRP [12], which fully corresponds to our patient's case. Various skin conditions, developed in the course of the SARS-CoV-2 infection, have been previously dealt with in the studies described by dermatologists. However, the conditions occurring in the oral cavity have rarely been described, particularly in young infected children. It is noteworthy mentioning that there has been no available study dealing with the non-respiratory symptoms only, such as high temperature, vomitting and oral mucosa lesions. Our young SARS-CoV-2 positive patient had all of the above symptoms, but no respiratory symptoms.

The atypical clinical manifestations of SARS-CoV-2 are becoming more frequent, especially those including dermatological and oral manifestations [10, 13–15]. The first recorded instance of oral mucosa condition arising from the SARS-CoV-2 infection was described by Martin Carreras-Presas. His three elderly patients developed painful oral changes in the form of ulcerations and oral blisters on the lower lip and hard palate [16].

Although the pathogenesis of skin and mucosal conditions have not been fully researched, there are hypotheses linking the above mentioned changes to blood vessels disorders caused by the virus [17]. The connection between the SARS-CoV-2 infection and oral lesions is still unknown, which is understandable, considering that the biopsies of the noticed changes have not been performed, with the exception of Soares [18] and Anasari's [19] cases. These two researchers have been able to histologically confirm the presence of inflammatory infiltrate in their patients' samples, thus suggesting that it was SARS-CoV-2 infection that caused oral changes in their patients.

One of the issues that all COVID-19 positive patients face is not being able to visit their dentists due to the self-isolation protocol. Consequently, during the pandemic, we have mostly relied on telemedicine, as was the case with our young patient, who reported oral changes in the earliest stage of infection.

Conclusion

Early reaction and response to all changes occurring within the oral cavity is crucial, particularly in asymptomatic patients. Even the earliest stages of oral manifestations may be a symptom of the coronavirus disease 2019, predominantly in young children who show a mild clinical course. Early detection is the key to prevent subsequent virus transmission.

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Institute of Child and Youth Health Care of Vojvodina, Novi Sad
Clinic of Pediatric Surgery[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]

Case report
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CONGENITAL DUODENAL ATRESIA ASSOCIATED WITH INTRAUTERINE INTESTINAL VOLVULUS AND MECONIUM PERITONITIS – A CASE REPORT

ATREZIJA DUODENUMA UDRUŽENA SA INTRAUTERINIM CREVNIM VOLVULUSOM I MEKONIJALNIM PERITONITISOM – PRIKAZ SLUČAJA

Svetlana BUKARICA[1, 2], Jelena ANTIĆ[1, 2], Nenad ŽAKULA[1], Ivana LUKIĆ[1, 2] and Marina MILENKOVIĆ[1, 2]

Summary

Introduction. Duodenal atresia is one of the most common small bowel anomalies usually diagnosed in utero. We present a case of a newborn with duodenal atresia associated with intestinal volvulus and meconium peritonitis. **Case Report.** A premature newborn with a birth weight of 1970 g was admitted due to radiological signs of duodenal atresia. Intraoperatively, in addition to duodenal atresia, we found that almost all intestinal loops were adherent to each other and to the liver in the form of conglomerates, as a consequence of intestinal (jejunal) volvulus and meconium peritonitis. A minimal intestinal resection was performed with creation of duodeno-jejunal anastomosis. The postoperative course was prolonged due to serious complications including cardiac tamponade and sepsis. After 77 days, with full enteral feeding, spontaneous bowel movement, and after appropriate weight gain, the child was discharged from the clinic. **Conclusion.** Treating congenital anomalies of the newborn is a challenge, even for an experienced surgeon, especially when associated with premature birth and low birth-weight. Despite adequate surgical techniques and intensive treatment, complex congenital anomalies are associated with high morbidity and mortality rates.

Key words: Intestinal Atresia; Duodenal Obstruction; Intestinal Volvulus; Meconium; Peritonitis; Infant, Premature; Congenital Abnormalities; Neonatology; Surgical Procedures, Operative; Prenatal Diagnosis

Sažetak

Uvod. Atrezija dvanaestopalačnog creva jedna je od najčešćih anomalija tankog creva koja se prenatalno dijagnostikuje. Prikazujemo slučaj atrezije dvanaestopalačnog creva kod novorođenčeta udružen sa crevnim volvulusom i mekonijalnim peritonitisom. **Prikaz slučaja.** Prevremeno rođeno novorođenče porođajne mase 1.970 g primljeno je zbog kliničkih i radioloških znakova atrezije dvanaestopalačnog creva. Intraoperativno, pored atrezije duodenuma, nailazimo na crevne vijuge koje su slepljene međusobno kao i sa jetrom u vidu konglomerata, a kao posledica volvulusa dela jejunuma i mekonijalnog peritonitisa. Načinjena je minimalna resekcija crevnih vijuga uz kreiranje duodeno-jejunalne anastomoze. Postoperativni tok je prolongiran komplikacijama u vidu srčane tamponade i razvoja sepse. Nakon 77 dana, uz uspostavljen enteralni unos u punom obimu, dete ima spontane stolice i napreduje u telesnoj masi, te se otpušta sa klinike. **Zaključak.** Lečenje urođenih anomalija novorođenčeta predstavlja izazov i za iskusnog hirurga, pogotovo kada su udružene sa malom porođajnom masom i prevremenim rođenjem. I pored adekvatne hirurške tehnike i intenzivnog tretmana novorođenčeta, kompleksne urođene anomalije su praćene visokim stepenom morbiditeta i mortaliteta.

Ključne reči: atrezija creva; opstrukcija dvanaestopalačnog creva; crevni volvulus; mekonijum; peritonitis; prevremeno rođeno dete; kongenitalne anomalije; neonatologija; operativne hirurške procedure; prenatalna dijagnostika

Introduction

Congenital duodenal atresia is the most common small bowel anomaly and it occurs in 1 in 3,000 - 10,000 live births [1, 2]. This anomaly affects male infants more frequently than females [3]. In theory, it represents an obliteration of the duodenal lumen and it is usually described as a result of failure of recanalization between the 8th and 10th week of gestation. Another possible cause of duodenal atresia is annular pancreas, which occurs as a result of extraluminal duodenal obstruction by the surrounding pancreatic tissue [4, 5]. Congenital duodenal atresia can be observed in newborns with Down syndrome, VACTERL (vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies and limb abnormalities) anomalies, intestinal malrotation, biliary tract anomalies, mandibulofacial anomalies, but also as an isolated malformation [2, 6].

In newborns with clinical signs of high intestinal obstruction, midgut volvulus must be considered as well. Although it is known that the incidence of symptomatic intestinal malrotation is 1 in 6,000 births, it is not precisely published how many of these present with neonatal intestinal volvulus [2]. Intrauterine intestinal volvulus represents a pathologic intestinal and/or proximal colon rotation around superior mesenteric artery, with subsequent

Corresponding Author: Prof. dr Svetlana Bukarica, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, Medicinski fakultet, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: svetlana.bukarica@mf.uns.ac.rs

intestinal venous congestion, followed by bowel ischemia and finally necrosis. The most frequent type of intestinal volvulus (also called "classic") is a result of intestinal malrotation, that is, clockwise rotation of the small bowel and ascending colon around the superior mesenteric artery. Another type of intestinal volvulus, called segmental, occurs when intestinal loops are twisted due to presence of meconium ileus, mesenteric or intestinal cysts, mesenteric defects, intestinal atresia, or it may be idiopathic. The rarest type of intestinal volvulus is without malrotation and malposition, which is usually found in premature and/or low birth weight newborns [7]. Unlike intestinal atresia, this condition is rarely discovered before birth, but must be considered in differential diagnosis of acute abdominal distension in a newborn [2].

In infants with bowel perforation due to intestinal atresia, volvulus, hemochromatosis, cystic fibrosis or viral infection, a condition known as meconium peritonitis may occur. This condition represents a sterile peritoneal inflammation, which usually has poor prognosis, with mortality of 80% [3, 4].

The presence of all the three above-mentioned pathologic conditions is quite rare, and just a few cases have been described in the literature so far [8 –10]. They are considered to be a consequence of the regulatory factor X6 gene mutation, and may also be associated with neonatal diabetes, gallbladder agenesis and anomalies of the pancreas. Long-tem prognosis in these patients is poor, with high mortality in the first months of life [8–10].

Case Report

We present a preterm newborn in his very first hours of life. He was born at 34 weeks of gestation weighing 1970 g. The intrauterine ultrasound showed polyhydramnios, so intestinal obstruction was suspected.

The infant presented with vomiting and mildly distended meteoristic abdomen in the upper quadrants. A double bubble sign was seen on an abdominal X-ray **(Figure 1)**, while abdominal ultrasound revealed distended stomach with no detectable passage into the small intestine.

After hydro-mineral and acid-base regulation, nasogastric probe was placed, and the patient was prepared for surgery. Under general anesthesia, right transverse supraumbilical laparotomy was made. Intestinal loops adherent to each other and to the liver in the form of conglomerate of intestinal loops were visible immediately after entering the peritoneal cavity **(Figure 2)**. After conglomerates were carefully separated, we found out that they were formed as a consequence of intrauterine intestinal volvulus **(Figure 3)** associated with meconium peritonitis. Careful intestinal and mesenteric detorsion was performed, bowel loops were wrapped in warm gauze and abdominal cavity was properly cleaned. We initially expected to find a duodenal

Figure 1. A double bubble sign
Slika 1. *Znak dvostrukog mehura*

atresia, with a typically dilated proximal and obliterated distal portion, i. e., type II duodenal atresia **(Figure 4)**. Considering that part of the jejunum (not longer than 10 cm) was ischemic and nonviable, it had to be resected, while anastomosis was created between the duodenum and the rest of the viable jejunal loops. Nasojejunal probe was placed as a stent through the site of anastomosis.

The postoperative recovery included antibiotic therapy, blood transfusions and internal homeostasis maintenance was continued in surgical intensive care

Figure 2. Intraoperative finding of "conglomerate of intestinal loops" adherent to the liver
Slika 2. *Intraoperativni nalaz konglomerata crevnih vijuga adherentnog za jetru*

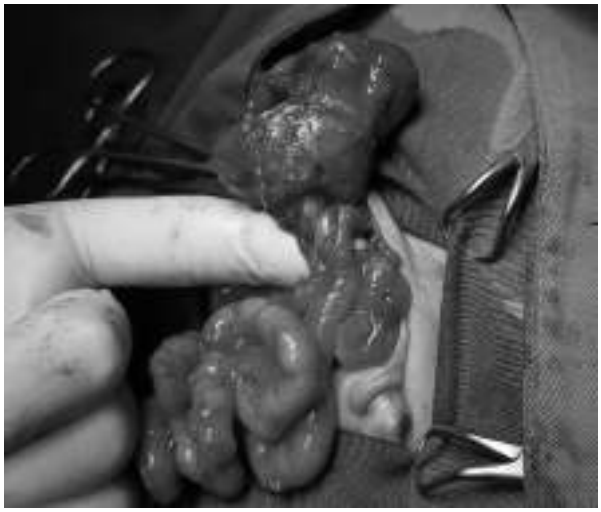

Figure 3. Midgut volvulus found inside the "conglomerate of intestinal loops"
Slika 3. *Tankocrevni volvulus unutar konglomerata crevnih vijuga*

Figure 4. Duodenal atresia – intraoperative finding
Slika 4. *Atrezija duodenuma – intraoperativni nalaz*

unit. Two weeks after the surgery, the baby suddenly deteriorated due to a cardiac tamponade. After cardiopulmonary resuscitation, pericardiocentesis was performed and clear fluid evacuated. Six days later, the baby was extubated, with sufficient oxygen saturation. After several weeks, he developed sepsis, which was successfully treated with antibiotic therapy. After 77 days of hospitalization, with full enteral feeding, the patient was discharged. At this moment, he is a one year old boy, still regularly controlled.

Discussion

Advances in prenatal diagnosis have facilitated early recognition of congenital anomalies. Prenatal ultrasound differentiates approximately one third of congenital intestinal obstructions. Accounting for 54% of prenatally detected cases, duodenal atresia is the most common anomaly of this type. Ultrasound characteristic of congenital duodenal atresia includes the double bubble sign, which is a presentation of distended stomach and duodenal pouch separated by the pylorus, with or without polyhydramnios [6]. Postnatal diagnosis of duodenal atresia, besides clinical signs and symptoms such as bilious vomiting sometimes with upper abdominal quadrants distension, relies on native abdominal X-ray as well. These findings are generally similar to the prenatal ones [11]. Similar clinical signs and symptoms (vomiting and mildly distended, meteoristic abdomen in its upper quadrants) as well as radiological finding of double bubble sign and distended stomach with no detectable passage into the small intestine, were present in our patient.

Reviewing the literature, we found several articles describing cases where radiological (double bubble sign) and even clinical findings suggested duodenal atresia, but patients have subsequently been found to have midgut volvulus [12, 13]. That is why in a newborn with acute abdominal distension, intestinal volvulus must be suspected as one of the possible etiologic causes. In patients with midgut volvulus, prenatal ultrasonography may detect dilated bowel loops, as well as polyhydramnios. Postnatal radiological findings include lack of intestinal air in the right abdomen, with all the loops displaced to the left [14]. In cases where consequent intestinal ischemia occurs, distended, "tubularized" bowel loops can be seen, sometimes with digitiform impressions as a result of wall edema [15]. As a result of intestinal volvulus, meconium peritonitis can also be seen. This condition, found in our newborn as well, despite its high mortality, may not always be an indication for surgical treatment. Approximately one third of these patients can be treated conservatively. Numerous studies proved that radiological findings, such as intestinal obstruction, volvulus or pneumoperitoneum may point to the need for surgical intervention [16, 17].

Treatment of duodenal atresia, after initial nasogastric tube placement, fluid and mineral balance regulation, relies on operative treatment via laparoscopic or open approach. Depending on the affected part of the duodenum, as well as intestinal lumen disproportion, intestinal continuity is established by creating duodeno-duodenal or duodeno-jejunal, end-to-side or side-to-side anastomosis [2].

Surgical strategies for treating intestinal volvulus include complete intestinal and mesenteric detorsion by counterclockwise rotation, wrapping the affected bowels with warm gauze and checking for viability after several minutes, followed by placing loops of small intestine to the right and colon to the left, as well as performing appendectomy (Ladd procedure). In cases where intestinal viability is unclear, second-look surgery can be performed within 24 – 48 hours. If a nonviable bowel is still present, it can be resected, followed by creating end-to-end anastomosis, or intestinal stoma [18]. In our patient, due to nonviable bowel loops, resection of this part of the intestine followed by a creation of anastomosis between proximal part of the duodenum and the rest of the jejunum seemed to be the best possible option.

Any congenital anomaly in the newborn period is a diagnostic-therapeutic challenge, even for an experienced surgeon. Association of two or more anomalies represents a specific form of challenge, which is commonly associated by numerous complications in affected organs or other organ systems.

Considering that radiological findings in our patient revealed a certain double bubble sign, we expected an isolated duodenal atresia. After intraoperative finding of conglomerate of intestinal loops, intestinal volvulus and meconium peritonitis, our decision to perform intestinal resection with primary anastomosis seemed as an appropriate solution for managing both, duodenal atresia and volvulus. However, meconium peritonitis was probably an important factor complicating the surgical course and postoperative recovery.

Conclusion

Treating congenital anomalies of the newborn is a challenge, even for an experienced surgeon, especially when associated with premature birth and low birthweight. Despite adequate surgical techniques and intensive treatment, complex congenital anomalies are associated with high morbidity and mortality rates.

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UP-TO-DATE BREAST CANCER IMAGING

SAVREMENI IMIDŽING KARCINOMA DOJKE

Nataša PRVULOVIĆ BUNOVIĆ, Viktorija VUČAJ ĆIRILOVIĆ, Nikola ANĐELIĆ and Jasmina BOBAN

Summary

Introduction. Breast cancer is a major health and economic problem in Serbia. On the one hand, most patients see a the doctor at an advanced stage of the disease, and on the other hand, screening response rate is low. Early detection increases the chances of survival. **Digital mammography** is the gold standard in breast cancer imaging, together with supplemental ultrasound and tomosynthesis. Mammography combined with tomosynthesis has a greater detection rate regardless of breast density, although the difference is more pronounced in high-density lesions, and it has fewer false-negative results than mammography alone. **Ultrasound**, apart from being a complementary method, is ideal for ultrasound-guided breast biopsy. **Magnetic resonance mammography** is an imaging method with the highest sensitivity in the detection of invasive breast cancer and has an important role in the evaluation of the post-therapeutic response and in preoperative preparation. **Magnetic resonance spectroscopy** measures the choline levels and helps to differentiate malignant from benign lesions. It is also a promising method for early assessment of the post-therapeutic response. **Positron emission tomography** is likely to gain more significant roles in breast cancer imaging in the near future, especially in measuring the treatment response.

Key words: Breast Neoplasms; Early Diagnosis; Diagnostic Imaging; Mammography; Ultrasonography, Mammary; Magnetic Resonance Imaging; Spectrum Analysis; Positron-Emission Tomography

Sažetak

Uvod. Karcinom dojke predstavlja ozbiljan zdravstveni, pa i ekonomski problem u Srbiji. U većini slučajeva žene se javljaju lekaru u odmaklom stadijumu bolesti, a sa druge strane imamo problem relativno niskog odziva žena na poziv u skrining program. Rana detekcija bolesti povećava šansu za preživljavanje. **Digitalna mamografija** je zlatni standard u imidžingu karcinoma dojke, uz dopunu ultrazvukom i tomosintezom. Mamografija kombinovana sa tomosintezom uspešnija je u detekciji lezija nezavisno od gustine dojke, mada je razlika izraženija kod denznih dojki i ima manje lažno-negativnih rezultata u odnosu samo na mamografiju. **Ultrazvuk**, osim što je dopunska metoda, je idealan za navođenje biopsija lezija dojke. **Magnetnorezonantna mamografija** je imidžing metoda sa najvećom senzitivnošću u detekciji invazivnog karcinoma dojke i ima važnu ulogu u evaluaciji postterapijskog odgovora i u preoperativnoj pripremi. **Magnetnorezonantnom spektroskopijom** se meri nivo holina na osnovu čega je moguća distinkcija malignih od benignih lezija. Takođe, obećavajuća je i kao metoda rane procene postterapijskog odgovora. **Pozitronska emisiona tomografija** će vrlo verovatno u bliskoj budućnosti dobiti značajnije uloge u imidžingu karcinoma dojke, pogotovo kao alat za merenje postterapijskog odgovora.

Ključne reči: karcinom dojke; rana dijagnoza; dijagnostički imidžing; mamografija; ultrazvuk dojke; magnetno rezonantni imidžing; spektroskopija; pozitronska emisiona tomografija

Introduction

Imaging has become an essential tool in the management of cancer patients. It has a key role in the disease detection, characterization of pathologic processes and precise localization, treatment response evaluation, guided biopsy, and other therapeutic and diagnostic procedures.

Breast cancer is the most common malignancy in the female population and the second leading cause of cancer death in Serbia, with annual morbidity of approximately 4,600 and mortality of 1,600 patients. It is a major health and economic problem in Serbia, because in 70% of cases patients see a doctor at an advanced stage of the disease (T2 stage or higher). The second part of the problem is low response to mammography screening which started in 2012 and is continuously performed in most regions of the country as an organized decentralized program [1].

Early detection of breast cancer leads to full recovery or transition to chronic disease. **Mammography** is the gold standard for the detection of breast

Corresponding Author: Prof. dr Nataša Prvulović Bunović, Institut za onkologiju Vojvodine, Univerzitet u Novom Sadu, Medicinski fakultet, 21204 Sremska Kamenica, Put dr Goldmana 4, E-mail: natasa.prvulovic-bunovic@mf.uns.ac.rs

Abbreviations

MR – magnetic resonance
PET – positron emission tomography
CEDM – contrast-enhanced digital mammography
DWI – diffusion-weighted imaging
ADC – apparent diffusion coefficient
PEM – positron emission mammography
SUV – standard uptake values

cancer, being the only diagnostic method that has proven to reduce the mortality rate **(Figure 1)**. It has been estimated that mammography reduces the mortality rate by more than 30% in the countries which have implemented mammography screening programs. By the end of the century, the breast cancer mortality rate is predicted to be lower by more than 50% due to mammography [2].

The goal of screening mammography is early detection of breast cancer in asymptomatic patients, especially carcinoma in situ, precancerous lesions, and lesions of uncertain malignant potential (B3 lesions), since treatment in these cases may prevent progression to invasive diseases [3]. However, increased availability of screening mammography is associated with overdiagnosis, an increase in unnecessary invasive procedures, and more false-positive and false-negative results. Despite a relatively high false-negative rate of 15 – 20% reported by some studies, mammography remains the only diagnostic test whose continued application has proven to reduce breast cancer mortality [4]. False-negative mammography results are more common in patients with radiologically dense breasts, in premenopausal and young patients, in patients with a history of previous breast biopsy, those with positive breast cancer family history, patients on estrogen replacement therapy, as well as in patients with atypical disease presentation or cancers with specific growth pattern (e.g., lobulated cancer). All of the mentioned leads to further testing, unnecessary biopsy, screening cost increase, as well as the psychological distress in affected women [5, 6]. Patients treated for breast cancer are referred for annual follow-up mammography of the same breast (if sparing surgery was performed) and of the contralateral breast, because of the 5 – 10% risk of same or contralateral breast disease in the first 10 years after cancer detection, regardless of age, cancer size or pathological type [7, 8].

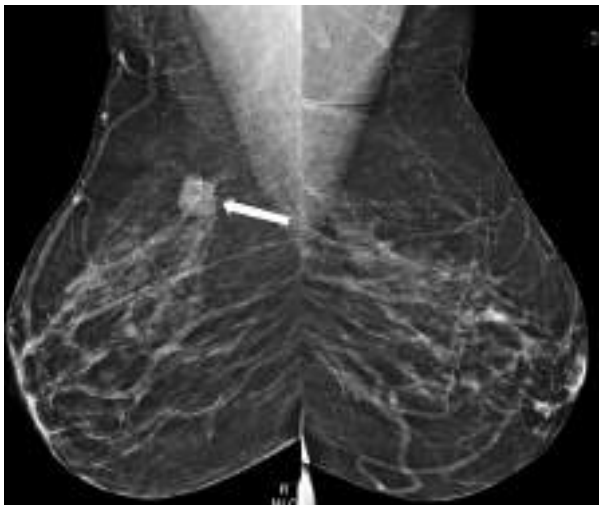


Figure 1. Digital mammography, mediolateral oblique projection. A highly suspicious spiculated shadow is seen in the upper quadrant of the right breast (arrow)
Slika 1. *Digitalna mamografija, mediolateralna kosa projekcija. U gornjem kvadrantu desne dojke uočava se visokosuspektna spikulisana senka (strelica)*

The advantages of modern, digital imaging over the classical conventional mammography, include the possibility of image archiving (which allows comparison with previous images, thus increasing the diagnostic value of the examination), the usage of different software tools that aid detection of breast abnormalities (e.g., computer-aided detection), and implementation of 3D mammography - tomosynthesis. **Tomosynthesis** improves lesion detection by allowing examination of breast tissue slice by slice and therefore reduces false-positive as well as false-negative results. Through the minor increase of acquired dose and examination duration, effects of tissue superpositioning, the drawback of standard 2D mammography, are eliminated. The inclusion of tomosynthesis as a supplementary method in breast cancer screening programs has shown to reduce the recall rate (number of repeated examinations) without changing the method sensitivity [9]. A 5-year study, carried out at the Diagnostic Imaging Center of the Oncology Institute of Vojvodina in Sremska Kamenica, compared standard 2D mammography with mammography supplemented by tomosynthesis (2D + 3D mammography), demonstrated an increase in breast cancer detection rate independent of breast density from 82.4% to 94.4% when the combined method is used. The detection rate increase is even greater in high-density breasts - from 67.8% to 88.1%, which is a difference over 20%. The same study showed a false-negative rate of 17.6% for 2D mammography and 5.6% for 2D + 3D mammography, furthermore confirming the importance of implementing tomosynthesis after digital mammography in symptomatic, but also in asymptomatic patients [10].

Contrast-enhanced digital mammography (CEDM) is a relatively new technique that combines full field digital mammography with the use of iodinated contrast in dual-energy subtraction technique [11]. The CEDM of both breasts lasts for about 10 minutes, which is much shorter compared to other available contrast techniques. It is commercially available and approved only in the United States. Since it is an emerging technique, it has certain limitations: lack of structured reporting lexicon and the biopsy-option [12].

Supplemental ultrasound breast examination is an ideal supplement to mammography in 45-year-old patients and older, and it is usually the only required method for breast evaluation of young women, preg-

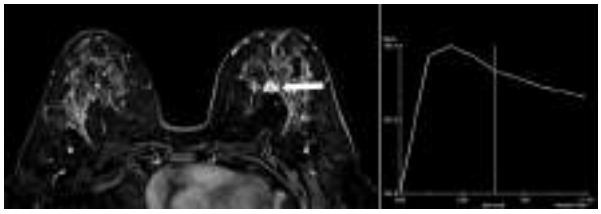
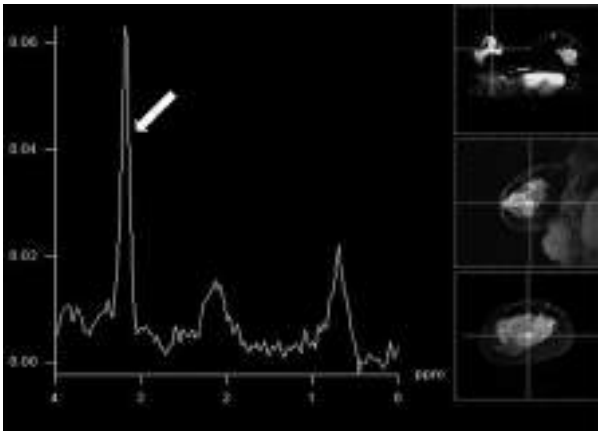


Figure 2. MR mammography. An infiltrative lesion in the central left breast (arrow) shows a curve of the dynamic contrast enhancement typical for malignant lesions
Slika 2. *Magnetnorezonantna mamografija. Infiltrativna lezija u centralnom aspektu leve dojke (strelica) prikazuje krivu posle kontrastnog pojačanja intenziteta signala tipičnu za maligne lezije*



Graph 1. MR spectroscopy. High choline peak shown at 3.2 ppm (arrow) is typical for malignant lesions
Grafikon 1. *Magnetnorezonantna spektroskopija. Visok pik holina na 3.2 ppm skale (strelica) pokazuje tipičan spektar za leziju malignih karakteristika*

nant and breastfeeding women, as well as in the evaluation of early post-treatment complications and sequelae (seromas, abscesses, liponecrosis, hematomas etc.). Being a non-invasive, simple and fast method, the main purpose of ultrasound breast examination is to differentiate whether the lesion is solid or cystic and to classify it in one of the six categories of the breast imaging reporting and data system according to the American College of Radiology recommendations [13–15]. Ultrasonography has a significant role in breast cancer screening as a supplementary examination to mammography, especially in patients with high-density breasts and in those who are at a high risk of breast cancer but cannot undergo breast magnetic resonance (MR) imaging. According to the Breast Imaging Society and the American College of Radiology, there is insufficient evidence that would support inclusion of breast ultrasonography in routine breast cancer screening programs in the above mentioned population [16]. Due to its harmlessness, ultrasound is an ideal guiding method for percutaneous core biopsy and fine-needle aspiration biopsy, thus enabling fast pathological and cytological diagnostics and further management.

Contrast-enhanced ultrasound of the breast has a limited role in everyday clinical practice. There are numerous studies currently taking place in the United States and Japan, but there is still no classification system for characterization of lesions [17]. Both exact quantitative and qualitative parameters remain controversial, since there is significant overlapping of enhancing features in both benign and malignant lesions [18].

The third modern breast imaging modality is **MR mammography** which is highly sensitive for breast lesions in comparison with standard mammography and ultrasonography **(Figure 2)**. Studies have shown that the sensitivity of MR mammography in invasive breast cancer detection is higher than 90%, the highest among breast imaging modalities. Due to its high cost and low availability, as well as relatively low sensitivity in the detection of breast cancer in situ, which is 40 - 80% according to different authors, MR mammography is still not implemented in big screening programs [19, 20]. The MR mammography shows a great potential in the detection of breast cancer in patients after breast-conserving surgery, radiation and neoadjuvant chemotherapy, in women with high-density breasts, and high-risk patients. In prosperous and developed countries, MR mammography is used as a supplementary or screening method for above mentioned patients. MR mammography is used in detailed preoperative assessment of lesion location and number of lesions, disease extension, and neoadjuvant treatment response. In preliminary staging, MR mammography detects an additional lesion in about one-third of patients. In patients who underwent breast-conserving surgery, it can be used as a screening method for the contralateral breast - in about 5% of cases an additional lesion is detected that has been previously missed on mammography and ultrasound. The MR mammography has a high specificity (more than 90%) and relatively low sensitivity (about 60%) in predicting the pathological complete remission after preoperative therapy, a task in which standard mammography, ultrasound, and physical examination have limited accuracy [21]. Therefore, MR mammography is suggested for all patients diagnosed with breast cancer [20, 22, 23]. The use of MR mammography is limited in some physiological and pathological conditions of breast tissue, which may render the examination uninformative. General contraindications (pacemakers and ferromagnetic foreign bodies) are also limitations of this imaging method. In pregnant and lactating patients, patients with confirmed mammary dysplasia or patients on hormone replacement therapy, there is an intensified hormonal stimulation of glandular tissue. Consequential increased vascular permeability, similar to that in malignant or non-malignant inflammations, causes diffuse contrast enhancement of breast tissue. This may produce a false-positive or false-negative result by masking an otherwise enhancing lesion.

Kuhl et al. introduced a concept of an abbreviated protocol for breast MR imaging for breast cancer

screening, which required only two sequences: one pre- and one postcontrast acquisition and two derived images (first postcontrast subtracted and maximum intensity projections images) [24]. This protocol significantly reduces acquisition and reading time burden (lasts about 3 minutes), has a very high negative predictive value (99.8%) but requires an expert radiologist. Nevertheless, there is an important issue related to breast tumors that do not induce neoangiogenesis and do not yield this crucial initial postcontrast enhancement.

The role of **diffusion-weighted imaging (DWI)** in MR mammography is still under a lot of discussion mostly due to lack of standardization and validation since the protocols vary among the centers. This led to the establishment of the International Breast DWI working group. The latest paper published by this group provides basic requirements for routine clinical application of breast DWI and defines the diffusion levels in typical breast lesions [25]. It should be performed on MRI units of 1.5T or more, before the contrast-enhanced part of the protocol, in the axial plane, using echo-planar imaging (single- or multi-shot) obtained in at least three orthogonal directions. The choice of b-values is a challenging decision, given that higher values can increase the specificity but reduce the signal-to -noise ratio. Therefore, a consensus was made to use a b-value of 800s/mm^2. Regarding characterization of the lesion, it is crucial to analyze both DWI images and derived apparent diffusion coefficient (ADC) maps together, to avoid misinterpretation. The position of the region of interest should always be performed in the same manner: in the field with lowest ADC values ("the darkest" points) avoiding cystic, necrotic, noisy, and non-enhancing parts of the lesion. There are no real cut-off values that can be used for lesion discrimination, but it is known that invasive ductal and lobular cancers, as well as ductal carcinoma in situ with microinvasion exhibit the lowest ADC values. However, mucinous and triple negative breast cancers can show high to very high ADC values especially if necrotic [26, 27]. Given that some highly cellular benign lesions can also yield low ADC values, the interpretation of DWI is not recommended alone, but in combination with morphologic and dynamic features of the lesions [25]. In conclusion, even though it should not be used as a stand-alone imaging technique, it is a valuable option in patients that have contraindications for application of gadolinium-based contrast agents, since the sensitivity of this methods in cancer detection exceeds that of mammography or ultrasound alone [28].

MR spectroscopy is a valuable tool for assessing the biochemical properties of tissues in vivo, measuring the levels of choline compounds found in the cell membrane. An elevated level of choline metabolites indicates a malignant nature of the lesion, since it correlates with cell membrane turnover, which is accelerated in proliferative states **(Graph 1)**. The goal of supplementary MR spectroscopy after MR mammography is reducing the number of negative biopsy results, as well as quantification of neoadjuvant therapy response by following the changes in choline levels. MR spectroscopy is supposed to increase the positive predicting value of MR mammography, especially in monitoring chemotherapy response, as the decrease in choline levels should precede any detectable changes in lesion size and morphology [20, 29, 30]. In a recent study by Prvulović Bunović et al., a relatively high sensitivity (0.8) and specificity (0.741) was shown for detection of choline peak as a biomarker of breast lesion malignancy [31]. However, caution must be present in interpreting certain types of both malignant (lobular cancer) and benign lesions (adenoid fibroadenomas), since a significant number of both false-positive and false-negative findings was found.

In recent years, the advancement of **Positron Emission Tomography** (PET) and **Positron Emission Mammography** (PEM) made a significant impact on the management of locally advanced breast cancer. The PET provides evaluation of early treatment response, as shown by the latest studies, but protocol standardization and comparison of results is necessary for its implementation into routine clinical practice. Nevertheless, assessing treatment response by measuring standard uptake values (SUV) of primary as well as secondary lesions before, during and after chemotherapy has already established PET as a valuable tool in breast cancer management. The absence or decrease of SUV in a lesion after treatment most likely indicates that the current drug should be discontinued and additional treatment options considered. New multicentric studies have shown that PEM, as a supplement to digital mammography, and physical examination show a sensitivity of 91% and a specificity of 93% in breast cancer detection. The limitation of PET and PEM, however, is ionizing radiation which disables large sample studies and screening of asymptomatic patients. The PET/MRI shows promising early results in treatment response prediction, but further development and larger sample studies are necessary [32–34].

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University of Belgrade, Belgrade
Faculty of Special Education and Rehabilitation[1]
Health Center Zvečan, Zvečan[2]

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EATING AND SWALLOWING DISORDERS IN CHILDREN WITH CEREBRAL PALSY

POREMEĆAJI HRANJENJA I GUTANJA KOD DECE SA CEREBRALNOM PARALIZOM

Mile VUKOVIĆ[1] and Jelena TODOROVIĆ[2]

Summary

Introduction. Cerebral palsy is characterized by abnormalities of muscle tone, movement and motor abilities caused by disorders in brain development. Many children with cerebral palsy have severe swallowing problems. **Cerebral Palsy.** Cerebral palsy is a neurodevelopmental disorder characterized by abnormalities in brain development. Swallowing is a process by which a bolus that is formed within the oral cavity is transported through the pharynx into the esophagus and stomach. It has four phases: preparatory oral, oral, pharyngeal and esophageal. **Swallowing disorders in children with cerebral palsy.** Swallowing disorders vary depending on the type of cerebral palsy. Children with spastic paralysis have a more pronounced disorder of the voluntary phases of swallowing, while children with athetoid paralysis are expected to have a disorder at the oral-motor level. Neurological lesions may affect the muscle function of the jaw, cheeks, lips, tongue, palate and pharynx, which is manifested by difficulties in controlling saliva and swallowing. **Diagnosis and treatment of dysphagia in cerebral palsy.** Diagnosis and treatment of dysphagia is best accomplished by a team of experts including a pediatrician, neurologist, otorhinolaryngologist, gastroenterologist, radiologist, dental specialist, speech therapist, nutritionist, and a specialist in physical medicine and rehabilitation. **Conclusion.** Dysphagia is a common comorbidity in children with cerebral palsy. Although swallowing disorders often correlate with the type of cerebral palsy, the most prevalent signs of dysphagia include: coughing, prolonged feeding time, laryngotracheal penetration and aspiration, suffocation, which leads to dehydration, malnutrition, but also to the need for alternative feeding methods. It is important to emphasize the importance of early treatment by a team of experts, with a speech therapist as a team leader.

Key words: Cerebral Palsy; Child; Feeding and Eating Disorders; Deglutition Disorders; Diagnosis; Treatment Outcome

Sažetak

Uvod. Cerebralnu paralizu karakterišu abnormalnosti mišićnog tonusa, pokreta i motoričkih sposobnosti usled poremećaja u razvoju mozga. Mnoga deca sa cerebralnom paralizom imaju izražene smetnje u gutanju. **Cerebralna paraliza** je neurorazvojni poremećaj za koji su karakteristične abnormalnosti u razvoju mozga. **Gutanje** podrazumeva akt formiranja bolusa u usnoj duplji i njegov tranzit kroz ždrelo u jednjak i želudac. Ima četiri faze: pripremnu oralnu, oralnu, faringealnu i ezofagealnu. **Poremećaji gutanja kod dece sa cerebralnom paralizom** variraju u zavisnosti od tipa cerebralne paralize. Deca sa spastičnom paralizom imaju izraženiji poremećaj voljnih faza gutanja, dok se kod dece sa atetoidnom paralizom očekuje poremećaj na oralno-motoričkom nivou. Prisustvo neurološke lezije može da utiče na mišiće vilice, obraze, usne, jezik, nepce i ždrelo, što se manifestuje teškoćama u kontroli pljuvačke i u gutanju. **Dijagnostika i tretman disfagije kod cerebralne paralize** sprovodi se timski. Stručni tim uključuje pedijatra, neurologa, otorinolaringologa, gastroenterologa, radiologa, specijalistu dentalne medicine, logopeda, nutricionistu i specijalistu fizikalne medicine i rehabilitacije. **Zaključak.** Disfagija predstavlja značajan komorbiditet kod dece sa cerebralnom paralizom. Iako smetnje u gutanju često korelišu sa tipom cerebralne paralize, u opšte znake disfagije mogu se izdvojiti: kašljanje, produženo vreme hranjenja, laringotrahealna penetracija i aspiracija, gušenje, što dovodi do dehidracije, neuhranjenosti, ali i do potrebe za alternativnim metodama hranjenja. Važno je naglasiti značaj ranog lečenja u koje je uključen tim stručnjaka, pri čemu je logoped obično rukovodilac tima.

Ključne reči: cerebralna paraliza; dete; poremećaji hranjenja; poremećaji gutanja; dijagnoza; ishod lečenja

Introduction

Cerebral palsy (CP) is a neurodevelopmental disorder characterized by abnormalities in muscle tone, movement, and motor ability caused by disorders in brain development [1]. It is a heterogeneous group of nonprogressive motor disorders associated with muscle weakness, limited range of motion, spasticity, and pathological reflexes [2]. It is a consequence of various etiological factors that caused brain damage before or during birth, or in the first years of life [3].

In addition to impairments in motor skills, disorders of sensation, perception, cognition, speech and behavior, epilepsy and musculoskeletal disorders are also often observed in CP. Disorders of swallowing may also be present, leading to changes in the anticipatory, preparatory, oral, pharyngeal, and esophageal phases of swallowing [4]. Thus, eating and swallowing difficulties affect the nutritional status of persons with CP [5].

Corresponding Author: Dr Jelena Todorović, Dom zdravlja Zvečan,
38227 Zvečan, Bube Mihailovića BB, E-mail: jelena.milisavljevic90@gmail.com

Abbreviations
CP – cerebral palsy
HRM – high-resolution manometry

Cerebral Palsy

According to the current definition, developed by an international team of experts, CP is a group of permanent, but not unchanging, disorders of movement and/or posture and motor function, which are the result of non-progressive disorders, lesions or abnormalities of the developing brain [6]. The CP is one of the leading causes of neurological impairment in childhood [7]. The incidence of CP is 2 – 3 per 1000 term, live births, while the incidence in preterm infants it ranges from 40 to 200 per 1000 live births [3, 8, 9].

The etiology of CP is multifactorial, but in 92% of cases it is thought to occur in the perinatal period [10]. The risk factors include congenital malformations in the development of the cortex, hypoxia, asphyxia, while injury and central nervous system infections are the most common postnatal causes of CP [11]. Despite the identification of risk factors, in 80% of cases the cause of CP is unclear and it is considered idiopathic [12].

Due to the heterogeneity of the clinical presentations, CP is classified according to the type of disorder and the topography. From the clinical aspect and based on the type of motor disorder, spastic, dyskinetic, and ataxic types of CP are distinguished, while the hypotonic type is not included in the classification because it progresses into one of the three types [1].

The spastic type of CP is the most common, occurring in as many as 85% of cases [13]. It is characterized by increased muscle tone, increased resistance to passive movements, abnormal posture and movements, and scissor gait [14]. Instead of fine and individual movements, the movements are massive, while the voluntary movements are slower and are performed with effort [1]. This type of CP is further broken into three subtypes: 1) spastic hemiplegia, 2) spastic diplegia, and 3) spastic quadriplegia [1].

The dyskinetic type of CP occurs in about 7% of cases [13]. Motor disorders in this type are much more severe than in other forms, and are manifested by difficulties in performing targeted movements, uncontrolled movements, while repetitive movements are often observed [14]. Certain forms of non-motor comorbidity are also observed in CP, such as intellectual development disorders, epilepsy, impaired vision, hearing, and dysphagia [15]. The dyskinetic type of CP is manifested as choreoathetoid and dystonic type of CP [1].

The ataxic type of CP is the rarest and occurs in about 4% of cases [13]. It is manifested by decreased muscle tone, tremor, and disturbances in the performance of goal-directed movements [14]. In addition, children with the ataxic CP often exhibit abnormal patterns of posture or movement and loss of orderly muscle coordination, which affects the strength, rhythm, and accuracy of the arm, leg, and torso movements [16].

Swallowing and phases of swallowing

Ingestion is the process of bolus formation in the oral cavity and its transport through the pharynx into the esophagus and stomach [17]. This complex process requires precise coordination of more than 30 muscles located within the oral cavity, pharynx, larynx, and esophagus [18]. Understanding the normal physiology and pathophysiology of swallowing is the basis for the detection and treatment of swallowing disorders.

Different authors present different phases of the swallowing process. According to Logemann [19], swallowing has four phases: a) preparatory oral, b) oral, c) pharyngeal and e) esophageal. Some authors additionally divide the oral phase into three more phases: food transfer through the oral cavity, food processing by chewing and saliva, and food transfer to the oropharynx.

The preparatory oral phase involves chewing movements and the formation of a bolus in the oral cavity. The patterns of movement in the preparatory oral phase vary depending on the viscosity of the food, its quantity, as well as the degree of pleasure [20]. The oral phase has the role of preparing food completely and facilitating the pharyngeal phase. The tip of the tongue is raised, it touches the alveolar ridge, and the posterior part is lowered, opening the passage to the pharynx. The dorsal surface of the tongue moves upwards, expanding the area of contact with the palate and pressing the fluid along the palate [18]. The pharyngeal phase begins by inducing a pharyngeal swallowing reflex. The velopharyngeal sphincter rises and closes the path to the epipharynx, the epiglottis closes and thus prevents the penetration of food inside the larynx and further into the airways [18]. These actions separate the digestive and respiratory tracts. When it comes to swallowing fluids, this phase begins during the oral phase [21]. The esophageal phase is the involuntary phase of swallowing.

Ingestion consists of a series of activities that require highly integrated sensorimotor coordination of multiple structures: cranial nerves, muscles, centers in the brainstem, as well as bilateral areas in the cortex [22]. Studies have shown that the left hemisphere plays a greater role in motor planning and the components of voluntary swallowing. In contrast, the right hemisphere is more involved in the automatic aspects of the swallowing process, during the pharyngeal phase. Although the role of individual hemispheres in the act of swallowing has not been fully elucidated, empirical data testify to the existence of bilateral control of the swallowing process [22].

From the point of view of development, it can be said that in newborns and younger infants, none of the four phases of swallowing is voluntary and that voluntary control of the oral phase is established at a later age. In older children, chewing is a voluntary activity, relying on appropriate sensory bolus registration and motor response [23].

Swallowing disorders in children with cerebral palsy

Dysphagia is often seen in children with CP. It is a swallowing disorder that may occur at any stage, oral preparatory, oral, pharyngeal, or esophageal phase [24]. The incidence of dysphagia in children with CP ranges from 19 to 99%. It often results in inadequate food intake, aspiration, and subsequent respiratory tract infections [25]. Some authors believe that all people with CP have some gastrointestinal disorders at some point of life [26]. The variability in reporting the prevalence of dysphagia in CP probably reflects differences in the level of motor impairment, intellectual disability, and the presence of other comorbid impairments.

Lucchi et al. [27] reported presence of dysphagia in most people with CP. According to some data, about 66% of children with moderate dysphagia are on a specific semi-liquid diet, while 95% of those with severe dysphagia use alternative feeding methods. Difficulties in chewing solid food are present in as many as 70% of children with CP, and 60% have difficulties in drinking from a glass [28].

Empirical data show that the severity of swallowing disorders varies depending on the type of cerebral palsy [29]. The difference in the severity of swallowing disorders may be related to the extent and location of the neurological damage. Spastic paralysis occurs due to bilateral injury of the upper motor neuron (pyramidal and extrapyramidal pathway) and these children have a more pronounced disorder of the voluntary phases of swallowing. The athetoid type of CP occurs as a consequence of lesions of the basal ganglia, and in these children, the swallowing disorder occurs at the oral-motor level [29].

Proper oral skills, as well as coordination of the movements of the muscles of the orofacial region, especially the tongue, are required for the normal development of sucking, swallowing and chewing [30]. It is known that a neurological lesion associated with CP can affect the muscles of the jaw, cheek, lips, tongue, palate, and pharynx, which is functionally manifested by difficulties in saliva control, swallowing, and speech [31]. Bilateral damage to the upper motor neuron usually causes a swallowing disorder, which manifests itself in problems in the formation of food bolus and a delay in the transfer of solid and liquid food from the oral cavity to the digestive tract [32].

Studies about the characterization of dysphagia in CP point out that swallowing disorder occurs both due to problems in voluntary oral movements and in the reflex pharyngeal phase of swallowing. Signs of dysphagia, such as delayed onset and segmented swallowing (voluntary movement), have been shown to occur due to damage to cortical neural networks. On the other hand, the signs of disorders of the pharyngeal component of swallowing, i.e., automatic components of deglutination, such as throat clearing, suggest subcortical brain injury and/or basal ganglion necrosis [33].

It has also been shown that children with CP due to poor lip control show difficulties in receiving bolus and sucking. In addition, poor lip closure leads to food loss as well as excessive salivation [34]. Uncontrolled salivation, i.e., spillage from the mouth to the lips, chin, neck and clothes, is present in 40% of people with CP, and in 15% of cases, it manifests itself in a severe form [35]. Studies have shown that children with uncontrolled salivation have greater difficulty in forming a bolus, inability to completely close the lips, and more residual contents in the oral cavity after swallowing [36]. It is believed that there is a significant correlation between the inability to close the lips and uncontrolled salivation [37].

The spastic type of CP is also associated with spasticity of the respiratory musculature, rigidity of the chest wall, impaired posture and abnormal time of muscle activation [38]. These factors may also contribute to insufficient intrathoracic and subglottic pressure. It is therefore not surprising that children with CP use compensatory strategies while eating. The oral transit time in children with CP is longer if they have a severe motor impairment [5].

Empirical data show that disorders at any stage of swallowing affect the safety and efficacy of oral intake required for adequate nutrition and hydration [25]. Swallowing disorders correlate with prolonged meals, poor growth and nutritional status, and potential respiratory consequences [28].

Disorders during the pharyngeal phase may include delayed or incomplete airway closure during swallowing, or pharyngeal aspiration of food or fluid, and food debris in the pharynx [31]. Aspiration may occur before swallowing (due to incoordination of the tongue, which allows the bolus to spill prematurely over the base of the tongue or a delayed swallowing reflex); during swallowing (associated with inefficient laryngeal closure); or after ingestion [21]. In children with CP who have swallowing difficulties, silent aspiration is common, when food or fluid enters below the right vocal folds, without clinical signs and symptoms [31]. The overall incidence of pulmonary aspiration in children with CP due to oral motor dysfunctions is not precisely known, but frequent hospital admissions due to presumed aspiration pneumonia are reported [33].

The incidence of gastroesophageal reflux is estimated in over 50% of children with CP, which can be explained by lesions in the neuronal-anatomical swallowing center located in the medulla oblongata, which leads to reflex dysfunction [33]. Reflux episodes have been shown to cause not only gastrointestinal symptoms, such as regurgitation or vomiting, but also respiratory problems, such as recurrent respiratory infections, persistent cough, life-threatening episodes of apnea, and respiratory failure [39].

Diagnosis and treatment of dysphagia in cerebral palsy

Clinical and instrumental assessment is used to diagnose dysphagia in children with CP [40]. Clinical assessment includes evaluation of medical records, a thorough review of medical history, and heteroanamnesis.

Clinical assessment is often supported by instrumental diagnostic procedures [41]. Diagnostic methods of dysphagia in children are videofluoroscopy, flexible endoscopy, and if no other diagnostic intervention is possible, manometric assessment of swallowing is used [41].

Videofluoroscopy is considered the gold standard in the diagnosis of dysphagia. This method allows real-time insight and visualization of the bolus through the oral cavity, oropharynx, hypopharynx, and esophagus, using modified barium [42]. It also provides information on the existence of absorption/penetration into the airways (before, during and after ingestion), the amount and localization of food residues in the oral cavity and pharynx [41].

The next diagnostic procedure is *flexible endoscopy*, which is used to assess the structures and functions of the upper respiratory tract, secretions, as well as pharyngeal phase of swallowing. It is performed using a flexible laryngoscope placed through the nose and then through the pharynx, in order to see the pharyngeal and laryngeal structures during swallowing [43]. It enables recording of the superior part of the pharynx and larynx. The obtained are color images [41].

One of the diagnostic methods is *high-resolution manometry (HRM)*. This method is used to objectively measure the swallowing pressure generated by muscle force along the pharynx and esophagus. The main indication for using HRM is the impossibility to assess swallowing differently, in cases of aspiration, nasal regurgitation, and coordination of breathing and swallowing [41].

After detecting signs of swallowing disorders and diagnosing dysphagia, children are included in the appropriate treatment program. Treatment of dysphagia in children with CP is performed by a professional team that includes doctors of appropriate specialties (pediatrician, neurologist, otorhinolaryngologist, gastroenterologist, radiologist, and dental specialist), speech therapist, nutritionist and a specialist in physical medicine and rehabilitation. Due to the nature of swallowing disorders, a speech therapist is usually the supervisor of the therapeutic process [41]. A speech therapist assesses oral-motor abilities and determines the most appropriate feeding techniques [40]. Also, the speech therapist, in cooperation with the physiotherapist, determines the best position when feeding the child with CP. From the therapeutic aspect of swallowing disorders in children, techniques for strengthening the muscles of the lips, tongue and jaws [44], as well as proper positioning during feeding, are most important. Also, impaired hand movement with inadequate body posture may disable self feeding, so they often need parental support or the support of a therapist [45]. Parental attitude towards the child's diagnosis is very important for the success of therapeutic interventions [46].

Conclusion

Data on the incidence of dysphagia in children with cerebral palsy vary widely and range from 19% to 99%. Despite the lack of precise data on the prevalence, it should be noted that most empirical studies show that dysphagia is a significant comorbid disorder in children with cerebral palsy. It has also been shown that eating and swallowing disorders vary in severity and depend on the type of cerebral palsy. Dysphagia in children with cerebral palsy is characterized by a whole set of different signs, some of which occur due to problems in the oral phase, and others in the pharyngeal phase of swallowing. Some signs of swallowing disorders, such as choking, coughing, prolonged feeding time, laryngotracheal penetration and aspiration, can lead to dehydration, malnutrition, but also the need for alternative feeding methods. Due to the complexity of the disorder, it is important to emphasize the importance of early diagnosis and treatment of swallowing disorders. Early detection of disturbances and early intervention in the area of feeding and swallowing can prevent many problems. Early counseling with parents and timely selection of good feeding techniques are of particular importance for the treatment of dysphagia in children with cerebral palsy. Although different techniques are used in the treatment of dysphagia in children with cerebral palsy, empirical data show that there is still no solid, scientifically verified evidence of the effectiveness of existing interventions in the field of eating and swallowing disorders in children with cerebral palsy. Therefore, future research should be directed towards obtaining as objective evidence as possible about the effects of existing therapeutic methods. Part of future research in this area should be dedicated to the development of new therapeutic procedures. We are sure that the implementation of appropriate therapeutic interventions leads to an improvement in the quality of life of children and their family members. Also, improvement of eating and swallowing contributes to better emotional and physical health of these children.

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University of Belgrade, Belgrade
Faculty of Special Education and Rehabilitation[1]
Clinical Hospital Center Zvezdara, Belgrade[2]

Seminar for physicians
Seminar za lekare u praksi
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SENSORY INTEGRATION AND ITS SIGNIFICANCE FOR FUNCTIONING AND DEVELOPMENT OF CHILDREN'S SPEECH

SENZORNA INTEGRACIJA I NJEN ZNAČAJ ZA FUNKCIONISANJE I RAZVOJ GOVORA DECE

Ivana ILIĆ SAVIĆ[1], Mirjana PETROVIĆ LAZIĆ[1] and Radmila RESIMIĆ[2]

Summary

Introduction. Sensory integration involves organizing sensory stimuli that are processed by the brain to produce adaptive responses to environmental demands. For a significant minority of children, sensory processing of information on daily basis may be a huge challenge. Sensory integration dysfunction occurs when the ability of different sensory systems for recognition, processing, and integration of stimuli and combination of information with modulations received from other systems is impaired. **Sensory processing therapy**. Sensory processing therapy is one of the newest, comprehensive therapeutic methods used in children with various pathologies. Sensory and perceptual development makes the basis to which sensory impressions, woven into social experience and neurological processing, are added to make a perception. That is why it is important to include young children in a stimulating environment that encourages active participation, enabling them to strengthen established neural connections, establish patterns of behavior, and properly understand past and anticipate future challenges. The aim of this study was to present the link between sensory integration and speech. The introduction provided an overview of the role of sensory processing and its significance for the overall child development. Also, the importance of researching sensory processing for the functioning and development of speech in children was emphasized. **Conclusion.** Finally, theoretical considerations on speech development in some disorders including sensory integration disorder were discussed.

Key words: Feedback, Sensory; Sensation Disorders; Perception; Speech; Child Development; Patient Participation

Sažetak

Uvod. Senzorna integracija podrazumeva organizovanje senzornih stimulusa koje obrađuje mozak kako bi se proizveli adaptivni odgovori na zahteve okoline. Za značajnu manjinu dece senzorna obrada svakodnevnih unosa može biti ogroman izazov. Disfunkcija senzorne integracije se javlja kada je poremećena sposobnost različitih senzornih sistema da prepoznaju, obrade i integrišu stimuluse i da kombinuju informacije sa modulacijama primljenim iz drugih sistema. **Terapija senzorne obrade** jedna je od najnovijih, sveobuhvatnih terapijskih metoda koja se koristi kod dece različitih patologija. Senzorni i perceptivni razvoj čine bazu na koju se nadovezuju čulne impresije koje su protkane kroz socijalno iskustvo i neurološku preradu i kao takve tvore doživljaj. Zato je važno uključiti decu ranog uzrasta u stimulativno okruženje koje ih „poziva" na aktivno učešće, omogućavajući im osnaživanje uspostavljenih neuronskih veza, utvrđivanje obrazaca ponašanja, pravilno razumevanje prethodnih i predviđanje budućih izazova. Cilj ove studije je da predstavi vezu između senzorne integracije i govora. U uvodnom delu dat je pregled shvatanja uloge senzorne obrade i njen značaj za celokupni detetov razvoj. Nakon toga istaknut je značaj istraživanja senzorne obrade za funkcionisanje i razvoj govora kod dece. **Zaključak**. Na samom kraju izvršena je elaboracija teorijskih razmatranja o razvoju govora kod nekih poremećaja koji uključuju poremećaj senzorne integracije.

Ključne reči: senzorna obrada; senzorna disfunkcija; percepcija; govor; razvoj deteta; aktivno učešće pacijenta

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Introduction

Sensory integration enables our brain to process, organize and select all received information from the environment in order to adequately respond to them with some purposeful activity [1]. Sensory integration in healthy individuals is spontaneous and the reception of multisensory information is integrated effortlessly, leading to faster and better performance on detection and discrimination of the task related to the performance of individual sensory inputs [2].

In some people, reactions of their own body are unclear and may distract them. In this case, we are talking about a sensory integration disorder. Sensory integration dysfunction (SID), previously called a sensory processing dysfunction, leads to multiple problems in communication and social interaction in affected children, with abnormal patterns of behavior. The senses are sensory systems that function on the principle of creating neural connections between

Corresponding Author: Asist. dr Ivana Ilić Savić, Univerzitet u Beogradu, Fakultet za specijalnu edukaciju i rehabilitaciju, 11000 Beograd, Visokog Stevana 2, E-mail: ivana.ilic558@gmail.com

Abbreviations
SID – sensory integration dysfunction
CP – cerebral palsy

receptors and afferent nerve pathways, basal ganglia and subcortical structures [3]. Inefficient sensory integration includes impaired stimulus reception, processing, and modulation within different sensory systems, as well as impaired data integration from different sources.

Investigating the characteristics of SID, previous research shows that dysfunction manifests as hypersensitivity or hyposensitivity (excessive and insufficient reactivity). Hypersensitivity or hypersensitivity to stimuli occurs when the sensory threshold is lower than normal, detecting and exciting even the weakest stimuli. Hyposensitivity, on the other hand, involves a high sensory threshold, which requires a much stronger force or number of stimuli to stimulate the brain [4]. Sensory integration therapy is one of the newest, comprehensive methods of therapy used in children with speech disorders, psychomotor impairments and learning difficulties [5].

We experience the world through seven senses: tactile sense (touch, pressure, pain, vibrations, warm, cold), vestibular (movement, balance, establishing adequate muscle tone, awareness of spatial orientation), proprioceptive (conscious movements of muscles and joints) perception of the position of different parts of the body of one in relation to the other and the range of motion of different parts of the body), auditory, visual, oral-gustatory and olfactory sense [3].

As the sensory integration processes start intrauterine [5], early deficits at the sensory processing level may determine further developmental pathways [6]. Hypersensitivity of the vestibular system is associated with the child's ability to perform daily activities independently and is typically manifested in the child's unwillingness to change head position, maintain body balance, concentration and oculomotor control while trying to follow the written text with his eyes, which makes him excessively tired [7].

The tactile system receives information from receptors located in the skin throughout the body. Feedback signals received from the tactile system facilitate motor planning and greatly affect emotional stability and social functioning [8]. Dysfunction of the tactile system is characterized by abnormal perception which is classified as hypersensitivity during everyday activities such as bathing, showering, washing, brushing, and cutting hair. These children cannot tolerate stiff or coarse textiles, tight clothing and clothing tags [7]. On the other hand, children hyposensitive to touch crave intense physical contact, tend to squeeze or hug other people, but also clap hands, stamp feet and bang their head on purpose. They tend to rub their bodies with various objects, showing weakened physical reactions, including a lack of pain response to injuries such as blows, cuts and bruises. Their sensory searches are often manifested by self-beating, self-biting, self-scratching, banging of the head or convulsions of the movement in order to release internal tension. Tactile deficits negatively affect learning, concentration and emotions [9].

Previous research shows that tactile and vestibular dysfunction in children is usually accompanied by uncoordinated proprioception. The proprioceptive system (also known as the deep sensation system) largely cooperates with the vestibular system. Its receptors are distributed through muscles, ligaments, joints and connective tissue. An uncoordinated deep sensation is usually presented as an everyday "clumsiness", e.g. constantly dropping objects such as toothpaste or toothbrush, too much or too little pressure on various objects, difficulties when aligning body parts when dressing [7].

Visual perception is essential for any activity that requires supervision, control or care. Basic visual functions are the basis for psychomotor and visual-perceptual development of a child [1]. Dysfunction of visual perception manifests itself as abnormal sensitivity to light and colors, inconsistency in putting together puzzles, because the child concentrates on detail and is not able to see the picture as a whole [2].

Auditory perception is a process in which our ear collects sounds of different frequencies and sends them through the auditory pathways to the brain. The brain processes them and stores them as needed. We hear with our ears and listen with our brains [1]. Practical examples of auditory perception dysfunction include irritability due to noise, difficulty in understanding verbal commands and localization of sound, or fascination with a sound that the child constantly repeats [6].

Olfactory hypersensitivity (hyperosmia) is manifested by vomiting or even "suffocation" in response to strong odors, which can be felt from a great distance, avoiding food (especially hot) with strong aromas and accepting only certain foods and ways of serving. These persons are bothered by perfumes, cosmetics or cleaning products and other people's natural body odors. Olfactory hyposensitivity, on the other hand, is manifested by searching for strong odors, sniffing objects and people, eating inedible substances, licking hands, etc. [9].

Early in his professional career, A. Jean Ayres recognized the importance of systematic and comprehensive assessment and measuring sensory, motor, and practical function and dysfunction. She designed and adapted standardized tests that assess sensory perception, practice, bilateral integration, and balance, as well as nonstandard observational measures of functions such as sensory reactivity and postural mechanisms. Ayres developed individual tests and then published Southern California Sensory Integration Tests that were later revised and reclassified to become sensory integration tests. This set of tests has been standardized on approximately 2,000 children aged 4 to 8 years and it is the only published set of tests that collectively addresses sensory integration functions that have been identified to date. Today, these tests show strong

reliability and validity and represent the gold standard for assessing sensory integrative functions in children [10]. In addition to this test, some of the questionnaires regarding sensory functioning and integration are used today, in order to complete the assessment with a functional assessment [1].

A comprehensive assessment of sensory, motor, and practical functions that may affect professional performance is crucial for evidence-based intervention. The research-based assessment process allows adequate characterization of a person's strengths and challenges for planning individually tailored interventions.

The role of sensory processing in speech neurodevelopment

Speech production is a highly specialized motor behavior that involves precisely coordinated movements of the articulator muscles, and relies on the integration of sensory feedback into vocal motor systems [11]. Multisensory perception affects an individual's ability to integrate tactile, auditory, visual, vestibular, proprioceptive, gustatory, and olfactory information, which can subsequently affect speech perception [12]. The main function of a multisensory integration system is to combine signals entering the brain through a separate sensory epithelium, so that different forms of energy emanating from the same object or event are treated as a unified perception [13].

Neurobiological research shows that speech perception triggers articulatory action through sensory modalities which over time creates a neural network for sensorimotor integration of speech. Auditory and visual speech information is often strongly integrated resulting in improved perception of audiovisual speech through auditory and visual stimuli. The integration of audiovisual speech is performed by the upper temporal sulcus and the lower frontal gyrus [14].

Recent clinical studies show that individuals with speech production deficits may show significant improvement in the neural network of speech during mimicry of the audiovisual speech signal, indicating the existence of a visuomotor pathway for speech motor control [15].

Although previous research shows that sensory processing abnormalities are often associated with neurodevelopmental disorders, there is no reason to expect that they occur exclusively in individuals who meet the criteria for one of the established diagnostic categories (developmental dysphasia, dyslexia and dysgraphia, autism, attention deficit hyperactivity disorder, apraxia). Therefore, it is accepted that there is a significant number of children who have a problem with sensory processing, without meeting the criteria for any disorder of neurological development. These children are of great clinical concern, because in the absence of a clearly identified diagnostic category, their access to services and appropriate treatments is often limited, which should be the subject of future research [16].

Sensory processing dysfunctions and speech disorders in cerebral palsy

Cerebral palsy (CP) is a combination of deficits caused by injury to the central nervous system, manifested by various disorders [19]. From the International Classification of Functioning, Disability and Health perspective, CP affects the person's "functioning" (including bodily structures – e.g., limbs – bodily functions – e.g., intellectual function – and activities – e.g., walking – which in turn causes "secondary disability," or limited participation in everyday activities – e.g., playing sports). Each person with CP lives in a personalized environment and thus its context also contributes to determining their independence, including personal factors – e.g., motivation) and environmental factors (e.g., architectural accessibility) [17].

Investigating the dysfunction of sensory processing, previous research shows that dysfunctions of surface and deep sensations in CP interfere with the perception and development of the body scheme, cause difficulties in motor planning and bilateral motor coordination, which leads to tactile hypersensitivity [8]. The resulting tactile defensiveness affects the whole body and limits the orofacial area [18].

Research on speech and language development in children with CP conducted in Poland shows that speech and language development in children with CP on the one hand depends on the location and extent of the impairment, and on the other - on the level of intellectual development of the child. The results of these studies show that speech disorders occur as a consequence of disorders of higher cortical functions, which affect the perceptual level or the ability to recognize and form a word structure (lack of capacity to recognize and remember acoustic or kinesthetic and motor word structure) or the expressive level or ability of verbal derivation (inability to pronounce or write a sentence structure). These findings suggest that patients with CP have limited mobility of the tongue and palate due to paresis or paralysis, as well as variable muscle tone which interferes with the coordination of the articulation process, manifested by disorders of the sensorimotor and efferent systems [19].

Analyzing different types of CP and the age of the individual, the findings of various studies so far confirm that the symptoms of dysarthria vary depending on the affected structures, and are less pronounced in children compared to adults [5]. Dysarthria is a symptom of CP. Dysarthria is defined as a neurogenic speech disorder characterized by slow, weak, inaccurate and uncoordinated movements of the speech musculature [20]. Dysarthria can also be a consequence of respiratory dysfunctions that include the ability of air to pass through the speech organs to modulate speech, affecting phonation, articulation and prosody. Thus, dysarthria impairs the control and coordination of muscle function necessary for breathing, phonation and articulation, which is involved in the speech process. In the mixed type of CP (pyramidal-extrapyramidal type), moderate spastic dysarthria is present [19].

Studies show that such poor motor control of the articulator muscles in CP often leads to hyper-salivation and jaw instability (involuntary jaw discharge). In the athetoid (extrapyramidal) form of CP, involuntary facial contractions, such as lip and cheek cramps, also interfere with articulation [2].

Sensory processing dysfunctions and speech disorders in autism

The latest classification system of the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, includes sensory problems as one of the diagnostic criteria for autism spectrum disorders [21]. According to Patient Screening and Assessment, autism spectrum disorders are neurodevelopmental disorders that occur before the third year of life and are characterized by difficulties in social interactions, social communication and the presence of repetitive actions and behavioral stereotypes associated with sensory disorders [22].

Altered sensory processing may negatively affect the cognitive function and clinical symptoms [23]. This assumption was confirmed by several studies that used subjective assessment measures, such as self-assessment questionnaires completed by parents. Studies have shown that atypical sensory processing is associated with a number of clinical problems, including anxiety and stereotypical behavior [24, 25].

Recent clinical studies show that the most prominent problem of sensory integration processing in children with autism is impaired visual perception by linking hyposensitivity with the ability to perceive details [26]. The results of recent research confirm these hypotheses, pointing out that children with autism have a less precise multisensory time perception of social stimuli [27], which in turn negatively affects their social communication [14].

Symptoms such as limited verbal contact and difficulty engaging in conversation that predominate in the clinical picture of autism are signs of deficits in both the communication and social dimensions. Research shows that children with autism who have relatively normal language skills often show other communication deficiencies, such as limited facial expressions and difficulty making eye contact, which hinders or completely prevents them from initiating and maintaining social interactions [28].

Speech development in children with infantile autism varies from one child to another. Analyzing auditory processing, research shows that problems in speech development occur due to the inability to differentiate sounds, especially emphasizing the inability to discriminate voice and speech [29]. Expressive language may be impaired or may develop with considerable delay to the point that the child does not speak at all. Research shows that approximately 30 - 40% of children with autism do not use expressive language for communication at all [8]. In recent years, speech development in children with autism has been described as disharmonious, with frequent regressions, i.e., loss of already acquired skills. Research also shows that later acquisition of language skills has negative consequences on the articulation of children with autism. The articulation is damaged in the form of omissions, substitutions and distortions [14]. Speech disorders that are common in autism include echolalia, intonation disorder, and modulation [29].

Analyzing the language competences of children with autism, many studies point out that at the lexical level, a specific vocabulary at the level of nouns and verbs prevails. The main characteristic of their pronunciation is the absence of personal, possessive, demonstrative pronouns and prepositions. At the syntactic level, simple sentences, incomplete contents and telegraphic speech prevail [29].

Research studying nonverbal communication of children with autism shows that nonverbal communication of these children is characterized by inability to compensate for pronounced language deficiency, inadequate response or complete absence of reactions expressed by gesture, facial expressions and body language [23].

Sensory processing dysfunctions and speech disorders in children with intellectual disabilities

The term "intellectual disability" means below-average intellectual functioning, which includes a wide range of different dysfunctions, deficits and difficulties of speech and language development, adaptive functioning, motor skills, motivation, emotional regulation disorders, attention and memory disorders. It is classified as mild, moderate, severe and profound [30].

Studies show that sensory processing dysfunction in children with intellectual disability affects the modulation of vestibular, proprioceptive, tactile, visual and auditory input. Impaired sensory integration manifests by deficits in the registration of vestibular stimuli resulting in decreased muscle tone, impaired balance reactions, and poor movement tolerance. Proprioceptive damage leads to low muscle tone, joint hypermobility, impaired sense of body position and inadequate movement registration [31]. Tactile dysfunctions include hyposensitivity to tactile stimuli and impaired tactile discrimination. The clinical picture of the senses is characterized by astigmatism, nystagmus or strabismus. Recent research has linked the degree of hearing loss with abnormal ear anatomy (narrow ear canals) and a tendency to persistent otitis media, which interferes with speech development [30].

Studies show that speech disorders in children with intellectual disabilities are more likely to occur as complex syndromes of various etiologies with various pathomechanisms and the resulting clinical picture. Some speech disorders occur in the central nervous system and are associated with brain pathology, i.e., injury to the cortical speech centers [32]. Analyzing the condition of the peripheral speech organs of children with intellectual disabilities, it was concluded that any anatomical and physiological change results in impaired phonation, articulation and breathing rhythm. Malformations of the lips and

pharyngeal cavity have a very negative impact on the overall intelligibility of speech. The most common anatomical defects include cleft palate, malocclusion, tongue defects (hypotonia), low muscle tone of the soft palate, larynx, and decreased mobility of the temporomandibular joints. All these deficiencies contribute to problems with chewing and swallowing food, which is an implication for future research [33].

Recent research shows that children with intellectual disabilities have receptive impairments in communication, i.e., difficulties with comprehension, and an inappropriate response to spoken language. The level of comprehension varies from individual to individual depending on intellectual capacity, reception capacity, sensory input processing, and the level of receptive vocabulary [17].

The results of previous research confirm that speech development in children with intellectual disabilities is delayed. In severe and profound intellectual disability, the first words appear at the age of 3 or 4, and simple sentences at the age of 4 – 5. Sometimes expressive speech is limited to the use of individual words, and nonverbal communication is insufficiently differentiated [34].

Conclusion

Sensory integration processes underlie the relationship between neurological functions and speech development. Sensory integration dysfunction is the result of inadequate reception, processing, modulation, perception, and response to sensory information. Adequate sensory processing is necessary for functioning and development of speech in children. Due to the crucial role of motor function, appropriate muscle tone and the acquisition of fine motor skills for the process of speech development in children, it seems that the early application of adequate therapy performed by an interdisciplinary team of specialists in relevant fields is of great importance.

This paper points to the existence of empirical and theoretical evidence of atypical sensory perception in children with cerebral palsy, autism, and intellectual disability. Based on the findings of previous research, we found that impaired sensory processing in these children affects multisensory integration, which indirectly affects the ability to perceive speech, which is impaired in these children. These data support hypotheses that point out that sensory perception abilities in children with sensory processing disorders may contribute to their basic diagnostic characteristics. These data also confirm the assumptions of many contemporary theoretical reviews of cerebral palsy, autism and intellectual disability that recognize the role of atypical sensory processing in their clinical picture.

Knowledge and understanding of sensory processing dysfunctions and their impact on the functioning and development of children with different clinical conditions is essential for accurate diagnosis of a given child's deficit, thus enabling adequate choice of therapeutic techniques and treatment modalities to be introduced as early as possible to stimulate optimal early development. From the theoretical study of the impact of sensory integration on the development of speech, its practical significance arises, since no practical solution is adequate if it does not have its own theoretical basis. The fact that processing disorder at the level of one sense is sufficient to cause sensory integration problems confirms the complexity of sensory processing, which is important for both theory and practical work in the field of special education and rehabilitation.

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BOOK REVIEWS
PRIKAZI KNJIGA

Dobanovački D, Marušić G, et al. Adolescent urology - Selected lectures (*Urologija adolescenata – Odabrana poglavlja).* Novi Sad: Laser Futog; 2021.

"Adolescence is a phase of transition from childhood to adulthood, between the ages of 10 and 19. Adolescents experience rapid physical, cognitive and emotional development, and sexual and reproductive maturity. Adolescence is also a period associated with increased illness and injury risks, but most of them are preventable and treatable."* Adolescent health and wellbeing is the actual goal of school-pediatricians on daily basis.

Two surgeons, professors and authors, specialists in pediatric and adult urology, have written the handbook *Adolescent Urology – Selected Chapters* that provides valuable information on important topics in adolescent urology. This book is intended for young primary care physicians who treat children aged 10 – 19 years, and all beginners in pediatric urology. The reviewers' comments emphasized the precious contribution this book offers not only to all the physicians who work with adolescents, but also to all who are interested in this field of medicine. The book is easy to read, gives a clear presentation of health issues, as well as comments and suggestions. The reference list is at the end of each chapter.

The book has 118 pages and contains nine lectures with synthesized information on urologic conditions and diseases in male adolescents with a lot of clinical photographs the authors have accumulated over the years of their clinical practice. The first two chapters are an introduction to relevant clinical anatomy and physiology topics. Chapter 3 covers history taking, clinical examination and diagnostic procedures. Chapter 4 discusses several specific conditions and issues (gynecomastia, nocturnal emission, etc). Chapter 5 deals with the very important experience of testicular pain, and some other acute conditions. The following chapter describes the diagnostics and therapy of some congenital reproductive anomalies, the focus being on early diagnosis. Chapter 7 contains brief information on sexually transmitted infections and their diagnosis and therapy. The last two chapters offer information on testicular tumors and genital injuries with the appropriate first aid in such cases.

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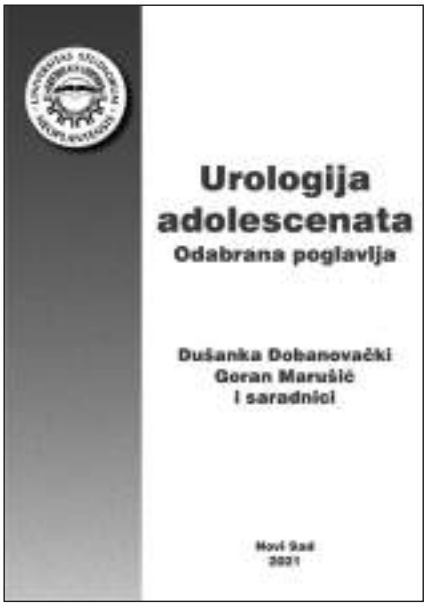

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*Adolescent Health – The Missing Population in Universal Health Coverage. UNICEF; 2018:9. (available on: https://www.unicef.org>media>file)

Aleksandra Stojadinović, MD, PhD

IN MEMORIAM
IN MEMORIAM

Prof. dr BRANISLAVA SOLDATOVIĆ STAJIĆ (1951–2021)

Prof. dr Branislava Soldatovic Stajić rođena je 5. 6. 1952. godine u Novom Sadu u porodici umetnika i književnika. U Novom Sadu je kao istaknuti đak završila osnovnu školu i gimnaziju Jovan Jovanović Zmaj. Na Medicinski fakultet u Novom Sadu upisala se 1971. godine, a diplomirala je 1976. sa prosečnom ocenom 9,41.

Posle obavljenog lekarskog staža, radila je na Klinici za interne bolesti. Od 1979. pa sve do odlaska u penziju, 2016. godine, bila je zaposlena kao neuropsihijatar na Klinici za psihijatriju u Novom Sadu, niz godina bila je načelnik Odeljenja za anksiozne poremećaje. Magistrirala je 1983, a doktorirala 1999. godine iz oblasti psihijatrije. U nastavu na Medicinskom fakultetu Novi Sad uključila se od 1991. godine kao asistent sa doktoratom i u pedagoškom radu dala svoj doprinos na Katedri za psihijatriju i medicinsku psihologiju sve do odlaska u penziju u zvanju vanredni profesor. Tokom čitave profesionalne karijere učestvovala je u međunarodnim projektima i bila autor velikog broja stručnih publikacija koje su objavljivane u domaćim i međunarodnim časopisima.

Branislava Soldatović Stajić je bila omiljeni asistent, a zatim i profesor Medicinskog fakulteta u Novom Sadu, a svoje veliko znanje iz oblasti medicine i psihijatrije prenosila je na sebi svojstven, šarmantan način, velikodušno i sadržajno nizu generacija studenata i postdiplomaca. Bila je omiljeni član Klinike za psihijatriju, uvek staložena, dobronamerna, plenila je mudrošću i razumevanjem. Sa zahvalnošću i poštovanjem i velikim žaljenjem opraštamo se od prof. dr Branislave Soldatović Stajić.

Prof. dr Mina Cvjetković

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

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Prijava rada treba da se učini na adresi:
http://aseestant.ceon.rs/index.php/medpreg/

U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu.

Elektronsko uređivanje časopisa obezbeđuje korišćenje sistema *CrossCheck*, koji prijavljene radove automatski proverava na plagijarizam i autoplagijarizam. Autori ne bi smeli da pošalju isti rad u više časopisa istovremeno. Ukoliko se to desi, glavni urednik časopisa *Medicinski pregled* ima pravo da rad vrati autorima bez prethodnog slanja rada na recenziju; da odbije štampanje rada; da se obrati urednicima drugih časopisa u koje je rad poslat ili da se obrati direktoru ustanove u kojoj su autori rada zaposleni.

Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.