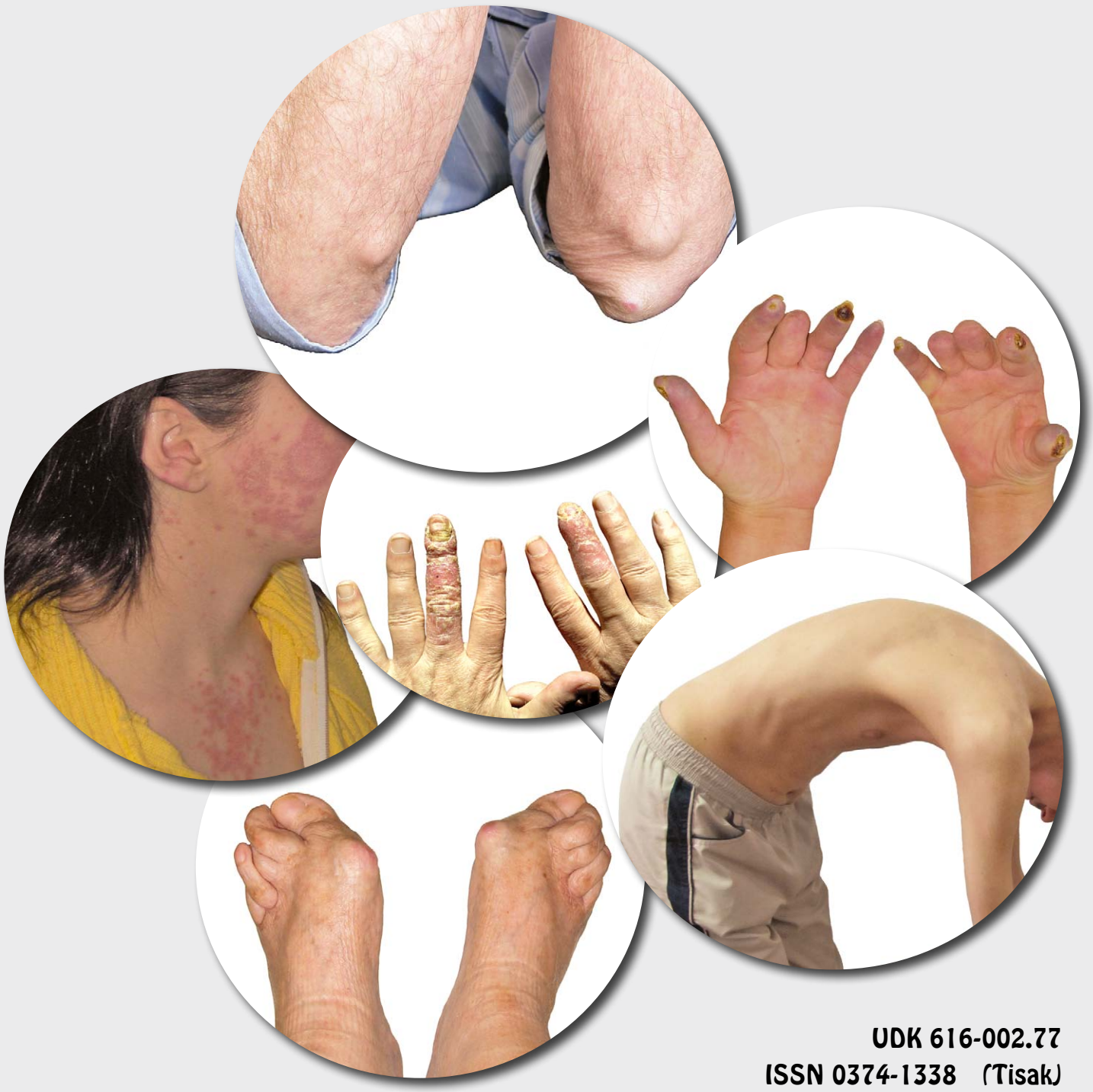
Časopis Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora
Journal of the Croatian Rheumatology Society Croatian Medical Association

REUMATIZAM

Volumen 66 Broj 2 Godina 2019.



UDK 616-002.77
ISSN 0374-1338 (Tisak)
ISSN 2459-6159 (Online)

DECEMBER 2019
VOLUME 66 • NUMBER 2

REUMATIZAM

Journal of the Croatian Rheumatology Society of the CMA

Publisher
Hrvatsko reumatološko društvo HLZ-a, Zagreb

Editor-in-Chief
Simeon Grazio
glavni-urednik-reumatizam@reumatologija.org

Editor
Nadica Laktašić-Žerjavić
urednik-reumatizam@reumatologija.org

Secretary
Hana Skala Kavanagh
tajnik-reumatizam@reumatologija.org

Scientific consultant
Armen Yuri Gasparyan

Educational and social media editor
Olena Zimba

Editors-in-Chief
Drago Čop (1954.–1963.)
Theodor Dürrigl (1963.–1990.)
Ivo Jajić (1991.–1998.)
Goran Ivanišević (1999.–2013.)
Simeon Grazio (2014.–)

Editorial address
REUMATIZAM
Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju,
KBC Sestre milosrdnice,
Vinogradska 29,
10000 Zagreb, Hrvatska

Croatian language editing
Branko Erdeljac

English language editing
Aleksandra Žmegač Horvat

Translation
Darija Čubelić, Lucija Milolović

Front page design
Zvonimir Barišić

Graphic design and typesetting
Gredice, Zagreb

Printing
Printera, Sveta Nedelja

Circulation
400

Printed finished
December 2019

Reumatizam (Rheumatism) is the official peer-reviewed journal of the Croatian Society for Rheumatology of the Croatian Medical Association. The journal is published twice a year.

Reumatizam publishes editorials, scientific papers, professional papers, brief communications (reports), reviews, preliminary reports and case reports. It informs professionals in the field of rheumatology on developments that affect clinical and nonclinical aspect of their practices.

Periodically, supplements with abstracts or full-texts presented at the congresses or symposia are published. The journal brings relevant information on the evaluation of diagnostic and therapeutic procedures, as well as on comprehensive care for individuals with rheumatic diseases.

Papers are published in English and Croatian, provided they are not already published elsewhere.

Free On-line Access to Internet Edition
http://www.reumatologija.org/engCasopis.aspx
http://reumatizam.hlz.hr/
https://hrcak.srce.hr/reumatizam

LISTOPAD 2019.
VOLUMEN 66 • BROJ 2

REUMATIZAM

Časopis Hrvatskoga reumatološkog društva HLZ-a

Izdavač
Hrvatsko reumatološko društvo HLZ-a, Zagreb

Glavni urednik
Simeon Grazio
glavni-urednik-reumatizam@reumatologija.org

Urednica
Nadica Laktašić-Žerjavić
urednik-reumatizam@reumatologija.org

Tajnica redakcije
Hana Skala Kavanagh
tajnik-reumatizam@reumatologija.org

Savjetnik za znanost
Armen Yuri Gasparyan

Urednik za izobrazbu i društvene medije
Olena Zimba

Glavni urednici
Drago Čop (1954.–1963.)
Theodor Dürrigl (1963.–1990.)
Ivo Jajić (1991.–1998.)
Goran Ivanišević (1999.–2013.)
Simeon Grazio (2014.–)

Adresa uredništva
REUMATIZAM
Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju,
KBC Sestre milosrdnice,
Vinogradska 29,
10000 Zagreb, Hrvatska

Lektor za hrvatski jezik
Branko Erdeljac

Lektor za engleski jezik
Aleksandra Žmegač Horvat

Prijevod
Darija Čubelić, Lucija Milolović

Rješenje naslovne stranice
Zvonimir Barišić

Grafički dizajn i slog
Gredice, Zagreb

Tisak
Printera, Sveta Nedelja

Naklada
400

Tiskanje dovršeno
Prosinac 2019.

Reumatizam, službeno glasilo Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora, je recenzirani časopis, koji redovito izlazi dva puta godišnje.

Reumatizam objavljuje uvodnike, znanstvene radove, stručne radove, kratka priopćenja, pregledne radove, prethodna izvješća i prikaze bolesnika. Časopis obavještava reumatologe o novostima u kliničkom i nekliničkom djelokrugu rada.

Reumatizam povremeno, kao suplement, objavljuje sažetke i/ili cjelovite radove s kongresa i simpozija. Časopis čitatelju daje bitne obavijesti u svezi evaluacije dijagnostičkih i terapijskih postupaka, odnosno pružanja sveobuhvatne skrbi osobama s reumatskim bolestima i stanjima.

Radovi se objavljuju na engleskom i hrvatskom jezikom uz uvjet da već nisu u istom obliku objavljeni drugdje.

Besplatan pristup internet izdanju časopisa
http://www.reumatologija.org/Casopis.aspx
http://reumatizam.hlz.hr/
https://hrcak.srce.hr/reumatizam

CONTENT / *SADRŽAJ*

Reumatizam 2019;66(2):53–63
https://doi.org/10.33004/reumatizam-66-2-7

ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

COMPARISON OF RADIOGRAPHIC AND ULTRASONOGRAPHIC FEATURES OF PAINFUL SHOULDER IN RHEUMATOID ARTHRITIS IN RELATION TO PAINFUL SHOULDER OF NON-INFLAMMATORY CAUSE

USPOREDBA RADIOGRAFSKIH I ULTRASONOGRAFSKIH OBILJEŽJA BOLNOG RAMENA U REUMATOIDNOM ARTRITISU U ODNOSU PREMA BOLNOM RAMENU NEUPALNOG UZROKA

Miroslav Barišić[1], Ivan Vlak[2], Ivan Šimundža[3], Tonko Vlak[2,4], Jure Aljinović[2,5], Igor Barišić[4,6]

[1]Community Health Center of Split-Dalmatia County, Split, Croatia / Dom zdravlja Splitsko-dalmatinske županije, Split, Hrvatska
[2]Institute of Rehabilitation Medicine and Rheumatology, Clinical Hospital Center Split, Split, Croatia / Zavod za fizikalnu medicinu i rehabilitaciju s reumatologijom Kliničkoga bolničkog centra Split, Split, Hrvatska
[3]Department of Thoracic Surgery, Clinical Hospital Center Split, Split, Croatia / Odjel torakalne kirurgije Kliničkoga bolničkog centra Split, Split, Hrvatska
[4]University of Split School of Medicine, Split, Croatia / Medicinski fakultet Sveučilišta u Splitu, Split, Hrvatska
[5]Department of Health Studies, University of Split / Odjel zdravstvenih studija Sveučilišta u Splitu
[6]Clinical Department of Diagnostic and Interventional Radiology, Clinical Hospital Center Split / Klinički zavod za dijagnostičku i intervencijsku radiologiju Kliničkoga bolničkog centra Split, Split, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Prof. dr. sc. Tonko Vlak, dr. med.,
Institute of Rehabilitation Medicine and Rheumatology
/ Zavod za fizikalnu medicinu i rehabilitaciju s reumatologijom
University of Split, School of Medicine / Medicinski fakultet Sveučilišta u Splitu
Clinical Hospital Center Split / Klinički bolnički centar Split
Šoltanska 1
21000 Split, Hrvatska
E-mail: tonkovlak@gmail.com

Received / Primljeno: September 3, 2019/ 3. rujna 2019.
Accepted / Prihvaćeno: November 22, 2019./ 22. studenoga 2019.

Abstract

Painful shoulder is an important public health problem present in various population groups, both the young as well as the elderly. Patients with rheumatoid arthritis (RA) and patients with non-inflammatory painful shoulder are two representative groups. The aim of this study was to estimate the differences in morphological parameters between the two patient groups and a possible predomination of one over the other. In 40 patients with RA both shoulders, and in 80 patients with non-inflammatory painful shoulders one shoulder, were radiographically and sonographically examined and the morphological parameters were compared. The patients with RA had a greater diameter of the biceps tendon sheath and the capsule-bone distance. More patients with RA had effusion of the biceps tendon sheath, subacromial-subdeltoid bursal effusion, and diffuse osteopenia. There were no differences between the groups in parameters usually associated with painful shoulder of non-inflammatory cause such as rotator cuff calcifications, supraspinatus tendon inhomogeneity, rotator cuff partial and total thickness tears, glenohumeral and acromioclavicular osteoarthrosis, large tuberculum sclerosis, and subacromial osteophytes. Patients with RA were then divided in two groups, the first involving patients with biceps tendon sheath effusion and subacromial-subdeltoid bursal effusion, and the second comprising patients without those symptoms. There was no significant difference among the parameters of painful shoulder in the second group and the parameters of non-inflammatory painful shoulder. Despite a significant difference in some parameters between the groups, the RA patients showed many parameters associated with non-inflammatory painful shoulder. They are obviously not "protected" against other intrinsic and extrinsic factors affect-

ing the shoulder; thus the cause of painful shoulder in the group of patients with RA may be multifactorial. Therefore, morphological analysis of the shoulder is required to evaluate the therapy after clinical estimates. A different combination of morphological shoulder parameters implies an individualized approach to the therapy.

Keywords: Arthritis, rheumatoid – complications, diagnostic imaging; Shoulder pain – diagnostic imaging, etiology; Shoulder joint – diagnostic imaging, pathology; Tendinopathy – etiology; Bursa, synovial – pathology; Inflammation – etiology; Ultrasonography; Radiography

Sažetak

Bolno rame važan je javnozdravstveni problem, koji se javlja u populacijskim skupinama različite dobi. Bolesnici s reumatoidnim artritisom (RA) skupina su s upalnom etiologijom bolnog ramena u odnosu prema bolesnicima s bolnim ramenom neupalne etiologije. Ciljevi istraživanja bili su utvrditi razliku u morfološkim parametrima između tih dviju skupina bolesnika i utvrditi eventualnu predominaciju nekih od praćenih parametara. Radiografski i ultrazvučno pregledana su oba ramena u 40-ero bolesnika s RA (bilateralna bol ramena) i po jedno rame u 80-ero bolesnika s bolnim ramenom neupalnog uzroka (unilateralna bol ramena). Bolesnici s RA imali su veći promjer ovojnice tetive duge glave bicepsa i veću distanciju kapsula – kost. Utvrđeno je da je više bolesnika s RA imalo izljev u ovojnici tetive duge glave bicepsa, izljev u subakromijskoj-subdeltoidnoj burzi i difuznu osteopeniju u odnosu prema drugoj skupini. Nije bilo razlike između skupina s obzirom na parametre koji su najčešće vezani za klinički entitet bolnog ramena neupalne etiologije kao što su kalcifikacije rotatorne manšete, inhomogenost tetive supraspinatusa, parcijalne i totalne rupture rotatorne manšete, osteoartritis akromioklavikularnog i humeroskapularnog zgloba, sklerozacije velikog tuberkula glave nadlakatne kosti te subakromijski osteofiti. Nakon utvrđivanja razlika između skupina bolesnici s RA podijeljeni su u dvije podskupine: onu s izljevom i onu bez izljeva u ovojnici tetive duge glave bicepsa i u subakromijskoj-subdeltoidnoj burzi, a kako bi se i oni usporedili s bolesnicima čija je bol u ramenu bila neupalne etiologije. Nije bilo znatne razlike među parametrima bolnog ramena između druge skupine i parametara bolnog ramena neupalne etiologije. Unatoč znatnoj razlici u nekim parametrima između dviju skupina bolesnici s RA imaju mnogo parametara povezanih s bolnim ramenom neupalnog uzroka. Oni, očigledno, nisu bili „zaštićeni" od ostalih promjena ramenoga zgloba, tako da uzrok bolnog ramena kod njih može biti multifaktorski. Za procjenu učinka i odabir terapije, a poslije i kliničku prosudbu, potrebna je morfološka analiza ramena. Različita kombinacija morfoloških parametara ramena implicira individualan pristup terapiji.

Ključne riječi: Reumatoidni artritis – dijagnostički slikovni prikaz, komplikacije; Bolno rame – dijagnostički slikovni prikaz, etiologija; Rameni zglob – dijagnostički slikovni prikaz, patologija; Tendinopatija – etiologija; Sinovijalna burza – patologija; Upala – etiologija; Ultrazvučno snimanje; Radiografija

INTRODUCTION

Approximately 90% of all rheumatoid arthritis (RA) patients have painful shoulder symptoms (1). The painful shoulder was found to be affected by inflammatory changes in the first two years of the disease in about 50% of patients, and in 83% of patients in 14 years of the disease (2).

Chronic inflammation in RA affects the articular synovial membrane and spreads to other articulated structures, such as bursae, tendons, and tendon sheaths. When examining such patients, conventional ultrasound with high-resolution probes is a reliable method for assessing all pathological changes of the above-mentioned joint structures, including the shoulder joint (3).

Proliferative synovitis therefore affects not only the humeroscapular joint, but also the other joints and bursae of the shoulder complex, especially the subacromial-subdeltoid bursa, as well as the long head of the biceps tendon (4).

Significant bone changes in the joints are expected in RA patients. However, unlike the small joints of the

UVOD

Simptome bolnog ramena ima oko 90% bolesnika koji boluju od reumatoidnog artritisa (RA) (1). Pritom je utvrđeno da je tijekom prve dvije godine bolesti rame zahvaćeno upalnim promjenama u oko 50% takvih bolesnika, a nakon 14 godina bolesti u njih 83% (2).

Kronična upala u RA zahvaća zglobnu sinovijalnu membranu i širi se u druge zglobne strukture kao što su burze, tetive i tetivne ovojnice. Pri pregledu takvih bolesnika konvencionalni ultrazvuk s visokorezolucijskim sondama pouzdana je metoda za procjenu svih patoloških promjena navedenih zglobnih struktura, pa tako i u ramenom zglobu (3).

Proliferativni sinovitis pritom zahvaća ne samo humeroskapularni zglob nego i ostale zglobove i burze ramenog kompleksa, poglavito subakromijsko-subdeltoidnu burzu, kao i ovojnicu tetive duge glave bicepsa (4).

U bolesnika s RA očekuju se znatne koštane promjene na zglobovima, ali za razliku od malih zglobova šaka i stopala, periartikularne promjene ramena utječu

hands and feet, periarticular shoulder changes affect the joint function much earlier than the bone structure (5, 6, 7). As a result, classical radiography reveals only late changes in advanced cases of the disease (8).

In contrast, diagnostic ultrasound can detect early changes in the soft tissues of the shoulder, subacromial-subdeltoid bursal effusion (9, 10), as well as effusion of the long head of the biceps tendon sheath (11), changes in the humeroscapular joint (12), and erosion of the humeral head (13, 14).

Painful shoulder which occurs due to a non-inflammatory etiology is often referred to as periarthritis humeroscapularis (PHS) in everyday practice. This diagnosis should be avoided, because it covers a large number of different clinical entities, which are all treated differently (15).

Therefore, we use the term painful shoulder of non-inflammatory cause, which means that it occurs without an underlying systemic inflammatory condition reported by patients that can be clinically determined. The cause of 60% cases of painful shoulder is subacromial impingement syndrome with consequential subacromial bursitis or supraspinatus muscle tendinitis. According to the research, 12% of these cases show adhesive capsulitis, 10% present with partial or complete rupture of the rotator cuff, 7% manifest with acromioclavicular joint osteoarthritis, 5% of cases are tendinitis of the long head of the biceps muscle, and 7% of cases are the result of some other causes (15).

Some of these causes occur on their own, and some occur in various combinations (16). Consequently, many morphological parameters occur together in both RA patients as well as in patients with non-inflammatory painful shoulder.

The purpose of this research was to investigate and possibly confirm the existence of a significant difference between the morphological parameters of painful shoulder in RA patients as compared to patients with painful shoulder of non-inflammatory etiology by using numerous radiographic and ultrasonographic diagnostic parameters.

MATERIALS AND METHODS

Description of the research

A cross-sectional study was conducted on patients diagnosed with RA presenting with a painful shoulder and patients with a painful shoulder of non-inflammatory etiology.

A conventional radiogram and ultrasound of both shoulders were performed in the RA patients, whereas in the patients with a non-inflammatory etiology the diagnostic procedures were done unilaterally, only on the painful shoulder. Additionally, the obtained parameters were analyzed and the findings of patients

na zglobnu funkciju prije nego koštane promjene (5 – 7). Klasična radiografija zbog toga otkriva tek kasne promjene u uznapredovalim slučajevima bolesti (8).

Za razliku od toga, dijagnostički ultrazvuk može otkriti vrlo rane promjene mekih tkiva ramena – i izljeve u subakromijskoj-subdeltoidnoj burzi (9, 10) i u ovojnici tetive duge glave bicepsa (11), promjene humeroskapularnog zgloba (12) te koštane erozije glave humerusa (13, 14).

Bolno rame koje nastaje zbog neupalne etiologije često se u svakodnevnoj praksi naziva humeroskapularni periartritis (PHS), što je dijagnoza koju valja izbjegavati jer se pod tim imenom skriva velik broj različitih kliničkih entiteta, koji se različito tretiraju (15).

Stoga u svojem radu rabimo izraz bolno rame neupalnog uzroka, što znači da je ono bilo dokazano bez sustavne upalne podloge tegoba koje bolesnici javljaju, a mi klinički utvrđujemo. U 60% slučajeva takvoga bolnog ramena uzrok je subakromijski sindrom sraza s posljedičnim subakromijskim burzitisom ili tendinitisom supraspinatusa. Prema provedenim istraživanjima, u 12% bolesnika radi se o adhezivnom kapsulitisu, u 10% o parcijalnoj ili potpunoj rupturi rotatorne manšete, u njih 7% o osteoartritisu akromioklavikularnog zgloba, u 5% o tendinitisu duge glave bicepsa, a u 7% bolesnika o „nekim drugim uzrocima“ (15).

Neki se od tih uzroka javljaju samostalno, a neki u različitim kombinacijama (16). Mnogi se morfološki parametri pritom javljaju zajedno – i kod bolnog ramena bolesnika s RA i u bolesnika s bolnim ramenom neupalnog uzroka.

Ciljevi ovog istraživanja bili su istraživanje i potvrđivanje postojanja znatne razlike između morfoloških parametara bolnog ramena bolesnika s RA i u onih s bolnim ramenom neupalnog uzroka, primjenjući pritom brojne radiografske i ultrasonografske dijagnostičke parametre.

ISPITANICI I METODE

Opis istraživanja

Provedena je presječna studija u bolesnika koji boluju od RA i imaju bolno rame te u onih što imaju bolno rame neupalne etiologije. U bolesnika s RA analiziran je konvencionalni radiogram i obavljen ultrazvučni pregled obaju ramena, a kod bolesnika s neupalnom etiologijom dijagnostika je obavljena jednostrano, samo na bolnom ramenu.

Nakon toga analizirali smo dobivene parametre te usporedili parametre bolesnika s bolnim ramenom u RA i parametre bolesnika s bolnim ramenom neupalne etiologije.

Ispitanici

Ultrazvučni pregled 160 ramena proveo je iskusan radiolog i ultrasoničar, koji u dijagnostici muskuloske-

with painful shoulder in rheumatoid arthritis were compared with the parameters of patients with painful shoulder of non-inflammatory etiology.

Respondents

An ultrasound examination of 160 shoulders was performed by an experienced ultrasound radiologist who had been working in the musculoskeletal system diagnostics field for more than 20 years. The diagnostic devices used were a Shimadzu SDU 1200 (Kyoto, Japan) with a 10-MHz linear probe, a Toshiba Nemio (Tokyo, Japan) with a linear probe of 11 and 14 Mhz, and Logic 8 (General Electrics) with an 8-Mhz linear probe.

Clinical examinations were carried out in 40 RA patients, examining both shoulders (bilateral painful shoulder in 28 women and 12 men, mean age 59.4 ± 11.9 years, average disease duration 4.3 years). In the same way, 80 patients with painful shoulder of non-inflammatory etiology were examined (unilateral shoulder pain in 54 women and 26 men, mean age 53.2 ± 7.2 years).

Before the examination, all patients stated that the pain had been present for more than 6 weeks, with no record of trauma.

The patients in the first group had been diagnosed with RA, supported by data on elevated CRP values and with no prior record of painful shoulder, while those in the second group had no record of possible RA.

Methods

For all 160 shoulders, the thickness of the supraspinatus tendon was measured in the transverse and longitudinal sections, in the neutral shoulder position as well as in adduction and internal rotation of the shoulder. The mean values in both cross-sections and both positions were measured.

Transverse cross-section: the upper part of the humeral head, above the intertubercular sulcus, was measured in the thickest medial part.

Longitudinal cross-section: measured in the place where the tendon emerges under the shadow of the acromion. The tendon diameter of the long head biceps muscle was measured on the upper edge of the intertubercular sulcus, in both the transverse and longitudinal cross-sections.

The humeroscapular joint effusion (capsule-bone distance), measured transaxillary, approached the part of the humerus not covered by the rotator cuff.

The presence of the subacromial bursal effusion has also been detected in the long head biceps tendon.

Data on the rotator cuff echo structure was analyzed during the examination, particularly the inhomogeneity of the supraspinatus tendon, as well as small deposits of calcium salts and the partial or complete rupture

letnog sustava radi dulje od 20 godina, rabeći pritom dijagnostičke uređaje Shimadzu SDU-1200 (Kyoto, Japan) s linearnom sondom od 10 MHz, Toshiba Nemio (Tokio, Japan) s linearnom sondom od 11 MHz i 14 MHz te Logiq 8 (General Electric, SAD) s linearnom sondom od 8 MHz.

U 40-ero bolesnika s RA pregledana su oba ramena (obostrano bolno rame u 28 žena i 12 muškaraca, srednje dobi 59,4 ± 11,9 godina, prosječnog trajanja bolesti 4,3 godine). Na isti je način pregled obavljen i kod 80-ero bolesnika s bolnim ramenom neupalne etiologije (jednostrana bol ramena, kod 54 žene i 26 muškaraca, srednje dobi 53,2 ± 7,2 godine).

Svi su bolesnici prije pregleda naveli da im boli traju dulje od 6 tjedana, bez evidencije o traumi. Bolesnici iz prve skupine imali su dokazan RA, praćen podatkom o povišenim vrijednostima CRP-a, bez prethodne evidencije o bolnom ramenu, dok su oni iz druge skupine bili bez evidencije o mogućem RA.

Metode

Kod svih 160 ramena istovjetno je mjerena debljina tetive supraspinatusa u transverzalnom i longitudinalnom presjeku, u neutralnoj poziciji ramena te pri adukciji i unutarnjoj rotaciji. Mjerene su srednje vrijednosti u oba presjeka i obje pozicije.

Transverzalni presjek: gornji dio glave humerusa, iznad intertuberkularnog žlijeba, mjerio se na najdebljem medijalnom dijelu.

Longitudinalni presjek: mjerio se na mjestu gdje tetiva izlazi ispod sjene akromiona. Promjer tetive duge glave bicepsa mjerio se na gornjem rubu intertuberkularnog žlijeba, u transverzalnom i longitudinalnom presjeku.

Izljev u humeroskapularnom zglobu (udaljenost zglobna ovojnica – kost) mjerio se transaksilarno, prilazeći dijelu humerusa koji nije pokriven rotatornom manšetom.

Registrirala se prisutnost izljeva u subakromijskoj burzi i u ovojnici tetive duge glave bicepsa.

Tijekom pregleda analizirali su se podatci o ehostrukturi rotatorne manšete, poglavito o inhomogenosti tetive supraspinatusa, malenim depozitima kalcijevih soli te o djelomičnoj ili potpunoj rupturi rotatorne manšete. Tetiva supraspinatusa definira se kao homogena ako je očuvana regularna fibrilarna struktura i ako je granica prema subdeltoidnoj burzi jasno očuvana. Tetiva se definira kao inhomogena ako je njezina fibrilarna struktura narušena bez jasne granice prema subdeltoidnoj burzi.

Analizirao se konvencionalni radiogram ramena, osobito s obzirom na prisutnost kalcifikacija tetiva i burza, cističnih formacija i uzura kosti te generalizirane osteopenije. Bilježili su se osteoartritis akromioklavikularnog i humeroskapularnog zgloba, sklerozacija

of the rotator cuff. The supraspinatus tendon is defined as homogeneous if the regular fibrillar structure is preserved along with the border towards the subdeltoid bursa. A tendon is defined as inhomogeneous if the fibrillar structure of the tendon is disturbed without a clear border to the subdeltoid bursa.

Conventional radiography of the shoulder was mainly analyzed on the presence of calcifications in the tendons and bursae, cystic formations, bone sulci, and generalized osteopenia. Osteoarthritis of the acromioclavicular and humeroscapular joints, greater tubercle sclerosis, and subacromial osteophytes were noted.

Statistical data analysis

A T-test for independent samples was used to determine statistically significant differences between numerical parameters. The correlation between category variables was determined by the χ^2 test.

The calculation of the sample size was carried out using an online program available on http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html to calculate the number of respondents. The distance from the articulated sheath to the bone was taken as the main measure of the outcome. Preliminary measurements gave us a value of 3.1 mm in the painful shoulder of inflammatory cause group, and a value of 2.5 mm in the non-inflammatory painful shoulder group. The standard deviation was about 0.5 mm. With a significance level of 0.05 and a statistical power of 0.8, the sample size was calculated to be 11 participants for each group of independent data sets. The Statistica 6 software package (StatSoft Inc, Tulsa, USA) was used.

RESULTS

Paraarticular sulci were found on 24 shoulders in 12 RA patients, whilst in the group of patients with non-inflammatory painful shoulders only one sulcus was found in one patient's shoulder.

Our study showed that there was no significant difference in the supraspinatus tendon thickness and long head biceps tendon in RA patients compared to the patients with a painful shoulder of non-inflammatory etiology.

The joint capsule-bone distance (an indicator of the intra-articular synovial fluid amount) was significantly higher in RA patients than in the group of patients with a painful shoulder of non-inflammatory etiology (Table 1).

Considerably more RA patients had a long head biceps tendon effusion ($\chi^2 = 16.78$; $P < 0.01$) as well as subdeltoid bursal effusion (($\chi^2 = 33.63$; $P < 0.01$) (Table 2).

There was no significant difference between the two groups of patients considering diffuse osteopenia ($\chi^2 = 2.66$; $P = 0.10$), rotator cuff calcification ($\chi^2 = 1.51$; $P =$

Table 1. Comparison of metric parameters of painful shoulder in patients with RA and patients with non-inflammatory painful shoulder. Results obtained by ultrasound

Tablica 1. Usporedba metričkih parametara bolnog ramena u bolesnika s RA i u onih s bolnim ramenom neupalne etiologije, dobivenih ultrazvučnim pregledom

Analyzed parameter / Analizirani parametar	Patients with painful shoulder; findings (x ± SD) / Nalazi (x ± SD) u pacijenata s bolnim ramenom		*P**
	RA (n = 80)	Non-inflammatory etiology / Neupalna etiologija (n = 80)	
Supraspinatus muscle tendon thickness (left) (mm) / Debljina tetive supraspinatusa (lijevo) (mm)	6,56 ± 1,11	6,3 ± 1,08	0,409
Supraspinatus muscle tendon thickness (right) (mm) / Debljina tetive supraspinatusa (desno) (mm)	6,51 ± 1,3	6,5 ± 0,96	0,98
Long head of the biceps muscle tendon (left) (mm) / Debljina tetive duge glave bicepsa (lijevo) (mm)	4,96 ± 0,74	4,64 ± 0,7	0,127
Long head of the biceps muscle tendon (right) (mm) / Debljina tetive duge glave bicepsa (desno) (mm)	4,93 ± 0,09	4,85 ± 0,97	0,16
Joint capsule-bone distance (left) (mm) / Udaljenost zglobna ovojnica – kost (lijevo) (mm)	3,12 ± 0,53	2,48 ± 0,55	< 0,001
Joint capsule-bone distance (right) (mm) / Udaljenost zglobna ovojnica – kost (desno) (mm)	3,3 ± 0,6	2,68 ± 0,56	< 0,001

**t-test*

velikog tuberkula nadlakatne kosti te subakromijski osteofiti.

Statistička raščlamba podataka

Za utvrđivanje statistički značajne razlike među numeričkim parametrima upotrijebljen je t-test za nezavisne uzorke. Korelacija između kategorijskih varijabla utvrđena je χ^2-testom.

Izračun veličine uzorka proveli smo s pomoću mrežnog programa za izračun broja ispitanika koji je dostu-

Table 2. Comparison of categorical parameters of painful shoulder in patients with RA and patients with non-inflammatory painful shoulder. Results obtained by ultrasound and radiography

Tablica 2. Usporedba kategorijskih parametara bolnog ramena u bolesnika s RA i u onih s neupalnim uzrokom prema rezultatima dobivenim ultrazvukom i radiografijom

Analyzed parameter / Analizirani parametar	Diagnostic method / Dijagnostička metoda	Number (%) of shoulders with positive findings / Broj (%) ramena s pozitivnim nalazom		χ^2	*P*
		RA (n = 80)	Non-inflammatory etiology / Neupalna etiologija (n = 80)		
Long head of biceps muscle sheath effusion / Izljev u ovojnici duge glave bicepsa	Ultrasound / Ultrazvuk	42/80 (52,5)	17/80 (21,2)	16,78	< 0,01
Subdeltoid bursal effusion / Izljev u subdeltoidnoj burzi	Ultrasound / Ultrazvuk	42/80 (52,5)	8/80 (10,0)	33,63	< 0,01
Diffuse osteopenia / Difuzna osteopenija	Radiography / Radiografija	25/80 (31,5)	16/80 (20,0)	2,66	0,10
Rotator cuff calcifications / Kalcifikacije rotatorne manšete	Radiography / Radiografija	6/80 (7,5)	11/80 (13,7)	1,51	0,22
Supraspinatus muscle tendon inhomogeneity / Inhomogenost tetive supraspinatusa	Ultrasound / Ultrazvuk	23/80 (28,5)	28/80 (35,0)	0,72	0,39
Partial rupture of the rotator cuff / Djelomična ruptura rotatorne manšete	Ultrasound / Ultrazvuk	21/80 (26,2)	24/80 (30,0)	0,28	0,59
Complete rupture of the rotator cuff / Potpuna ruptura rotatorne manšete	Ultrasound / Ultrazvuk	9/80 (11,2)	12/80 (15,0)	0,49	0,48
Greater tuberous sclerosis / Sklerozacija velikog tuberkula	Radiography / Radiografija	50/80 (62,5)	52/80 (65,0)	0,11	0,74
Subacromial osteophytes / Subakromijski osteofiti	Radiography / Radiografija	44/80 (55,0)	59/80 (73,7)	6,13	0,05
Acromioclavicular joint ostheoarthritis / Osteoartritis akromioklavikularnog zgloba	Radiography / Radiografija	26/80 (32,5)	30/80 (37,5)	0,44	0,51
Humeroscapular joint ostheoarthritis / Osteoartitis humeroskapularnog zgloba	Radiography / Radiografija	15/80 (18,5)	16/80 (20,0)	0,04	0,84

0.22), supraspinatus muscle tendon inhomogeneity ($\chi^2 = 0.72$; $P = 0.39$), partial rupture of the rotator cuff ($\chi^2 = 0.28$; $P = 0.59$), complete rupture of the rotator cuff ($\chi^2 = 0.49$; $P = 0.48$), sclerotic lesion of the greater tubercle of the humerus ($\chi^2 = 0.11$; $P = 0.75$), acromioclavicular joint osteoarthritis ($\chi^2 = 0.44$; $P = 0.51$), and humeroscapular joint osteoarthritis ($\chi^2 = 0.04$; $P = 0.84$) (Table 2).

In a significantly higher number of patients with non-inflammatory shoulder pain subacromial osteophytes were found compared to the RA patients (Table 2).

The RA shoulders were later divided into two groups:
- the first group with subdeltoid bursa and long head biceps tendon sheath effusion, which always appeared in conjunction, and
- the second group without an effusion.

There were notably fewer shoulders with subacromial osteophytes ($\chi^2 = 23.11$; $P < 0.01$) and acromioclavicular joint osteoarthritis ($\chi^2 = 4.37$; $P < 0.05$) in the first group compared to the painful shoulder of the non-inflammatory cause group (Table 3).

pan na: http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html. Kao glavnu mjeru ishoda uzeli smo udaljenost od zglobne ovojnice do kosti; preliminarna mjerenja dala su nam vrijednosti od 3,1 mm u skupini s bolnim ramenom upalnog uzroka i od 2,5 mm u skupini s bolnim ramenom neupalnog uzroka, dok je standardna devijacija bila oko 0,5 mm. S razinom značajnosti od 0,05 i snagom studije od 0,8 program je za ustroj studije od dvije skupine nezavisnih podataka dao veličinu svake skupine od 11 ispitanika. Upotrijebljen je softverski paket Statistica 6 (StatSoft Inc, Tulsa, SAD).

REZULTATI

Paraartikularne uzure nađene su u 24 ramena kod 12-ero bolesnika s RA, dok su u skupini bolesnika s bolnim ramenom neupalnog uzroka nađene samo u jednom ramenu, kod jednog bolesnika. Naše je istraživanje pokazalo da nema znatne razlike u debljini tetive supraspinatusa i tetive duge glave bicepsa u bolesnika s RA u odnosu prema bolesnicima s bolnim ramenom neupalne etiologije. Udaljenost zglobna kapsula – kost (in-

Table 3. Comparison of categorical parameters of painful shoulder in patients with RA with subdeltoid bursal effusion and biceps tendon sheath effusion versus parameters of patients with non-inflammatory painful shoulder. Results obtained by ultrasound and radiography

Tablica 3. Usporedba kategorijskih parametara bolnog ramena u bolesnika s RA s izljevom u subdeltoidnoj burzi i u ovojnici tetive duge glave bicepsa i parametara bolesnika s bolnim ramenom neupalne etiologije prema rezultatima dobivenim ultrazvukom i radiografijom

Analyzed parameter / Analizirani parametar	Diagnostic method / Dijagnostička metoda	Number (%) of shoulders with positive findings / Broj (%) ramena s pozitivnim nalazom		χ^2	P
		RA with effusion / RA s izljevom (n = 42)	Non-inflammatory etiology / S neupalnom etiologijom (n = 80)		
Diffuse osteopenia / Difuzna osteopenija	Radiography / Radiografija	14/42 (33,3)	16/80 (20,0)	1,55	0,21
Rotator cuff calcifications / Kalcifikacije rotatorne manšete	Radiography / Radiografija	4/42 (9,5)	11/80 (13,7)	0,36	0,55
Supraspinatus muscle tendon inhomogeneity / Inhomogenost tetive supraspinatusa	Ultrasound / Ultrazvuk	6/42 (14,3)	28/80 (35,0)	3,51	0,06
Partial rupture of the rotator cuff / Djelomična ruptura rotatorne manšete	Ultrasound / Ultrazvuk	8/42 (19,1)	24/80 (30,0)	1,71	0,19
Complete rupture of the rotator cuff / Potpuna ruptura rotatorne manšete	Ultrasound / Ultrazvuk	4/42 (9,5)	12/80 (15,0)	0,73	0,39
Greater tuberous sclerosis / Sklerozacija velikog tuberkula	Radiography / Radiografija	20/42 (47,6)	52/80 (65,0)	3,44	0,06
Subacromial osteophytes / Subakromijski osteofiti	Radiography / Radiografija	12/42 (28,6)	59/80 (73,7)	23,11	< 0,01
Acromioclavicular joint ostheoarthritis / Osteoartritis akromioklavikularnog zgloba	Radiography / Radiografija	8/42 (19,1)	30/80 (37,5)	4,37	< 0,05
Humeroscapular joint ostheoarthritis / Osteoartitis humeroskapularnog zgloba	Radiography / Radiografija	8/42 (19,1)	16/80 (20,0)	0,02	0,89

There was no significant difference between morphological parameters in the RA patients from the second group compared to the patients with non-inflammatory painful shoulder (Table 4).

DISCUSSION

The results of our study, in which we compared ultrasound and radiographic parameters of patients with painful shoulder in rheumatoid arthritis and patients with painful shoulder of non-inflammatory etiology, showed that there was a significant morphological difference between these two groups.

Moreover, our study has shown that the capsule-bone distance (an indicator of the intra-articular synovial fluid amount) was significantly higher in RA patients in comparison to the group of patients with non-inflammatory etiology of the painful shoulder.

In particular, more RA patients had an effusion of the long head biceps tendon sheath and a subdeltoid bursal effusion.

In a significantly higher number of patients with painful shoulder of non-inflammatory etiology subacromial osteophytes were found, in contrast to RA patients.

dikator količine intraartikularne sinovijalne tekućine) bila je bitno veća u bolesnika s RA nego u skupini bolesnika s bolnim ramenom neupalne etiologije (tablica 1.). Znatno više bolesnika s RA imalo je izljeve u ovojnici tetive duge glave bicepsa ($\chi^2 = 16,78$; $P < 0,01$) i u subdeltoidnoj burzi ($\chi^2 = 33,63$; $P < 0,01$) (tablica 2.).

Nije bilo bitne razlike između skupina bolesnika s obzirom na difuznu osteopeniju ($\chi^2 = 2,66$; $P = 0,10$), kalcifikacije rotatorne manšete ($\chi^2 = 1,51$; $P = 0,22$), inhomogenost tetive supraspinatusa ($\chi^2 = 0,72$; $P = 0,39$), djelomičnu rupturu rotatorne manšete ($\chi^2 = 0,28$; $P = 0,59$), potpunu rupturu rotatorne manšete ($\chi^2 = 0,49$; $P = 0,48$), kao ni s obzirom na sklerozaciju velikog tuberkula humerusa ($\chi^2 = 0,11$; $P = 0,75$), osteoartritis akromioklavikularnog zgloba ($\chi^2 = 0,44$; $P = 0,51$) i humeroskapularnog zgloba ($\chi^2 = 0,04$; $P = 0,84$) (tablica 2.).

U bolesnika s bolnim ramenom neupalnog uzroka nađen je znatno veći broj subakromijskih osteofita nego u bolesnika s RA (tablica 2.).

Ramena bolesnika s RA podijeljena su poslije u dvije skupine:

- prva skupina s izljevima u subdeltoidnoj burzi i u ovojnici tetive duge glave bicepsa, koji se uvijek javljaju u kombinaciji
- druga skupina bez izljeva.

Table 4. Comparison of categorical parameters of painful shoulder in patients with RA without subdeltoid bursal effusion and biceps tendon sheath effusion versus parameters of patients with non-inflammatory painful shoulder. Results obtained by ultrasound and radiography

Tablica 4. Usporedba kategorijskih parametara bolnog ramena u bolesnika s RA bez izljeva u subdeltoidnoj burzi i u ovojnici tetive duge glave bicepsa i parametara bolesnika s bolnim ramenom neupalne etiologije prema rezultatima dobivenim ultrazvukom i radiografijom

Analyzed parameter / Analizirani parametar	Diagnostic method / Dijagnostička metoda	Number (%) of shoulders with positive findings / Broj (%) ramena s pozitivnim nalazom		χ^2	*P*
		RA without effusion / RA bez izljeva (n = 38)	Non-inflammatory etiology / Neupalna etiologija (n = 80)		
Diffuse osteopenia / Difuzna osteopenija	Radiography / Radiografija	11/38 (28,9)	16/80 (20,0)	1,17	0,28
Rotator cuff calcifications / Kalcifikacije rotatorne manšete	Radiography / Radiografija	2/38 (5,3)	11/80 (13,8)	1,89	0,17
Supraspinatus muscle tendon inhomogeneity / Inhomogenost tetive supraspinatusa	Ultrasound / Ultrazvuk	17/38 (44,7)	28/80 (35,0)	1,04	0,31
Partial rupture of the rotator cuff / Djelomična ruptura rotatorne manšete	Ultrasound / Ultrazvuk	13/38 (34,2)	24/80 (30,0)	0,21	0,64
Complete rupture of the rotator cuff / Potpuna ruptura rotatorne manšete	Ultrasound / Ultrazvuk	5/38 (13,2)	12/80 (15,0)	0,07	0,79
Greater tuberous sclerosis / Sklerozacija velikog tuberkula	Radiography / Radiografija	30/38 (78,9)	52/80 (65,0)	2,36	0,12
Subacromial osteophytes / Subakromijski osteofiti	Radiography / Radiografija	32/38 (84,2)	59/80 (73,8)	1,59	0,21
Acromioclavicular joint osteoarthritis / Osteoartritis akromioklavikularnog zgloba	Radiography / Radiografija	18/38 (47,4)	30/80 (37,5)	1,04	0,31
Humeroscapular joint ostheoarthritis / Osteoartitis humeroskapularnog zgloba	Radiography / Radiografija	7/38 (18,4)	16/80 (20,0)	0,04	0,84

In a survey conducted in 2010, researchers Milutinović and Zlatković-Švenda showed by using ultrasound that RA patients are more likely to be associated with subdeltoid bursal and long biceps tendon sheath effusions, a bigger capsule-bone distance, cartilage reduction, and humerus head erosion in comparison to patients with a non-inflammatory etiology of painful shoulder (17). These results are similar to the results of our study, as expected.

It is known that chronic and progressive inflammatory diseases of the joint such as RA affect the synovial membrane and extend to extra-articular components (bursae, tendons, and tendon sheaths), causing damage to the joint cartilage (3, 18).

The non-inflammatory painful shoulder symptoms most often originate from a subacromial bursa irritation in subacromial impingement syndrome, as well as from calcium salt deposits in calcifying tendinitis.

According to the available data, in RA patients it can be expected to find a greater diameter of the supraspinatus muscle tendon, as well as the long head biceps tendon, and a bigger capsule-bone distance (which represents a higher amount of intra-articular synovial fluid). However, our study only found a greater cap-

U prvoj je skupini bilo znatno manje ramena sa subakromijskim osteofitima ($\chi^2 = 23,11$; $P < 0,01$) i osteoartritisom akromioklavikularnog zgloba ($\chi^2 = 4,37$; $P < 0,05$) nego u skupini bolnih ramena neupalnog uzroka (tablica 3.).

Nije bilo bitne razlike između morfoloških parametara u bolesnika s RA iz druge skupine i onih s bolnim ramenom neupalne etiologije (tablica 4.).

RASPRAVA

Rezultati našeg istraživanja, u kojem smo uspoređivali ultrazvučne i radiografske parametre bolnih ramena u bolesnika s RA i onih s bolnim ramenima neupalne etiologije, pokazali su da postoje znatne morfološke razlike između bolnih ramena upalne i neupalne etiologije. Naše je istraživanje pokazalo da je udaljenost zglobna kapsula – kost (indikator količine intraartikularne sinovijalne tekućine) znatno veća u bolesnika s RA nego u skupini bolesnika s bolnim ramenom neupalne etiologije. Bitno više bolesnika s RA imalo je izljev u ovojnici tetive duge glave bicepsa i izljev u subdeltoidnoj burzi. Subakromijske osteofite imao je znatno veći broj bolesnika s bolnim ramenom neupalnog uzroka u odnosu prema bolesnicima s RA.

sule-bone distance in RA patients, whilst the supraspinatus muscle tendon thickness and the long head biceps tendon thickness showed no statistically significant differences between the patient groups. The explanation of that result may be the shorter duration of the inflammatory rheumatic disease and the fact that the supraspinatus muscle and long head biceps tendon thickening is already recorded in the first stage of subacromial impingement syndrome, especially in younger patients (19–22). This fact diminishes the value of metric parameters in distinguishing changes in RA patients from those with painful shoulder of non-inflammatory etiology.

The long head biceps tendon and subdeltoid bursal effusions, as a common finding in RA patients, predominated in that group as expected. According to the experience and available literature, effusion can be also found in patients with a non-inflammatory etiology of the painful shoulder, especially in subacromial impingement syndrome, with consequential long biceps tendon bursitis and tendinitis, which may be found in asymptomatic patients as well. In cases of massive rupture of the rotator cuff, a passive effusion from the articulated area into the bursa can be detected (15, 21, 23, 24).

Diffuse osteopenia of the shoulder bones was found in both the RA patients and patients with non-inflammatory shoulder pain, with no statistically significant difference. An inflammatory component and access to earlier local corticosteroid administration, as well as the lack of movement in the painful shoulders, can be an explanation.

Other parameters associated with painful shoulder of non-inflammatory etiology, such as calcifications, partial and complete ruptures of the rotator cuff, inhomogeneity of the supraspinatus tendon, humeroscapular and acromioclavicular joint osteoarthritis, sclerosis of the greater tuberosity of the humerus, and the presence of subacromial osteophytes, surprisingly showed no statistically significant difference between the two groups. Even the number of RA shoulders with soft tissue calcifications was higher in comparison with the other group (25, 26).

Inhomogeneity of the supraspinatus tendon with an abnormal fibrillar structure and without a clear border towards the subdeltoid bursa can be also found in subacromial impingement syndrome (16, 27).

Although partial and complete rupture of the rotator cuff are strongly associated with subacromial impingement syndrome in elderly patients (28, 29), they can be found in advanced RA as well. Painful shoulder of non-inflammatory etiology is strongly associated with acromioclavicular osteoarthritis, large tuberous sclerosis, and the presence of subacromial osteophytes (30).

U istraživanju koje su 2010. g. provele Milutinović i Zlatković-Švenda pokazano je da ultrazvučnom dijagnostikom u bolesnika s bolnim ramenom u RA znatno češće nalazimo izljev u subdeltoidnoj burzi i ovojnici tetive duge glave bicepsa, veću udaljenost zglobna kapsula – kost, smanjenje hrskavice i erozije glave humerusa nego u bolesnika s neupalnom etiologijom bolnog ramena (17). Ovi su rezultati očekivano slični rezultatima našeg istraživanja.

Poznato je da kronična i progresivna upalna zglobna bolest kao što je RA zahvaća sinovijalnu membranu i širi se na izvanzglobne komponente (burze, tetive i tetivne ovojnice) te u zglobu oštećuje zglobnu hrskavicu (3, 18). Tegobe u bolnom ramenu neupalne etiologije potječu najčešće od iritacije subakromijske burze pri subakromijskom sindromu sraza te od prisutnih depozita kalcijevih soli u kalcificirajućem tendinitisu. Prema dostupnim podatcima očekivalo bi se da se kod bolesnika s RA zabilježe veći promjer tetive supraspinatusa i tetive duge glave bicepsa te veća udaljenost zglobna ovojnica – kost (koja znači veću količinu intraartikularne sinovijalne tekućine). Međutim, tijekom našeg istraživanja u bolesnika s RA našli smo samo veću udaljenost zglobna ovojnica – kost, dok debljine tetive supraspinatusa i tetive duge glave bicepsa nisu pokazale statistički značajne razlike među skupinama naših bolesnika. To možemo objasniti kraćim trajanjem upalne reumatske bolesti, kao i činjenicom da se zadebljanje tetive supraspinatusa i tetive duge glave bicepsa bilježi već u prvoj fazi subakromijskog sindroma sraza, poglavito među mlađim bolesnicima (19 – 22). Ta činjenica smanjuje vrijednost navedenih metričkih parametara pri razlikovanju promjena u bolesnika s RA i kod onih s bolnim ramenom neupalnog uzroka.

Izljev u ovojnici tetive duge glave bicepsa i subdeltoidnoj burzi, kao čest nalaz u bolesnika s RA, očekivano je dominirao u toj skupini bolesnika. Prema iskustvu i dostupnoj literaturi, on se može naći i u bolesnika s bolnim ramenom neupalne etiologije, osobito u onih sa subakromijskim sindromom sraza i posljedičnim burzitisom i tendinitisom tetive duge glave bicepsa, ali i u asimptomatskih bolesnika. U slučajevima masivne rupture rotatorne manšete nalazi se pasivni izljev u burzu iz zglobnog prostora (15, 21, 23, 24). Difuzna osteopenija kostiju ramena nađena je i u bolesnika s RA i u onih s bolnim ramenom neupalnog uzroka, bez statistički značajne razlike. Objašnjenje su upalna komponenta i moguća prijašnja lokalna administracija kortikosteroida, kao i manjak kretanja bolnih ramena. Ostali parametri povezani s bolnim ramenom neupalne etiologije (kalcifikacije rotatorne manšete i inhomogenost tetive supraspinatusa, djelomične i potpune rupture rotatorne manšete, osteoartritis humeroskapularnog i akromioklavikularnog zgloba, sklerozacija velikog tuberkula te subakromijski osteofiti) iznena-

The RA patient shoulders were divided into two groups in the second phase of the survey. The first group was associated with subdeltoid bursa and long biceps tendon sheath effusions in conjunction, whilst the second group had no such affiliation.

Comparing the shoulders of both the RA and non-inflammatory groups, a statistically significantly higher number of shoulders with acromioclavicular joint osteoarthritis and subacromial osteophytes were observed in the non-inflammatory painful shoulder group.

A comparison of the shoulders of the second group with RA and the non-inflammatory painful shoulders showed no statistically significant difference between the parameters. The multifactorial characteristic of the painful shoulder in RA is additionally emphasized by this fact.

CONCLUSION

RA patients are not protected from the usual harmful effects, especially in the older population, and therefore the etiology of painful shoulder in the stated group can be multifactorial. Due to that fact, painful shoulder treatment should be modified and adapted to each patient individually, based on radiological (X-ray and ultrasound) diagnostics. The significance of the results obtained by this study emphasizes the importance of a constant analysis of the morphological shoulder parameters after a clinical assessment in determining the prognosis and therapy of patients with a painful shoulder.

Conflict of interest statement: Authors declare no conflict of interest.

Translated on English/Prijevod na engleski
Lucija Milović

đujuće i neočekivano nisu pokazali statistički značajnu razliku među skupinama naših bolesnika. Čak je broj ramena s kalcifikacijama mekih česti bio veći u skupini bolesnika s RA (25, 26). Inhomogenost tetive supraspinatusa s poremećajem normalne fibrilarne strukture, bez jasne granice prema subdeltoidnoj burzi, može se naći i pri subakromijskom sindromu sraza (16, 27). Djelomične i potpune rupture rotatorne manšete veoma su povezane sa subakromijskim sindromom sraza u starijih bolesnika (28, 29), ali se mogu naći i u uznapredovalom RA. Bolno rame neupalne etiologije često je povezano s prisutnošću osteoartritisa akromioklavikularnog zgloba, sklerozacijom velikog tuberkula i sa subakromijskim osteofitima (30).

Ramena bolesnika s RA podijeljena su u drugoj fazi istraživanja u dvije skupine: u prvoj su skupini bila ramena s izljevima u subdeltoidnoj burzi i ovojnici tetive duge glave bicepsa, koji se javljaju uvijek u kombinaciji, dok je druga skupina ramena bila bez izljeva.

Usporedimo li ramena iz prve skupine bolesnika s RA s onima iz skupine bolesnika s bolnim ramenom neupalnog uzroka, vidimo da je statistički značajno veći broj ramena s osteoartritisom akromioklavikularnog zgloba i subakromijskim osteofitima nađen u skupini bolesnika s bolnim ramenom neupalnog uzroka. Ako, pak, usporedimo ramena iz druge skupine bolesnika s RA s onima iz skupine bolesnika s bolnim ramenom neupalne etiologije, vidimo da nema statistički značajne razlike među parametrima. To dodatno ističe multifaktornost bolnog ramena kod RA.

ZAKLJUČAK

Bolesnici s RA nisu „zaštićeni" ni od drugih, uobičajenih noksa koje pogađaju posebno starije ljude, tako da uzrok bolnog ramena kod njih može biti multifaktorski. Terapija bolnog ramena trebala bi, stoga, biti modificirana prema svakomu pojedinom bolesniku i individualno prilagođena, uz prethodno napravljenu radiološku (RDG i UZ) dijagnostiku. Rezultati dobiveni ovom studijom ističu važnost analize morfoloških parametara ramena poslije kliničke prosudbe, a radi određivanja prognoze i terapije u bolesnika s bolnim ramenom.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Petersson CJ. Painful shoulders in patients with rheumatoid arthritis. Prevalence, clinical and radiological features. Scand J Rheumatol. 1986;15:275–9.
2. Hämäläinen M. Epidemiology of upper limb joint affections in rheumatoid arthritis. U: Baumgartner H, Dvorak J, Grob D, Munziger U, Simmen BR (ur.). Rheumatoid arthritis. Current trends in diagnostics, conservative treatment, and surgical reconstruction. Stuttgart: George Thieme Verlag; 1995., str. 158–61.
3. Midiri M, Iovane A, Finazzo M, Brancatelli G, Gallo C, Lagalla R. Color Doppler-echo in rheumatoid arthritis with extra-articular location. Preliminary experience. Radiol Med. 1999;98: 123–6.
4. Coari G, Paoletti F, Iagnocco A. Shoulder involvement in rheumatic diseases. Sonographic findings. J Rheumatol. 1999;26: 668–73.
5. Iagnocco A, Filippucci E, Meenagh G, Delle Sedie A, Riente L, Bombardieri S i sur. Ultrasound imaging for the rheumatologist. I. Ultrasonography of the shoulder. Clin Exp Rheumatol. 2006;24:6–11.
6. Lenza M, Buchbinder R, Takwoingi Y, Johnston RV, Hanchard NC, Faloppa F. Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. Cochrane Database Syst Rev. 2013;2013(9): CD009020.
7. Shinagawa S, Okamura K, Yonemoto Y, Shitara H, Suto T, Sakane H i sur. Shoulder tenderness was associated with the inflammatory changes on magnetic resonance imaging in patients with rheumatoid arthritis. Sci Rep. 2019;9:19599.
8. Hunter DJ, Conaghan PG. Imaging outcomes and their role in determining outcomes in osteoarthritis and rheumatoid arthritis. Curr Opin Rheumatol. 2006;18:157–62.
9. van Holsbeeck M, Strouse PJ. Sonography of the shoulder: evaluation of the subacromial-subdeltoid bursa. Am J Roentgenol. 1993;160:561–4.
10. Farin PU, Jaroma H, Harju A, Soimakallio S. Shoulder impingement syndrome: sonographic evaluation. Radiology. 1990;176:845–8.
11. Middleton WD, Reinus WR, Totty WG, Melson GL, Murphy WA. Ultra-sonographic evaluation of the rotator cuff and biceps tendon. J Bone Joint Surg Am. 1986;68:440–50.
12. Koski JM. Axillar ultrasound of the glenohumeral joint. J Rheumatol. 1989;16:664–7.
13. Hodler J, Terrier B, von Schulthess GK, Fuchs WA. MRI and sonography of the shoulder. Clin Radiol. 1991;43:323–7.
14. Amin MF, Ismail FM, El Shereef RR. The role of ultrasonography in early detection and monitoring of shoulder erosions, and disease activity in rheumatoid arthritis patients; comparison with MRI examination. Acad Radiol. 2012;19:693–700.
15. Čičak N. Periarthritis humeroscapularis – dijagnoza koju valja odbaciti. Liječ Vjesn. 1999;121:87–93.
16. Iagnocco A, Coari G, Leone A, Valesini G. Sonographic study of painful shoulder. Clin Exp Rheumatol. 2003;21:355–8.
17. Milutinović S, Zlatković-Švenda M. Ultrasonographic study of the painful shoulder in patients with rheumatoid arthritis and patients with degenerative shoulder disease. Acta Reumatol Port. 2010;35:50–8.
18. McMahon PJ, Sallis RE. The painful shoulder. Zeroing in on the most common causes. Postgrad Med. 1999;106:36–8, 41–3, 47–9.
19. Neer CS. Impingement lesions. Clin Orthop Relat Res. 1983; 173:70–7.
20. Lyons PM, Orwin JF. Rotator cuff tendinopathy and subacromial impingement syndrome. Med Sci Sports Exerc. 1998;30 (Supl. 4):S12–7.
21. Almekinders LC. Impingement syndrome. Clin Sports Med. 2001;20:491–504.
22. Čičak N. Rame i nadlaktica. U: Pećina M (ur.). Ortopedija. Zagreb: Naklada Ljevak; 2004., str. 232–50.
23. van Holsbeeck MT, Kolowich PA, Eyler WR, Craig JG, Shirazi KK, Habra GK i sur. US depiction of the partial-thickness tear of the rotator cuff. Radiology. 1995;197:443–6.
24. Farin PU, Jaroma H. Sonographic findings of rotator cuff calcifications. J Ultrasound Med. 1995;14:7–14.
25. Woodward TW, Best TM. The painful shoulder. II. dio. Acute and chronic disorders. Am Fam Physician. 2000;61:3291–300.
26. Chiou HJ, ChouYH, Wu JJ, Huang TF, Ma HL, Hsu CC, Chang CY. The role of high-resolution ultrasonography in management of calcific tendonitis of the rotator cuff. Ultrasound Med Biol. 2001;27:735–43.
27. Mack LA, Gannon MK, Kilcoyne RF, Matsen RA. Sonographic evaluation of the rotator cuff. Accuracy in patients without prior surgery. Clin Orthop Relat Res. 1988;234:21–7.
28. Papatheodorou A, Ellinas P, Takis F, Tsanis A, Maris I, Batakis N. US of the shoulder; rotator cuff and non-rotator cuff disorders. Radiographics. 2006;26(1):e23.
29. Moosikasuwan JB, Miller TT, Burke BJ. Rotator cuff tears: clinical, radiographic, and US findings. Radiographics. 2005;25: 1591–607.
30. Warner JP. Pathophysiology and findings in impingement and rotator cuff tears. Presentation at the annual AMSSM (American Medical Society for Sports Medicine) meeting. Hilton Head Island, S.C., April 1995.

Reumatizam 2019;66(2):64–70
https://doi.org/10.33004/reumatizam-66-2-8

ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

ULTRASOUND EVALUATION OF THE ANKLE JOINTS AND TENDONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

ULTRAZVUČNA EVALUACIJA ZGLOBOVA I TETIVA GLEŽNJA U SUSTAVNOM ERITEMSKOM LUPUSU

Ljiljana Smiljanić Tomičević[1], Darija Čubelić[1], Miroslav Mayer[1], Branimir Anić[1]

[1]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb, School of Medicine, University Hospital Center Zagreb, Croatia / Zavod za kliničku imunologiju i reumatologiju, Klinika za unutarnje bolesti, Klinički bolnički centar Zagreb, Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Hrvatska

Corresponding author / Adresa autora za dopisivanje:
Ljiljana Smiljanić Tomičević, MD
Division of Clinical Immunology and Rheumatology / Zavod za kliničku imunologiju i reumatologiju
Department of Internal Medicine / Klinika za unutarnje bolesti
University of Zagreb, School of Medicine / Medicinski fakultet Sveučilišta u Zagrebu
University Hospital Center Zagreb / Klinički bolnički centar Zagreb
Kišpatićeva 12
10000 Zagreb, Croatia / Hrvatska
Tel: 00385 98 648712
E-mail / e-pošta: lilimef@gmail.com

Received / Primljeno: September 1, 2019 / 1. 9. 2019.
Accepted / Prihvaćeno: October 6, 2019 / 6. 10. 2019.

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with musculoskeletal involvement as one of the most common clinical manifestations. High-resolution ultrasound (US) has been proven to be a useful diagnostic tool for the evaluation of joints and tendons in the majority of inflammatory rheumatic diseases.

The aim of this study is to assess the frequency of ankle joint and tendon involvement in SLE patients with the use of US, and correlate the findings with the physical examination, laboratory tests, and disease activity scores. Here we will show preliminary results of the survey in the first 10 out of 60 included patients. Ten consecutive SLE patients were enrolled in the study and underwent clinical evaluation, laboratory tests, and bilateral high-resolution US on the same day.

Gray-scale and power Doppler (PD) US were performed for imaging of the talocrural (TC) and subtalar joints (ST), ankle tendons, second and third metacarpophalangeal (MCP) joints, second and third proximal interphalangeal (PIP) joints, second and third metatarsophalangeal (MTP) joints, and wrists.

A total of 180 joints and 200 tendons were examined. Preliminary results showed US-detected inflammatory joint abnormalities in 7/10 (70%) patients and tendon involvement in 1/10 (10%). Both the MTP and TC joints were affected in 60% of the patients, MCP joints in 50%, ST in 40%, wrists in 30%, and PIP joints in 10% of the patients. The most prevalent pathological US finding was joint effusion, less frequently synovial hypertrophy, while a positive PD signal was rarely detected. Effusion in the TC joints was present in 60% of the patients, synovial hypertrophy in 40%, and a positive PD in 10%. As many as 62.5% of the patients without inflammatory joint symptoms had pathological US findings in the ankle joints.

The results showed a high prevalence of US-verified inflammatory joint changes in SLE patients. Surprisingly, the MTP and ankle joints were most commonly affected. Additionally, a great number of asymptomatic patients also had pathological US findings in the ankle joints.

Keywords: Lupus erythematosus, systemic – complications; Ankle joint – diagnostic imaging; Joint diseases – diagnostic imaging, etiology; Synovitis – diagnostic imaging, etiology; Tenosynovitis – diagnostic imaging, etiology; Metacarpophalangeal joint – diagnostic imaging; Metatarsophalangeal joint – diagnostic imaging; Ultrasonography

Sažetak

Sustavni eritemski lupus (SLE) kronična je autoimunosna bolest s afekcijom muskuloskeletnog sustava kao jednom od najčešćih manifestacija. Ultrazvuk visoke rezolucije (UZ) dokazao se kao korisno dijagnostičko sredstvo pri evaluaciji zglobnih i tetivnih promjena u većini upalnih reumatskih bolesti.

Cilj je ove studije odrediti učestalost zahvaćanja zglobova i tetiva gležnja u bolesnika sa SLE-om koristeći se UZ-om te korelirati rezultate s fizikalnim pregledom, laboratorijskim nalazima i mjerama aktivnosti bolesti. Prikazali smo preliminarne rezultate studije na prvih 10 od ukupno 60 bolesnika. Uključeno je 10 uzastopnih pacijenata sa SLE-om koji su istog dana podvrgnuti kliničkoj evaluaciji, laboratorijskom ispitivanju i ultrazvučnom pregledu. Ultrazvučno su obostrano pregledani talokruralni (TC) i suptalarni (ST) zglobovi, tetive gležnja, drugi i treći metakarpofalangealni (MCP) zglobovi, drugi i treći proksimalni interfalangealni (PIP) zglobovi, drugi i treći metatarzofalangealni (MTP) zglobovi te ručni zglobovi.

Ukupno je pregledano 180 zglobova i 200 tetiva. Preliminarni rezultati pokazuju ultrazvučno detektirane upalne zglobne promjene u 7/10 (70%) bolesnika i zahvaćenost tetiva u 1/10 (10%). MTP i TC zglobovi bili su zahvaćeni u 60% bolesnika, MCP zglobovi u njih 50%, ST u 40%, ručni zglobovi u 30%, dok su PIP zglobovi bili zahvaćeni u 10% bolesnika. Najčešći patološki ultrazvučni nalaz bio je zglobni izljev, nešto rjeđe sinovijalna hipertrofija, dok je pozitivan PD signal rijetko bio prisutan. Izljev u TC zglobovima detektiran je u 60% bolesnika, sinovijalna hipertrofija u njih 40%, a pozitivan PD u 10% bolesnika. Čak 62,5% asimptomatskih bolesnika imalo je patološki nalaz na UZ-u gležnjeva.

Rezultati pokazuju veliku prevalenciju ultrazvučno verificiranih upalnih promjena zglobova u pacijenata sa SLE-om. Iznenađuje da su najčešće bili zahvaćeni zglobovi stopala i gležnja. Također, bitno je naglasiti da je velik broj asimptomatskih bolesnika imao patološki ultrazvučni nalaz zglobova gležnja.

Ključne riječi: Sistemski eritemski lupus – komplikacije; Gležanjski zglob – dijagnostički slikovni prikaz; Zglobne bolesti – dijagnostički slikovni prikaz, etiologija; Sinovitis – dijagnostički slikovni prikaz, etiologija; Tenosinovitis – dijagnostički slikovni prikaz, etiologija; Metakarpofalangealni zglob – dijagnostički slikovni prikaz; Metatarzofalangealni zglob – dijagnostički slikovni prikaz; Ultrasonografija

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of complex pathogenesis with a wide range of clinical manifestations (1). It is characterized by multi-system inflammation with the production of autoantibodies and the formation of immune complexes and their deposition into tissues. Affection of the musculoskeletal system is one of the most common and earliest manifestations of the disease, occurring in 95% of patients (1, 2). The joint involvement may range from mild arthralgia and arthritis to a rare non-erosive deforming arthropathy (Jaccoud arthropathy) (1), and almost all joints can be affected. In older studies, the most commonly affected joints were the small joints of the hands, the wrist, and the knee, while recent studies point to the frequent involvement of the joints of the feet (3, 4). Periarticular structures may also be affected by inflammation. Tendonitis, tenosynovitis, and changes or ruptures of the tendons have also been described in SLE patients, sometimes being the only cause of pain and instability in these patients. Affection of the ankle often occurs in patients with inflammatory rheumatic diseases. Clinical examination of the ankle may underestimate the type and distribution of the pathological changes due to the complexity of the anatomical structures of that area. Conventional radiological examination of the ankle provides bone structure data while providing

UVOD

Sustavni eritemski lupus (SLE) kronična je autoimunosna bolest kompleksne patogeneze koja se manifestira širokim spektrom simptoma (1). Karakteriziraju je multiorganska upalna zbivanja uz proizvodnju protutijela i stvaranje imunokompleksa te odlaganje njihovih depozita u tkiva. Zahvaćanje muskuloskeletnog sustava među najčešćim je i najranijim manifestacijama, a javlja se u oko 95% slučajeva (1, 2). Zahvaćanje zglobova može varirati od blage artralgije, preko artritisa, do rijetko prisutne neerozivne deformirajuće artropatije (takozvane Jaccoudove artropatije) (1), a mogu biti zahvaćeni gotovo svi zglobovi. Prema prijašnjim studijama, kao najčešće zahvaćeni zglobovi navode se mali zglobovi šaka, ručni zglobovi i koljena, dok novije studije upućuju i na čestu zahvaćenost zglobova stopala (3, 4). I periartikularne strukture mogu biti zahvaćene upalnim zbivanjem. Tendinitis, tenosinovitis i promjene ili rupture tetiva također su opisani kod pacijenata sa SLE-om, što katkad može biti jedini uzrok boli i nestabilnosti u ovih pacijenata. U pacijenata s upalnim reumatskim bolestima gležanj je često zahvaćen bolešću. Klinički pregled gležnja može podcijeniti tip i distribuciju patoloških promjena zbog kompleksnosti anatomskih struktura tog područja. Konvencionalni radiološki pregled gležnja donosi podatke o strukturi kosti, ali ne daje mnogo podataka o okolnom mekom tkivu. Magnetska rezonancija (MR) slikovna je metoda

very little information about the surrounding soft tissue. Magnetic resonance imaging (MRI) is a high-resolution imaging that can show both bone and soft tissue structures. It is very sensitive to changes in joints, but it is expensive and often unavailable in routine clinical practice.

High resolution Power Doppler (PD) and musculoskeletal ultrasound (MSUS) has been proven to be a useful and non-invasive diagnostic technique for assessing and tracking pathological changes in joints, tendons, and entheses (5). There is extensive literature on the benefits of MSUS in various inflammatory rheumatic diseases, mostly in rheumatoid arthritis, psoriatic arthritis, and other spondyloarthropathies (6, 7). However, so far few ultrasound studies have been conducted that evaluate the joints in SLE patients (4, 8, 9).

PATIENTS AND METHODS

The pilot study included 10 consecutive SLE patients diagnosed according to the 1997 revised ACR criteria, who were treated at the Division of Clinical Immunology and Rheumatology at the University Hospital Center Zagreb (10). The study protocol included an ultrasound and physical examination performed the same day as the regular rheumatologist follow-up and laboratory reevaluation. The MSUS examination was performed in all patients, regardless of the presence or absence of pain and swelling in the joints and tendons. The study was conducted according to the guidelines of good clinical practice as well as the Helsinki Declaration. All patients signed an informed consent form.

Clinical and demographical data (date of diagnosis, disease duration, system involvement, current and previous therapy, previous presence of pain and swelling of the ankle) were collected from each study patient. All patients were subjected to a standardized physical examination that evaluated the presence of painful and swollen joints and deformities (44 joints), with the evaluation of tendons and joints of the feet and ankles. To assess the disease activity, the SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000) and ECLAM (European Consensus Lupus Activity Measurement) were used (11, 12). For the purposes of the study, data on patients with SLE included in the hospital register were used as well. A single rheumatologist, who was blinded to the clinical and laboratory data, performed the MSUS examination and scored the static images. The images were also scored by another independent rheumatologist expert in MSUS.

A high-resolution US equipped with a multifrequency linear array transducer (4–15 MHz) with PD was used. Multiplanar examination techniques were performed in accordance with the International Guide-

visoke rezolucije koja može prikazati i strukturu kosti i mekih tkiva te ima visoku osjetljivost na promjene u zglobovima, ali je često nedostupna i preskupa za uporabu u rutinskoj kliničkoj praksi. *Power Doppler* visoke rezolucije (PD) i muskuloskeletni ultrazvuk (MSUS) dokazali su se kao korisne i neinvazivne dijagnostičke metode za procjenu i praćenje promjena zglobova, tetiva i enteza (5). Postoje opsežni literaturni podatci o pozitivnim stranama primjene MSUS-a u raznim upalnim reumatskim bolestima, većinom pri reumatoidnom i psorijatičnom artritisu te spondiloartropatijama (6, 7). Za razliku od toga, nije provedeno mnogo studija koje su proučavale zahvaćenost zglobova u pacijenata sa SLE-om (4, 8, 9).

ISPITANICI I METODE

U pilot-studiju bilo je uključeno 10 uzastopnih ambulantnih bolesnika koji se liječe u Zavodu za kliničku imunologiju i reumatologiju Kliničkoga bolničkog centra Zagreb, a kojima je dijagnoza SLE-a postavljena u skladu s kriterijima ACR-a (*American College of Rheumatology*), revidiranima 1997. godine (10). Protokol studije uključivao je ultrazvučni i fizikalni pregled koji su bili obavljeni na dan redovite reumatološke kontrole i rutinske laboratorijske reevaluacije. Pregled MSUS-om obavljen je u svih bolesnika, neovisno o tome jesu li u tom trenutku imali boli ili oticanje zglobova i tetiva. Studija je provedena prema pravilima dobre kliničke prakse i u skladu s Helsinškom deklaracijom. Svi pacijenti potpisali su pristanak kojim potvrđuju da su informirani o sudjelovanju u studiji.

Za svakog uključenog pacijenta prikupljeni su klinički i demografski podatci (datum postavljanja dijagnoze, trajanje bolesti, zahvaćenost pojedinih organskih sustava, trenutačna i prijašnja terapija, oticanje i bol gležnja u prošlosti). Svim je bolesnicima učinjen standardizirani fizikalni pregled kojim je evaluirana prisutnost bolnih i otečenih zglobova te deformiteta (44 zgloba), uz evaluaciju tetiva na gležnjevima. Za procjenu aktivnosti bolesti upotrijebljeni su indeksi SLEDAI-2K (engl. *Systemic Lupus Erythematosus Disease Activity Index 2000*) i ECLAM (engl. *European Consensus Lupus Activity Measurement*) (11, 12). Za potrebe studije upotrijebljeni su i podatci o bolesnicima iz bolničkog registra oboljelih od SLE-a. Ultrazvučni pregled uz bodovanje slikovnih nalaza izveo je reumatolog koji nije bio upoznat s kliničkim i laboratorijskim podatcima o bolesniku. Dobivene ultrazvučne slike bodovao je i drugi neovisni reumatolog koji je stručnjak u uporabi MSUS-a. Rabljen je ultrazvučni uređaj visoke rezolucije s linearnom sondom frekvencije 4 – 15 MHz uz upotrebu PD-a. Za prikazivanje TC i ST zglobova, tetiva gležnja, drugog i trećega MCP zgloba, drugog i trećega PIP zgloba, drugog i trećega MTP zgloba, drugog i trećega MCP zgloba te ručnoga zgloba

lines for MSUS in Rheumatology for imaging of the TC and ST joints, ankle tendons, second and third MCP joints, second and third PIP joints, second and third MTP joints, and wrists (13). A total of 18 joints and 20 tendons were examined in each patient and the inflammatory US score and global inflammatory US score were calculated. The joints for global inflammatory US scoring were selected according to the shown frequency of the joint involvement in recent studies. The presence of joint effusion, synovial hypertrophy, bone erosion, tenosynovitis, and enthesitis was defined according to the OMERACT definitions (13). US-detected elementary lesions were evaluated with a dichotomous score (absence/presence). A semi-quantitative scale (0–3) was used for scoring joint effusion, synovial proliferation, and PD.

RESULTS

Ten consecutive patients, all females, were enrolled in the study. The mean age was 45.3 years and the mean disease duration 164 months. Half of the enrolled subjects did not have musculoskeletal symptoms at the time of examination. The demographic, clinical, and serologic data are reported in Table 1. For the majority of patients, treatment was based on corticosteroids alone or combined with various different disease-modifying anti-rheumatic drugs.

Ultrasonographic findings

A total of 180 joints and 200 tendons were examined. Preliminary results in 10 patients showed US-detected inflammatory joint abnormalities in 7/10 (70%) patients and tendon involvement in 1/10 (10%). Both the MTP and TC joints were affected in 60% of the patients, MCP joints in 50%, ST in 40%, wrists in 30%, and PIP joints in 10% of the patients. According to these findings, the TC and MTP were the most frequently involved joints. The most severely affected joints were the TC and MCP, with clinical and ultrasound synovitis at the time of evaluation. The most prevalent pathological US findings in all examined joints were joint effusion and synovial hypertrophy (present in 80% of the patients), while a positive PD signal was rarely detected (30%). Only one patient had bone erosion verified. Furthermore, the most prevalent pathological US finding in the ankles was also joint effusion (60%), less frequently synovial hypertrophy (40%), while a positive PD signal was present in 10% of the patients. As many as 62.5% of the patients without inflammatory joint symptoms had pathological US findings in the ankle joints. The mean value of the global US inflammatory score was 5.6, while the mean value of the ankle US inflammatory score amounted to 2.9.

primijenjene su multiplanarne tehnike pregleda prema međunarodnim smjernicama za MSUS u reumatologiji (13). Ukupno je svakom bolesniku pregledano 18 zglobova i 20 tetiva te su izračunani upalni ultrazvučni zbroj (skor) za svaki pregledani zglob i opći ultrazvučni upalni zbroj. Zglobovi za izračun općeg ultrazvučnog upalnog zbroja odabrani su prema učestalosti zahvaćanja zglobova opisanoj u dosad objavljenim studijama. Prisutnost zglobnog izljeva, sinovijalne hipertrofije, koštanih erozija, tenosinovitisa i entezitisa određena je prema OMERACT-ovim definicijama (13). Osnovne lezije dijagnosticirane ultrazvukom evaluirane su dihotomnim sustavom (odsutnost/prisutnost). Semikvantitativna ljestvica (0 – 3) upotrijebljena je za izračun (skoriranje) zglobnog izljeva, sinovijalne proliferacije i PD-a.

REZULTATI

U studiju je uključeno deset uzastopnih bolesnika, a svi su bili ženskog spola. Srednja dob bolesnica bila je 45,3 godine, uz prosječno trajanje bolesti od 164 mjeseca. Polovina uključenih bolesnica nije imala aktualnih tegoba s muskuloskeletnim sustavom u trenutku pregleda. Demografski, klinički i serološki podatci prikazani su na tablici 1. Kod većine bolesnica terapija je bila bazirana na glukokortikoidima u monoterapiji ili u kombinaciji s različitim antireumaticima koji modificiraju bolest.

Ultrazvučni nalazi

Ukupno je pregledano 180 zglobova i 200 tetiva. Preliminarni rezultati na prvih 10 pacijentica pokazali su ultrazvučno verificirane upalne zglobne promjene u 7/10 bolesnica (70%) i zahvaćenost tetiva u 1/10 bolesnica (10%). I MTP i TC zglobovi bili su zahvaćeni kod 60% pacijentica, MCP u njih 50%, ST u 40%, ručni zglobovi u 30%, a PIP zglobovi u 10% pacijentica. Prema ovim podatcima, TC i MTP zglobovi bili su najčešće te ujedno i najteže zahvaćeni, s kliničkim i ultrazvučnim znakovima sinovitisa u vrijeme evaluacije. Najčešći patološki ultrazvučni nalaz kod svih pregledanih zglobova bili su zglobni izljev i sinovijalna hipertrofija (oboje prisutno u 80% bolesnica), dok je pozitivan PD signal rijetko bio prisutan (30%). Kod jedne bolesnice verificirana je erozija kosti. Nadalje, najčešći patološki ultrazvučni nalaz gležnja također je bio zglobni izljev (60%), nešto rjeđe sinovijalna hipertrofija (40%), dok je pozitivan PD signal bio prisutan kod samo 10% bolesnica. Među bolesnicama koje nisu imale simptome sinovitisa, u njih čak 62,5% ultrazvukom su detektirane patološke promjene zgloba gležnja. Srednja vrijednost općeg ultrazvučnog upalnog zbroja iznosila je 5,6, a srednja vrijednost ultrazvučnog upalnog zbroja gležnja iznosila je 2,9.

Table 1. Demographic, clinical, and serologic data of enrolled patients according to musculoskeletal disease status
Tablica 1. Demografski, klinički i serološki podatci o bolesnicima prema statusu zahvaćenosti muskuloskeletnog sustava

Feature / Obilježje	All patients / Svi bolesnici n = 10	Patients with MSK symptoms / Bolesnici s MSK simptomima n = 5	No MSK symptom / Bez MSK simptoma n =5
Age, years, mean (range) / Dob, godine, srednja vrijednost (raspon)	45.3 (24–67)	44.8	45.8
Disease duration, months, mean (S.D.) / Trajanje bolesti, mjeseci, srednja vrijednost (S. D.)	164 (121.01)	133.2 (116.5)	194.8 (130.4)
Joint involvement, n (%) / Zahvaćenost zglobova, n (%)	5 (50)	5 (100)	0(0)
CRP, mg/L, mean value (range) / CRP, mg/L, srednja vrijednost (raspon)	8.36 (0.9–57)	1.26	15.46
ESR mm/h, mean value (range) / SE, mm/h, srednja vrijednost (raspon)	34 (8–80)	34.2	33.8
ANA, n (%)	9 (90)	4 (80)	5 (100)
Anti-dsDNA, n (%) / AntidsDNK, n (%)	4 (40)	2 (40)	2 (40)
C3, mg/L, mean value (range) / C3, mg/L, srednja vrijednost (raspon)	1.168 (0.88–1.5)	1.156	1.186
C4, mg/L, mean value (range) / C4, mg/L, srednja vrijednost (raspon)	0.176 (0.05–0.35)	0.134	0.218
Glucocorticoids, n (%) / Glukokortikoidi, n (%)	9 (90)	4 (80)	5 (100)
Glucocorticoids, mean daily dosage, mg / Glukokortikoidi, prosječna dnevna doza, mg	13.25	17.5	12.5
Hydroxychloroquine and chloroquine, n (%) / Hidroksiklorokin i klorokin, n (%)	8 (80)	4(50)	4 (50)
MTX, AZA, MMF, CyA, CyC, n (%)	4 (40)	2(40)	2(40)
SLEDAI-2K, mean value (range) / SLEDAI-2K, srednja vrijednost (raspon)	3.6 (0–10)	5.6	1.6
ECLAM, mean value (range) / ECLAM, srednja vrijednost (raspon)	2.05 (0–5.5)	3	1.1
Number of tender joints, mean value (range) / Broj bolnih zglobova, srednja vrijednost (raspon)	2 (0–10)	4	–
Number of swollen joints, mean value (range) / Broj otečenih zglobova, srednja vrijednost (raspon)	1.3 (0–3)	2.6	–

DISCUSSION

Existing studies indicate a high prevalence of joint and tendon inflammatory changes in SLE patients and it is apparent that ultrasound changes of the hand and wrist joints are common in those patients, depending on the type of arthropathy (4, 8, 9, 14, 15). Furthermore, most studies have shown that there is significant subclinical joint involvement in SLE patients (4, 14, 15). This leads to the conclusion that reliance on the physical examination of the joints can underestimate the presence of active joint inflammation. In the systematic review by Lins and Santiago from 2015, which included a literature overview from 1950 to 2015, the high frequency of subclinical joint and tendon US pathology was also shown (14). Most articles in this re-

RASPRAVA

Dosad objavljene studije upućuju na veliku učestalost upalnih promjena zglobova i tetiva kod bolesnika sa SLE-om, a dokazano je i da se često ultrazvučno mogu detektirati promjene malih zglobova šaka i ručnih zglobova, ovisno o tipu artropatije (4, 8, 9, 14, 15). Također, istraživanja su upozorila na znatnu supkliničku prisutnost patoloških promjena zglobova kod bolesnika sa SLE-om (4, 14, 15). Ovo vodi do zaključka da oslanjanje samo na fizikalni pregled zglobova može dovesti do podcjenjivanja prisutnosti zglobne upale. U preglednom članku Caroline Lins i Mittermayera Santiaga, objavljenom 2015. godine, koji je obuhvatio literaturu od 1950. do 2015. godine, primijećena je velika učestalost supkliničkih ultrazvučnih promjena zglobo-

view demonstrated hand and wrist joint changes (14). In the research by Iagnocco et al. in 2014, ultrasonographic changes of the joints were described in a large proportion of patients (87%), while only 40% of them presented with clinical involvement of the joints. That study unexpectedly showed that the MTP joints were more commonly affected (72% of the patients) compared with the wrist (53%), MCP (46%), and PIP joints (19%) (4). In addition, the MTP joints were affected by more severe inflammatory changes compared with other examined joint levels. There are very few other studies that have evaluated the MTP joint region (4, 15). The high prevalence of MTP joint ultrasound pathology was also demonstrated in a pilot study by Mukherjee in 2016 (15). This study also showed a high frequency of US-detected forefoot bursal prevalence and bursal PD (100% of patients). Significant associations between bursal prevalence and MTP joint PD were noted (15).

Studies conducted in other rheumatic diseases have found US with PD a useful tool for the assessment of pathologies in ankle joint and tendons, as well as the differentiation of inflammatory and degenerative changes (16). To the best of our knowledge, this is the first US study aimed at an analysis of inflammatory changes in the ankle joints and tendons in SLE patients. In our study we found that the most commonly affected joints were the TC and MTP joints (60% of the patients). That correlates with the research of Iagnocco et al., although it has to be noted that ankle joints were not analyzed in that study. Gabba et al., in a study that was conducted in 108 SLE patients with musculoskeletal symptoms, found that patients with active musculoskeletal disease had more US pathology in the joints, while asymptomatic subjects had more pathological findings in the tendons (9). Our findings showed that the most common changes in joints were joint effusion followed by synovial hypertrophy, while a positive PD signal was rarely observed, which correlates with other studies (4, 5). It is important to emphasize that joint effusion was also present in 40% of asymptomatic patients in our study.

Data on the correlation between ultrasound findings and the inflammatory activity index SLEDAI-2k are contradictory. In our study both the SLEDAI-2k and ECLAM indexes were higher in the group of patients with pathological ultrasound findings in the ankle joints than in the group of patients without US changes. SLEDAI was 4.66/2 and ECLAM 2.5/1.375.

CONCLUSION

Results of the preliminary study show a high prevalence of US-verified inflammatory joint changes in SLE patients. Surprisingly, the foot and ankle joints were most commonly affected and a great number of as-

va i tetiva (14). Većina radova u spomenutom članku opisala je promjene u zglobovima šaka te u ručnom zglobu (14). Annamaria Iagnocco i suradnici opisali su u istraživanju objavljenom 2014. godine ultrazvučne promjene zglobova kod velikog dijela bolesnika (87%), dok je njih samo 40% imalo kliničke znakove aktivne zglobne upale. Ta je studija došla do neočekivanih rezultata prema kojima su MTP zglobovi češće zahvaćeni (72%) od ručnih zglobova (53%), MCP zglobova (46%) i PIP zglobova (19%) (4). Isto tako, MTP zglobovi bili su zahvaćeni težim upalnim promjenama u usporedbi s drugim ispitivanim zglobovima. U literaturi se može naći tek nekoliko studija u kojima je evaluirana zahvaćenost MTP zglobova (4, 15). Jedna je od njih pilot-studija iz 2016. godine gdje su Mukherjee i suradnici pokazali veliku prevalenciju patoloških ultrazvučnih promjena MTP zglobova (15). Ta je studija također pokazala veliku učestalost ultrazvučno detektiranih burza prednjeg dijela stopala, kao i veliku učestalost pozitivnog PD-a burza (100% bolesnika). Primijećena je znatna povezanost pojavnosti burza prednjeg dijela stopala i pozitivnog PD signala u MTP zglobovima (15).

Istraživanja provedena pri drugim reumatskim bolestima pokazala su da su UZ i PD korisne metode za procjenu patoloških promjena zglobova i tetiva, kao i za razlikovanje upalnih promjena od degenerativnih (16). Prema našim spoznajama, ovo je prva ultrazvučna studija s ciljem analiziranja upalnih promjena zglobova i tetiva gležnja kod pacijenata sa SLE-om. Naši podatci upozoravaju na to da su najčešće bili zahvaćeni TC i MTP zglobovi (60%). To se slaže s podatcima istraživanja koje su objavili Annamaria Iagnocco i suradnici 2014. godine, uz naglasak da u toj studiji nisu bili ispitivani zglobovi gležnja. Alessandra Gabba i suradnici pokazali su u studiji provedenoj na 108 lupusnih bolesnika s muskuloskeletnim manifestacijama u tijeku bolesti da su bolesnici s aktivnom muskuloskeletnom bolešću ultrazvučno dominantno imali zglobne promjene, dok su asimptomatski bolesnici imali više MSUS promjena na tetivama (9). Naši rezultati pokazuju da su najčešće zglobne promjene bile zglobni izljev i sinovijalna hipertrofija, dok je pozitivan PD signal rijetko detektiran, što odgovara podatcima iz drugih studija (4, 5). Valja naglasiti da je zglobni izljev također bio prisutan kod 40% asimptomatskih bolesnica.

U dosadašnjim studijama podatci o korelaciji ultrazvučnog nalaza i indeksa upalne aktivnosti – SLEDAI-2k prijeporni su. U našoj studiji oba indeksa, SLEDAI-2k i ECLAM, bila su viša u grupi bolesnika koja je imala patološki nalaz ultrazvuka zglobova nego u grupi koja nije imala ultrazvučnih promjena zglobova. SLEDAI je bio 4,66/2, a ECLAM 2,5/1,375.

ZAKLJUČAK

Rezultati ove preliminarne studije pokazuju veliku prevalenciju ultrazvučno verificiranih upalnih promje-

ymptomatic patients also had pathological US findings in the ankle joints.

Conflict of interest statement: Authors declare no conflict of interest.

na zglobova kod bolesnika sa SLE-om. Iznenađuje da su najčešće bili zahvaćeni zglobovi stopala i gležnja te da je velik broj asimptomatskih bolesnika imao patološke promjene opisane ultrazvučnim pregledom gležnjeva.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. Eur J Intern Med. 2008;19(7): 482–7.
2. Cerovec M, Anić B, Padjen I, Cikes N. Prevalence of the American College of Rheumatology classification criteria in a group of 162 systemic lupus erythematosus patients from Croatia. Croat Med J. 2012;53(2):149–54.
3. Grossman JM. Lupus arthritis. Best Pract Res Clin Rheumatol. 2009;23(4):495–506.
4. Iagnocco A, Ceccarelli F, Rizzo C, Truglia S i sur. Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology. 2014;53(3):465–72.
5. Joshua F, Lassere M, Bruyn GA, Szkudlarek M i sur. Summary findings of a systematic review of the ultrasound assessment of synovitis. J Rheumatol. 2007;34(4):839–47.
6. Hoving JL, Buchbinder R, Hall S, Lawler G i sur. A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. J Rheumatol. 2004;31(4):663–75.
7. Riente L, Delle Sedie A, Filippucci E, Iagnocco A i sur. Ultrasound imaging for the rheumatologist IX. Ultrasound imaging in spondyloarthritis. Clin Exp Rheumatol. 2007;25(3):349–53.
8. Iagnocco A, Ossandon A, Giulio C, Fabrizio C i sur. Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. Clin Exp Rheumatol. 2004;22(5):621–4.
9. Gabba A, Piga M, Vacca A, Porru G i sur. Joint and tendon involvement in systemic lupus erythematosus: an ultrasound study of hands and wrists in 108 patients. Rheumatology. 2012;51(12):2278–85.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
11. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2): 288–91.
12. Mosca M, Bencivelli W, Vitali C, Carrai P i sur. The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. Lupus. 2000;9(6): 445–50.
13. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E i sur. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485–7.
14. Lins CF, Santiago MB. Ultrasound evaluation of joints in systemic lupus erythematosus: a systematic review. Eur Radiol. 2015;25(9):2688–92.
15. Mukherjee S, Cherry L, Zarroug J i sur. A pilot investigation of the prevalence of US-detectable forefoot joint pathology and reported foot-related disability in participants with systemic lupus erythematosus. J Foot Ankle Res. 2016;9:27.
16. Suzuki T. Power Doppler ultrasonographic assessment of the ankle in patients with inflammatory rheumatic diseases. World J Orthop. 2014;5(5):574–84.

Reumatizam 2019;66(2):71–74
https://doi.org/10.33004/reumatizam-66-2-9

BRIEF PAPER KRATKO PRIOPĆENJE

ATYPICAL PRESENTATION OF ANTISYNTHETASE SYNDROME – CASE REPORT

ATIPIČNA PREZENTACIJA ANTISINTETAZNOG SINDROMA – PRIKAZ BOLESNIKA

Irma Ovčina[1], Marina Vukčević[1], Boris Prodanović[2]

[1]Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina / Univerzitetski klinički centar Republike Srpske, Banja Luka, Republika Srpska, Bosna i Hercegovina
[2]Institute for Physical Medicine and Rehabilitation "Dr Miroslav Zotović", Banja Luka, Republic of Srpska, Bosnia and Herzegovina / Institut za fizikalnu medicinu i rehabilitaciju „Dr. Miroslav Zotović", Banja Luka, Republika Srpska, Bosna i Hercegovina

Corresponding author / Adresa autora za dopisivanje:
Irma Ovčina, MD
Clinical Center of the Republic of Srpska / Univerzitetski klinički centar Republike Srpske
Dvanaest beba bb
Banja Luka
Bosnia and Herzegovina / Bosna i Hercegovina
Phone:+387 65/499-196
E-mail: irma.o93@hotmail.com

Received / Primljeno: September 8, 2019. / 8. rujna 2019.
Accepted / Prihvaćeno: October 18, 2019. / 18. listopada 2019.

Abstract

Anti-synthetase syndrome is an autoimmune disease characterized by myositis and interstitial lung disease. In this paper we report on a middle-aged male patient with an uncommon anti-synthetase syndrome, presenting with pulmonary manifestation before myositis. It is important to identify these patients, because early diagnosis and appropriate treatment are essential for optimal care.

Keywords: Autoimmune diseases – immunology; Myositis – diagnosis, immunology; Lung disease, interstitial – diagnosis, immunology; Autoantibodies – blood; Amino acyl – TRNA synthetase – immunology; Histidine – TRNA ligase – immunology; Glucocorticoids – therapeutic use; Immunosuppressive agents – therapeutic use

Sažetak

Antisintetazni sindrom autoimunosna je bolest koju karakteriziraju miozitis i intersticijska plućna bolest. U ovom radu prikazujemo sredovječnog pacijenta sa sindromom antisintetaze koji se, neuobičajeno, manifestirao plućnim promjenama prije miozitisa. Važno je da takvi bolesnici budu identificirani, jer su rana dijagnoza i odgovarajuće liječenje nužni radi optimalne skrbi za njih.

Ključne riječi: Autoimunosne bolesti – imunologija; Miozitis – dijagnoza, imunologija; Intersticijska plućna bolest – dijagnoza, imunologija; Autoantitijela – u krvi; Aminoacil transportna RNK sintetaza – imunologija; Histidin transportna RNK ligaza – imunologija; Glukokortikoidi – terapijska uporaba; Imunosupresivi – terapijska uporaba

INTRODUCTION

Antisynthetase syndrome (ASS) is a systemic autoimmune syndrome characterized by the presence of autoantibodies to aminoacyl-transfer RNA (tRNA) synthetases (antisynthetase antibodies) (1). Antibodies to anti-histidil (anti-Jo-1) antibodies are the most commonly detected antisynthetase autoantibodies (2). The clinical presentation typically includes: constitu-

UVOD

Antisintetazni sindrom (ASS) skupina je sustavnih autoimunosnih poremećaja koje karakterizira prisutnost protutijela na aminoacil-tRNK sintetazu (antisintetazna protutijela) (1). Najčešća antisintetazna protutijela jesu ona na histidil (anti-Jo1) (2). Tipična klinička slika uključuje miozitis, artralgije ili artritis, Raynaudov fenomen, „mehaničarske ruke" i intersticijsku

tional symptoms, myositis, arthralgias or arthritis, Raynaud phenomenon, mechanic's hands, and interstitial lung disease (ILD). ASS makes up about 30% of inflammatory myopathies (3). The presence of anti-aminoacyl-tRNA synthetase antibodies and *two major* or *one major and two minor criteria are necessary f*or a diagnosis. Major criteria are ILD, polymyositis, or dermatomyositis, while minor criteria are arthritis, Raynaud phenomenon, and mechanic's hands (4). Initial treatment are glucocorticoids, but if necessary, they are combined with immunosuppressive agents such as cyclophosphamide, azathioprine, or mycophenolate mofetil (3).

CASE REPORT

A 45-year-old man presented with a two-month history of general weakness, exhaustion, and chest pain. He had been treated at the Department for Respiratory Diseases under the diagnosis of bilateral pneumonia. The symptoms of general weakness were associated with long-lasting inactivity and bed rest. On discharge, 20-milligram prednisolone tablets once daily were prescribed for further home treatment. At the next follow-up with the pulmonologist one month after discharge from the hospital, an intensification of the previous symptoms with occasional dyspnea was reported. On that occasion, ILD was verified and the chest X-ray showed characteristics of pulmonary fibrosis. Prednisolone was excluded from the therapy. The patient was examined by a rheumatologist who indicated hospitalization for additional diagnostic workup. At the time of hospitalization, pain in the muscles of the pelvis and shoulders occured. The physical examination revealed tachycardia, weak handshake, and difficulty standing up from the squatting position (Gower sign). The initial laboratory workup showed leukocytosis 17x10^9/l (3.4-9.7 10^9/L), as well as elevated aspartate-aminotransferase (AST) 177 U/L (<50U/L), alanine-aminotransferase (ALT) 188U/L (<50U/L), lactate-dehydrogenase (LDH) 548 U/L (<248), creatine kinase (CK) 3184 U/L (0-171 U/L), creatine kinase-MB 112 U/L (0-24 U/L), and C-reactive protein (CRP) 27.2 mg/L (0-5 mg/L). In the urinanalysis total 24-hour urine protein was 0.238 g/24h (<0.15 g/24h). The immunological workup showed negative rheumatoid factor (RF), *anti*-cyclic citrullinated peptide (anti-CCP) antibody, antinuclear antibody (ANA), *anti-double stranded DNA (anti-dsDNA) antibody, anti-ribonuclear protein (RNP) antibody, anti-Smith (Sm) antibody,* and anti-topoisomerase I (anti-Scl-75) antibody, but positive anti-histidil (anti-Jo-1) antibodies, which were 200 (<1 U/l). Spirometry showed a mild restrictive ventilatory disorder, and carbon monoxide diffusing capacity (DLCO) was mildly reduced as well. Serum tumor markers, high-resolution chest CT (HRCT), and ultra-

plućnu bolest (IPB). ASS čini oko 30% upalnih miopatija (3). Dijagnoza se postavlja na temelju prisutnosti protutijela na aminoacil-tRNK sintetazu i dvaju velikih kriterija ili jednoga velikog i dvaju malenih kriterija. Veliki kriteriji jesu IPB, polimiozitis ili dermatomiozitis, a u malene se kriterije ubrajaju artritis, Raynaudov fenomen i „mehaničarske ruke" (4). Osnovnu terapiju ASS-a čine glukokortikoidi, ali oni se, prema potrebi, mogu kombinirati s imunosupresivima kao što su ciklofosfamid, azatioprin ili mikofenolat mofetil (3).

PRIKAZ BOLESNIKA

Naš je pacijent bio 45-godišnji muškarac s dvomjesečnom anamnezom opće slabosti, iscrpljenosti i boli u prsima. Liječen je na Odjelu pulmologije pod dijagnozom bilateralne pneumonije. Simptomi opće slabosti shvaćeni su kao posljedica dugotrajne neaktivnosti i ležanja u krevetu. Otpušten je iz bolnice uz preporuku uzimanja prednizona u dozi od 20 mg na dan. Pri sljedećem pregledu pulmologa, mjesec dana nakon otpusta iz bolnice, primijećeno je intenziviranje prijašnjih simptoma s povremenom dispnejom. Na ovom je pregledu utvrđen IPB, a na RDG-u prsnog koša opisana je plućna fibroza. Prednizon je isključen iz terapije.

Bolesnika je zatim pregledao reumatolog koji je indicirao hospitalnu obradu. Tijekom hospitalizacije javila se bol u mišićima zdjelice i ramena. Fizikalnim pregledom otkriveni su tahikardija, oslabljen stisak šake i teškoće pri ustajanju iz čučnja (Gowersov znak). Inicijalna laboratorijska obrada pokazala je leukocitozu 17 × 10^9/L (3,4 – 9,7 × 10^9/L), kao i povišene vrijednosti aspartat-aminotransferaze (AST) 177 U/L (< 50 U/L), alanin-aminotransferaze (ALT) 188 U/L (< 50 U/L), laktat-dehidrogenaze (LDH) 548 U/L (< 248), kreatin kinaze (CK) 3184 U/L (0 – 171 U/L), kreatin kinaze-MB 112 U/L (0 – 24 U/L) i C-reaktivnog proteina (CRP) 27,2 mg/L (0 – 5 mg/L). Ukupni proteini u 24-satnom urinu iznosili su 0,238 g/24 h (< 0,15 g/24 h). Imunološka obrada pokazala je negativan reumatski faktor (RF). Protutijela na ciklički citrulinski peptid (anti-CCP), antinuklearna protutijela (ANA), protutijela na dvolančani DNK (anti-dsDNK), protutijela na ribonuklearni protein (anti-RNP), anti-Smith protutijela (anti-Sm) i protutijela na topoizomerazu I (anti-Scl 75) bila su negativna, ali su otkrivena pozitivna protutijela na histidil (anti-Jo1), čija je razina bila 200 U/L (< 1 U/L). Spirometrija je pokazala blagi restriktivni poremećaj ventilacije, a difuzijski kapacitet za CO (DLCO) također je bio blago smanjen. Nalazi serumskih tumorskih markera, visokorezolucijskog CT-a toraksa (HRCT) te ultrazvuka srca i mišićno-koštanog sustava bili su normalni. Elektromioneurografija je pokazala malen postotak niskonaponskih polifaznih akcijskih potencijala.

sound of the heart and musculoskeletal system were normal. Electromyoneurography showed a small percentage of low-voltage polyphasic action potentials.

The patient was treated with high doses of corticosteroids, methylprednisolone 1 mg/kg/day, and methotrexate tbl a 15 mg once a week. An improvement was observed in the clinical and laboratory parameters. The corticosteroid dose was gradually reduced and switched to oral prednisolone 60 mg per day, divided in two doses (30 mg + 30 mg). On the last follow-up, six months after hospitalization, the laboratory findings were: CK 66, CK-MB 10.7, AST 14, and ALT 18. The other parameters were within the reference limits, and the prednisolone dose was reduced to 15 mg daily with the same metothrexate dose.

DISCUSSION

ASS is a rare systemic autoimmune disease that affects multiple organs. The prevalence is 1.5 per 100,000 population. The mean age at diagnosis is 50 years, with a predominance in females (2 : 1) (5). Myositis, ILD, and polyarthritis followed by fever and skin involvement are the classic clinical manifestations of ASS (6). The hallmark of the disease are antibodies against aminoacyl-tRNA synthetase, most commonly anti-Jo-1 antibodies, in 80% of cases (3). ILD occurs in more than 60% of cases and is the major cause of morbidity (7). Routine testing for ASS antibodies in all patients with ILD without an obvious etiology is important because they have implications regarding the choice of therapy (8). Myositis occurs in 90% of cases, but it is of note that it may not be part of the initial clinical presentation of ASS. In one series of ILD patients with ASS, myositis as an initial symptom was present in only 31% of them. Myositis can occur months and even years after ILD (9). In our case, ILD preceded myositis. A literature review shows that it occurs at a percentage of 10-30%, which is not negligible (10). In our patient, in the initial stages of the disease ILD presented on X ray as fibrosis according to the radiologist's report, but clinically it was more consistent with interstitial pneumonitis, as an early stage of ILD. Because of that, we started treatment with prednisolone, with a favorable response verified by the chest HRCT done after admission to the Rheumatology Department, which was normal. Pulmonary function tests showed a mild restrictive ventilation disorder, supporting the initial findings (FVC 78%; FEV1 73%; DLCO 65%).

Joint involvement occurs in more than 50%, mechanic's hands in 30%, and Raynaud phenomenon in 40% of ASS cases (6).

A similar case report was published by Priyangika et al. In that case the patient initially presented with progressive exertional dyspnea. HRCT was performed, as

Bolesnik je liječen visokim dozama kortikosteroida (metilprednizolon u dozi od 1 mg/kg/dan) i peroralnim metotreksatom u dozi od 15 mg na tjedan, nakon čega dolazi do poboljšanja kliničkih i laboratorijskih parametara. Doza kortikosteroida postupno je snižena i promijenjena iz intravenskoga u peroralni prednizon od 60 mg na dan, podijeljena na dvije doze (30 mg + 30 mg). Pri posljednjoj kontroli, šest mjeseci poslije hospitalizacije, vrijednost CK bila je 66, CK-MB 10,7, AST-a 14, ALT-a 18, uz uredne vrijednosti ostalih mjerenih parametara, a doza prednizona snižena je na 15 mg, uz istu dozu metotreksata.

RASPRAVA

ASS rijetka je sustavna autoimunosna multiorganska bolest. Prevalencija iznosi 1,5 na 100.000 stanovnika. Prosječna dob bolesnika pri dijagnozi jest 50 godina, a češće se javlja u žena (2 : 1) (5). Miozitis, IPB i poliartritis praćeni febrilitetom i afekcijom kože tipična su klinička manifestacija ASS-a (6). Za bolest su karakteristična protutijela na aminoacil-tRNK sintetazu od kojih je najčešće protutijelo na histidil (anti-Jo1) koje se javlja u 80% bolesnika (3). Intersticijska plućna bolest javlja se u više od 60% bolesnika i glavni je uzrok morbiditeta (7). Rutinsko određivanje protutijela na ASS u svih bolesnika s IPB-om nejasne etiologije važno je radi odabira terapije (8). Miozitis se javlja u 90% bolesnika, ali valja naglasiti da ne mora biti jedan od početnih kliničkih simptoma ASS-a. U jednoj seriji bolesnika s IPB-om u ASS-u miozitis je kao početni simptom bio prisutan u njih samo 31%. Miozitis se može javiti mjesecima, pa i godinama poslije pojave IPB-a (9). U našeg je bolesnika IPB prethodio miozitisu. Uvidom u literaturu može se primijetiti da se to događa kod čak 10 – 30% pacijenata, što nije zanemariv postotak (10). Našem je pacijentu u početnoj fazi bolesti čak i na RDG-u pluća opisan IPB u obliku fibroze, kao što je navedeno u radiološkom nalazu, dok je klinički nalaz govorio više u prilog intersticijskom pneumonitisu kao ranoj fazi IPB-a. Zbog toga smo liječenje počeli prednizonom, uz povoljan odgovor, na što je upućivao i uredan nalaz HRCT-a toraksa, učinjenoga nakon prijma na Odjel za reumatologiju. Testovi plućne funkcije pokazali su blag restriktivni poremećaj ventilacije, u skladu s početnim nalazima (FVC 78%; FEV1 73%; DLCO 65%).

Afekcija zglobova javlja se u više od 50% bolesnika s ASS-om, „mehaničarske ruke" u njih 30%, a Raynaudov fenomen u 40% takvih pacijenata (6).

Sličan prikaz bolesnika objavili su Priyangika i suradnici. Njihov se pacijent inicijalno javio zbog progresivne dispneje pri naporu. Učinjeni su HRCT toraksa i transbronhalna biopsija pluća te je postavljena dijagnoza kriptogene organizirane pneumonije. Dvije godine poslije pacijentu su se javile boli u mišićima.

well as transbronchial lung biopsy, and the diagnosis of organizing pneumonia was made. Two years later the patient presented with muscle pain, and the diagnosic workup revealed elevented CK and CRP with positive anti-Jo-1 antibodies, but without arthritis or arthralgias, Raynaud phenomenon, or mechanic's hands. With high-dose prednisolone and azathioprine, the patient's CK and inflammatory markers normalized (11). He had positive anti-Jo-1 antibodies with ILD and muscle involvement, but without Raynaud phenomenon, joint involvement, and mechanics hands, which does not exclude the possibility of their occurrence in the future.

In conclusion, our case shows that in patients with ILD without a known etiology the presence of ASS must be considered. Early diagnosis and the adequate treatment are essential for optimal patient care.

Acknowledgments: None.

Conflict of interest statement: Authors declare no conflict of interest.

Dijagnostičkom obradom nađeni su: povišene vrijednosti CK i CRP-a, pozitivna protutijela na histidil (anti-Jo1) bez prisutnosti artritisa ili artralgija, Raynaudov fenomen i „mehaničarske ruke". Uz liječenje visokim dozama prednizona i azatioprina vrijednosti CK i upalnih parametara normalizirale su se (11). Naš je bolesnik bio pozitivan na anti-Jo1, imao je IPB i zahvaćenost mišića, ali bez Raynaudova fenomena, afekcije zglobova i „mehaničarskih ruku", što ne znači da se te manifestacije možda neće pojaviti u budućnosti.

Zaključno, naš prikaz upozorava na to da bi kod bolesnika s idiopatskim IPB-om trebalo razmotriti i ASS kao mogući uzrok. Rano dijagnosticiranje i prikladno liječenje nužni su radi optimalne skrbi za bolesnika.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

Prijevod na hrvatski/Translated on Croatian
Darija Čubelić

REFERENCES / LITERATURA

1. Targoff IN. Autoantibodies and their significance in myositis. Curr Rheumatol Rep. 2008;10(4):333–40.
2. Cojocaru M, Cojocaru IM, Chicos B. New Insights into Antisynthetase Syndrome. Maedica (Buchar). 2016;11(2):130–5.
3. Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. Curr Rheumatol Rep. 2011;13(3):175–81.
4. Witt LJ, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. Clin Pulm Med. 2016;23(5):218–26.
5. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol. 2011;37(1):100–9.
6. Chatterjee S, Prayson R, Farver C. Antisynthetase syndrome: not just an inflammatory myopathy. Cleve Clin J Med. 2013; 80(10):655–66.
7. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology (Oxford). 2009;48(8):968–71.
8. Aslam F, Russell EB. Fellow's forum case report: diagnosing antisynthetase syndrome. Rheumatologist. 2013;1–6.
9. Tillie-Leblond I, Wislez M, Valeyre D i sur. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. Thorax. 2008;63:53–9.
10. Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M i sur. Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature. Medicine. 2012;91(4):206–11.
11. Thanuja Nilushi Priyangika SM, Karunarathna WGSG, Liyanage I i sur. Organizing pneumonia as the first manifestation of anti-synthetase syndrome. BMC Res Notes. 2016;9:290.

Reumatizam 2019;66(2):75–80
https://doi.org/10.33004/reumatizam-66-2-10

CASE REPORT PRIKAZ BOLESNIKA

GIANT CELL ARTERITIS IN A PATIENT WITH BILATERAL PAROTID SWELLING AS THE FIRST SIGN OF THE DISEASE: A CASE REPORT

GIGANTOCELULARNI ARTERITIS: PRIKAZ BOLESNICE S OTEKLINOM PAROTIDNIH ŽLIJEZDA KAO PRVOM MANIFESTACIJOM BOLESTI

Diana Bajo[1], Ana Begović[1], Katarina Borić[1], Mijo Meter[2], Dijana Perković[1]

[1]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Split, School of Medicine, University Hospital Center Split / Zavod za kliničku imunologiju i reumatologiju, Klinika za unutarnje bolesti, Medicinski fakultet Sveučilišta u Splitu, Klinički bolnički centar Split
[2]Department of Cardiovascular Diseases, University of Split, School of Medicine, University Hospital Center Split / Klinika za bolesti srca i krvnih žila, Medicinski fakultet Sveučilišta u Splitu, Klinički bolnički centar Split

Corresponding author / Adresa autora za dopisivanje:
prim. doc. dr. sc. Dijana Perković, dr. med.
Division of Clinical Immunology and Rheumatology / Zavod za kliničku imunologiju i reumatologiju
Department of Internal Medicine / Klinika za unutarnje bolesti
University of Split, School of Medicine / Medicinski fakultet Sveučilišta u Splitu
University Hospital Centre Split / Klinički bolnički centar Split
Šoltanska 1
21000 Split
E-mail / e-pošta: dijana.perkovic@hotmail.com

Received / Primljeno: July 17, 2019 / 17. srpnja 2019.
Accepted / Prihvaćeno: November 18, 2019 / 18. studenoga 2019.

Abstract

We report a case of a patient with vision loss, whose diagnosis of temporal arteritis was confirmed by temporal artery biopsy. The patient presented with bilateral parotid swelling, *amaurosis fugax,* jaw claudication, and then headache. After the introduction of glucocorticoid therapy, the symptoms of the disease subsided, but there was a permanent loss of vision in one eye. This case indicates that it is important to consider temporal arteritis as a differential diagnosis in patients older than 50 with *amaurosis fugax* or other atypical symptoms that may precede the headache. A multidisciplinary approach involving neurologist, otorhinolaryngologist, infectiologist, ophthalmologist, and rheumatologist is key to early diagnosis and start of appropriate treatment that reduces the risk of permanent vision loss.

Keywords: Giant cell arteritis – complications, diagnosis, drug therapy; Temporal arteries – pathology; Amaurosis fugax – etiology; Optic neuropathy, ischemic – etiology; Parotid diseases – etiology; Temporomandibular joint disorders – etiology; Headache – etiology; Glucocorticoids – therapeutic use

Sažetak

U ovom radu prikazali smo bolesnicu s gubitkom vida u sklopu temporalnog arteritisa potvrđenog biopsijom temporalne arterije. Klinički se bolest prezentirala oteklinom parotidnih žlijezda, *amaurosis fugax* i klaudikacijama čeljusti, a potom i glavoboljom. Nakon uvođenja glukokortikoidne terapije simptomi bolesti su regredirali, no zaostao je gubitak vida na jedno oko. Ovaj slučaj nas upozorava da je važno razmotriti temporalni arteritis kao diferencijalnu dijagnozu u bolesnika starijih od 50 godina s *amaurosis fugax* i ostalim atipičnim simptomima koji se mogu razviti prije pojave glavobolje. Dobra suradnja između neurologa, otorinolaringologa, infektologa, oftalmologa i reumatologa ključna je za rano postavljanje dijagnoze i početak odgovarajućeg liječenja koji smanjuje rizik od trajnog gubitka vida.

Ključne riječi: Gigantocelularni arteritis; Amurosis fugax; Oteklina parotidnih žlijezda; Glavobolja

INTRODUCTION

Giant cell arteritis (GCA), or temporal arteritis, is a chronic inflammatory disease affecting the large and medium-sized arteries in persons over the age of 50, with the highest incidence between the ages of 70 and 80 years (1). Most symptoms and signs of GCA are the result of affected cranial branches of arteries originating from the aortic arch, but given the systemic nature of the disease, other blood vessels can be affected too. The diagnosis of GCA should be considered in older patients who complain of new-onset headache, sudden onset of vision disturbances, especially the transient monocular vision loss, jaw claudication, fever of unknown origin, anemia or other systemic symptoms and signs. Elevated erythrocyte sedimentation rate (ESR) is usually present, frequently accompanied by high level of C-reactive protein (CRP) in the serum Current or previous diagnosis of polymyalgia rheumatica (PMR) increases the likelihood of either of these results (2). In approximately 50% of patients, GCA manifests with various visual disturbances. Among the most common ones are the monocular vision loss and anterior ischemic optic neuropathy (AION). It is estimated that binocular blindness will occur in 25–50% of untreated patients with monocular vision loss (3–5).

The main treatment is a high dosage of systemic glucocorticoids, which must be introduced as soon as GCA is diagnosed, especially in patients with recent or imminent vision loss. Treatment should not be delayed while waiting for the results of other diagnostic methods such as temporal artery biopsy, i.e. the results of histological examination of biopsy specimen. For patients who have developed side effects or who depend on high doses of glucocorticoids, treatment can be augmented with methotrexate (MTX) or, as of more recently, interleukin 6 (IL-6) inhibitor tocilizumab (TCZ) (6–9).

In this paper, we present a case of a patient with swollen parotid glands and visual disturbances as part of GCA, with both symptoms manifesting before the onset of headache.

CASE REPORT

The 66-year-old patient was hospitalized at the Department of Ophthalmology due to a monocular vision loss. Two months before admission, the patient experienced parotid gland swelling and thickening of th temporal arteries. A month before admission, she noticed visual disturbances in the left eye on several occasions. The disturbances took the form of transitory "curtain effect" that lasted no longer than 10 minutes, followed by gradual weakening of vision that developed over the course of around 10 days. The patient was examined in another hospital by otorhinolaryn-

UVOD

Gigantocelularni arteritis (GCA) ili arteritis divovskih stanica je kronična upalna bolest koja zahvaća velike i srednje velike arterije u osoba starijih od 50 godina, s najvećom incidencijom u sedmom desetljeću života (1). Većina simptoma i znakova GCA rezultat su zahvaćanja kranijalnih ogranaka arterija koje potječu iz luka aorte, ali budući da je bolest sistemska, mogu biti zahvaćene i ostale krvne žile. Dijagnozu GCA treba razmotriti u starijih bolesnika koji se žale na novonastalu glavobolju, nagli početak poremećaja vida, posebno prolazni monookularni gubitak vida, klaudikaciju čeljusti, neobjašnjivu temperaturu, anemiju ili druge sistemske simptome i znakove. Obično je prisutna ubrzana sedimentacija eritrocita (SE) i / ili visokim C-reaktivnim proteinom (CRP) u serumu. Trenutna ili prethodna dijagnoza reumatske polimialgije (PMR) povećava šansu bilo kojeg od ovih nalaza (2). GCA se u oko 50% bolesnika prezentira različitim poremećajima vida. Među najčešćima je monookularni gubitak vida i prednja ishemijska optička neuropatija [*engl. anterior ischemic optic neuropathy* (AION)]. Procjenjuje se da će se obostrano sljepoća razviti u 25 do 50 % neliječenih bolesnika s jednostranim gubitkom vida (3–5).

Visoke doze sistemskih glukokortikoida okosnica su terapije, a liječenje treba započeti odmah nakon što se postavi dijagnoza GCA, osobito u bolesnika s nedavnim ili prijetećim gubitkom vida. Liječenje ne treba odlagati dok se čeka nalaz drugih dijagnostičkih metoda kao što je biopsija temporalne arterije, odnosno rezultati patohistološke analize bioptata. U bolesnika koji su razvili nuspojave ili su ovisni o visokim dozama glukokortikoida u terapiju se može dodati metotreksat (MTX), a u novije vrijeme inhibitor interleukina – 6 (IL-6), tocilizumab (TCZ) (6–9).

U ovom radu prikazujemo bolesnicu s oteklinom parotidnih žlijezda i smetnjama vida u sklopu GCA, koji su nastali prije pojavljivanja glavobolje.

PRIKAZ BOLESNIKA

Šezdesetšestogodišnja bolesnica hospitalizirana je na Klinici za oftalmologiju zbog jednostranog gubitka vida. Dva mjeseca pred prijam pojavila joj se oteklina parotidnih žlijezda uz zadebljanja u predjelu temporalnih arterija. Mjesec dana pred prijam je u više navrata primijetila poremećaje vida lijevog oka u obliku kratkotrajnih „efekata zavjese" u trajanju do desetak minuta, a potom i postupno slabljenje vida koje se razvijalo kroz desetak dana. Pregledana je u drugoj ustanovi od strane specijalista otorinolaringologije, neurologije i oftalmologije. Tada joj je učinjena kompjutorizirana tomografija (CT) glave i otkrivena upala lijevog maksilarnog sinusa, zbog čega joj je ordiniran cefuroksim tijekom 10 dana, ali bez učinka. Nekoliko dana pred

gology, neurology and ophthalmology specialists. She underwent the computed tomography (CT) of the head at the same time, which revealed the inflammation of the left maxillary sinus. She was prescribed a 10-day course of cefuroxime, to no effect. Several days before admission to our hospital, she was subfebrile (axillary temperature up to 37.6°C) and began to experience pain in the jaw and temporal regions. After completely losing vision in her left eye, she was hospitalized at the Department of Ophtalmology, where she was diagnosed with anterior ischemic optic neuropathy (AION) of the left eye. During her hospital stay, we noticed that her right-eye vision was weakening too, so 3 days after hospitalization she was examined by a rheumatology specialist and transferred to the Department of Rheumatology. The patient received intravenous pulse glucocorticoid therapy on the same day (Solu-Medrol, 500 mg/day for 3 days). The treatment was continued with the dosage of 1 mg/kg, with gradual tappering. Her right-eye vision normalized 2 days after the start of the treatment, but left-eye vision loss persisted throughout her hospital stay. The patient had been treated for arterial hypertension and bronchial asthma, and she suffered two cerebrovascular insults (CVI) in 2013 due to the left carotid artery stenosis, for which she underwent a thromboendarterectomy. Upon admission, the patient was afebrile, her vital signs were normal, and she had several crusts that remained after herpes zoster infection in the parieto-occipital region Laboratory test results showed increased ESR (80 mm/h), elevated CRP (41.1 mg/L), leukocytosis (11.5×10^9/L) with neutrophilia (92.7%) and mild hyperglycemia (7.0 mmol/L). Other hematological and biochemistry parameters (erythrocytes, thrombocytes, transaminases, creatinine, electrolytes, C3 and C4 complement) were within normal reference ranges. Color Doppler ultrasound (CDUS) of the temporal arteries showed hypoechoic *halo* of both temporal arteries. Temporal artery biopsy was performed, and the histological examination determined that the media was thickened, with inflammatory lymphocyte and histiocyte infiltration and presence of multinuclear giant cells (CD68-positive). Magnetic resonance imaging of the brain showed a left supratentorial parietooccipital area of malacia/atrophy of the parenchyma, resembling the sequelae of the chronic vascular lesion, and a smaller chronic lacunar vascular lesion in the left frontal region subcortically. Results of microbiological tests (urine culture, hemoculture), tumor markers (carcinoembryonic antigen [CEA], CA 19-9, CA 125, CA 15-3, alpha fetoprotein [AFP]) and immunological parameters (antinuclear antibodies [ANA], rheumatoid factor [RF], antineutrophil cytoplasmic antibodies [ANCA]) all came back normal. Eight days after the start of the glucocorticoid therapy, follow-up testing

prijam u našu ustanovu je bila subfebrilna (Tax do 37,6 °C) te je počela osjećati bolove u čeljusti i u temporalnim regijama. Zbog potpunog gubitka vida na lijevo oko hospitalizirana je na Klinici za očne bolesti gdje je utvrđen AION lijevog oka. Tijekom hospitalizacije je primijetila slabljenje vida i na desnom oku, te je tri dana nakon hospitalizacije konzilijarno pregledana od strane reumatologa i premještena u Zavod za reumatologiju. Isti dan je primijenjena intravenska pulsna terapija glukokortikoidom (Solu-Medrol, 500 mg/dan kroz tri dana), a potom je nastavljeno liječenje u dozi od 1 mg/kgTT, uz postupno snižavanje doze. Dva dana nakon početka terapije vid na desno oko se normalizirao, no na lijevom oku je zaostao gubitak vida do kraja hospitalizacije. Bolesnica se inače liječila zbog arterijske hipertenzije i bronhijalne astme, a u dva navrata je 2013. godine preboljela cerebrovaskularni inzult (CVI), zbog stenoze lijeve karotidne arterije, te joj je učinjena trombendarterektomija. Prilikom prijma bila je afebrilna, s urednim vitalnim parametrima, a parijetookcipitalno je bilo vidljivo nekoliko krustoznih efloroscencija u sklopu herpes zoster infekcije, koja je bila u fazi sanacije. U laboratorijskim nalazima zabilježena je ubrzana SE (80 mm/h), povišena vrijednost CRP (41,1 mg/L), leukocitoza ($11,5 \times 10^9$/L) s neutrofilijom (92,7%) i blaga hiperglikemija (7,0 mmol /L). Ostali hematološki i biokemijski nalazi (eritrociti, trombociti, transaminaze, kreatinin, elektroliti, C3 i C4 komplement) bili su u granicama referentnih vrijednosti. Kolor dopler ultrazvuk (CDUS) temporalnih arterija je pokazao hipoehogeni *halo* obje temporalne arterije. Učinjena je i biopsija temporalne arterije, a patohistološkom analizom je utvrđeno zadebljanje medije s upalnim infiltratom limfocita i histiocita uz multinuklearne divovske stanice (CD68 pozitivne). Magnetska rezonancija (MR) mozga je pokazala lijevo supratentorijalno parijetookcipitalno zonu malacije / atrofije parenhima u smislu sekvele kronične vaskularne lezije, te manju kroničnu lakunarnu vaskularnu leziju lijevo frontalno subkortikalno. Nalazi mikrobioloških pretraga (urinokulture, hemokulture), tumorskih biljega [karcinoembrionalni antigen (CEA), CA 19-9, CA 125, CA 15-3, alfa-fetoprotein (AFP)] i imunoloških parametara [antinuklearna protutijela (ANA), reumatoidni faktor (RF), anti-neutrofilna citoplazmatska protutijela (ANCA)] bili su uredni. Osam dana od početka terapije glukokortikoidima ponovljene laboratorijske pretrage su pokazale normalizaciju upalnih parametara (CRP 2,6 mg/L), a bolesnica je otpuštena na kućnu njegu.

RASPRAVA

Prema Američkom reumatološkom društvu [*engl. American College of Rheumatology* (ACR)] za klasifikaciju GCA potrebni su dob od 50 godina ili više, novo-

showed normalization of inflammation parameters (CRP 2.6 mg/L), and the patient was discharged to home care.

DISCUSSION

According to the American College of Rheumatology (ACR), classification criteria for GCA includes age of 50 years or older, new-onset headache, temporal artery tenderness or decreased temporal artery pulsation, ESR of at least 50 mm/h, and positive artery biopsy results characterized by mononuclear infiltration or granulomatous inflammation (10). Definitive diagnosis is based on histological analysis of temporal artery or diagnostic imaging. Histological and immunohistochemical analyses show inflammation of the arterial wall dominated by CD4+ T lymphocytes and macrophages that frequently show granulomatous organization, forming giant cells. Vascular remodeling caused by inflammation leads to the intimal hyperplasia and occlusion of the lumen, which leads to ischemic complications. Histological specimen to prove GCA is most commonly obtained by the temporal artery biopsy (11). However, in the hands of experienced ultrasound specialists, CDUS can replace biopsy (12).

Our patient met all the criteria for the GCA diagnosis, but interestingly, the headache only began after the first manifestation of visual disturbances. Ordinarily, the onset of headache precedes visual disturbances and is present in approximately 90% of GCA patients. Available literature describes cases with atypical onset of the disease, such as occipital headache, limited range of jaw motion or orofacial pain (13–15). Such atypical onset of the disease, as was the case with our patient, hinders the timely diagnosis and beginning of treatment, which can have far-reaching consequences. The swelling of the parotid glands is an extremely rare symptom of this disease, caused by the vasculitis of the posterior auricular artery (16, 17). The patient in question experienced the swelling 2 months before hospitalization, and it subsided spontaneously over the course of approximately one month.

If GCA is suspected and visual disturbances have already manifested, the planned biopsy should not delay the start of the glucocorticoid treatment. According to some studies, temporal artery biopsy performed 1–4 weeks after the start of the glucocorticoid treatment reveals signs of inflammation typical for GCA, providing useful information for diagnosis even during that time (6). Negative biopsy results do not rule out the GCA diagnosis and can be expected in 10–15% of GCA patients (8, 12, 18). Positron emission tomography (PET), CT, CT angiography (CTA), and magnetic resonance angiography (MRA) lack the resolution for proper visualization of temporal artery (19). That may explain why our patient was not diagnosed with GCA after undergoing CT.

nastala glavobolja, osjetljivost temporalne arterije ili oslabljen puls temporalne arterije, brzina SE od najmanje 50 mm/h i pozitivna biopsija arterije obilježena mononuklearnom infiltracijom ili granulomatoznom upalom (10). Konačna dijagnoza se temelji na patohistološkoj analizi temporalne arterije ili slikovnom prikazu. Patohistološki i imunohistokemijski se nalazi upala stijenke arterije s prevladavanjem CD4+ T limfocita i makrofaga koji se često granulomatozno organiziraju te formiraju divovske stanice. Vaskularno remodeliranje uzrokovano upalom dovodi do hiperplazije intime i okluzije lumena što je izvor ishemijskih komplikacija bolesti. Histopatološki uzorak za dokazivanje GCA najčešće se dobiva biopsijom temporalne arterije (11). No, CDUS u rukama iskusnih ultrasoničara može zamijeniti biopsiju (12).

U naše bolesnice su zadovoljeni svi kriteriji za dijagnozu GCA, a zanimljivo je da je glavobolja počela nakon pojave prvih vidnih poremećaja. Naime, glavobolja se uglavnom javlja prije vidnih poremećaja i može se naći u oko 90% bolesnika s GCA. U dostupnoj literaturi su opisani prikazi bolesnika s atipičnim početkom bolesti, poput okcipitalne glavobolje, ograničenog otvaranja vilice ili orofacijalnih bolova (13–15). Ovakav atipičan početak bolesti, kao što je slučaj i u naše bolesnice, otežava pravovremeno postavljanje dijagnoze i početak liječenja što može imati dalekosežne posljedice. Oteklina parotidnih žlijezda je izrazito rijedak simptom bolesti koji nastaje kao posljedica vaskulitisa stražnje aurikularne arterije (16, 17). Takva oteklina se u prikazane bolesnice pojavila dva mjeseca prije hospitalizacije, a spontano se povukla kroz oko jedan mjesec.

Kod opravdane sumnje na GCA i pojave vidnih poremećaja planirana biopsija ne smije odlagati početak glukokortikoidne terapije. Prema nekim studijama, biopsija temporalne arterije uzeta 1–4 tjedna nakon početka liječenja glukokortikoidima otkriva upalne promjene tipične za GCA te i tada daje korisne informacije za dijagnozu (6). Negativni rezultati biopsije ne isključuju dijagnozu GCA, a očekuju se u 10–15% bolesnika s GCA (8, 12, 18). Pozitronska emisijska tomografija (PET), kmpjuterizirana tomografija (skr. CT), CT s angiografijom (CTA) i magnetna rezonancija s angiografijom (MRA) nemaju dovoljnu rezoluciju da omoguće vizualizaciju temporalne arterije (19). To može objasniti zašto našoj bolesnici nije dijagnosticiran GCA nakon što je bio učinjen CT.

Najozbiljnija komplikacija GCA je trajni gubitk vida koji je obično bezbolan i iznenadan, a može biti djelomičan ili potpun te jednostran ili obostran. Trajni gubitak vida u GCA rezultat je AION-a, okluzije središnje ili grane retinalne arterije [*engl. central retinal artery occlusion/branch retinal artery occlusion* (CRAO/BRAO)], stražnje ishemijske optičke neuropatije [*engl.*

The most serious GCA complication is permanent vision loss, which is usually painless and sudden. It can be partial or complete, monocular or binocular. Permanent vision loss in GCA is the result of AION, central retinal artery occlusion or branch retinal artery occlusion (CRAO/BRAO), posterior ischemic optic neuropathy (PION) or, rarely, cerebral ischemia. Fundoscopy is indicated in patients with subjective change in visual acuity (3,4,18). The first ophthalmological examination of our patient did not reveal anything unusual, while the follow-up examination found the AION of the left eye, which caused the permanent vision loss. The reported recurrence of CVI could also be a consequence of GCA, as CVI is described as part of GCA clinical presentation. However, it does not correspond with the GCA clinical presentation in our patient because it occurred several years earlier.

Given the fact that patients with undiagnosed GCA often "wander" between neurologists, ophthalmologists, infectiologists and rheumatologists, glucocorticoid therapy is usually not introduced in a timely manner in clinical practice (20, 21). It can lead to the permanent vision loss and other serious complications of this disease, as was the case with our patient.

CONCLUSION

In this paper we described the case of a patient with temporal arteritis who suffered irreversible vision loss in one eye as the result of delayed introduction of appropriate treatment. This case should alert us to the importance of taking temporal arteritis into consideration as a differential diagnosis in patients older than 50 with *amaurosis fugax*, even if typical symptoms are missing at the onset of disease. Additionally, bilateral parotid swelling, although exceedingly rare, can be one of the first manifestations of the disease. Good collaboration between ophthalmology and rheumatology specialists, as well as other specialists, is key to early diagnosis and start of appropriate treatment to reduce the risk of permanent vision loss and other effects of the disease.

Conflict of interest statement: Authors declare no conflict of interest.

posterior ischemic optic neuropathy (PION)] ili rijetko, cerebralne ishemije. Fundoskopija je indicirana u bolesnika sa subjektivnom promjenom oštrine vida (3,4,18). Prvi oftalmološki pregled naše bolesnice je bio uredan, dok je pri ponovljenom pregledu utvrđen AION lijevog oka, koji je doveo do trajnog gubitka vida. Podatak o recidivu CVI-a bi također mogao biti posljedica GCA. Naime, CVI se opisuje kao dio kliničke slike GCA, iako vremenski odmak od više godina se u ovom slučaju ne bi uklopio u kliničku sliku GCA.

Obzirom da bolesnici s neprepoznatim GCA često „lutaju" između neurologa, oftalmologa, infektologa i reumatologa, početak terapije glukokortikoidima u kliničkoj praksi nije pravovremen (20, 21), što može dovesti do trajnog gubitka vida i ostalih ozbiljnih komplikacija ove bolesti kao što je bio slučaj i u naše bolesnice.

ZAKLJUČAK

U ovom radu prikazali smo bolesnicu s temporalnim arteritisom u koje je zaostao gubitak vida na jedno oko zbog zakašnjele primjene odgovarajuće terapije. Ovaj slučaj upozorava nas da je važno razmotriti temporalni arteritis kao diferencijalnu dijagnozu u bolesnika starijih od 50 godina s *amaurosis fugax* čak i ako izostanu tipični simptomi u početku bolesti. Osim toga, oteklina u području parotidnih žlijezda, iako vrlo rijetka, može biti jedna od prvih manifestacija bolesti. Dobra suradnja specijalista oftalmologije i reumatologije, ali i drugih specijalista od ključne je važnosti za rano postavljanje dijagnoze i početak odgovarajućeg liječenja kako bi se smanjio rizik od trajnog gubitka vida i ostalih posljedica bolesti.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol. 2017;13(10):578.
2. Nordborg E, Nordborg C. Giant cell arteritis: strategies in diagnosis and treatment. Curr Opin Rheumatol 2004;16:25–30.
3. Miller NR. Visual manifestations of temporal arteritis. Rheum Dis Clin North Am. 2001;27(4):781.
4. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol. 1998;125(4):509.
5. Barbazan C, Gonzalez-Gay MA, Aspe B, Fucionos L, Mantecon-Apariocio JM. Visual recovery after retinal stroke due to giant cell arteritis. Clin Exp Rheumatol. 2000;18:425–6.
6. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703.
7. Villiger PM, Adler S, Kuchen S, i sur. Tocilizumab for induction and maintenance of remission in giant cell arteritis: A phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387(10031):1921. Epub 2016 Mar 4.
8. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA. 2016;315(22):2442–58.
9. Hellmich B, Agueda A, Monti S, i sur. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020 Jan;79(1):19–30.
10. Hunder GG, Bloch DA, Michel BA, i sur. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
11. Cid MC, Campo E, Ercilla G, i sur. Immunohistochemical analysis of lymphoid and macrophage cell subsets and their immunologic activation markers in temporal arteritis. Influence of corticosteroid treatment. Arthritis Rheum. 1989;32(7):884.
12. Luqmani R, Lee E, Singh S, i sur. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess 2016;20:1–238.
13. Rana AQ, Saeed U, Khan OA, Qureshi AR, Paul D. Giant cell arteritis or tension-type headache?: A differential diagnostic dilemma. J Neurosci Rural Pract. 2014;5(4):409–11.
14. Reiter S, Winocur E, Goldsmith C, Emodi-Perlman A, Gorsky M. Giant cell arteritis misdiagnosed as temporomandibular disorder: A case report and review of the literature. J Orofac Pain. 2009;23:360–5.
15. Kraemer M, Metz A, Herold M, Venker C, Berlit P. Reduction in jaw opening: A neglected symptom of giant cell arteritis. Rheumatol Int. 2011;31:1521–3.
16. Amor-Dorado JC, Llorca J, Garcia-Porrua C, Costa C, Perez-Fernandez N, Gonzalez-Gay MA. Audiovestibular manifestations in giant cell arteritis: a prospective study. Medicine (Baltimore). 2003;82(1):13–26.
17. Czihal M, Tatò F, Hoffmann U, Kuhlencordt PJ. Juvenile temporal arteritis. Clin Exp Rheumatol. 2013;31(1 Suppl 75):S89.
18. Hayreh SS, Biousse V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? J Neuroophthalmol. 2012;32(3):278.
19. Duftner C, Dejaco C, Sepriano A, i sur. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD open. 2018;4(1):e000612. doi: 10.1136/rmdopen-2017-000612. eCollection 2018.
20. Laskou F, Coath F, Mackie SL, Banerjee S, Aung T, Dasgupta B. A probability score to aid the diagnosis of suspected giant cell arteritis. Clin Exp Rheumatol 2019; 37 (Suppl. 117):S104–S108.
21. Lyons HS, Quick V, Sinclair AJ, Nagaraju S, Mollan SP. A new era for giant cell arteritis. Eye. https://doi.org/10.1038/s41433-019-0608-7.

Reumatizam 2019;66(2):81–91
https://doi.org/10.33004/reumatizam-66-2-11

CASE REPORT PRIKAZ BOLESNIKA

PANDAS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES, CASE REPORT, AND LITERATURE REVIEW

PANDAS: DIJAGNOSTIČKI I TERAPIJSKI IZAZOVI, PRIKAZ BOLESNICE I PREGLED LITERATURE

Kristian Hodak[1], Mario Šestan[1], Marija Jelušić[1]

[1]Division of Clinical Immunology, Rheumatology and Allergology, Centre of Reference for Paediatric and Adolescent Rheumatology of Ministry of Health of the Republic of Croatia, University Department for Paediatrics, University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia / Zavod za kliničku imunologiju, reumatologiju i alergologiju, Referentni centar za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske, Klinika za pedijatriju, Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

Adresa autora za dopisivanje/Corresponding author:
Prof. dr. sc. Marija Jelušić, dr. med.
Division of Clinical Immunology, Rheumatology and Allergology / Zavod za kliničku imunologiju, reumatologiju i alergologiju
Rheumatology of Ministry of Health of the Republic of Croatia / Referentni centar za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva RH
University Department for Paediatrics / Klinika za pedijatriju
University of Zagreb School of Medicine / Medicinski fakultet Sveučilišta u Zagrebu
University Hospital Centre Zagreb / Klinički bolnički centar Zagreb
Kišpatićeva ulica 12, 10000 Zagreb
Tel.: 01 2388 701
E-mail / e-pošta: marija.jelusic@mef.hr

Received / Primljeno: August 8, 2019/ 8. kolovoz 2019.
Accepted / Prihvaćeno: November 22, 2019/ 22. studeni 2019.

Abstract

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a controversial clinical entity in medical practice due to insufficiently known etiopathogenesis, lack of specific markers for confirmation of the diagnosis, and difficult-to-prove causal relationship between a group A β-haemolytic streptococcal (GABHS) infection and the onset of symptoms. It presents with a sudden onset of symptoms and signs of obsessive-compulsive disorder (OCD) and/or tics, which are associated with a recent GABHS infection. We presented a patient with PANDAS as well as a brief overview of the literature concerning the etiopathogenesis, diagnostics and treatment while emphasizing the complexity of this disorder due to the large variations in clinical presentation, the inability to make a reliable diagnosis, and the controversies in choosing effective treatment methods. It is evident that many of the issues surrounding PANDAS remain open and that further research and a multidisciplinary approach are needed to better understand this complex clinical entity.

Keywords: Autoimmune diseases – complications, diagnosis, drug therapy; Streptococcal infections – complications, diagnosis, drug therapy; Streptococcus pyogenes; Obsessive-compulsive disorder – drug therapy, etiology; Tic disorders – drug therapy, etiology; Immunoglobulins, intravenous – therapeutic use; Amoxicillin-potassium clavulanate combination – therapeutic use; Anti-bacterial agents – therapeutic use

Sažetak

Pedijatrijski autoimunosni neuropsihijatrijski poremećaji udruženi sa streptokoknom infekcijom (engl. *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections* – PANDAS) prijeporan su klinički entitet u medicinskoj praksi zbog nedovoljno poznate etiopatogeneze, nepostojanja specifičnog biljega za potvrdu dijagnoze te teško dokazive uzročno-posljedične veze između infekcije β-hemolitičkim streptokokom skupine A (BHSA) i pojave simptoma ovog poremećaja. Očituje se naglo nastalim simptomima i znakovima opsesivno-kompulzivnog poremećaja (OKP) i/ili tikovima, koji su povezani s nedavnom infekcijom BHSA-om. U radu smo prikazali bolesnicu

s PANDAS-om i kratak pregled literature vezane uz etiopatogenezu, dijagnostiku i liječenje ovog poremećaja pri čemu smo željeli naglasiti njegovu složenost zbog velikih različitosti u kliničkoj slici, nemogućnosti postavljanja sigurne dijagnoze i prijepora pri odabiru učinkovitih metoda liječenja. Iz navedenoga je razvidno da mnoga pitanja u svezi s PANDAS-om ostaju otvorena te da su potrebna daljnja istraživanja i multidisciplinarni pristup kako bi se bolje upoznao ovaj kompleksan klinički entitet.

Ključne riječi: Autoimunosne bolesti – dijagnoza, farmakoterapija, komplikacije; Streptokokne infekcije – dijagnoza, farmakoterapija, komplikacije; Streptococcus pyogenes; Opsesivno-kompulzivni poremećaj – etiologija, farmakoterapja; Tikovi – etiologija, farmakoterapja; Intravenski imunoglobulini – terapijska uporaba; Amoksicilin – klavulanska kiselina – terapijska uporaba; Protubakterijski lijekovi – terapijska uporaba

INTRODUCTION

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) still represents a controversial syndrome in clinical medicine manifested by sudden onset of symptoms and signs of obsessive-compulsive disorder (OCD) and/or tics but temporally associated with a group A β-hemolytic streptococcal (GABHS) infection. This is why PANDAS is thought to be essentially associated with an impaired immune response of the organism against GABHS antigens (1–3).

PANDAS was first described as a disorder in a 1998 paper by Swedo et al., when the first criteria for its diagnosis were proposed (1). Although the exact incidence of this syndrome is not known, it is estimated that it affects approximately 1% of children, and according to information in foreign literature, around one to three new patients may be expected annually in an average primary care unit (4). The syndrome is more common in boys, with a 2.6 : 1 ratio, and usually occurs between ages 3 and 12, most commonly between ages 6 and 8 (1).

The etiopathogenesis of the disorder is not fully understood. One of the more popular hypotheses is that the disorder is based on the creation of antibodies which, due to their similarity with streptococcal antigens and neural tissue antigens, produce a cross-reaction with epitopes in the central nervous system (CNS) (5, 6).

The disorder usually has an abrupt onset. Apart from the OCD symptoms, it can manifest itself with tics, hyperactivity, choreatic movements, anxiety, frequent urination, and writing difficulties, as well as with a deterioration in school performance (1). OCD is manifested by forced thoughts and actions that the affected person perceives as foreign and imposed. Tics are involuntary, sudden, repetitive movements that are short-lasting and occur in attacks (7, 8).

The therapy is diverse because of the insufficiently clarified pathogenesis; it includes antibiotics, psychotherapy, psychopharmaceuticals, intravenous immunoglobulins (IVIGs), glucocorticoids, plasmapheresis, and monoclonal antibodies (9–12).

UVOD

Pedijatrijski autoimunosni neuropsihijatrijski poremećaji udruženi sa streptokoknom infekcijom (engl. *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections* – PANDAS) i dalje su prijeporan sindrom u kliničkoj medicini koji se očituje naglo nastalim simptomima i znakovima opsesivno-kompulzivnog poremećaja (OKP) i/ili tikova što su vremenski povezani s infekcijom β-hemolitičkim streptokokom skupine A (BHSA), zbog čega se pretpostavlja da se u osnovi radi o poremećenom imunosnom odgovoru organizma na antigene BHSA (1 – 3).

PANDAS je prvi put opisan 1998. godine u radu Susan Swedo i suradnika, kada su i predloženi prvi kriteriji za njegovu dijagnozu (1). Iako točna incidencija ovog sindroma nije poznata, procjenjuje se da zahvaća oko 1% djece, a u stranoj literaturi nalazi se podatak da bi se u jednoj prosječnoj ambulanti primarne zdravstvene zaštite moglo očekivati između jednog i tri nova bolesnika na godinu (4). Pojavljuje se češće u dječaka s omjerom 2,6 : 1, obično između 3. i 12. godine, a češće između 6. i 8. godine (1).

Etiopatogeneza poremećaja nije do kraja razjašnjena. Jedna od popularnih hipoteza jest da je u osnovi nastanka ovog poremećaja stvaranje protutijela koja zbog sličnosti streptokoknih antigena s antigenima neuralnog tkiva dovode do ukrižene reaktivnosti s epitopima središnjega živčanog sustava (SŽS) (5, 6).

Poremećaj tipično ima nagli početak. Osim simptomima OKP-a, može se manifestirati tikovima, hiperaktivnošću, koreatičnim kretnjama, anksioznošću, učestalim mokrenjem te teškoćama pisanja i slabijim školskim uspjehom (1). OKP se očituje prisilnim mislima i radnjama koje oboljela osoba doživljava kao strane i nametnute. Tikovi su nevoljne, nagle, repetitivne kretnje koje su kratkotrajne i nastupaju u napadajima (7, 8).

Terapija koja se primjenjuje raznovrsna je zbog nedovoljno razjašnjene patogeneze, a obuhvaća antibiotike, psihoterapiju, psihofarmake, intravenske imunoglobuline (IVIG), glukokortikoide, plazmaferezu i monoklonska protutijela (9 – 12).

The aim of this study was to present a clinical case as well as the complexity of the diagnostic procedure and the choice of therapy in a patient with PANDAS.

CASE PRESENTATION

We are presenting a female patient who was admitted to our Department at 12 years of age. Until she presented with first symptoms at the age of 9, she was not seriously ill. The family history was unremarkable. The illness started around a month after a pharyngeal inflammation empirically treated with amoxicillin. First, there was a sudden onset of all-day, involuntary, stereotypical body movements, more precisely twitching of the arms and legs, bouncing while walking, and involuntary movements of the torso. Afterwards vocal tics appeared in the form of mumbling, frequent throat clearing, and screams. The symptoms were most evident in the evening hours and during the night, and were present every day. The neuropediatric analysis was done in another institution. The initial electroencephalogram (EEG) as well as the EEG after a sleepless night were unremarkable. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. A repeated EEG was focally changed and the EEG after a sleepless night showed epileptogenic changes. The proposed psychiatric and psychological assessment showed psychomotor restlessness, impulsiveness, low frustration threshold, aggressive outbursts tendencies with elements of anxiety and depression, as well as somewhat immature behavior for the patient's age. A working diagnosis of Tourette syndrome was made. Use of the antidepressant sertraline, the antiepileptics oxcarbazepine and carbamazepine, the antipsychotics quetiapine and risperidone, as well as diazepam did not have a therapeutic effect. After a year, the symptoms spontaneously withdrew and did not return for the next 7-8 months.

The second episode of the illness occurred before the age of 11 years with a sudden relapse of the previously described symptoms, but this time with alternating periods of more intense and milder clinical presentation. Haloperidol therapy was introduced, but removed due to worsening of the symptoms. Pimozide and levetiracetam therapy was then started; it was successful for 5 to 6 months, when the symptoms recurred in a milder form as tics of the left leg and arm as well as vocal tics. Besides that, the girl's school performance deteriorated and she became excessively anxious and increasingly withdrawn. Considering the relapse of symptoms and failure of the antipsychotic and antiepileptic therapy, a repeated assessment excluded epilepsy, autoimmune encephalitis, and structural damage of the brain as the cause of the symptoms. From that assessment it is important to single out a positive GAB-

Cilj je rada prikazati kliničku sliku te složenost postupaka postavljanja dijagnoze i izbora terapije u bolesnika s PANDAS-om.

PRIKAZ BOLESNICE

Prikazujemo bolesnicu koja je prvi put primljena u naš Zavod u dobi od 12 godina. Do pojave prvih simptoma bolesti u dobi od 9 godina nije bila teže bolesna. Obiteljska anamneza bila je neupadljiva. Bolest je započela oko mjesec dana nakon preboljele upale ždrijela koja je empirijski liječena amoksicilinom. Najprije su naglo nastupili cjelodnevni nevoljni, stereotipni pokreti tijela, odnosno trzaji rukama i nogama, poskakivanja pri hodu te nevoljni pokreti trupa. Naknadno su se pojavili vokalni tikovi u obliku mumljanja, učestalog pročišćivanja grla i krikova. Navedeni simptomi bili su najizraženiji u večernjim satima i tijekom noći te prisutni svakodnevno. U drugoj ustanovi učinjena je neuropedijatrijska obrada. Inicijalni elektroencefalogram (EEG), kao i EEG nakon neprospavane noći bili su uredni. Nalaz magnetske rezonancije (MR) mozga bio je uredan. Međutim, ponovljeni EEG bio je žarišno promijenjen, a EEG nakon neprospavane noći epileptogeno promijenjen. Preporučena je psihijatrijska i psihološka obrada kojom su utvrđeni psihomotorički nemir, impulzivnost, niski frustracijski prag, sklonost agresivnim ispadima uz elemente anksioznosti i depresivnosti te nešto nezrelije ponašanje za dob. Postavljena je radna dijagnoza Touretteova sindroma. Primjena antidepresiva sertralina, antiepileptika okskarbazepina i karbamazepina, antipsihotika kvetiapina i risperidona te diazepama nije postigla terapijski učinak. Nakon jedne godine simptomi su se spontano povukli te se nisu pojavljivali sljedećih 7 – 8 mjeseci.

Druga epizoda bolesti manifestirala se u dobi od nepunih 11 godina naglim recidivom prethodno opisanih simptoma, ali ovaj put s izmjenom perioda intenzivnije i blaže kliničke slike. Uvedena je terapija haloperidolom koja je zbog pojačanja simptoma ukinuta. Zatim je započela terapija pimozidom i levetiracetamom koja je djelovala tijekom 5 do 6 mjeseci nakon čega se simptomi ponovo javljaju, ali u blažem obliku tikova lijevom nogom i rukom te vokalnih tikova. Uz to, djevojčica je popustila u školi, postala je izraženije anksiozna te se počela povlačiti u sebe. S obzirom na recidiv simptoma i neuspjeh terapije antipsihoticima i antiepilepticima, ponovljena je obrada kojom su isključeni epilepsija, autoimunosni encefalitis te strukturna oštećenja mozga kao uzrok tegoba, a iz tada učinjenih nalaza valja izdvojiti pozitivan BHSA iz obriska ždrijela i povišen titar protutijela na streptolizin O (ASO) (prva izmjerena vrijednost 671 IJ/mL; ponovljena vrijednost nakon 4 tjedna 1703 IJ/mL; referentne vrijednosti ≤ 200 IJ/mL), dok su protutijela na deoksiribonu-

HS pharyngeal swab and an elevated antistreptolysin O (ASO) antibody titer (first measured value: 671 IU/mL; repeated value after 4 weeks: 1703 IU/mL; reference value: ≤ 200 lU/mL), while anti-deoxyribonuclease B (anti-DNase B) antibodies were negative. On repeat brain MRI, there were minor changes in diffusibility with signal hyperintensity present in the area of the head of the *nucleus caudatus* as well as in the left part of the *globus pallidus*, more specifically in its inner part and the left subthalamic nucleus. Morphological analysis showed a small increase in the basal ganglia volume in comparison to the standard values.

Based on the confirmed streptococcal infection with sudden tic onset that started before puberty and disrupted everyday functionality, manifesting episodically with the presence of associated psychiatric comorbidities at the age of 12, the PANDAS diagnosis was made. Antimicrobial treatment by amoxicillin with clavulanic acid was introduced for 10 days during which the symptoms decreased, only to relapse after the discontinuation of treatment. Due to the progression and failure of the previous therapy, IVIG therapy was initiated. Continuation of the prophylactic therapy by amoxicillin with clavulanic acid was recommended. In the following 5 years, the vocal tics disappeared completely; occasional mild twitches of the legs and arms remained, but they did not interfere with the patient's daily functionality.

After that period, at the age of 17, there was a recurrent but minor exacerbation in the form of stereotypical extremity movements with tingling in the legs and insomnia. The antipsychotic risperidone was introduced following the recommendation of a psychiatrist who diagnosed an emotional disorder, but due to the fact that the patient and her parents were disinclined to the recommended therapy, they discontinued it themselves. The girl was feeling well and able to follow her classes.

The following exacerbation occurred after pharyngitis at the age of 19, when, with the existing twitching of the arms and legs, there was a sudden onset of facial tics in the form of grimacing as well as vocal tics in the form of throat clearing. GABHS was again found in a pharyngeal swab. The symptoms were reduced by antimicrobial therapy with cefuroxime, but recurred after the discontinuation of the drug. Therefore, another IVIG therapy was initiated and it was recommended to continue the prophylactic amoxicillin with clavulanic acid therapy, resulting with symptom regression.

DISCUSSION

We have presented a patient with PANDAS. This disorder continues to cause controversy since its mechanism is still unresolved, there are no diagnostic markers, it is not possible to associate streptococcal infection and

kleazu B (antiDNaza B) bila negativna. Na ponovljenome MR-u mozga bile su vidljive manje promjene difuzibilnosti s hiperintenzitetom signala u području obiju glava nukleusa kaudatusa te u lijevom dijelu globusa palidusa odnosno njegovu unutarnjem dijelu i lijevoj suptalamičkoj jezgri. Morfološkom analizom uočen je blagi porast volumena bazalnih ganglija u odnosu prema standardnim vrijednostima.

Na osnovi potvrđene streptokokne infekcije i nagle pojave tikova koji su započeli prije puberteta, ometali svakodnevno funkcioniranje, a javljali su se epizodno, te uz prisutne pridružene psihijatrijske komorbiditete u dobi od 12 godina postavljena je dijagnoza PANDAS-a. Provedeno je antimikrobno liječenje amoksicilinom s klavulanskom kiselinom u trajanju od 10 dana tijekom kojeg su se simptomi ublažili, ali su nakon prestanka liječenja ponovo progredirali. Zbog te progresije simptoma i neuspjeha prethodne terapije provedena je terapija intravenski primijenjenim imunoglobulinima (IVIG-om) te je preporučeno nastaviti profilaktičku terapiju amoksicilinom s klavulanskom kiselinom. Sljedećih 5 godina vokalni su tikovi potpuno prestali, dok su se povremeno pojavljivali blagi trzaji nogu i ruku, ali nisu ometali svakodnevno funkcioniranje.

Nakon tog perioda, u dobi od 17 godina, dolazi do ponovnog, ali blažeg pogoršanja u obliku stereotipnih pokreta ekstremiteta, uz trnce u nogama i nesanicu. Prema preporuci psihijatra, koji je postavio dijagnozu emocionalnog poremećaja, započeta je primjena antipsihotika risperidona, no budući da bolesnica i roditelji nisu bili skloni navedenoj terapiji, samoinicijativno su je prekinuli. Bolesnica se subjektivno dobro osjećala i mogla je pratiti nastavu.

Sljedeće pogoršanje nastupilo je nakon faringitisa u dobi od 19 godina, kada uz postojeće trzaje nogu i ruku dolazi do nagle pojave facijalnih tikova, odnosno grimasa i vokalnih tikova u obliku pročišćavanja grla. Iz obriska ždrijela ponovo je dokazan BHSA. Simptomi su se ublažili primjenom antimikrobne terapije cefuroksimom, ali su se prestankom uzimanja lijeka ponovo intenzivirali. Zbog toga je drugi put provedena terapija IVIG-om te je preporučeno nastaviti profilaktičku terapiju amoksicilinom s klavulanskom kiselinom nakon čega je došlo do regresije simptoma.

RASPRAVA

U radu smo prikazali bolesnicu s PANDAS-om. Ovaj poremećaj i dalje izaziva prijepore budući da je mehanizam njegova nastanka nerazjašnjen, nema biljega za potvrdu dijagnoze, ne može se sa sigurnošću utvrditi povezanost između streptokokne infekcije i nastanka simptoma, a k tomu ne postoji ni definirano razdoblje između ovih događaja (13, 14).

the onset of symptoms with certainty, and there is no defined period between symptomatic events (13, 14).

The essence of the disorder is thought to be an autoimmune event after a GABHS infection, during which antibodies can be generated that may affect the function of the basal ganglia (5, 6). Some GABHS antigens are thought to be homologous with human brain proteins. This leads to a disrupted immune response due to molecular mimicry and a subsequent cross-reaction with CNS epitopes. Consequently, damage occurs that is sometimes visualized on brain MRI as basal ganglia edema. The so-called orbitofrontostriatal circle is affected, whose damage is associated with a behavioral disorder manifesting as OCD. Recent studies using neuroimaging methods (15, 16) have shown that patients with PANDAS can show an increased volume of grey matter in the structures that belong to the said anatomical area, such as the *putamen*, *nucleus caudatus*, *amygdala*, *globus pallidus*, etc. On a repeat brain MRI, our patient showed a minor increase in basal ganglia volume, which is consistent with the results of the above studies.

Some authors believe that the results of a good therapeutic effect of IVIG and plasmapheresis support the underlying autoimmune disease theory. This is limited by the small number of patients, the concomitant administration of antibiotics, the short duration of the studies, as well as by the unspecific IVIG effect (13, 17). Furthermore, the presence of antibodies does not mean a direct association with the disease. Besides, it has not been proven which antibodies exactly are responsible for the onset of the disease. Various studies have shown the existence of autoantibodies in the serum of patients with PANDAS. On the one hand, there are nonspecific antineuronal antibodies (18–20) for which there is no proven causal-outcome association with PANDAS; also, it is not known whether these antibodies can cross the blood-brain barrier, whether they can form intrathecally, and how long they are present in the patient's serum before the onset of the disease. On the other hand, in patients with PANDAS increased levels of serum antibodies have been found that were created against neuron antigens such as tubulin, lisogangliosid, and dopamine D1 and D2 receptors. But so far there is still insufficient evidence that these antibodies are the cause of symptoms in patients (21–24).

Our patient's immunology workup showed a positive ASO titer and a negative anti-DNase B. These tests were done in combination with a pharyngeal swab to prove a recent GABHS infection. ASO titer and anti-DNAse B are serological tests used to confirm recent *Streptococcus pyogenes* bacterium infections, and they are especially useful in cases of suspected complications caused by the mentioned infection, such as rheu-

Smatra se da je u osnovi poremećaja autoimunosno zbivanje poslije infekcije BHSA-om, pri čemu zbog infekcije može doći do stvaranja protutijela koja onda mogu utjecati na funkciju bazalnih ganglija (5, 6). Pretpostavlja se da su neki antigeni BHSA homologni s proteinima ljudskog mozga. To dovodi do poremećenog imunosnog odgovora zbog molekularne mimikrije te, posljedično, ukrižene reaktivnosti s epitopima SŽS-a. Posljedično dolazi do oštećenja, što se katkad na MR-u mozga prikazuje kao edem bazalnih ganglija. Zahvaćen je tzv. orbitofrontostrijatalni krug s čijim je oštećenjem povezan poremećaj ponašanja u obliku OKP-a. Primjenom neuroslikovnih metoda (15, 16) recentna su istraživanja pokazala da se u bolesnika s PANDAS-om može opaziti povećan volumen sive tvari u strukturama koje pripadaju navedenom anatomskom području kao što su putamen, nukleus kaudatus, amigdala, globus palidus itd. Naša je bolesnica na ponovljenome MR-u mozga imala blagi porast volumena bazalnih ganglija, što se može uklopiti u rezultate navedenih istraživanja.

Neki autori smatraju da bi u prilog autoimunosnoj podlozi bolesti išli rezultati istraživanja o dobromu terapijskom učinku IVIG-a i plazmafereze, koji su ipak ograničeni malenim brojem bolesnika, popratnom primjenom antibiotika, kratkim trajanjem istraživanja, kao i mogućnosti nespecifičnog učinka IVIG-a (13, 17). Nadalje, postojanje protutijela ne znači nužno i direktnu povezanost s pojavom bolesti, a također nije dokazano koja su to točno protutijela odgovorna za nastanak bolesti. Tako su različita istraživanja upozorila na postojanje autoprotutijela u serumu bolesnika s PANDAS-om. S jedne strane, radi se o nespecifičnim antineuronalnim protutijelima (18 – 20) za koja nije dokazana uzročno-posljedična povezanost s PANDAS-om, a nije poznato ni mogu li ta protutijela prijeći krvno-moždanu barijeru, mogu li se stvarati intratekalno te koliko su vremena prije nastanka bolesti ta protutijela prisutna u serumu bolesnika. S druge strane, u bolesnika s PANDAS-om utvrđena je povišena serumska razina protutijela usmjerenih na antigene neurona poput tubulina, lizogangliozida, dopaminskih receptora D1 i D2. No, zasad još ne postoji dovoljno dokaza da su ta protutijela uzrok tegoba u bolesnika (21 – 24).

Naša je bolesnica od imunološke obrade imala pozitivan ASO titar i negativnu antiDNazu B. Ti su testovi učinjeni da bi se, u kombinaciji s obriskom ždrijela, dokazala recentna infekcija BHSA-om. ASO titar i antiDNaza B serološki su testovi koji služe za dokazivanje prethodne infekcije uzrokovane bakterijom *Streptococcus pyogenes*, a osobito su korisni pri sumnji na komplikacije navedene infekcije kao što su reumatska vrućica i akutni poststreptokokni glomerulonefritis (25). U literaturi su opisane diskrepancije između vri-

matic fever and acute post-streptococcal glomerulonephritis (25). The literature shows discrepancies between ASO titer and anti-DNase B values, as was the case with our patient (25, 26). Namely, situations are possible where the ASO titer is positive, but the anti-DNase B negative, and vice versa. For example, up to 20% of patients with a proven GABHS pharyngitis will not have increased ASO titer values, probably due to the different expression of streptolysin O in different strands of GABHS (25). It is also possible that some strands do not have an expressed DNase B gene, or that its expression is very weak, which could be the cause of the negative anti-DNase B titers (25, 26). Other autoantibodies done in the immunological analysis of our patient were negative.

PANDAS was first defined in 1998 in a study by Swedo et al. (1) that proposed five diagnostic criteria that must be met in order to make a diagnosis: 1. presence of OCD and/or a tic disorder; 2. symptom onset after the age of 3 but before puberty; 3. episodic course of symptom severity characterized by an abrupt onset and exacerbations, while in between exacerbations the patient can be without symptoms; 4. association with a GABHS infection (positive throat culture and/or positive ASO titer); 5. association with neurological abnormalities, especially motor hyperactivity and adventitious movements such as choreiform movements and tics.

In our patient motor and vocal tics were present, the symptoms appeared abruptly at the age of 9 with periods of worsening and diminishment, there was a proven GABHS infection, and involuntary stereotypical movements were present. According to the above, the patient fulfilled all five diagnostic criteria for a PANDAS diagnosis.

The study by Swedo highlighted the differences between patients with PANDAS and those with similar clinical presentations (1). Symptoms in PANDAS patients begin about 3 years earlier on average than OCD and tics typical of children. These symptoms have sudden and dramatic characteristics. It is also mentioned that every subsequent exacerbation of the disease is not necessarily associated only with a GABHS infection, but may also be linked to a viral infection or some other disease. Although they are not diagnostic criteria, some other common conditions associated with PANDAS are listed: attention deficit hyperactivity disorder (ADHD), common after 6 years of age, emotional lability, separation anxiety, inappropriate behavior for age, and nocturnal problems. Those states are also episodic and associated with a GABHS infection. We found that our patient also had psychiatric comorbidities, more specifically emotional disorders, sleep problems, anxiety, and inappropriate behavior for age.

While an association with GABHS is thought to be an important feature of PANDAS, even prior to definjednosti ASO titra i antiDNaze B kao što je to bilo i u naše bolesnice (25, 26). Naime, moguće su situacije u kojima je ASO titar pozitivan, a antiDNaza B negativna i obrnuto. Primjerice, i do 20% bolesnika s faringitisom dokazano uzrokovanim BHSA-om neće imati povišene vrijednosti ASO titra, vjerojatno zbog različite ekspresije streptolizina O u različitim sojevima BHSA (25). Također, moguće je da neki sojevi nemaju izražen gen za DNazu B ili je on vrlo slabo eksprimiran, što bi moglo biti uzrokom negativnih vrijednosti antiDNaze B (25, 26). Ostala autoprotutijela određena u sklopu imunološke obrade u prikazane bolesnice bila su negativna.

PANDAS je prvi put definiran u radu Susan Swedo i suradnika, a autori su predložili pet dijagnostičkih kriterija koji moraju biti ispunjeni za postavljanje dijagnoze: 1. prisutnost simptoma i znakova OKP-a i/ili tikova; 2. početak simptoma nakon 3. godine, a prije puberteta; 3. epizodni tijek bolesti karakteriziran naglim početkom i pogoršanjima, dok između napadaja bolesnik može biti bez simptoma; 4. povezanost s infekcijom BHSA-om (pozitivna kultura obriska ždrijela i/ili pozitivan ASO titar); 5. povezanost s neurološkim poremećajima, posebno motoričkom hiperaktivnošću i nehotimičnim pokretima kao što su koreiformni pokreti i tikovi (1).

U naše su bolesnice bili prisutni motorički i vokalni tikovi, simptomi su naglo započeli u 9. godini, s razdobljima egzacerbacije i ublažavanja simptoma, uz dokazanu infekciju BHSA-om, a imala je i nevoljne stereotipne pokrete. Prema navedenomu, bolesnica je ispunjavala svih pet kriterija za postavljanje dijagnoze PANDAS-a.

Istraživanje koje je provela Swedo istaknulo je razlike bolesnika s PANDAS-om u odnosu prema onima sa sličnom kliničkom slikom (1). Tako simptomi u bolesnika s PANDAS-om počinju u prosjeku oko 3 godine prije od OKP-a uobičajenoga za dječju dob te tikova. Ti su simptomi naglog i burnog karaktera. Navodi se i da svaka daljnja egzacerbacija bolesti ne mora biti povezana samo s infekcijom BHSA-om, već to može biti virusna infekcija ili neka druga bolest. Iako nisu dio kriterija za dijagnozu, navedena su još neka česta stanja koja prate PANDAS: poremećaj pozornosti s hiperaktivnošću (engl. *Attention deficit hyperactivity disorder* – ADHD), često nakon 6. godine, emocionalna labilnost, separacijska anksioznost, neprimjereno ponašanje za dob i noćne more. Ta su stanja također bila epizodna i povezana s infekcijom BHSA-om. I u svoje smo bolesnice zamijetili postojanje psihijatrijskih komorbiditeta u obliku emocionalnog poremećaja, poremećaja spavanja, anksioznosti i nezrelijeg ponašanja za dob.

Dok se povezanost s BSHA-om smatra bitnim obilježjem PANDAS-a, još prije definiranja ovoga klinič-

ing this clinical entity it was known that infections could trigger neuropsychiatric disorders. This is how in 1995 PITANDs (pediatric, infection-triggered, autoimmune neuropsychiatric disorders) was defined, in which symptoms similar to those of PANDAS appear, but in this case they do not have to be associated with GABHS (17). The criteria for PITANDs are: 1. symptom onset in the pediatric population between 3 years of age and puberty; 2. sudden onset and/or presentation of impulsive, recurrent, clinically significant symptom exacerbation and remission; 3. exacerbations are not exclusively associated with stress or illness, should be pervasive and of sufficient severity to suggest the need for treatment modifications, untreated exacerbation lasts for a minimum of 4 weeks; 4. evidence of an antecedent or concomitant infection, such as a positive GABHS throat culture, positive streptococcal serological findings (e.g., ASO titer or anti-DNase B), or a history of illness (e.g., pharyngitis, sinusitis, or flulike symptoms); 5. at some time in life, the patient must have met the diagnostic criteria for OCD and/or a tic disorder; 6. during OCD and/or tic exacerbations, most patients have abnormal neurological findings, most often with adventitious movements; 7. patients may not have significant symptoms between episodes of their OCD and/or tic disorder.

Our patient presented with tics that appeared in exacerbations and ceased in remission periods; periods of disease worsening were not associated only with states of stress or illness and lasted longer than 4 weeks. She was given therapy and she had involuntary movements of the extremities during disease exacerbation. Right before the disease onset she had pharyngitis, and at one point she had a working diagnosis of Tourette syndrome. She had a series of positive ASO titers. Between worsening episodes there were periods of complete absence of the disease, but also of minor symptoms, more specifically tics. According to this, the patient also fulfilled the criteria for the diagnosis of PITANDs.

After PITANDs and PANDAS were defined, definitions of new clinical entities emerged that manifested with neuropsychiatric symptoms associated with infection, but with a wider age range at which the disorder could occur, as well as a wider range of symptoms. Studies suggesting that infection with *Mycoplasma pneumoniae* could be associated with OCD symptoms and tics probably contributed to this idea, and similar theories also exist regarding infections with *Borrelia burgdorferi* (27, 28). This is how in 2012 PANS (pediatric acute-onset neuropsychiatric syndrome) was proposed (29). The criteria for this entity are: 1. abrupt, dramatic onset of OCD symptoms and signs or severely restricted food intake; 2. concurrent presence of additional neuropsychiatric symptoms from at least two of the following several categories: a) anxiety, b) emo-

kog entiteta spoznalo se da infekcije mogu biti okidači neuropsihijatrijskih poremećaja. Tako su još 1995. godine definirani pedijatrijski autoimunosni neuropsihijatrijski poremećaji potaknuti infekcijom (engl. *Pediatric, infection-triggered, autoimmune neuropsychiatric disorders* – PITANDs), pri kojima se javljaju slični simptomi kao u PANDAS-u, ali ne moraju biti uzrokovani BHSA-om (17). Kriteriji za PITANDs jesu: 1. pojava simptoma poremećaja u pedijatrijskoj populaciji između 3. godine i puberteta; 2. iznenadna pojava i/ili slika naglih, ponavljanih, klinički važnih simptoma egzacerbacije i remisije; 3. egzacerbacije nisu povezane samo sa stresom ili bolesti, trebaju biti prodorne, dovoljno teške da se predloži liječenje, a neliječena egzacerbacija traje minimalno 4 tjedna; 4. postojanje dokaza o prethodnoj ili istodobnoj infekciji kao što su pozitivan nalaz obriska ždrijela na BHSA, pozitivan nalaz serologije na streptokok (npr., ASO titar ili antiDNaza B) ili anamnestički podatci koji upućuju na infekciju (npr., faringitis, sinusitis ili simptomi slični gripi); 5. u nekom trenutku života postavljena je dijagnoza OKP-a i/ili tikova prema kriterijima; 6. tijekom egzacerbacije OKP-a i/ili tikova većina bolesnika ima poremećen neurološki nalaz, često s nevoljnim pokretima; 7. bolesnici mogu, ali ne moraju, imati znatne simptome između epizoda OKP-a i/ili tikova.

Ako analiziramo bolesnicu koju smo prikazali, u nje su prisutni tikovi koji se pojavljuju u egzacerbacijama te nestaju u razdobljima remisije bolesti, a pogoršanja bolesti nisu povezana samo sa stanjima stresa ili bolesti te su trajala dulje od 4 tjedna. Primala je terapiju i imala nevoljne pokrete ekstremitetima tijekom egzacerbacije bolesti. Između epizoda pogoršanja bila su prisutna razdoblja potpune odsutnosti bolesti, ali i manjih smetnja u obliku tikova. Neposredno prije početka bolesti imala je upalu ždrijela, a u jednom trenutku postavljena joj je radna dijagnoza Touretteova sindroma. Imala je pozitivne nalaze ASO titra. Prema tomu, ova je bolesnica ispunjavala i kriterije za postavljanje dijagnoze PITANDs-a.

Nakon što su definirani PITANDs i PANDAS pojavile su se i definicije novih kliničkih entiteta koji se manifestiraju neuropsihijatrijskim simptomima, a povezani su s infekcijom, ali sa širim rasponom dobi u kojoj se poremećaj može pojaviti te širim spektrom simptoma. Vjerojatno su tomu pridonijeli i rezultati istraživanja prema kojima bi i infekcija s *Mycoplasma pneumoniae* mogla biti povezana sa simptomima OKP-a i tikovima, a takve sumnje postoje i za infekciju s *Borrelia burgdorferi* (27, 28). Tako se 2012. iskristalizirao PANS (engl. *Pediatric acute-onset neuropsychiatric syndrome*), odnosno pedijatrijski akutni neuropsihijatrijski sindrom (29). Kriteriji za ovaj entitet uključuju: 1. iznenadnu, burnu pojavu simptoma i znakova OKP-a ili izraženu restrikciju unosa hrane; 2. istodob-

Table 1. Comparison of clinical features of PANDAS, PITANDs, and PANS
Tablica 1. Usporedba kliničkih značajki PANDAS-a, PITANDs-a i PANS-a

	PANDAS[1]	PITANDs[2]	PANS[3]
Glavni simptomi i znakovi / Main symptoms and signs	OKP[4] i/ili tikovi / oCD[4] and/or tics	OKP[4] i/ili tikovi / OCD[4] and/or tics	OKP[4] ili restrikcija unosa hrane / OCD[4] or food intake restriction
Ostali simptomi i znakovi / Other symptoms and signs	većina bolesnika ima neurološke poremećaje (posebno motoričku hiperaktivnost i nehotimične pokrete) / most patients experience neurological disorders (especially motor hyperactivity and involuntary movements)	većina bolesnika ima neurološke poremećaje (posebno motoričku hiperaktivnost i nehotimične pokrete) / most patients experience neurological disorders (especially motor hyperactivity and involuntary movements)	obvezatno prisutna dva od ovih simptoma: anksioznost, emocionalna labilnost i/ili depresija, iritabilnost, agresivnost i/ili izrazito oporbeno ponašanje, regresija u ponašanju, pogoršanje u školskom uspjehu, senzoričke ili motoričke abnormalnosti, somatski znakovi ili simptomi uključujući poremećaj spavanja, enurezu ili učestalo mokrenje / must include two of the following symptoms: anxiety, emotional instability and/or depression, irritability, aggression and/or marked oppositional behavior, regressive behavior, deteriorating school performance, sensory or motor abnormalities, somatic signs or symptoms including sleep disorders, enuresis, or frequent urination
Početak simptoma / Symptom onset	naglo / sudden	naglo / sudden	naglo / sudden
Dob / Age	nakon 3. godine, a prije puberteta / after age 3 and before puberty	nakon 3. godine, a prije puberteta / after age 3 and before puberty	simptomi obično započinju u školskoj dobi, ali mogu početi i u adolescenciji / symptoms commonly start at school age, but may also occur in adolescence
Tijek / Course	epizodan (epizode akutne egzacerbacije simptoma i remisije) / episodic (bouts of acute exacerbation of symptoms and remission)	može biti epizodan, ali ne nužno / may be episodic, but not necessarily	tijek može biti sličan PANDAS-u[1] / course may be similar to PANDAS[1]
Između napadaja / Between attacks	obično bez simptoma ili blaži simptomi / usually without or with mild symptoms	može biti bez simptoma, ali mogu biti prisutni i znatni simptomi / may be asymptomatic, or with marked symptoms	tijek može biti sličan PANDAS-u[1] / course may be similar to PANDAS[1]
Infekcija BHSA-om[5] / BHSA[5] infection	pozitivna kultura obriska ždrijela i/ili pozitivan ASO[6] titar / positive throat swab and/or positive ASO[6] titer	nije nužna povezanost sa streptokoknom infekcijom, već može biti i neka druga infekcija / no necessary association with streptococcal infection, may be another type of infection	nije povezan s infekcijom; simptomi se ne mogu bolje objasniti nekim drugim medicinskim poremećajem / not infection-associated; symptoms cannot be better explained by any other medical disorder

[1]PANDAS – pedijatrijski autoimunosni neuropsihijatrijski poremećaji udruženi sa streptokoknom infekcijom / pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; [2]PITANDs – pedijatrijski autoimunosni neuropsihijatrijski poremećaji potaknuti infekcijom / pediatric, infection-triggered, autoimmune neuropsychiatric disorders; [3]PANS – pedijatrijski akutni neuropsihijatrijski sindrom / pediatric acute-onset neuropsychiatric syndrome; [4]OKP/OCD – opsesivno-kompulzivni poremećaj / obsessive-compulsive disorder; [5]BHSA – β-hemolitički streptokok grupe A / group A β-hemolytic streptococci; [6]ASO – antistreptolizin O / antistreptolysin O

tional lability and/or depression, c) irritability, aggression, and/or severely oppositional behavior, d) behavioral regression, e) deterioration in school performance, f) sensory or motor abnormalities, g) somatic signs or symptoms, including sleep disorders, enuresis, or frequent urination; 3. symptoms are not better explained by known neurological or medical disorders, such as Sydenham chorea, systemic lupus erythematosus, Tourette syndrome, or others.

nu pojavu barem dvaju od ovih neuropsihijatrijskih simptoma: a) anksioznost, b) emocionalnu labilnost i/ili depresiju, c) iritabilnost, agresivnost i/ili izrazito oporbeno ponašanje, d) regresiju u ponašanju, e) pogoršanje u školskom uspjehu, f) senzoričke ili motoričke abnormalnosti, g) somatske znakove ili simptome uključujući poremećaj spavanja, enurezu ili učestalo mokrenje; 3. simptomi nisu bolje objašnjeni nekim drugim neurološkim ili medicinskim poremećajem

Although our patient had symptoms such as anxiety, emotional lability, irritability, aggressive behavior, behavioral regression, deterioration in school performance, and motor abnormalities, she does not fit the criteria for PANS as there were no symptoms or signs of OCD or anorexia.

The clinical features of all three syndromes (PANDAS, PANS, and PITANDs) are summarized in Table 1.

Therapy for PANDAS includes antibiotics, psychotherapy, psychopharmaceuticals, IVIG, glucocorticoids, plasmapheresis, and monoclonal antibodies (rituximab) (9–12).

Haloperidol and risperidone are recommended for the treatment of tics (8). The presented patient was taking both medications before she was diagnosed with PANDAS. There was no regression of symptoms during the therapy with risperidone, while haloperidol treatment led to worsening of the symptoms. In support of this, an interesting observation was made in experimental animals in a 2000 study about the positive effects of haloperidol and paroxetine on reducing similar symptoms in animals caused after exposure to streptococcal infection (30). In our patient, pimozide and levetiracetam had a favorable effect on symptom reduction. Pimozide has been shown effective in reducing tic symptoms in Tourette syndrome, although less than the atypical antipsychotic olanzapine (31).

Amoxicillin with clavulanic acid therapy showed a positive effect on the reduction of symptoms, but with therapy discontinuation, the symptoms reappeared. Success was also achieved in another attempt with antibiotics, but this time with cefuroxime from the cephalosporine group. These results are supported by studies that have shown a positive effect on the reduction of symptoms after antibiotic usage. With penicillin and amoxicillin symptoms disappear after 10 days of use, but usually recur after reinfection (13, 32). Studies show a beneficial effect of antibiotics, namely penicillin, cephalosporin, clindamycin, and macrolide on symptom reduction. Our patient was advised twice to use prophylactic antibiotics because during antimicrobial therapy the symptoms were less severe, and they progressed with the discontinuation of the antimicrobial therapy. In the literature, however, there are questionable data about the efficacy of prophylactic antibiotic usage (33, 34).

IVIG and plasmapheresis therapy have shown favorable long-term results in some studies, while others have not confirmed that (13, 35–37). It is important to emphasize that immunomodulator therapy is not the first choice of treatment, but reserved only for severe cases in which previous therapy did not give effect. IVIG therapy was applied two times in our patient. The first time it showed a positive effect on her symptoms, primarily on the vocal tics, which completely disap-

kao što su Sydenhamova koreja, sustavni eritematozni lupus, Touretteov sindrom ili drugi.

Iako je naša bolesnica imala simptome poput anksioznosti, emocionalne labilnosti, iritabilnosti, agresivnog ponašanja, regresije u ponašanju, popuštanja u školi i motoričkih abnormalnosti, ona se ne uklapa u kriterije za PANS jer nema simptoma ni znakova OKP-a, kao ni anoreksije.

Klinička obilježja triju opisanih sindroma (PANDAS, PITANDs i PANS) sažeto su prikazana na tablici 1.

Terapija PANDAS-a obuhvaća antibiotike, psihoterapiju, psihofarmake, IVIG, glukokortikoide, plazmaferezu i monoklonska protutijela (rituksimab) (9 – 12).

U liječenju tikova preporučuje se rabiti haloperidol i risperidon (8). Prikazana bolesnica primala je oba lijeka dok još nije bila postavljena dijagnoza PANDAS-a. Na risperidon nije došlo do regresije simptoma, a primjena haloperidola dovela je do njihova pogoršanja. U svezi s tim zanimljivo je opažanje na eksperimentalnim životinjama o pozitivnom djelovanju haloperidola i paroksetina pri ublažavanju sličnih simptoma izazvanih nakon izlaganja streptokoknoj infekciji (30). U naše je bolesnice primjena pimozida i levetiracetama imala povoljan učinak na ublažavanje simptoma. Pimozid se pokazao učinkovit pri smanjenju tikova u Touretteovu sindromu iako manje od atipičnog antipsihotika olanzapina (31).

Terapija amoksicilinom s klavulanskom kiselinom u nje je pokazala pozitivan učinak na redukciju simptoma, ali s prestankom uzimanja terapije oni su se vratili. Uspjeh je bio postignut i u drugom navratu primjene antibiotika, ali ovaj put cefuroksima iz skupine cefalosporina. Ovakve rezultate podupiru i istraživanja koja su pokazala pozitivne učinke pri ublažavanju simptoma zbog primjene antibiotika. Djelovanjem penicilina i amoksicilina simptomi nestaju nakon 10 dana davanja, ali često recidiviraju poslije reinfekcije (13, 32). Istraživanja pokazuju dobro djelovanje antibiotika, tj. penicilina, cefalosporina, klindamicina i makrolida na ublažavanje simptoma. Našoj bolesnici bila je u dva navrata preporučena profilaktička primjena antibiotika, budući da su tijekom uzimanja antimikrobne terapije simptomi bili manje izraženi, a progredirali su prestankom antimikrobnog liječenja. U literaturi, međutim, postoje dvojbeni podatci o učinkovitosti profilaktičke primjene antibiotika (33, 34).

Terapija IVIG-om i plazmafereza pokazale su u nekim istraživanjima dobre dugoročne rezultate, dok druga istraživanja to nisu potvrdila (13, 35 – 37). Bitno je naglasiti da navedena imunomodulacijska terapija nije prvi izbor u liječenju, već je rezervirana samo za teške bolesnike u kojih prethodna terapija nije bila uspješna. U naše je bolesnice terapija IVIG-om provedena dva puta. Prvi je put pokazala pozitivan učinak na njezine simptome, i to ponajprije na vokalne tikove

peared, while there was a reduction in leg and arm twitching. After the second IVIG therapy, there was also a reduction in symptoms. A study from 1998 showed a better and faster effect of plasmapheresis on tic and OCD symptom reduction, while IVIG therapy had an effect on OCD symptoms but not so much on tics, possibly due to a lesser expression in that group of patients (35).

A study on the effect of tonsillectomy showed that there was no significant difference in the course of the disease between those who had tonsillectomies and adenectomies as compared to the control group (38). In the patient we presented here this therapy modality was not recommended.

CONCLUSION

PANDAS is a specific but still controversial clinical entity that should not be ignored due to its association with a common pathogen in the population, GABHS. We should consider this in children who present with a sudden onset of symptoms and signs such as tics and OCD associated with a recent GABHS infection. It is difficult to make a reliable diagnosis due to the fact that there are neither biomarkers nor a clear time frame between the streptococcal infection and the symptoms of the disease, as well as because of the difficulty in determining a causal-consequential relation between them. Due to the small number of patients as well as difficulties in determining the diagnosis and evaluating available therapy, further research is needed to address many open questions about the etiopathogenesis and treatment of this complex disease in the future.

Conflict of interest statement: Authors declare no conflict of interest.

koji su potpuno nestali, dok se pojavnost trzaja nogu i ruku smanjila. Poslije druge primjene IVIG-a također je došlo do ublažavanja simptoma. U istraživanju iz 1998. godine pokazalo se bolje i brže djelovanje plazmafereze na smanjenje tikova i simptoma OKP-a, dok je terapija IVIG-om djelovala na simptome OKP-a, ali ne toliko na tikove, možda zbog njihove manje izraženosti u toj skupini ispitanika (35).

Istraživanje o učinku tonzilektomije pokazalo je da nema znatne razlike u tijeku bolesti između tonzilektomiranih i adenoidektomiranih u odnosu prema kontrolnoj skupini (38). Bolesnici koju smo prikazali ovaj modalitet liječenja nije preporučen.

ZAKLJUČAK

PANDAS je specifičan, ali i dalje prijeporan klinički entitet koji ne treba zanemariti zbog njegove povezanosti s čestim patogenom u populaciji, BHSA-om. Na njegovo postojanje treba posumnjati u djece koja se prezentiraju naglo nastalim simptomima i znakovima kao što su tikovi i OKP, a povezani su s nedavnom infekcijom BHSA-om. Postavljanje sigurne dijagnoze bolesti otežano je nepostojanjem biomarkera i jasnoga vremenskog okvira između streptokokne infekcije i simptoma bolesti te otežanog utvrđivanja uzročno-posljedične povezanosti između njih. Zbog male količine informacija u stručnoj literaturi, istraživanja koja su dosad provedena na malenom broju bolesnika, kao i teškoća pri postavljanju dijagnoze i evaluaciji učinaka dostupne terapije potrebna su daljnja istraživanja kako bi se u budućnosti odgovorilo na mnoga otvorena pitanja o etiopatogenezi i liječenju ove kompleksne bolesti.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Swedo SE, Leonard HL, Garvey M i sur. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998;155:264–71.
2. Gilbert DL, Mink JW, Singer HS. A Pediatric Neurology Perspective on Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection and Pediatric Acute-Onset Neuropsychiatric Syndrome. J Pediatr. 2018;199:243–51.
3. Barišić N. Neurološke manifestacije reumatoloških bolesti. U: Jelušić M, Malčić I (ur.). Pedijatrijska reumatologija. 1. izd. Zagreb: Medicinska naklada; 2014., str. 333–40.
4. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med. 2002;156:356–61.
5. Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. JAMA Psychiatry. 2017;74:740–6.
6. Perez-Vigil A, Fernandez de la Cruz L, Brander G i sur. The link between autoimmune diseases and obsessive-compulsive and

tic disorders: a systematic review. Neurosci Biobehav Rev. 2016;71:542–62.

7. Jakovljević M. Anksiozni poremećaji. U: Begić D, Jukić V, Medved V (ur.). Psihijatrija. 1. izd. Zagreb: Medicinska naklada; 2015., str. 183–98.
8. Begovac I. Psihički poremećaji dječje i adolescentske dobi. U: Begić D, Jukić V, Medved V (ur.). Psihijatrija. 1. izd. Zagreb: Medicinska naklada; 2015., str. 291–310.
9. Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. Neurosci Biobehav Rev. 2018;86: 51–65.
10. Swedo SE, Frankovich J, Murphy TK. Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome. J Child Adolesc Psychopharmacol. 2017;27:562–65.
11. Williams KA, Swedo SE, Farmer CA i sur. Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. J Am Acad Child Adolesc Psychiatry. 2016; 55:860–7.
12. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med. 2002;156:356–61.
13. Chiarello F, Spitoni S, Hollander E, Matucci Cerinic M, Pallanti S. An expert opinion on PANDAS/PANS: highlights and controversies. Int J Psychiatry Clin Pract. 2017;21:91–8.
14. Stemberger Marić L, Tešović G. PANDAS sindrom. U: Tješić--Drinković D, Senečić-Čala I, Vuković J (ur.). Pedijatrija danas: Od šume informacija do stabla pedijatrijskog znanja. 1. izd. Zagreb: Medicinska naklada; 2019., str. 71–5.
15. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. BJ Psychiatry. 2009;195:393–402.
16. Cabrera B, Romero-Rebollar C, Jiménez-Ángeles L i sur. Neuroanatomical features and its usefulness in classification of patients with PANDAS. CNS Spectr. 2019;24:533–43.
17. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection--triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1995; 34:307–11.
18. Pavone P, Bianchini R, Parano E i sur. Anti-brain antibodies in PANDAS versus uncomplicated streptococcal infection. Pediatr Neurol. 2004;30:107–10.
19. Dale RC, Church AJ, Candler PM, Chapman M, Martino D, Giovannoni G. Serum autoantibodies do not differentiate PANDAS and Tourette syndrome from controls. Neurology. 2006;66:1612.
20. Nicholson TRJ, Ferdinando S, Krishnaiah RB i sur. Prevalence of anti-basal ganglia antibodies in adult obsessive-compulsive disorder: cross-sectional study. Br J Psychiatry. 2012;200: 381–86.
21. Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. J Neuroimmunol. 2006;179:173–9.
22. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol. 2007;178:7412–21.
23. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS One. 2013;8:e73516.
24. Cox CJ, Zuccolo AJ, Edwards EV i sur. Antineuronal antibodies in a heterogeneous group of youth and young adults with tics and obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2015;25:76–85.
25. Parks T, Smeesters PR, Curtis N, Steer AC. ASO titer or not? When to use streptococcal serology: a guide for clinicians. Eur J Clin Microbiol Infect Dis. 2015;34:845–9.
26. Walker MJ, Barnett TC, McArthur JD i sur. Disease manifestations and pathogenic mechanisms of group A Streptococcus. Clin Microbiol Rev. 2014;27:264–301.
27. Kim Y, Ko TS, Yum MS, Jung AY, Kim HW. Obsessive-compulsive disorder related to mycoplasma-associated autoimmune encephalopathy with basal ganglia involvement. J Child Adolesc Psychopharmacol. 2016;26:400–2.
28. Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. Psychiatr Clin North Am. 1998;21:693–703.
29. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatr Ther. 2012;2:2.
30. Brimberg L, Benhar I, Mascaro-Blanco A i sur. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. Neuropsychopharmacology. 2012;37:2076–87.
31. Onofrj M, Paci C, D'Andreamatteo G, Toma L. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. J Neurol. 2000;247: 443–6.
32. Lotan D, Cunningham M, Joel D. Antibiotic treatment attenuates behavioral and neurochemical changes induced by exposure of rats to group a streptococcal antigen. PLoS One. 2014; 9:e101257.
33. Garvey MA, Perlmutter SJ, Allen AJ i sur. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry. 1999;45:1564.
34. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry. 2005;57:788–92.
35. Perlmutter SJ, Leitman SF, Garvey MA i sur. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. 1999;354:1153–8.
36. Nave AH, Harmel P, Buchert R, Harms L. Altered cerebral glucose metabolism normalized in a patient with a pediatric autoimmune neuropsychiatric disorder after streptococcal infection (PANDAS)-like condition following treatment with plasmapheresis: a case report. BMC Neurol. 2018;18:60.
37. Williams KA, Swedo SE, Farmer CA i sur. Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. J Am Acad Child Adolesc Psychiatry. 2016; 55:860–867.e2.
38. Murphy TK, Lewin AB, Parker-Athill EC, Storch EA, Mutch JP. Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus. Pediatr Infect Dis J. 2013;32: 834–8.

Reumatizam 2019;66(2):92
https://doi.org/10.33004/reumatizam-66-2-12

PROFESSOR NADA ČIKEŠ, PHD HAS BEEN ELECTED FOR VICE PRESIDENT OF UEMS (UNION EUROPEENNE DES MEDECINS SPECIALISTES)

Our renowned clinical immunologist and rheumatologist, Professor Nada Čikeš, member of the Croatian Rheumatology Society, President of the European Committee for Rheumatology and Rheumatology Section of UEMS (Union Europeenne des Medicins Specialistes) in the five years period and member of the Working Group for Postgraduate Specialist Training for seven years, and Central Delegate of the Commission for International Cooperation with UEMS of the Croatian Medical Association, was elected Vice-President of UEMS at a meeting of the UEMS Council held from 18 to 19 October 2019 in London.

Congratulations to Professor Čikeš on this great achievement and we are proud that, as a member of the Croatian Rheumatological Society, she spread the reputation of Croatian rheumatology.

Editorial Board
of the journal Rheumatizam

PROF. DR. SC. NADA ČIKEŠ JE IZABRANA ZA DOPREDSJEDNICU UEMS-a (UNION EUROPEENNE DES MEDECINS SPECIALISTES)

Naša priznata klinička imunologinja i reumatologinja, profesorica Nada Čikeš, članica Hrvatskog reumatološkog društva, predsjednica Europskog odbora za reumatologiju i Reumatološke sekcije UEMS-a (Union Europeenne des Medicins Specialistes) tijekom pet godina i članica Radne skupine za poslijediplomsko specijalističko usavršavanje tijekom sedam godina te središnji delegat Povjerenstva za međunarodnu suradnju s UEMS-om Hrvatskog liječničkog zbora je na sastanku Vijeća UEMS-a održanom od 18. do 19. listopada 2019. godine u Londonu izabrana za dopredsjednicu UEMS-a.

Čestitamo profesorici Čikeš na ovom velikom postignuću i ponosni smo da je kao članica Hrvatskog reumatološkog društva pronijela i ugled hrvatske reumatologije.

Uredništvo
časopisa Reumatizam

http://www.reumatologija.org
http://www.reumatizam.hlz.hr

INSTRUCTIONS FOR AUTHORS

ABOUT THIS JOURNAL

Reumatizam (Rheumatism) is the platinum open-access peer-reviewed biannual journal of the Croatian Society for Rheumatology. The journal publishes practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items. Priority is given to evidence-based research reports in rheumatology, physical medicine and rehabilitation, orthopedics, and allied health specialties to provide the readership with new scientific information on diagnostic and therapeutic procedures as well as comprehensive care for patients with autoimmune and autoinflammatory rheumatic diseases.

Although the journal primarily serves the interests of rheumatologists and physiatrists from Croatia and other Adriatic-Ionian countries, the editors welcome high-quality submissions from all over the world. The aim of the journal's internationalization is to publicize the best rheumatology research and practice, and monitor the progress in rheumatology and allied health professions in Croatia and neighboring countries.

Reumatizam regularly publishes biannual issues and supplements that include abstracts and full texts of papers presented at national and regional congresses and symposia as part of lifelong medical training. The journal also publishes news from scientific literature (in the form of extended abstracts) and brief information on the professional activities of rheumatology societies and other related associations in Croatia and neighboring countries. Submissions in Croatian and English are welcome, with papers published bilingually to attract the readership in Croatia and other countries. Duplicate items that are processed or published elsewhere in any languages are not considered.

The journal is published in print and electronic versions, employing the platinum open-access model, without processing, publication, and view charges. Publication expenses are covered by the Croatian Society for Rheumatology. The English version of *Reumatizam* is available in electronic format at: http://reumatizam.hlz.hr/ and http://www.reumatologija.org/engCasopis.aspx?link=Reumatizam_pdf_en). All contents of the journal *Reumatizam* are archived in Hrčak, the central portal of Croatian scientific journals, which offers free access to the journals following the Open Access Initiative (https://hrcak.srce.hr/reumatizam).

Instructions for Authors follow the updated recommendations of the International Committee of Medical Journal Editors (ICMJE) (http://icmje.org/icmje-recommendations.pdf) and the World Association of Medical Editors (WAME) (http://www.wame.org). Ethical standards comply with those of the Committee on Publication Ethics (COPE) (https://publicationethics.org/resources) and the Council of Science Editors (CSE) (https://bit.ly/2WvbCxK).

All contributors are also advised to consult the relevant research reporting standards of the EQUATOR Network, which are available at http://www.equator-network.org/.

The *Reumatizam* editorial board supports the principles of integrity, transparency, and quality in pre- and post-publication communication, in compliance with the Sarajevo Declaration on Integrity and Visibility of Scholarly Publications (https://bit.ly/2qVgJvs).

The contents of *Reumatizam* can be used free of charge for educational and research purposes, with full reference to the primary source, in line with the Creative Commons license (https://creativecommons.org/licenses/by-nc/4.0/). Any other use is prohibited without permission by the publisher.

PAPER SUBMISSION / MANUSCRIPT PUBLICATION

Manuscripts should be submitted electronically to the following addresses: glavni-urednik-reumatizam@reumatologija.org and urednik-reumatizam@reumatologija.org). Alternatively, if agreed with the editor, they may be submitted on paper (in one computer printout), including an electronic version on CD, DVD, or USB

UPUTE AUTORIMA

O ČASOPISU

„Reumatizam" je službeni recenzirani časopis Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora s platinum slobodnim pristupom koji izlazi dva puta godišnje. Objavljuje kliničke smjernice, uvodnike, originalne znanstvene radove, stručne radove, pregledne radove, dobro dokumentirane prikaze bolesnika, kratka priopćenja i preliminarna priopćenja.. Prioritet časopisa jesu radovi temeljeni na dokazima iz područja reumatologije, ali i srodnih struka (fizikalne medicine i rehabilitacije, ortopedije/kirurgije) čime se čitatelju daju bitne znanstvene informacije o dijagnostičkim i terapijskim procedurama, odnosno pružanju sveobuhvatne skrbi osobama oboljelima od autoimunih i autoinflamatornih reumatskih bolesti.

Iako je časopis otvoren svim kvalitetnim člancima iz cijelog svijeta, naglasak je na autorima i specifičnostima iz Hrvatske i susjednih zemalja**, odnosno napretku reumatologije i srodnih struka u tim zemljama**. Cilj internacionalizacije časopisa je objavljivanje najboljih reumatoloških istraživanja i prakse te praćenje napretka reumatološke struke i pridruženih zdravstvenih profesija u Hrvatskoj i susjednim zemljama.

Reumatizam izlazi dva puta na godinu, a u njemu se kao suplement objavljuju sažetci ili cjeloviti radovi s nacionalnih i regionalnih kongresa i simpozija u sklopu trajne medicinske izobrazbe. Časopis objavljuje i novosti iz stručne literature (kao prošireni sažetak) i kratke informacije o stručnim aktivnostima reumatoloških i srodnih stručnih društava iz Hrvatske i susjednih država. Radovi mogu biti napisani hrvatskim ili engleskim jezikom, s pojedinim dijelovima napisanima na drugom jeziku, a objavljeni su na oba jezika kako bi se privuklo čitateljstvo iz Hrvatske i drugih zemalja. Radovi se objavljuju pod uvjetom da nisu prethodno drugdje publicirani.

Časopis se izdaje u tiskanom i elektroničkom obliku s *platinum* slobodnim pristupom, bez potrebe za registracijom. Autorstvo u časopisu i čitanje časopisa se ne naplaćuje. Troškove izdavanja časopisa pokriva Hrvatsko reumatološko društvo. Engleska inačica časopisa *Reumatizam* u elektroničkom obliku dostupna je na: http://reumatizam.hlz.hr/ i http://www.reumatologija.org/engCasopis.aspx?link=Reumatizam_pdf_en.). Svi sadržaji časopisa Reumatizam su pohranjeni na portalu Hrčak, središnjem portalu za hrvatske znanstvene i stručne časopise koji nude otvoreni pristup svojim radovima (https://hrcak.srce.hr/reumatizam).

Upute autorima u skladu su s preporukama Međunarodnog odbora urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE; http://icmje.org/icmje-recommendations.pdf) i Svjetske udruge medicinskih urednika (*World Association of Medical Editors* – WAME; http://www.wame.org), a etički standardi sukladni su onima Odbora publicističke etike (*Committee on Publication Ethics* – COPE; https://publicationethics.org/resources) i Vijeća znanstvenih urednika (*Council of Science Editors* – CSE; http://bit.ly/2WvbCxK).

Također se mogu konzultirati relevantni znanstveni standardi EQUATOR mreže koji su dostupni na http://www.equator-network.org/.

Uredništvo *Reumatizma* podupire principe integriteta, transparentnosti i kvalitete u komunikaciji prije i nakon objavljivanja radova u skladu sa Sarajevskom deklaracijom (*Sarajevo Declaration on Integrity and Visibility of Scholarly Publications*; http://bit.ly/2qVgJvs/).).

Sadržaj iz časopisa *Reumatizam* smije se bez naknade rabiti u nastavne i istraživačke svrhe, uz potpuno navođenje izvora u skladu sa dozvolom Creative Commons (http://creativecommons.org/licenses/by-nc/4.0/). Svaka druga uporaba zabranjena je bez izričitog dopuštenja izdavača.

PREDAJA RADA / OBJAVA RUKOPISA

Rukopisi se dostavljaju elektroničkom poštom (glavni-urednik-reumatizam@reumatologija.org i urednik-reumatizam@reumato-

mailed to: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia.

The editorial board of the journal acts in accordance with the instructions of the International Committee of Medical Journal Editors (ICMJE) – Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) and the World Association of Medical Editors – WAME (http://www.wame.org). For texts in English, it is recommended that authors who are not native English speakers consult a professional for correct and good quality language revision and/or translation. The editor may provide such a service upon payment.

It is required to include with the manuscript a written statement indicating that the paper has not been previously published or submitted/accepted for publication in another journal, a statement that the authors of the paper agree to transfer their copyright to the journal, and a signed Statement of Authorship as well as a Conflict of Interest Statement.

AUTHORSHIP

Individuals designated as authors must meet the four ICMJE authorship criteria. The authors are required to include with the manuscript a written statement indicating that all co-authors have made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; that they have drafted the work or revised it critically for important intellectual content; that they give final approval of the version to be published; and that they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved (https://bit.ly/34nZotQ). The editors encourage the authors and the reviewers to register with ORCID (Open Researcher and Contributor iD; https://orcid.org) and present their informative ORCID iDs. There should not be any change in the authorship after the manuscript is submitted. In exceptional cases, when an omission occurred or substantial work is still being done while the submission is being revised, an author's name may be added or the order of authors can be rearranged with a written statement explaining the reasons for that and a confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal, or rearrangement. Individuals who do not meet the traditional authorship criteria, e.g., persons who provide special equipment or materials, technical assistance, statistical analyses, or funding, can be listed in the Acknowledgments.

PLAGIARISM AND RETRACTION OF PAPERS

All papers are screened for originality and plagiarism, copying, as well as duplicate and redundant submission/publication of texts and images from other sources (with checker tools such as Duplichecker, Plagiarism Checker, Plagium, PlagScan). Plagiarized papers or papers unethically published in any other way will be retracted following the COPE Retraction Guidelines (https://publicationethics.org/files/retraction%20guidelines.pdf).

CATEGORIZATION, FORMATTING, AND WORD LIMIT FOR PAPERS

Reumatizam publishes the following types of peer-reviewed articles: practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items.

Editorial: 1200 words maximum; up to 1 figure or table; up to 20 references; 3–6 Medical Subject Heading (MeSH) keywords of the National Library of Medicine of US; unstructured abstract up to 300 words (if applicable).

Original Research: 6,500 words maximum; up to 6 figures and 6 tables; unlimited number of references; 3 – 6 keywords; structured abstract up to 300 words (except for articles on the history of medicine that may have an unstructured abstract).

logija.org) ili u dogovoru s urednikom u papirnatom obliku (u računalnom ispisu), zajedno s elektroničkom verzijom na CD-u, DVD-u, USB-*sticku* na adresu: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Hrvatska.

Uredništvo časopisa slijedi upute Međunarodnog odbora urednika medicinskih časopisa – Preporuke za provedbu, prikazivanje, uređivanje i objavljivanje radova u medicinskim časopisima (*International Committee of Medical Journal Editors* (ICMJE) – *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*; http://www.icmje.org/icmje-recommendations.pdf) i Svjetske udruge medicinskih urednika (*World Association of Medical Editors* – WAME; http://www.wame.org). Za tekstove na engleskom jeziku preporučuje se da autori koji nisu izvorni govornici engleskog jezika potraže savjet stručnjaka radi točnog i kvalitetnog prijevoda. Izdavač može osigurati takvu uslugu uz plaćanje.

Uz rukopis treba priložiti pisanu izjavu da rad prethodno nije bio objavljen ili ponuđen/prihvaćen za objavu u nekome drugom časopisu, da autori rada prenose autorska prava na časopis, te priložiti potpisane Izjave o autorstvu i Izjave o sukobu interesa.

AUTORSTVO

Osobe određene kao autori moraju biti kvalificirane za autorstvo sukladno preporukama Međunarodnog odbora urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE). Autori trebaju uz rukopis priložiti pisanu izjavu da su svi koautori znatno sudjelovali u koncepciji ili nacrtu rada ili u prikupljanju, analizi i interpretaciji podataka i napisali prvu verziju rada ili su ga kritički revidirali u znatnom dijelu intelektualnog sadržaja i odobrili završnu verziju rada te su se složili da su odgovorni za sve značajke rada i jamče da će se pitanja koja se odnose na točnost i integritet bilo kojeg dijela rada prikladno istražiti i riješiti (http://bit.ly/34nZotQ). Uredništvo ohrabruje autore, kao i recenzente, da se registriraju kod ORCID-a (Open Researcher and Contributor iD;https://orcid.org) i prilikom prijave dostave ORCID-ov identifikacijski broj (ID). Idealno ne bi trebalo biti nikakvih promjena u autorstvu nakon upućivanja rada prema uredništvu. U situacijama kada je došlo do ispuštanja navođenja autora ili je obavljen značajan posao nakon što je rad revidiran može se dodati autor uz pisano objašnjenje razloga za to, kao i pisanu potvrdu (e-mail, faks, dopis) od strane svih autora da se slažu s dodavanjem, izostavljanjem ili promjenom redoslijeda autora.

Osobe koje ne zadovoljavaju kriterije za autorstvo poput osoba koje su pružile, tehničku pomoć ili osigurale specijalnu opremu i materijale, statističku analizu ili pokrile troškove istraživanja treba navesti u dijelu Zahvale.

PLAGIRANJE I POVLAČENJE RADOVA

Svi se radovi provjeravaju na originalnost i plagiranje, umnažanje, dupliciranje i prekomjernu prijavu/publikacije i teksta i slikovnih prikaza iz drugih izvora (pomoću, na primjer, programa Duplichecker, Plagiarism Checker, Plagium, PlagScan). Plagirani ili na bilo koji drugi neetički način objavljeni radovi bit će povučeni u skladu s COPE-ovim Uputama o povlačenju radova (COPE – *Retraction Guidelines*; https://publicationethics.org/files/retraction%20guidelines.pdf).

KATEGORIZACIJA, FORMAT I OPSEG RADOVA

Reumatizam objavljuje ove vrste radova kod kojih je potrebna recenzija : kliničke smjernice, uvodnike, originalne znanstvene radove, pregledne radove, stručne radove, kratka/preliminarna priopćenja, pregledne radove i dobro dokumentirane prikaze bolesnika (s pregledom literature).

Uvodnik (*Editorial*): maksimalno 1200 riječi; do 1 slike ili tablice; do 20 referencija; 3 – 6 MeSH ključnih riječi; nestrukturirani sažetak do 300 riječi (ako je primjenjivo).

Practice Guidelines, Review and Expert Opinion articles: 6,000 words maximum; up to 5 figures and 5 tables; unlimited number of references; 3 – 6 keywords; structured abstract up to 300 words (except for articles on the history of medicine that may have an unstructured abstract).

Letters (Short or Preliminary Communication, Brief Report): 1,500 words maximum; up to 3 figures or tables; up to 15 references; 3 – 6 keywords.

Case Report (Case Based Review): 6,000 words maximum; up to 5 figures or tables; unlimited number of references; 3–6 keywords; unstructured abstract up to 300 words.

Erratum: enables correction of errors made in writing, printing, or publication process of an article. To be sent to: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia, or via email: glavni-urednik-reumatizam@reumatologija.org and urednik-reumatizam@reumatologija.org.

ARTICLE / MANUSCRIPT PREPARATION

Reumatizam publishes articles in Croatian, including the title, abstract, keywords, and table and figure titles and legends in English, or articles in English (American standard), including the title, abstract, keywords, and table and figure titles and legends in Croatian. The writing style should be clear and concise. Articles should be structured following the EQUATOR Network principles (http://www.equator-network.org).

The text should be typed in 12-point font, on white A4 paper (210 x 297 mm), double-spaced, with a maximum of 30 lines per page, including the title page, abstract, text, acknowledgments, conflict of interest statement, references, tables, and legends. The left margin should be 35 mm, and the right, top and bottom margins 25 mm each. All the pages, including the title page, should be numbered in the bottom right corner.

Measurements, if needed, should be reported using the International System of Units (SI). Names that can be abbreviated should be spelled out in full followed by the abbreviation in parentheses at the first mention, and referred to only in the abbreviated form further in the text. Latin names should be italicized, with the full name at the first mention, and only the abbreviated form further in the text. Drugs should be referred to by their generic names, and trade names, if necessary, may follow in parentheses, with the manufacturer's name. Manufacturers of specific instruments or reagents (name and location) should be given in parentheses.

Except for reviews and letters to the editor, manuscripts should include the following: a title page (on a separate page), abstract and keywords (on a separate page), the main text (with the following sections: introduction, participants and methods, results, discussion, and conclusion), acknowledgments, funding, conflict of interest statement, references, list of tables, list of figures, tables and figures.

Title page

The title page should include the article title (concise, clear, and informative) both in Croatian and in English, and the full name of each author, followed by the full name of the author's affiliation, with full postal address (street, city, and country) of the institution. If the article was prepared by several authors of various affiliations, all authors should be linked to their corresponding affiliation(s) using superscript numerals after their respective names, and preceding the institution name.

This should be followed by the name, surname, and full contact address of the corresponding author responsible for the correspondence related to the article, with his/her telephone and fax numbers, and e-mail address.

Abstract and keywords

The second page should include the abstract, both in Croatian and in English, of up to 300 words, providing the purpose of the study/research, materials (participants) and methods, results, and conclusions.

Originalni rad (*Original Research Article*): maksimalno 6500 riječi; do 6 slika i 6 tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; strukturirani sažetak do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kliničke smjernice (Practical Guidelines), pregledni radovi (Review) i radovi temeljeni na mišljenju eksperata (Expert Opinion Articles): maksimalno 6 000 riječi; 5 slika i 5 tablica; neograničeni broj referencija; 3-6 ključnih riječi, strukturirani sažetas sa do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kratko priopćenje (*Short Communication*, *Brief Report*): maksimalno 1500 riječi; do 3 slike ili tablice; do 15 referencija; 3 – 6 ključnih riječi.

Prikaz bolesnika(*Case Based Review)* maksimalno 6000 riječi; do 5 slika ili tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; nestrukturirani sažetak do 300 riječi.

Ispravak (*Erratum*): omogućuje korekciju pogrješaka koje su se pojavile kod pisanja, printanja ili u procesu publikacije članaka. Šalje se na adresu: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Hrvatska ili elektroničkom poštom na: glavni-urednik-reumatizam@reumatologija.org i urednik-reumatizam@reumatologija.org.

PRIPREMA RADA / RUKOPISA

U časopisu *Reumatizam* objavljuju se članci na hrvatskom jeziku, s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku ili članci na engleskom jeziku (*UK spelling*), s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku. Stil pisanja treba biti jasan i jezgrovit. Radovi trebaju biti strukturirani sukladno principima EQUATOR Networka (http://www.equator-network.org).

Tekst treba biti napisan slovima veličine 12 točaka na bijelom papiru formata A4 (210 × 297 mm) s dvostrukim proredom, s najviše 30 redaka po stranici, uključujući i naslovnu stranicu, sažetak, tekst, zahvale, izjavu o sukobu interesa, referencije, tablice i legende. Lijeva margina treba biti široka 35 mm, a desna margina te gornji i donji rub 25 mm. Sve stranice, uključujući naslovnu, trebaju imati redni broj u donjem desnom kutu.

Pri potrebi izražavanja podataka rabe se SI mjerne jedinice. Kod naziva koji se mogu pisati kraticom pri prvom je pojavljivanju potrebno napisati puni naziv, s kraticom, a u daljnjem tekstu samo kraticu. Latinski nazivi pišu se načinom Italic, i to puni naziv kod prvog pojavljivanja u tekstu, a u daljnjem tekstu navodi se kratica. Lijekovi se navode generičkim imenom, a ako je nužno, može se u zagradi navesti tvorničko ime, s imenom proizvođača. Proizvođače specifičnih instrumenata ili reagensa (naziv i lokacija) treba navesti u zagradi.

Izuzev preglednih radova i pisama uredniku radovi trebaju imati slijedeće elemente: naslovna stranica (posebna stranica), sažetak i ključne riječi (posebna stranica), glavni tekst rada (s dijelovima: uvod, ispitanici i metode, rezultati, rasprava i zaključak), zahvale, financiranje, izjava o sukobu interesa, literatura, popis tablica i slika te tablice i slike.

Naslovna stranica

Na naslovnoj stranici trebaju biti naslov rada (sažet, jasan i informativan) na hrvatskom i engleskom jeziku te puno ime svakog od autora. U sljedećem retku treba navesti puni naziv ustanove, ulicu i broj, grad i državu. Ako su u izradi rada sudjelovali autori iz različitih ustanova, za svakog od njih poslije imena i prezimena te prije navoda ustanove treba napisati odgovarajući broj u superskriptu.

Slijede ime i prezime te puna adresa autora za dopisivanje u vezi s radom, njegov/njezin telefonski broj, broj faksa i e-mail adresa.

The abstract should emphasize new and important aspects of the study, or observations. Below the abstract, three to six keywords or short terms should be listed, both in Croatian and in English, to help index the article. The keywords may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine of US should be used for the keywords. General and plural terms, and multiple concepts (e.g., using "and", "or") should be avoided. The abstract should not include references.

Introduction

The introduction provides a brief outline of the context/background of the topic, as well as the purpose and rationale for conducting the study/research. It is recommended to cite only relevant references, which should be well-balanced and recent (not older than 10 years, if possible). At the end, the objective(s) of the study/research should be stated clearly and precisely. No data from the paper or conclusions should be given in the introduction.

Materials and methods

This section provides details about how the study/research was conducted: the place and time, as well as the eligibility criteria for selecting the experimental or observational participants (or laboratory animals), with all their important characteristics. The author(s) should provide a detailed outline of the study (e.g., a randomized–controlled study, an observational study, a prospective/retrospective study, etc.), the data collection methods applied, the meaning of the descriptors, and explain and identify the methods, devices (including the manufacturer's name in parentheses), and procedures, sufficiently detailed to enable others to reproduce the results. References should be given for established methods, and new or substantially modified methods should be described in detail, stating the reasons for using them, and evaluating their limitations.

Generic names should be used for drugs and chemicals. All measurements should be given in SI units. In Croatian texts a decimal comma should be used, and in texts in English a decimal point.

Ethics / Ethical standards

Studies involving human subjects or animals should have received the approval of the respective ethics committee. The work described should have been carried out in accordance with the ethical standards of an institutional or national committee responsible for experiments involving human subjects, as well as with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964 and its revisions) for experiments involving humans http://www.wma.net/en/30publications/10policies/b3/index.html; EU Directive 2010/63/EU and for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Also, it should be stated explicitly that informed consent was obtained from all participating adult subjects or from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (i.e., oral or written).

Participants' names and/or surnames should not appear, particularly in figurative/illustrative materials.

Statistics

Statistical methods should be described in detail, to enable a knowledgeable reader with access to the original data to verify the reported results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty. The statistical software used should be specified.

Results

Results should be presented in a logical sequence in the text, tables, and figures. In this section, the results are not interpreted nor are their implications discussed. In addition to absolute numbers

Sažetak i ključne riječi

Druga stranica treba sadržavati sažetak na hrvatskom i engleskom jeziku (do 300 riječi) u kojem su navedeni cilj studije/istraživanja, materijal (ispitanici) i metode, rezultati i zaključci.

U sažetku valja naglasiti nove i važne aspekte studije ili opservacije. Ispod sažetka autori trebaju navesti tri do šest ključnih riječi ili kratkih pojmova na hrvatskom i engleskom jeziku koji će pomoći pri indeksiranju članka. Ključne riječi se mogu objaviti uz sažetak. Za ključne riječi treba se koristiti pojmovima iz popisa *Medical Subject Headings* (MeSH) Indexa Medicusa. Općenite, množine i mnogostruke koncepte (primjerice uz uporabu „i", „ili") treba izbjegavati. Sažetak ne smije sadržavati navode referencija.

Uvod

U uvodu se ukratko navode kontekst/pozadinsko znanje o temi, svrha i razlog provođenja studije/istraživanja. Preporučuje se navesti samo relevantne referencije, koje trebaju biti uravnotežene i recentne (po mogućnosti ne starije od 10 godina). Na kraju treba jasno i točno navesti cilj/-eve studije/istraživanja. U uvodu se ne navode podatci iz rada niti zaključci.

Materijal i metode

Navode se detalji provedbe studije/istraživanja: gdje i kad je provedena, na koji je način učinjen odabir i sve važne karakteristike ispitanika (ili laboratorijskih životinja) koje su studirane ili opservirane. Treba detaljno specificirati nacrt studije (npr., randomizirana-kontrolirana studija, opservacijska studija, prospektivna/retrospektivna itd.), način prikupljanja podataka, značenje deskriptora te objasniti, identificirati metode, aparate (s nazivom proizvođača u zagradi) i postupke, dovoljno detaljno kako bi se rezultati mogli reproducirati. Za poznate metode treba navesti referencije, a nove metode ili metode koje su znatnije modificirane detaljno opisati, navodeći razlog njihove primjene i procjene njihovih ograničenja.

Za lijekove i kemikalije moraju se rabiti generička imena. Sve veličine trebaju biti izražene u SI jedinicama. U tekstovima na hrvatskom jeziku rabi se decimalni zarez, a u tekstovima na engleskome decimalna točka.

Etika / Etički standardi

Radovi koji uključuju ljude ili životinje trebaju imati odobrenje od odgovarajućeg etičkog povjerenstva. Takav rad treba biti proveden sukladno etičkim standardima intitucije ili nacionalnom povjerenstvu odgovornom za eksperimente koji uključuju ljude i s Etičkim kodeksom udruge World Medical Association (Helsinška deklaracija iz 1964. i njezine kasnije inačice) za istraživanja koja uključuju ljude http://www.wma.net/en/30publications/10policies/b3/index.html; EU Direktiva 2010/63/EU I za istraživanja na životnjama http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Također, treba jasno navesti da je dobiven informirani pristanak od strane svih odraslih ispitanika ili od strane roditelja ili zakonskih skrbnika za maloljetne ispitanike ili nesposobne odrasle osobe, kao i način na koji je taj pristanak dobiven (npr. usmeno ili pismeno).

Imena i /ili prezimena ispitanika ne smiju biti obznanjena, naročito u grafičkim/slikovnim materijalima.

Statistika

Treba iscrpno opisati statističke metode kako bi se obrazovanom čitatelju koji ima pristup originalnim podatcima omogućilo da potvrdi navedene rezultate. Gdje god je to moguće zaključke treba kvantificirati i prezentirati odgovarajućim indikatorima pogrješke ili odstupanja od mjerenja. Treba navesti upotrijebljeni računalni program.

Rezultati

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i slikama. U ovom se dijelu rezultati ne tumače niti se raspravlja o njiho-

and percentages, it is necessary to include the results of statistical analysis, by stating, for example, P values or other parameters. All the data from the tables or figures should not be repeated in the text, but rather only the most important observations should be emphasized or summarized. Redundant tables and figures (e.g., presenting the same data in different formats) should be avoided, as should the use of figures and tables when it is better to include the data in the textual part (e.g., when there is insufficient data for tables or figures).

Discussion

Most of this section is the interpretation of results. New and important aspects of the study, and its implications, should be emphasized. It is not recommended to repeat in detail data or any other material given in the Introduction or in the Results section. Own findings should be compared with the findings of other studies/research, showing the similarities and differences. It is also important to explain the significance of the results obtained, their limitations, and implications for future research, avoiding, however, making statements and drawing conclusions not completely confirmed by the obtained data. When necessary, new hypotheses may be given, but clearly labelled as such.

Conclusions

The main conclusions are drawn based on the author's or authors' own results (3 – 5 sentences maximum).

Abbreviations

Only standard abbreviations should be used. The spelled-out abbreviation followed by the abbreviation in parentheses should be used at the first mention unless the abbreviation is a standard unit of measurement. Abbreviations should be avoided in the manuscript title.

Symbols

Symbols used in the text should be explained. A detailed list of symbols may be given in an appendix.

Tables

Tables should be presented on a separate page. They should not be submitted as images/photographs. Each table should have a title and be numbered consecutively in the order it appears in the text. Tables should be self-explanatory and as simple as possible. Table legends should be given below the table, and may include a reference to data in the table indicated by a superscript figure or letter. Results presented elsewhere in the article (e.g., in an illustration), should not be repeated in the table. If a table originating from other sources is used, permission for such publication should be obtained from the respective publisher/author.

Figures / Illustrations

All figures should be professionally drawn or photographed. Letters, numbers, and symbols on figures should be clear enough to remain legible when the figure is reduced for publication. Figure titles and descriptions are considered to be a part of the text, and not part of the figure/illustration. Each figure/illustration should be numbered consecutively according to the order in which it appears in the text, and have a clear mark showing which is the upper side. Figures/illustrations should appear in a quality appropriate for print publication. Photocopied images or photographs are not suitable for reproduction. If submitted in electronic format, figures/illustrations should be in a high resolution TIFF or JPEG file format, a minimum of 1,500 pixels wide. Figures/illustrations submitted in other formats may be accepted only with the prior consent of the editorial board. The editorial board reserves the right not to publish any figures/illustrations that fail to meet the above requirevim implikacijama. Uz apsolutne brojeve i postotke potrebno je uključiti rezultate statističke analize, navođenjem obično p-vrijednosti ili drugog parametra. U tekstu se ne ponavljaju svi podatci iz tablica ili slika, već se naglašavaju ili sažimaju samo bitna opažanja. Potrebno je izbjegavati suvišne tablice i slike (npr. prikaz istih podataka u različitim formatima) ili uporabu slika i tablica u slučaju kada je informacije bolje uključiti u tekstualni dio (npr. kada nema dovoljno podataka za tablice ili slike).

Rasprava

Većina ovog dijela odnosi se na interpretaciju rezultata. Potrebno je naglasiti nove i bitne aspekte studije te implikacije koje iz nje proistječu. Ne preporučuje se detaljno ponavljati podatke ni bilo koje druge materijale koji su navedeni u uvodnom dijelu ili u dijelu s rezultatima. U dijelu za raspravu treba usporediti vlastite rezultate s rezultatima iz drugih studija/istraživanja te navesti sličnosti i razlike. Također, važno je objasniti značenje dobivenih rezultata, njihova ograničenja i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podatcima. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

Zaključci

Na osnovi vlastitih rezultata izvode se glavni zaključci (maksimalno 3 – 5rečenica).

Kratice

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u tekstu, osim ako je riječ o standardnim kraticama mjernih jedinica. Kratice treba izbjegavati u naslovu rada.

Simboli

U tekstu se simboli moraju objasniti. U dodatku se može navesti iscrpan popis simbola.

Tablice

Tablice se pišu na posebnoj stranici. Ne smiju se slati kao slike/fotografije. Svaka tablica mora imati naslov i redni broj prema redoslijedu pojavljivanja u tekstu. Tablica mora biti pregledna i jednostavna. Legende tablica trebaju biti napisane ispod tablice, uz oznaku u tablici u superskriptu. Tablice ne bi trebale ponavljati rezultate koji su prezentirani bilo gdje drugdje u radu (npr. u slici). Tablice preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihovih izdavača/autora.

Slike / Ilustracije

Sve slike trebaju biti profesionalno nacrtane ili snimljene. Slova, brojevi i simboli moraju biti čitki i u smanjenom obliku u kojem će se objaviti. Svaka slika mora imati broj prema redoslijedu pojavljivanja u tekstu, ime autora i označenu gornju stranu. Svaki crtež mora imati broj prema redoslijedu pojavljivanja u tekstu i označenu gornju stranu. Crteži trebaju biti dovoljno kvalitetno izrađeni za objavu u tisku. Fotokopije slika ili fotografija nisu pogodne za reprodukciju. Ako se dostavljaju u elektroničkom obliku, slike/ilustracije moraju biti u formatu TIFF ili JPEG visoke kvalitete, najmanje širine 1500 piksela. Slike/ilustracije u ostalim formatima mogu biti prihvaćene samo uz prethodni dogovor s uredništvom. Uredništvo pridržava pravo ne objaviti slike/ilustracije koje ne zadovoljavaju ove uvjete. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji (ili skrbnika) ili osoba mora biti neprepoznatljiva (prekrivanje očiju, lica i sl.). Slike preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihova izdavača/autora.

ments. Photographs of individuals will be published only with the written consent of the person photographed (or his/her guardian), or the individual should be rendered unrecognizable (concealing the eyes, face, etc.). If a figure is taken from other sources, permission for such reproduction obtained from the respective editor/author should be submitted.

Acknowledgments

All contributors who do not meet the ICMJE authorship criteria, such as persons who provide technical help, special equipment or materials, and statistical analyses should be listed in the Acknowledgments section. Funding and material support should also be listed, with details of the institution/organization/company that provided such support (including the grant numbers), and the beneficiary (a project, a program, an individual). The International Committee of Medical Journal Editors – ICMJE provides detailed guidelines as to who to list under this section (https://bit.ly/36oo0UZ).

Conflict of interest statement

The authors must declare whether there is a financial relationship between them and the organization/pharmaceutical company that sponsored the research. Conflicting non-financial relationships that may add bias in the journal submissions should be also transparently declared. All contributors of the journal are advised to consult the recommendations available at https://bit.ly/337vidA. The authors should fill and send the following form (WEB-MJESTO NA NAŠOJ STRANICI ILI http://www.icmje.org/conflicts-of-interest/.

The Statement will be included in a separate section of the paper before the References.

References

Comprehensive and systematic searches through Scopus, Web of Science, PubMed, Directory of Open Access Journals (DOAJ), and specialist bibliographic databases are strongly encouraged to cite highly relevant, updated, and evidence-based items. The following relevant recommendations could be consulted at https://rdcu.be/bVOOt and https://bit.ly/2PxEGDz.

References should be presented using the Vancouver style, a numeric citation style as recommended by the US National Library of Medicine. The most frequent examples can be consulted in the following recommendations: ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detailed instructions can be found in the following book: Citing Medicine (https://www.ncbi.nlm.nih.gov/books/NBK7256).

References in the text, tables, and legends should be numbered in Arabic numerals, in parentheses, consecutively in the order of appearance in the text. When more than one reference is given, these should be separated by a comma.

In the list of references, **authors** and/or **editors** are cited with the surname(s) and followed by the initial(s) of the name(s). Initials do not end with a full stop, unless the initial comes immediately before the title. For several authors/editors, their names are separated by a comma. For more than six authors/editors, the first six should be listed with surnames and initials followed by "et al.", and the others omitted. In **titles**, only the first word is capitalized, and any other words that are usually written with a capital. In pagination, repeated identical initial digits for page numbers are omitted (for example: 123-125 becomes 123-5). Each reference should end with a full stop.

For articles in **English**, it is recommended that titles of references published in other languages are cited in English (if available), or an English translation of the title provided (placed in square brackets), with an indication of the language of the original placed at the end.

Zahvale

U zahvali treba navesti sve suradnike koji nisu zadovoljili ICMJE kriterije za autorstvo poput osoba koje su pružile tehničku pomoć ili osigurale specijalnu opremu i materijale, ili statističku analizu. Financijska i materijalna potpora također trebaju biti navedene, s detaljima institucije/organizacije/tvrtke koja je takvu pomoć pružila (uključivo i identifikacijske brojeve pomoći) te tko je dobio takvu potporu (projekt, program, pojedinac). Međunarodni odbor urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE) ima detaljne smjernice koga valja navesti u Zahvalama (https://bit.ly/36oo0UZ).

Izjava o sukobu interesa

Autori moraju izjaviti postoji li financijski odnos između njih i organizacije/tvrtke koja je sponzorirala istraživanje. Ne financijski sukob interesa koji može također utjecati na prihvačanje rada bi također trebao biti jasno naznačen. Molimo pogledati preporuke na stranici http://bit.ly/337vidA. Autori moraju popuniti i poslati sljedeći obrazac (http://www.icmje.org/conflicts-of-interest/)

Izjava će stajati u posebnom dijelu prije navoda literature.

Literatura

Preporuča se sistematično petraživanje u bazama Scopus, Web of Science, PubMed i Directory of Open Access Journals (DOAJ) i specijaliziranim bazama podataka s ciljem citiranja relevantnih, novijih i radova utemeljenih na dokazima. Takve relevantne preporuke mogu se naći na http://rdcu.be/bVOOt i https://bit.ly/2PxEGDz.

Literatura se navodi primjenom Vancouverskih pravila koja propisuju numerički način citiranja, prema preporukama američke *National Library of Medicine*. Najčešći primjeri mogu se naći u preporukama: *ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles* (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detaljne upute mogu se naći u knjizi *Citing Medicine* (https://www.ncbi.nlm.nih.gov/books/NBK7256).

Literaturu u tekstu, tablicama i legendama treba navoditi arapskim brojevima u zagradi, prema redoslijedu pojavljivanja. Ako brojeva ima više, odvajaju se zarezima.

U popisu literature autori i/ili urednici navode se prezimenom/prezimenima i inicijalima imena. Iza inicijala ne stavlja se točka osim ako je riječ o inicijalu neposredno prije naslova. Ako autora/urednika ima više, odvajaju se zarezima. Ako ih ima više od šest, nakon prva tri t treba napisati „i sur.", a ostale ispustiti. U naslovu se velika slova rabe samo za početno slovo prve riječi u naslovu i u riječima koje se uobičajeno pišu velikim slovima. Kad se navode brojevi stranica, treba ispustiti iste početne znamenke stranica (npr. 123–125 postaje 123–5). Na kraju svake referencije stavlja se točka.

U tekstovima na engleskom jeziku pri navođenju radova objavljenih na drugim jezicima preporučuje se navesti naslov na engleskom (ako postoji) ili ga prevesti na engleski (u tom slučaju treba ga staviti u uglate zagrade), a na kraju se navodi izvorni jezik rada.

Pri navođenju prihvaćenih, ali još neobjavljenih radova na kraju treba dodati: „U tisku." Autori trebaju dobiti pismeno odobrenje za citiranje takvog rada zajedno s potvrdom da je rad prihvaćen za objavu.

Članak u časopisu

Naslovi časopisa trebaju se navoditi uobičajenim kraticama (*NLM Title Abbreviation*) koje se mogu naći u katalogu *National Library of Medicine* (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Za časopise se ne navodi izdavač. Obvezatno se navode godište, volumen i stranice časopisa. Ako časopis ima kontinuiranu paginaciju, mogu se izostaviti mjesec/broj u godištu časopisa i pripadajuća zagrada.

When referencing an accepted, but not yet published, article, "Forthcoming" should be added at the end. Authors should have written consent to cite such an article, with confirmation that the article has been accepted for publication.

Journal article

Journal titles should be cited with the usual abbreviations (NLM Title Abbreviation), to be found in the *National Library of Medicine Catalog* (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journal references omit information about the publisher. It is required to include the year of publication, volume, and page numbers. If the journal uses continuous pagination, the month/volume number of the journal indicated in parentheses may be omitted.

[Example] Journal article, more than six authors:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, et al. Proposal for biologic drugs therapy in rheumatoid arthritis. Reumatizam. 2010;57(1):29–35. Croatian.

[Example] Journal article, continuous pagination:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Example] Supplement article:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2):ii14–7.

Books

It is required to cite the place of publication, the publisher, and the year of publication. Pagination is provided only if part of a book is cited.

[Example] Book (authors):

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2nd ed. St. Louis: Saunders; 2004.

[Example] Book (editors):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, editors. Oxford textbook of rheumatology. 3rd ed. New York: Oxford University Press; 2004.

[Example] Chapter in a book:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, editor. Spondyloarthropathies. Orlando: Grune and Stratton; 1984. pp. 151–85.

Papers presented at meetings

If a conference paper is published in a journal or a supplement, the instructions for citing a journal or a supplement should be applied. If a conference paper is published in a book, the book title is followed by "Proceedings of", the conference title, date(s), and location (city and country) of the conference.

[Example] Papers presented at meetings, published in a supplement:

7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). Reumatizam. 1997;44(Suppl):1.

[Example] Papers presented at meetings, published in a book:

8. Babić-Naglić Đ. Fizička aktivnost i vježbe [Physical activities and exercises]. In: Ivanišević G, editor. Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj [Thalassotherapy, kinesitherapy and aromatherapy in Croatia]. Proceedings of the 14th Lošinj School of Natural Remedies; 2013 Sep 6–7; Veli Lošinj, Croatia. Zagreb: Hrvatski liječnički zbor; 2013, pp. 49–55. Croatian.

[Example] Conference proceedings (book):

9. Gordon DA, editor. Immune reactions and experimental models in rheumatic diseases. Proceedings of the Fourth Ca-

[Primjer] Članak iz časopisa, više od šest autora:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J i sur. Prijedlog primjene bioloških lijekova u reumatoidnom artritisu. Reumatizam. 2010;57(1):29–35.

[Primjer] Članak iz časopisa, kontinuirana paginacija:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Primjer] Članak iz suplementa:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Supl 2):ii14–7.

Knjige

Obvezatno se navode mjesto izdanja, izdavač i godina izdanja. Brojevi stranica navode se samo kada se citira dio knjige.

[Primjer] Knjiga (autori):

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2. izd. St. Louis: Saunders; 2004.

[Primjer] Knjiga (urednici):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (ur.). Oxford textbook of rheumatology. 3. izd. New York: Oxford University Press; 2004.

[Primjer] Poglavlje u knjizi:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. U: Calin A (ur.). Spondyloarthropathies. Orlando: Grune and Stratton; 1984., str. 151–85.

Izlaganje na znanstvenom skupu

Ako je izlaganje objavljeno u časopisu ili suplementu, treba slijediti upute za časopis ili suplement. Ako su izlaganja objavljena u knjizi, nakon naslova knjige dodaju se napomena „Zbornik izlaganja na", naziv skupa te vrijeme, mjesto (grad ili država) održavanja konferencije.

[Primjer] Izlaganje na znanstvenom skupu, objavljeno u suplementu:

7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). Reumatizam. 1997;44(Supl):1.

[Primjer] Izlaganje na znanstvenom skupu, objavljeno u knjizi:

8. Babić-Naglić Đ. Fizička aktivnost i vježbe. U: Ivanišević G (ur.). Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj. Zbornik izlaganja na 14. lošinjskoj školi prirodnih ljekovitih činitelja; 2013 Ruj 6–7; Veli Lošinj, Hrvatska. Zagreb: Hrvatski liječnički zbor; 2013., str. 49–55.

[Primjer] Zbornik izlaganja na znanstvenom skupu (knjiga):

9. Gordon DA (ur.). Immune reactions and experimental models in rheumatic diseases. Zbornik izlaganja na Četvrtoj kanadskoj konferenciji o istraživanju reumatskih bolesti; 1970 Lis 15–17; Toronto, Kanada. Toronto: University of Toronto Press; 1972.

Mrežne publikacije

Citati mrežnih publikacija trebaju uključivati URL i datum pristupa osim ako je riječ o publikaciji koja ima DOI.

[Primjer] Članak iz časopisa na internetu:

10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res [Internet]. 2014;2014:419029. Dostupno na: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881. [Pristupljeno: 25. 5. 2014.].

[Primjer] Članak iz časopisa na internetu, sadržava DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 Svi 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

nadian Conference on Research in Rheumatic Diseases; 1970 Oct 15–17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

Web publications

References for web publications should include the URL and date of access, unless it is a publication with a DOI.

[Example] Journal article on the Internet:

10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res [Internet]. 2014;2014:419029. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881. [cited: 2014 May 25].

[Example] Journal article on the Internet, with a DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 May 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

[Example] Book/monograph on the Internet:

12. Chen Q, editor. Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Available from: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [2013 Oct 8].

[Example] Web page:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Croatian Society for Rheumatology of the CMA; c2014. Available from: http://www.reumatologija.org/Pocetna.aspx. [cited: 2014 Apr 1].

REVIEW PROCESS

Each manuscript is treated as highly confidential material, and the review process is performed anonymously (double-blind peer review when identities of reviewer and authors are masked). The journal reviewers are required to adhere to the COPE ethical guidelines available at https://bit.ly/323WOHL

The editor-in-chief checks all the submitted manuscripts, and assigns the respective priority level: a) the manuscript is sent immediately for a double-blind peer review; b) the manuscript is returned to authors with suggestions for modifications; c) the manuscript is rejected outright without peer review. Each submitted manuscript is assigned a number and an ID. The authors are informed that the manuscript has been received and a number assigned. The authors are obliged to use such an ID number in all correspondence. A corresponding author acts on behalf of the others in the process related to the manuscript's publication. Manuscripts and other submitted material are not returned to senders.

Authors may suggest up to 5 potential reviewers (excluding coauthors and contributors for the past 3 years), or, providing reasons, ask for the exclusion of a particular reviewer. The editor-in-chief makes the final decision. A copy of the reviewers' opinion is sent to the authors, with the reviewers' identity blinded. The author should take into account the reviewers' opinions for the final version of the manuscript, or provide arguments for their own opinion.

Manuscripts are not published in the order in which they are received by the editorial board. The editorial board reserves the right to adjust the manuscript style to certain standards of uniformity.

Each published article is assigned a DOI (Digital Object Identifier), a unique identifier for every article published in *Reumatizam*. The editorial board provides one copy of *Reumatizam* for each author (or for the corresponding author, if the manuscript was submitted by a group of authors).

[Primjer] Knjiga/monografija na internetu:

12. Chen Q (ur.). Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Dostupno na: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [Pristupljeno: 8. 10. 2013.].

[Primjer] Mrežna stranica:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Hrvatsko reumatološko društvo HLZ-a; c2014. Dostupno na: http://www.reumatologija.org/Pocetna.aspx. [Pristupljeno: 1. 4. 2014.].

PROCES OCJENE RADA

Svaki se rukopis tretira kao strogo povjerljiv materijal, a proces ocjene rada provodi se anonimno (dvostruko slijepo gdje su identiteti i autora i recenzenata zamaskirani). Recenzenti časopisa trebaju se pridržavati COPE etičkih smjernica dostupnih na http://bit.ly/323WOHL.

Glavni i odgovorni urednik pročita sve prijavljene radove i označava njihovu općenitu razinu prioriteta: a) rukopis se odmah šalje dvojici recenzenata, b) rukopis se vraća autorima sa sugestijama za modifikaciju, c) rukopis se odbacuje smjesta bez prethodne recenzije. Svaki upućeni rad dobiva svoj broj i oznaku (ID), a autori će biti obaviješteni o prijamu rada i njegovu broju. Autori su se dužni tim ID brojem koristiti u svakoj budućoj korespondenciji. Autor kojega su ostali autori imenovali za korespondenciju djeluje u ime ostalih u procesu vezanom za publikaciju rada. Rukopisi i ostali dostavljeni materijali ne vraćaju se pošiljateljima.

Autori mogu predložiti do 5 potencijalnih recenzenata (osim koautora i suradnika u posljednje 3 godine) ili uz obrazloženje zatražiti isključenje određenih recenzenata. Glavni i odgovorni urednik donosi konačnu odluku. Preslika mišljenja recenzenata dostavlja se anonimno autoru. Autor treba uzeti u obzir mišljenja recenzenata pri izradi konačne verzije rada ili argumentirano obrazložiti svoje mišljenje.

Radovi se ne objavljuju prema redoslijedu prispijeća rukopisa u uredništvo časopisa. Uredništvo zadržava pravo prilagoditi stil rada određenim standardima ujednačenosti.

Svaki objavljeni članak dobiva svoj DOI (*Digital Object Identifier*) koji je jedinstven za svaki članak objavljen u *Reumatizmu*. Uredništvo će osigurati svakom autoru (ili autoru koji je zadužen za korespondenciju ako je grupa autora prijavila rad) jednu kopiju časopisa *Reumatizma*.