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.