NEUROPSIHIJATRIJSKI LUPUS – DVA LICA JEDNE BOLESTI (PRIKAZ DVA SLUČAJA)

PRIKAZ SLUČAJA

CASE REPORT

NEUROPSYCHIATRIC LUPUS – TWO FACES OF ONE DISEASE (TWO CASE REPORTS)

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SAŽETAK

Uvod: Neuropsihijatrijski lupus (neuropsihijatrijski sistemski eritemski lupus – NPSEL) je forma sistemske autoimunske bolesti – sistemskog eritemskog lupusa, sa dominantnim zahvatanjem centralnog i perifernog nervnog sistema. Nuklearna magnetna rezonanca (NMR) mozga se smatra zlatnim standardom za dijagnostiku pacijenata sa neuropsihijatrijskim lupusom. Lečenje NPSEL-a uključuje: visoke doze kortikosteroida, pulsnu terapiju metilprednizolonom, intravenske imunoglobuline, plazmaferezu, imunosupresive (ciklofosfamid, azatioprin, mikofenolat mofetil), te biološku terapiju – rituksimab.

Prikaz slučajeva: U ovom radu su prikazane dve pacijentkinje sa dijagnozom neuropsihijatrijskog lupusa, sa različitim kliničkim manifestacijama bolesti, kao i sprovedenu dijagnostika, te povoljni ishod imunosupresivne terapije postignut kod obe pacijentkinje.

Zaključak: Patogeneza NPSEL-a uključuje neuroinflamatorne (autoimunske) i ishemijske mehanizme. Neuroimidžing (engl. *neuroimaging*) je pokazao dobre rezultate u razlikovanju pacijenata sa sistemskim eritemskim lupusom (SEL) u odnosu na kontrolnu grupu. Cilj lečenja SEL-a je postizanje remisije ili niske aktivnosti bolesti kao i sprečavanje epizoda pogoršanja. Terapija intravenskim ciklofosfamidom, kao i sistemskim kortikosteroidima, pokazala je značajno pozitivne rezultate kod pacijenata sa NPSEL-om. Postoji velika potreba za novim biomarkerima u serumu i likvoru kao i inovativnijim radiološkim procedurama u budućnosti. Neophodna su dodatna klinička ispitivanja koja bi dovela do novih terapijskih opcija u lečenju NPSEL-a.

Ključne reči: neuropsihijatrijski lupus, NMR mozga, metilprednizolon, ciklofosfamid

ABSTRACT

Introduction: Neuropsychiatric lupus (neuropsychiatric systemic lupus erythematosus – NPSLE) is a form of a systemic autoimmune disease – systemic lupus erythematosus (SLE), with dominant central and peripheral nervous system involvement. Nuclear magnetic resonance imaging (NMRI) of the brain is considered the gold standard for diagnosing patients with NPSLE. Treatment of NPSLE includes the following: high doses of corticosteroids, methylprednisolone pulse therapy, intravenous immunoglobulins, plasmapheresis, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil), and biological therapy – rituximab.

Case reports: In this paper, we present two patients diagnosed with neuropsychiatric lupus, with different clinical manifestations of the disease, as well as the diagnostics performed, and the good clinical outcomes of immunosuppressive therapy achieved in both patients.

Conclusion: The pathogenesis of NPSLE involves neuroinflammatory (autoimmune) and ischemic mechanisms. Neuroimaging has shown good results in differentiating patients with SLE from controls. The goal of SLE treatment is to achieve remission or low disease activity and to prevent episodes of exacerbation. Treatment with intravenous cyclophosphamide as well as with systemic corticosteroids has shown significantly positive results in patients with NPSLE. There is great need, in the future, for new biomarkers in the serum and cerebrospinal fluid (CSF), as well as for more innovative radiological procedures. Additional clinical trials that would lead to new therapeutic options for the treatment of NPSLE are necessary.

Keywords: neuropsychiatric lupus, brain NMRI, methylprednisolone, cyclophosphamide

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UVOD

Neuropsihijatrijski lupus (neuropsihijatrijski sistemski eritemski lupus – NPSEL) je forma sistemske autoimunske bolesti – sistemskog eritemskog lupusa (SEL), sa dominantnim zahvatanjem centralnog i perifernog nervnog sistema [1]. Oko 50% pacijenata razvija neuropsihijatrijske simptome SEL-a, unutar jedne godine od početka sistemskog eritemskog lupusa [2]. NPSEL uključuje niz neuroloških i psihijatrijskih simptoma koji utiču na kvalitet života pacijenata, kao i na prognozu bolesti [3]. Kod pacijenata sa SEL-om, mortalitet od NPSEL-a je na drugom mestu, odmah iza lupusnog nefritisa [4]. Prevalencija NPSEL-a varira u rasponu od 37% do 95%. Na ovakav rezultat utiču različiti dijagnostički kriterijumi, dizajni studija, različite populacije i rase pacijenata, praćenje različitih kohorti pacijenata, kao i tipovi i težina kliničke slike bolesti [1]. Nuklearna magnetna rezonanca (NMR) mozga se smatra zlatnim standardom za dijagnostiku pacijenata sa NPSEL-om [5]. Lečenje NPSEL-a uključuje: visoke doze kortikosteroida, pulsnu terapiju metilprednizolonom, intravenske imunoglobuline, plazmaferezu, imunosupresive (ciklofosfamid, azatioprin, mikofenolat mofetil), te biološku terapiju – rituksimab [2].

Cilj ovog rada je da se prikažu dve potpuno različite manifestacije neuropsihijatrijskog lupusa, izazove u njihovoj dijagnostici, kao i postignuti povoljni odgovor na imunosupresivnu terapiju.

PRIKAZ DVA SLUČAJA

Prikaz prvog slučaja

Prvi slučaj jeste pacijentkinja stara 65 godina. Dijagnoza sistemskog eritemskog lupusa (SEL) je kod ove pacijentkinje postavljena 1991. godine, na osnovu kožnih promena, fotosenzitivnosti, poliartralgije, ranica u ustima i nosu, poliserozitisa, bicitopenije, + antinukleusnih antitela (ANA), + anti-Smit antitela (anti-Sm at), sniženih vrednosti C4 komponente komplementa, te zapaljenskog sindroma. U isto vreme je postavljena i dijagnoza sekundarnog Sjogrenovog sindroma, koja je potvrđena patohistološkim nalazom biopsije male pljuvačne žlezde.

Inicijalna terapija sa zadovoljavajućim efektom uključivala je primenu parenteralne (metilprednizolon 1 mg/kg) i *per os* (prednizon – doza održavanja 10 mg/dan) glukokortikosteroidne (GKS) terapije, uz antimalarik – hidroksihlorokin u dozi od 200 mg/dan. Tokom vremena javljala su se povremena pogoršanja u vidu poliserozitisa i kutanog diskoidnog lupusa sa dobrim odgovorom na pulsnu terapiju metilprednizolonom.

Novembra 2015. godine, po prvi put od početka bolesti, javlja se prvi *Grand mal* epileptični napad. Na

INTRODUCTION

Neuropsychiatric lupus (neuropsychiatric systemic lupus erythematosus – NPSLE) is a form of systemic autoimmune disease – systemic lupus erythematosus (SLE), with dominant involvement of the central and peripheral nervous system [1]. About 50% of patients develop neuropsychiatric symptoms of SLE within one year of the onset of systemic lupus erythematosus [2]. NPSLE includes a number of neurological and psychiatric symptoms that affect the quality of life of patients, as well as the prognosis of the disease [3]. In patients with SLE, mortality from NPSLE is second only to lupus nephritis [4]. The prevalence of NPSLE varies between 37% and 95%. This result is affected by different diagnostic criteria, study designs, different populations and races of patients, follow-up of different cohorts of patients, as well as the types and severity of the clinical presentation of the disease [1]. Nuclear magnetic resonance imaging (NMRI) of the brain is considered the gold standard for the diagnosis of patients with NPSLE [5]. Treatment of NPSLE includes the following: high doses of corticosteroids, pulse therapy with methylprednisolone, intravenous immunoglobulins, plasmapheresis, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil), and biological therapy – rituximab [2].

The aim of this study is to present two completely different manifestations of neuropsychiatric lupus, the challenges in their diagnosis, as well as the favorable response to immunosuppressive therapy.

TWO CASE REPORTS

Case report I

The first case is a 65-year-old female patient. The diagnosis of systemic lupus erythematosus (SLE) was established in this patient in 1991, based on skin changes, photosensitivity, polyarthralgia, sores in the mouth and nose, polyserositis, bicytopenia, + antinuclear antibodies (ANAs), + anti-Smith antibodies (anti- Sm at), decreased values of the complement component 4 (C4), and inflammatory syndrome. At the same time, a diagnosis of secondary Sjögren's syndrome was made, which was confirmed by the pathohistological findings of a small salivary gland biopsy.

Initial treatment, which achieved a satisfactory effect included the use of parenteral (methylprednisolone 1 mg/kg) and *per os* (prednisone – maintenance dose of 10 mg/day) glucocorticosteroid (GCS) therapy, together with an antimalarial drug – hydroxychloroquine at a dose of 200 mg/day. Over time, there were occasional exacerbations, in the form of polyserositis and cutaneous discoid lupus with a good response to pulse therapy with methylprednisolone.

elektroencefalogramu (EEG) su opisane epileptiformne promene sa paroksizmalnim šiljcima i oštrim talasima. U terapiju je uvedena valproinska kiselina, kao i natrijum valproat. Januara 2016. godine, urađena je NMR endokranijuma gde su opisane supratentorijalne multiple mikroangiopatske lezije bele mase, suspektno vaskulitisne etiologije uz kortikalne reduktivne promene. Istog meseca, pacijentkinja je imala još jedan *Grand mal* napad. Nije bilo kliničkih i laboratorijskih kriterijuma za dijagnozu sekundarnog antifosfolipidnog sindroma. Uz konsultaciju sa neurologom, postavljena je dijagnoza NPSEL-a.

Početkom 2016. godine, započeta je pulsna terapija ciklofosfamidom (500 mg/m^2 telesne površine (TP)) uz dva pulsa metilprednizolona od po 500 mg. Nakon mesec dana, pacijentkinja je imala treći i poslednji *Grand mal* napad. Kod pacijentkinje je primenjeno ukupno 12 ciklusa terapije ciklofosfamidom u kumulativnoj dozi od 10 grama. Po završetku terapije, na kontrolnom EEG-u nisu opisane epileptiformne promene, kontrolna NMR endokranijuma je bila bez bitnijih promena u odnosu na početak bolesti. Po završetku lečenja ciklofosfamidom, u terapiju je, pored prednizona u dozi od 10 mg/dan i hidroksihlorokina od 200 mg/dan, uveden i azatioprin u dozi od 100 mg/dan. U nekoliko navrata tokom lečenja ciklofosfamidom, detektovane su asimptomatske urinarne infekcije sa blažom hipogamaglobulinemijom, koje su, pored antibiotske terapije, lečene i primenom humanih intravenskih imunoglobulina (IVIG).

Prikaz drugog slučaja

Drugi slučaj jeste pacijentkinja stara 53 godine. Njoj je, 2016. godine, postavljena dijagnoza Sjogrenovog sindroma, na osnovu pozitivnih antinukleusnih antitela, povišenih anti SSA antitela (anti-SSA at), suvog oka (keratokonjuktivitis *sicca* – KK *sicca*; lat. *keratoconjunctivitis sicca*), patološkog nalaza scintigrafije pljuvačnih žlezda koji je dokazao postojanje smanjene akumulacione i ekskrecione sposobnosti pljuvačnih žlezda, PH nalaza biopsije pljuvačnih žlezda sa fokusima limfocitne infiltracije, kseroftalmije, kserostomije, te poliartralgije.

Pacijentkinja je inicijalno lečena prednizonom u dozi od 1 mg/kg, uz postepeno smanjivanje doze do 15 mg/dan, kao i hidroksihlorokinom u dozi od 300 mg/dan. Nakon nekoliko meseci, javilo se akutno konfuzno stanje uz kognitivnu disfunkciju. Pacijentkinja je pregledana od strane neurologa i inicijalno je postavljena sumnja na *Morbus Alzheimer*. Urađena je NMR endokranijuma, na kojoj su opisane punktiformne mikroangiopatske lezije, fronto-parijetalno, obostrano, uz kortikalne reduktivne promene.

In November 2015, for the first time since the onset of the disease, the first grand mal epileptic seizure occurred. Epileptiform changes with paroxysmal spikes and sharp waves were recorded on the electroencephalogram (EEG). Valproic acid and sodium valproate were introduced as a part of the therapy. In January 2016, an NMRI of the endocranium was performed recording supratentorial multiple microangiopathic white matter lesions of suspected vasculitis etiology, with cortical reductive changes. In the same month, the patient had another grand mal seizure. There were no clinical or laboratory criteria for the diagnosis of secondary antiphospholipid syndrome. In consultation with a neurologist, the diagnosis of NPSLE was established.

In early 2016, cyclophosphamide pulse therapy (500 mg/m^2 body surface area (BSA)) was started, with two pulses of methylprednisolone – 500 mg each. After one month, the patient had her third and final grand mal seizure. The patient received a total of 12 cycles of cyclophosphamide therapy, with a cumulative dose of 10 grams. After the end of the therapy, no epileptiform changes were described on the follow-up EEG, while the follow-up NMRI of the endocranium was without significant changes, as compared to the beginning of the disease. After the end of treatment with cyclophosphamide, in addition to prednisone at a dose of 10 mg/day and hydroxychloroquine at a dose of 200 mg/day, azathioprine at a dose of 100 mg/day was also introduced into the therapy. On several occasions during treatment with cyclophosphamide, asymptomatic urinary infections with mild hypogammaglobulinemia were detected, which, in addition to antibiotic therapy, were also treated with the use of human intravenous immunoglobulins (IVIGs).

Case report II

The second case is a 53-year-old female patient. In 2016, she was diagnosed with Sjögren's syndrome, based on a positive ANA test, elevated anti-SSA antibodies (anti-SSA at), dry eye syndrome (keratoconjunctivitis sicca – KC sicca), a pathological finding of salivary gland scintigraphy proving reduced accumulation and excretory capacity of the salivary glands, the PH finding of salivary gland biopsy with foci of lymphocytic infiltration, xerophthalmia, xerostomia, and polyarthralgia.

The patient was initially treated with prednisone at a dose of 1 mg/kg, which was gradually reduced to 15 mg/day, as well as with hydroxychloroquine at a dose of 300 mg/day. After several months, acute confusional state with cognitive dysfunction occurred. The patient was examined by a neurologist, and Alzheimer's disease was initially suspected. NMRI of the endocranium was performed and punctiform microangiopathic le-

Marta 2017. godine, tokom prve hospitalizacije na Klinici za alergologiju i imunologiju Univerzitetskog kliničkog centra Srbije (UKCS) postavljena je dijagnoza neuropsihijatrijskog lupusa, na osnovu fotosenzitivnosti, poliartralgije, + ANA, + lupus antikoagulans testa (LA), bicitopenije, te neuropsihijatrijskih manifestacija. Od strane psihijatra je postavljena dijagnoza anksiozno-depresivnog sindroma i u terapiju je uveden selektivni inhibitor preuzimanja serotonina (engl. *selective serotonin reuptake inhibitor – SSRI*) – sertralin, u dozi od 50 mg/dan. Elektromioneurografskim pregledom (EMNG) isključeno je postojanje polineuropatije (PNP). Pregledom neurologa konstatovana je desnostrana slabost uz hod na širokoj osnovi.

Jula 2017. godine, započeta je imunosupresivna terapija ciklofosfamidom u dozi od 500 mg/m^2 telesne površine, i ukupno ordinirano 12 ciklusa sa kumulativnom dozom od 7,2 grama, uz pulseve metilprednizolona od po1.000 mg po ciklusu. Od postavljanja dijagnoze, pored prednizona i antimalarika, u terapiju je uključena i acetilsalicilna kiselina u dnevnoj dozi 100 mg, zbog + lupus antikoagulansa (LA). Nakon završenih 12 ciklusa terapije ciklofosfamidom, urađena je kontrolna NMR endokranijuma, čiji nalaz je bio značajnije neizmenjen u odnosu na prethodni, pre započinjanja terapije.

Od strane psihijatra, krajem 2018. godine, iz terapije je isključen antidepresiv, dok je produžena terapija benzodiazepinom, po potrebi. Već nakon prvog ciklusa ciklofosfamidom, nisu se više javljali napadi akutnog konfuznog stanja, dok su kognitivne funkcije bile značajno poboljšane. Terapija održavanja je u daljem toku, pored prednizona u dozi od 10 mg/dan, hidroksihlorokina u dozi od 200 mg/dan i acetilsalicilne kiseline u dozi od 100 mg/dan, uključivala i azatioprin u dozi od 100 mg/dan.

DISKUSIJA

Neuropsihijatrijska forma sistemskog eritemskog lupusa je oduvek predstavljala izazov za kliničare, kako na dijagnostičkom tako i na terapijskom nivou [1]. NPSEL se češće javlja kod afričke i azijske populacije, ali je uočeno da su teži oblici bolesti češći kod bele rase [5]. NPSEL ima široki spektar i visoku heterogenost kliničkih fenotipova, uključujući glavobolju, epilepsiju, moždani udar, perifernu neuropatiju, kognitivne poremećaje, gubitak pamćenja, te psihijatrijske simptome. [2,4].

Američki koledž za reumatologiju (engl. *American College of Rheumatology – ACR*) je 1999. godine predložio 19 entiteta u sklopu NPSEL-a (12 u sklopu centralnog nervnog sistema (CNS) i 7 u sklopu perifernog nervnog sistema (PNS), uz podelu još i na difuznu i fokalnu zahvaćenost nervnog sistema (NS)), (Tabela 1) [1]. Moždane manifestacije SEL-a se definišu kao fokalni i

sions were registered, fronto-parietally, bilaterally, with cortical reductive changes.

In March 2017, during the patient's first hospital stay at the Clinic of Allergology and Immunology of the University Clinical Center of Serbia (UCCS), a diagnosis of neuropsychiatric lupus was made, based on photosensitivity, polyarthralgia, + ANA, + lupus anticoagulant test (LA), bicytopenia, and neuropsychiatric manifestations. A psychiatrist diagnosed anxiety-depressive syndrome and selective serotonin reuptake inhibitor (SSRI) – sertraline, at a dose of 50 mg/day, was introduced as a part of the therapy. The electromyoneurography (EMNG) finding ruled out polyneuropathy (PNP). An examination by a neurologist revealed right-sided weakness with broad-based gait.

In July 2017, the patient was started on immunosuppressive therapy with cyclophosphamide at a dose of 500 mg/m^2 of body surface area, and a total of 12 cycles were prescribed with a cumulative dose of 7.2 grams, with methylprednisolone pulses of 1,000 mg per cycle. Since the diagnosis, in addition to prednisone and antimalarial drugs, the therapy included acetylsalicylic acid at a daily dose of 100 mg, due to + lupus anticoagulant (LA). After completing 12 cycles of cyclophosphamide therapy, a follow-up NMRI of the endocranium was performed, and the findings were significantly unchanged, as compared to the previous one, performed before the beginning of therapy.

In late 2018, the patient's psychiatrist discontinued antidepressant treatment, but continued treatment with benzodiazepine, as needed. As early as the first cycle with cyclophosphamide was completed, attacks of acute confusional state no longer occurred, while cognitive functions were significantly improved. In addition to prednisone at a dose of 10 mg/day, hydroxychloroquine at a dose of 200 mg/day, and acetylsalicylic acid at a dose of 100 mg/day, further maintenance therapy also included azathioprine at a dose of 100 mg/day.

DISCUSSION

The neuropsychiatric form of systemic lupus erythematosus has always been a challenge for clinicians, both at the diagnostic and at the therapeutic level [1]. NPSLE occurs more often in African and Asian populations, however, more severe forms of the disease have been observed as more common in Caucasians [5]. NPSLE has a wide spectrum and high heterogeneity of clinical phenotypes, including headache, epilepsy, stroke, peripheral neuropathy, cognitive impairment, memory loss, and psychiatric symptoms. [2,4].

In 1999, the American College of Rheumatology (ACR) proposed 19 entities within NPSLE (12 with-

Tabela 1. Manifestacije neuropsihijatrijskog SEL-a, prema Američkom koledžu za reumatologiju (ACR)

	Centralni nervni sistem (CNS)	Periferni nervni sistem (PNS)
Difuzne manifestacije (psihijatrijski poremećaji)	Akutno konfuzno stanje Anksiozni poremećaji Kognitivne disfunkcije Poremećaji raspoloženja Psihoze	
Fokalne manifestacije (neurološki poremećaji)	Aseptični meningitis Cerebrovaskularne bolesti Demijelinizacioni sindrom Glavobolje Poremećaji pokreta Mijelopatija Epilepsija	Gilen Bareov sindrom Bolesti autonomnog nervnog sistema Mononeuropatije Mijastenija gravis Kranijalna neuropatija Pleksopatija Polineuropatija

Table 1. Manifestations of neuropsychiatric SLE according to the American College of Rheumatology (ACR)

	Central nervous system (CNS)	Peripheral nervous system (PNS)
Diffuse manifestations (psychiatric disorders)	Acute confusional state Anxiety disorders Cognitive dysfunction Mood disorders Psychoses	
Focal manifestations (neurological disorders)	Aseptic meningitis Cerebrovascular diseases Demyelination syndrome Headaches Movement disorders Myelopathy Epilepsy	Guillain-Barre syndrome Diseases of the autonomous nervous system Mononeuropathies Myasthenia gravis Cranial neuropathy Plexopathy Polyneuropathy

difuzni neurološki deficiti, pri čemu su fokalni poremećaji uglavnom posledica tromboembolijskih događaja prouzrokovanih prisustvom antifosfolipidnih antitela. Patogeneza difuznih poremećaja (afektivni i kognitivni poremećaji) značajno je kompleksnija i za sada nedovoljno razjašnjena [3]. Većina simptoma NPSEL-a može se javiti i u sklopu komorbiditeta ili može biti posledica terapije glukokortikosteroidima (GKS), što značajno otežava dijagnostiku ove bolesti [4].

Patogeneza NPSEL-a uključuje neuroinflamatorne (autoimunske) i ishemijske mehanizme. Patološki mehanizam kod SEL-a uključuje gubitak imunološke tolerancije na ćelijski nuklearni antigen, proizvodnju autoantitela i taloženje imunskih kompleksa, što dovodi do aktivacije komplementa, upale tkiva i ćelijske apoptoze. Izmenjena je aktivacija B i T ćelija kao i produkcija interferona tip I. U većini slučajeva koegzistiraju oba patogenetska mehanizma [5].

Disfunkcija krvno-moždane barijere sa posledičnim prolaskom antitela u cerebrospinalnu tečnost kao

in the central nervous system (CNS) and 7 within the peripheral nervous system (PNS), with an additional distinction between diffuse and focal involvement of the nervous system (NS)), (Table 1) [1]. Cerebral manifestations of SLE are defined as focal and diffuse neurological deficits, whereby focal disorders are mainly due to thromboembolic events caused by the presence of antiphospholipid antibodies. The pathogenesis of diffuse disorders (affective and cognitive disorders) is significantly more complex and, as yet, insufficiently understood [3]. Most of the symptoms of NPSLE can occur within comorbidities or can be a consequence of glucocorticosteroid (GCS) therapy, which significantly complicates the diagnosis of this disease [4].

The pathogenesis of NPSLE involves neuroinflammatory (autoimmune) and ischemic mechanisms. The pathological mechanism in SLE involves the loss of immune tolerance to the cell nuclear antigen, production of autoantibodies, and build-up of immune complexes, leading to complement activation, tissue inflamma-

i intratekalna sinteza antitela, jesu poremećaji koji se javljaju u sklopu NPSEL-a. Prisustvo antifosfolipidnih antitela povezano je pre svega sa pojavom trombotičkih događaja, kao što je moždani udar, u sklopu NPSEL-a, ali i sa pojavom epileptičnih napada, poremećaja pokreta, kognitivne disfunkcije i mijelopatije. Anti-akva porin 4 antitela su povezana sa pojavom transferzalnog mijelitisa i optičkog neuromijelitisa. Anti-P ribozomska antitela najčešće su povezana sa pojavom psihoze. U sklopu NPSEL-a se javljaju i anti-N metil D aspartat receptorska antitela koja zajedno sa anti-P ribozomalnim antitelima učestvuju u patofiziologiji difuznih oštećenja preko toksičnog oštećenja neurona i izazivanja apoptoze [1]. Kod difuznih formi NPSEL-a sa kliničkom slikom akutnog konfuznog stanja, uočen je povišen nivo IL-6 u cerebrospinalnoj tečnosti. Zbog nedostatka specifičnosti, za sada se ne radi rutinska provera prisustva ovog citokina u cerebrospinalnoj tečnosti [1,5].

Neuroimidžing je pokazao dobre rezultate u razlikovanju pacijenata sa SEL-om, u odnosu na kontrolnu grupu [3]. Neuroimidžing nije specifičan za postavljanje dijagnoze NPSEL-a, ali je od značaja za isključivanje drugih uzročnika (infektivni, neoplastični, aneurizme, i drugi) neuropsihijatrijskih simptoma kod ovih pacijenata [4]. Uobičajeni nalaz konvencionalnog NMR snimanja mozga kod pacijenata sa SEL-om uključuje hiperintenzivne promene bele mase kao i atrofiju mozga, ali ove promene nisu specifične [6].

Cilj lečenja SEL-a je postizanje remisije ili niske aktivnosti bolesti, kao i sprečavanje epizoda pogoršanja. Kod svih pacijenata sa SEL-om se preporučuje primena hidroksihlorokina u dozi ne većoj od 5 mg/kg telesne mase (TM). Doza održavanja prednizona ne treba da prelazi 7,5 mg/dan, sa tendencijom potpunog isključivanja kada se steknu uslovi. Primena imunomodulatornih agenasa (metotreksat, azatioprin, mikofenolat) može skratiti vreme potrebno za smanjenje doze GKS-a ili njihovo potpuno isključivanje iz terapije. Kod svih pacijenata sa pozitivnim antifosfolipidnim antitelima (aFL at) preporučuje se primarna profilaksa niskim dozama acetilsalicilne kiseline. Primena antikoagulante terapije – niskomolekularni heparini (engl. *low molecular weight heparins – LMWHs*), preporučuje se naročito tokom trudnoće kao i u postoperativnom toku. U zavisnosti od manifestacije bolesti, potrebna je i simptomatska terapija (antipsihotici, anksiolitici, i dr.) [7]. Hidroksihlorokin se koristi kao prva terapijska linija kod pacijenata sa SEL-om bez značajnijih oštećenja organskih sistema. Predložena je i njegova primena za primarnu prevenciju NPSEL-a, posebno za cerebrovaskularne događaje i epileptičke napade [2]. Terapija intravenskim ciklofosfamidom, kao i sistemskim kor-

tion, and cell apoptosis. The activation of B and T cells, as well as the production of interferon type I, is altered. In most cases, both pathogenetic mechanisms coexist at the same time [5].

Dysfunction of the blood-brain barrier with consequent passage of antibodies into the cerebrospinal fluid, as well as intrathecal synthesis of antibodies, are disorders that occur as a part of NPSLE. The presence of antiphospholipid antibodies is primarily associated with the occurrence of thrombotic events, such as stroke, in NPSLE, but also with the occurrence of epileptic seizures, movement disorders, cognitive dysfunction, and myelopathy. Anti-aqua porin 4 antibodies are associated with the occurrence of transverse myelitis and neuromyelitis optica. Anti-P ribosomal antibodies are most often associated with the onset of psychosis. As a part of NPSLE, anti-N methyl D aspartate receptor antibodies also appear, and, together with anti-P ribosomal antibodies, participate in the pathophysiology of diffuse damage through toxic damage to neurons and the induction of apoptosis [1]. In diffuse forms of NPSLE with clinical presentation of acute confusional state, an elevated level of IL-6 in the cerebrospinal fluid has been observed. Due to the lack of specificity, the presence of this cytokine in the cerebrospinal fluid is not routinely tested for, as yet [1,5].

Neuroimaging has shown good results in differentiating patients with SLE, as compared to the control group [3]. Neuroimaging is not specific for the diagnosis of NPSLE, but it is important for excluding other causes (infectious agents, neoplastic causes, aneurysms, and others) of neuropsychiatric symptoms in these patients [4]. A common finding of conventional NMRI brain imaging in patients with SLE includes hyperintense white matter changes as well as brain atrophy, but these changes are not specific [6].

The goal of SLE treatment is to achieve remission or low disease activity, as well as to prevent episodes of exacerbation. In all patients with SLE, the administration of hydroxychloroquine at a dose not exceeding 5 mg/kg of body weight (BW) is recommended. The maintenance dose of prednisone should not exceed 7.5 mg/day, with a tendency to completely discontinue the drug, when the conditions for this are met. The use of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can shorten the time required to reduce the dose of GCSs or to completely exclude them from therapy. In all patients with positive antiphospholipid antibodies (aPL at), primary prophylaxis with low doses of acetylsalicylic acid is recommended. The use of anticoagulant therapy – low molecular weight heparins (low molecular weight heparins – LMWHs) is recommended, especially during pregnancy,

tikosteroidima, pokazala je značajno pozitivne rezultate kod pacijenata sa NPSEL-om, i danas je u većini slučajeva ovo prva terapijska opcija kod formi bolesti sa zahvatanjem organskih sistema (bubrezi, centralni i periferni nervni sistem) [5]. U randomizovanim kontrolisanim studijama, poređena je primena ciklofosfamida sa pulsnim dozama kortikosteroida i zaključeno je da bolji efekat ima lečenje ciklofosfamidom. Pokazano je da primena azatioprina, kao terapije održavanja, smanjuje relapse bolesti [2]. Isti efekat sa još bezbednijim terapijskim profilom ima i primena mikofenolat mofetila. Rituksimab je anti-CD20 IgG1 monoklonsko antitelo koje uništava B limfocite delujući na CD20 molekule koji se nalaze na njihovoj površini [2]. Postoje ograničeni podaci o efikasnosti biološke terapije u lečenju NPSEL-a. Upotreba rituksimaba pokazala je povoljne efekte ali potrebne su dodatne studije o efikasnosti. Belimumab je pokazao pozitivan efekat kod pacijenata sa blažom formom bolesti [5]. Kod pogoršanja ekstrarenalne forme bolesti, može se primeniti belimumab, dok se kod pogoršanja i aktivnosti SEL-a sa potencijalnim ugrožavanjem organskih sistema, može primeniti rituksimab [7].

Novija saznanja pokazuju da farmakološka modulacija mikroglije može uticati na ublažavanje simptoma bolesti (imunomodulator fingolimod; modulator sfingozin 1 fosfat receptora, koji deluje na limfocite tako što ih sekvestrira u limfne čvorove i sprečava njihovu migraciju na mesto autoimunskog procesa) [3]. Postoji potreba za novim terapijskim opcijama koje bi bile usmerene na poremećaj krvno-moždane barijere, citokine i mikroglijalne ćelije [5].

Uprkos opsežnim kliničkim istraživanjima, do sada se nijedan laboratorijski ni neuroimidžing biomarker nije pokazao kao potpuno precizan u dijagnozi NPSEL-a. Postoji velika potreba za novim biomarkerima u serumu i likvoru kao i za inovativnijim radiološkim procedurama u budućnosti [5]. Neophodna su dodatna klinička ispitivanja koja bi dovela do novih terapijskih opcija u lečenju NPSEL-a.

SPISAK SKRAĆENICA

NPSEL – neuropsihijatrijski sistemski eritemski lupus
NMR – nuklearna magnetna rezonanca
SEL – sistemski eritemski lupus
ANA – antinukleusna antitela
Anti-Sm at – anti-Smit antitela
GKS – glukokortikosteroidi
EEG – electroencefalogram
IVIG – intravenski imunoglobulini
Anti-SSA at – anti-Sjogren sindrom A antigen
KK *sicca* – keratokonjuktivitis *sicca*
LA – lupus antikoagulans

as well as during postoperative recovery. Depending on the manifestation of the disease, symptomatic therapy is also necessary (antipsychotic drugs, anxiolytic drugs, etc.) [7]. Hydroxychloroquine is used as first-line treatment in patients with SLE without significant damage to organ systems. Its application has also been suggested for the primary prevention of NPSLE, especially for cerebrovascular events and epileptic seizures [2]. Therapy with intravenous cyclophosphamide, as well as with systemic corticosteroids, has shown significantly positive results in patients with NPSLE, and nowdays, in most cases, this is the therapeutic option of choice for forms of the disease that involve organ systems (kidneys, the central and peripheral nervous system) [5]. In randomized controlled trials, the use of cyclophosphamide was compared with pulsed doses of corticosteroids, and it was concluded that treatment with cyclophosphamide had a better effect. It has been shown that the use of azathioprine, as maintenance therapy, reduces disease relapses [2]. The use of mycophenolate mofetil has the same effect with an even safer therapeutic profile. Rituximab is an anti-CD20 IgG1 monoclonal antibody that destroys B lymphocytes by acting on CD20 molecules located on their surface [2]. There are limited data on the effectiveness of biological therapy in the treatment of NPSLE. The use of rituximab has shown favorable effects, but additional studies on efficacy are needed. Belimumab has shown a positive effect in patients with the mild form of the disease [5]. In case of exacerbation of the extrarenal form of the disease, belimumab can be used, while in the case of exacerbation and activity of SLE, with a potential threat to organ systems, rituximab can be used [7].

More recent findings have shown that pharmacological modulation of microglia can affect the alleviation of disease symptoms (immunomodulator fingolimod; modulator of the sphingosine 1 phosphate receptor, which acts on lymphocytes by sequestering them in lymph nodes and preventing their migration to the site of the autoimmune process) [3]. There is a need for new therapeutic options that would target the disruption of the blood-brain barrier, cytokines, and microglial cells [5].

Despite extensive clinical research, to date, no laboratory or neuroimaging biomarker has proven to be completely accurate in the diagnosis of NPSLE. There is great need for new biomarkers in the serum and CSF, as well as for more innovative radiological procedures in the future [5]. Additional clinical trials are necessary that would lead to new therapeutic options in the treatment of NPSLE.

SSRI – selektivni inhibitor preuzimanja serotonina (engl. *selective serotonin reuptake inhibitors*)
EMNG – elektromioneurografija
PNP – polineuropatija
CNS – centralni nervni sistem
PNS – periferni nervni sistem
IL-6 – interleukin-6
aFL at – antifosfolipidna antitela
LMWHs – niskomolekularni heparini (engl. *low molecular weight heparins*)

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LIST OF ABBREVIATIONS AND ACRONYMS

NPSLE - neuropsychiatric systemic lupus erythematosus
NMRI – nuclear magnetic resonance imaging
SLE – systemic lupus erythematosus
ANAs – antinuclear antibodies
Anti-Sm at – anti-Smith antibodies
GCSs – glucocorticosteroids
EEG – electroencephalogram
IVIGs – intravenous immunoglobulins
Anti-SSA at – anti-Sjogren syndrome A antigen
KC sicca – keratoconjunctivitis sicca
LA – lupus anticoagulant
SSRIs – selective serotonin reuptake inhibitors
EMNG – electromyoneurography
PNP – polyneuropathy
CNS – central nervous system
PNS – peripheral nervous system
IL-6 – interleukin-6
aPL at - antiphospholipid antibodies
LMWHs - low molecular weight heparins

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