NOVI TERAPIJSKI AGENSI U LEČENJU NEUROSARKOIDOZE

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REVIEW ARTICLE

NEW THERAPEUTIC AGENTS IN NEUROSARCOIDOSIS TREATMENT

Nikola Marić[1], Aleksa Golubović[1], Slobodan Belić[1], Nataša Đurđević[1], Ivan Milivojević[1], Miloš Geratović[1], Mihailo Stjepanović[1,2]

[1] Univerzitetski klinički centar Srbije, Klinika za pulmologiju, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[1] *University Clinical Center of Serbia, Clinic for Pulmonology, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

SAŽETAK

Neurosarkoidoza predstavlja relativno čestu ekstrapulmonalnu formu sarkoidoze. Karakterišu je prisustvo različite kliničke slike, mala verovatnoća spontane remisije, značajan uticaj na kvalitet života, kao i potencijalno povećanje mortaliteta. Pored kortikosteroida, u lečenju neurosarkoidoze se primenjuju i drugi lekovi, kao što su metotreksat, azatioprin, mikofenolat mofetil, inhibitori faktora nekroze tumora α (*TNF*-α), infliksimab i adalimumab. U ovom radu smo, pregledom dostupne literature, pokušali da objedinimo dosadašnja saznanja i novine u lečenju neurosarkoidoze, kako bismo olakšali svakodnevni rad lekarima klinicarima. Dosadašnje studije i dalje daju prednost pulsnim dozama kortikosteroida, dok je druga terapija pokazala prednost samo u pojedinim slučajevima. Ipak, treba napomenuti da su potrebna dodatna istraživanja, kako bi se uspešno razvila individualna terapija.

Ključne reči: sarkoidoza, neurosarkoidoza, kortikosteroidi

ABSTRACT

Neurosarcoidosis is a relatively common extrapulmonary form of sarcoidosis. It is characterized by variable clinical presentation, low probability of spontaneous remission, and significant impact on the quality of life, as well as potential increase in mortality. In addition to corticosteroids, other drugs are used in the treatment of neurosarcoidosis, such as methotrexate, azathioprine, mycophenolate mofetil, tumor necrosis factor α (TNF-α) inhibitors, infliximab and adalimumab. In this paper, by reviewing the available literature, we have attempted to consolidate the current knowledge and novelties in the treatment of neurosarcoidosis, for the purpose of assisting physicians in their day-to-day clinical work. Previous studies still favor pulsed doses of corticosteroids, while other forms of therapy have proven beneficial only in individual cases. However, it should be noted that additional research is needed in order to successfully develop individual therapy.

Keywords: sarcoidosis, neurosarcoidosis, corticosteroids

Autor za korespondenciju:
Mihailo Stjepanović
Klinika za pulmologiju, Univerzitetski klinički centar Srbije
Dr Koste Todorovića 26, 11000 Beograd, Srbija
Elektronska adresa: mihailostjepanovic@gmail.com

Corresponding author:
Mihailo Stjepanović
Clinic for Pulmonology, University Clinical Center of Serbia
26 Dr Koste Todorovića Street, 11000 Belgrade, Serbia
E-mail: mihailostjepanovic@gmail.com

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UVOD

Sarkoidoza predstavlja granulomatozno oboljenje koje može da zahvati bilo koji organ. Iako su najčešći simptomi malaksalost, zamaranje, neproduktivan kašalj i oticanje zglobova, klinička prezentacija može značajno da varira u zavisnosti od distribucije granuloma. Ukoliko ne dođe do spontane remisije (oko 30% slučajeva, u zavisnosti od populacije) [1], prva linija terapije su oralni kortikosteroidi, dok se u slučaju hronične forme, čestih recidiva ili pojave ekstrapulmonalne forme bolesti, mogu razmatrati i drugi terapijski modaliteti. Za dijagnostiku same bolesti, kao i za praćenje efikasnosti terapije, pored fizikalnog pregleda, koriste se i radiografska snimanja (klasična radiografija, kompjuterska tomografija, magnetna rezonanca ili pozitronska emisiona tomografija, u zavisnosti od forme bolesti), biomarkeri (angiotenzin konvertujući enzim (engl. angiotensin-converting enzyme – ACE)), hitotriozidaza (engl. chitotriosidase – ChT), kalcijum u dvadesetčetvoročasovnom urinu, kao i upitnici o kvalitetu života.

KLINIČKA SLIKA I DIJAGNOSTIKA NEUROSARKOIDOZE

Neurosakroidoza se javlja kod 5% do 15% pacijenata [2]. Klinička slika je različita i zavisi od lokalizacije granuloma u nervnom sistemu. Klinički se može manifestovati na sledeće načine: mono- ili polineuropatija, neuropatija malih nervnih vlakana (engl. *small fiber sensory neuropathy - SFSN*), epileptični napadi, meningitis, lezije hipotalamusa ili hipofize, poremećaji u ponašanju, cerebelarna ataksija, promene u kognitivnom funkcionisanju (Tabela 1) [3]. Zlatni standard za postavljanje dijagnoze je biopsija tkiva, ali treba napomenuti da je to u praksi skoro nemoguće, posebno ako se sumnja da je lezija locirana u centralnom nervnom sistemu. U svakodnevnoj kliničkoj praksi, za dijagnostiku se koriste: klinička slika, magnetna rezonanca (MR) endokranijuma ili kičme, te prisustvo povišenih biomarkera za sarkoidozu u likvoru. Verovatnoća dijagnoze neurosar-

INTRODUCTION

Sarcoidosis is a granulomatous disease which may affect any organ. Although the most common symptoms are malaise and weakness, fatigue, non-productive cough, and swollen joints, the clinical presentation may vary significantly, depending on the distribution of the granulomas. If spontaneous remission does not occur (in around 30% of cases, depending on the population) [1], oral corticosteroids are first-line treatment, while in case of the chronic form, frequent recurrence, or the development of the extrapulmonary form of the disease, other therapeutic modalities may also be considered. In addition to the physical exam, for diagnosing the disease itself, as well as for following-up on the efficiency of the therapy, the following are also used: radiographic imaging (standard X-ray imaging, computed tomography, magnetic resonance imaging, positron emission tomography - depending on the form of the disease), biomarkers (angiotensin-converting enzyme – ACE), chitotriosidase (ChT), 24-hour urine calcium, as well as questionnaires on the quality of life.

CLINICAL PRESENTATION AND DIAGNOSTICS OF NEUROSARCOIDOSIS

Neurosarcoidosis occurs in 5% to 15% of patients [2]. The clinical presentation varies, and it depends on the localization of the granuloma in the nervous system. Clinically, it can manifest in the following ways: mono- or polyneuropathy, small fiber sensory neuropathy (SFSN), epileptic seizures, meningitis, lesions of the hypothalamus or the hypophysis, behavioral disorders, cerebellar ataxia, changes in cognitive functioning (Table 1) [3]. The gold standard for establishing a diagnosis is tissue biopsy, however, it should be noted that, in practice, this is almost impossible, especially when there is a suspicion that the lesion is located within the central nervous system. In everyday clinical practice, the following are used in establishing the diagnosis: clinical presentation, magnetic resonance imaging (MRI) of the endocranium or the spine, as well

Tabela 1. Učestalost kliničkih manifestacija neurosarkoidoze

Table 1. Frequency of clinical manifestations of neurosarcoidosis

Manifestacija / *Manifestation*	Učestalost / *Frequency*
Zahvaćenost kranijalnih nerava / *Involvement of cranial nerves*	31 – 55%
Hronični aseptični meningitis / *Chronic aseptic meningitis*	16 – 37%
Zahvaćenost kičmene moždine / *Spinal cord disease*	18 – 23%
Cerebralna parenhimska bolest / *Cerebral parenchymal disease*	21%
Hipotalamohipofizna zahvaćenost / *Hypothalamic-pituitary disease*	6 – 9%
Hidrocefalus / *Hydrocephalus*	9 – 10%
Cerebralna infarkcija / *Cerebral infarction*	6%
Zahvaćenost perifernog nervnog sistema / *Peripheral nervous system disease*	17%

koidoze, ukoliko su prethodno pomenuti rezultati pozitivni, veća je, ako pacijent već ima prethodno patohistološki potvrđenu sarkoidozu drugog organa [4,5]. Iako relativno retka forma sarkoidoze, neurosarkoidoza dovodi do značajnog narušavanja kvaliteta života i ima višu stopu mortaliteta i morbiditeta, te je neophodno što pre započeti lečenje.

TERAPIJSKI AGENSI

Lečenje neurosarkoidoze gotovo uvek zahteva medikamentoznu terapiju, ali se odluka o tipu leka i dozi bazira na stručnom mišljenju i retkim prospektivnim studijama [3,6]. Primena kortikosteroidne terapije i dalje predstavlja prvu liniju terapije, ali su doze koje se primenjuju više u odnosu na plućnu formu. Parenteralna primena visokih doza kortikosteroida je indikovana u slučajevima kada postoji jasna rapidna klinička progresija. Treba napomenuti da je neuspeh lečenja monoterapijom čest, jednim delom zbog težine same bolesti, a drugim delom zbog izraženih neželjenih efekata kortikosteroida [7,8]. U tim slučajevima, indikovana je primena, u drugoj liniji, nekih od preparata koji štede kortikosteroide, od kojih se najčešće upotrebljava metotreksat (engl. *methotrexate – MTX*). Studije su pokazale da kombinovana upotreba kortikosteroida i *MTX*-a dovodi do snižavanja potrebnih doza kortikosteroida, kao i do smanjenja broja recidiva [9,10]. Drugi često primenjivan lek je mikofenolat, koji je pokazao sličan pozitivan efekat kao *MTX* u kontroli bolesti, ali se pokazao kao inferiorniji u odnosu na tendenciju recidiva bolesti [10].

Inhibitori faktora nekroze tumora α (*TNF*-α) su dugo razmatrani kao terapijska opcija u lečenju različitih formi sarkoidoze. Monoklonalno antitelo infliksimab se pokazalo kao potencijalna treća linija u lečenju refraktarne sarkoidoze, te su saveti vodećih stručnjaka da se može koristiti i u lečenju neurosarkoidoze. Studije sprovedene u Francuskoj i u Sjedinjenim Američkim Državama su pokazale uspeh infliksimaba u lečenju neurosarkoidoze, čak i u slučajevima kada druga terapija nije bila uspešna [11,12]. Ipak, upotreba infliksimaba je dovela do značajnih komplikacija u vidu razvoja infekcija, toksičnih efekata lečenja i relapsa bolesti nakon obustave terapije. Retrospektivna studija sprovedena u Holandiji je takođe pokazala značajne komplikacije, ali je isto tako pokazala da potencijalno postoji korelacija između redukcije doze leka i recidiva bolesti (postepena redukcija doze je dovela do smanjene verovatnoće za recidiv bolesti) [13]. S obzirom na potencijalne komplikacije primene *TNF*-α inhibitora, kao i na ekonomski faktor (cena proizvodnje leka), osmišljeni su analozi *TNF*-α inhibitora, koji su pokazali slične pozitivne efekte, uz odsustvo toksiciteta [14,15]. Kod pacijenata

as the presence of elevated biomarkers for sarcoidosis in the spinal fluid. The probability of neurosarcoidosis, in case the above-mentioned results are positive, is higher if the patient already has previous pathohistologically confirmed sarcoidosis of another organ [4,5]. Although a relatively rare form of sarcoidosis, neurosarcoidosis leads to significant deterioration of the quality of life and it has higher mortality and morbidity rates, which is why it is necessary to start with treatment as soon as possible.

THERAPEUTIC AGENTS

The treatment of neurosarcoidosis almost always requires medicamentous therapy, however, the decision on the type of drug and its dose is based on expert opinion and rare prospective studies [3,6]. The application of corticosteroid therapy still represents first-line treatment for neurosarcoidosis, however, the applied doses are higher than the pulmonary form. Parenteral application of high doses of corticosteroids is indicated in cases where there is a clear rapid clinical progression of disease. It should be noted that unsuccessful monotherapy treatment is frequent, in part because of the severity of the disease itself, and in part due to pronounced adverse effects of the corticosteroids [7,8]. In these cases, the second-line application of certain steroid-sparing agents is indicated; among them the one most commonly used is methotrexate (MTX). Studies have shown that the combined use of corticosteroids and MTX leads to the decrease in the necessary doses of corticosteroids, as well as to the decrease in the number of recurrences [9,10]. Another frequently applied medicament is mycophenolate, which has shown a positive effect similar to MTX in controlling the disease, however, it has proven to be inferior to MTX with respect to the tendency of disease recurrence [10].

Tumor necrosis factor α (TNF-α) inhibitors were being considered for a long time as a therapeutic option in the treatment of different forms of sarcoidosis. Infliximab, a monoclonal antibody, has shown to be potential third-line therapy in the treatment of refractory sarcoidosis, which is why leading experts advise that it may be used in the treatment of neurosarcoidosis. Studies carried out in France and the United States of America have shown successful treatment of neurosarcoidosis with infliximab, even in cases where other treatment had been unsuccessful [11,12]. However, the application of infliximab has led to significant complications in the form of infections, toxic effects of the treatment, and recurrence of disease after treatment cessation. A retrospective study carried out in the Netherlands showed significant complications, as well, but it also showed that there is a potential correlation between drug dose reduction and disease recurrence (gradual

kod kojih je primena *TNF*-α inhibitora kontraindikovana, ili se ne postiže zadovoljavajući terapijski odgovor, može se koristiti rituksimab, kao odgovarajuća zamena [16,17,18].

U svakodnevnoj kliničkoj praksi, pojedine forme neurosarkoidoze predstavljaju poseban izazov za lečenje.

CEREBRALNA PARENHIMSKA BOLEST I HIDROCEFALUS

Relativno česta forma neurosarkoidoze karakteriše se granulomima u beloj masi mozga, koji, u zavisnosti od veličine, mogu imitirati sklerozne ploče, zone mikroishemije ili tumore. Ukoliko se granulomi nalaze na granici između komornih sistema, u samim komorama ili ukoliko zahvataju leptomeninge, može doći do razvoja hidrocefalusa [19]. Lokalizacija i veličina ovih granuloma može da dovede do različitih senzitivnih, motornih i/ili kognitivnih ispada, kao i do porasta intrakranijalnog pritiska. Moguća je i pojava epileptičnih napada, koji ukazuju na to da se radi o fulminantnom toku, te je, pored primene antiepileptika, neophodno i što pre započeti sistemsku terapiju. Prisustvo hematoencefalne barijere, čija permeabilnost otežava prodor velikom broju lekova, predstavlja poseban izazov u lečenju ove forme sarkoidoze. Ukoliko medikamentozna terapija ne dovede do povoljnog terapijskog odgovora, može se sprovoditi radioterapija u niskim dozama (do 20 Gy) [20]. Hirurško lečenje je moguće ukoliko dolazi do akutnog razvoja hidrocefalusa ili ukoliko je neurosarkoidoza rezistentna na medikamentoznu terapiju [19,21].

HIPOTALAMUSNO-HIPOFIZNA ZAHVAĆENOST

Prisustvo granuloma u hipotalamusno-hipofiznoj regiji daje kliničku sliku sličnu nesekretujućim tumorima ove regije. Granulomi vrše kompresiju i destrukciju okolnog nervnog i žlezdanog tkiva i dovode do sekundarnog hipotiroidizma, hipogonadotropnog hipogonadizma, panhipopituitarizma i sindroma neadekvatne sekrecije antidiuretskog hormona (engl. *syndrome of inappropriate antidiuretic hormone* (*ADH*) *secretion – SIADH*). Sekundarni hipotiroidizam nastaje zbog destrukcije bazofilnih tireotropnih ćelija usled inflamacije, te se posledično smanjuje produkcija tireostimulišućeg hormona (TSH) i smanjenja stimulacije tiroidne žlezde [22]. Destrukcija bazofilnih gonadotropnih ćelija dovodi do smanjenja sekrecije gonadotropin-oslobađajućeg hormona (engl. *gonadotropin-releasing hormone – GnRH*), ukoliko je oštećenje na nivou hipotalamusa ili do smanjenja sekrecije lutenizirajućeg hormona (LH) i folikul-stimulišućeg hormona (FSH), ukoliko je lezija u adenohipofizi. S obzirom na to da se sarkoidoza retko javlja u prepubertetskom i pubertetskom dobu, deficiti ovih hormona primarno dovode do neplodnosti [23].

reduction of the dose led to decreased probability of disease recurrence) [13]. Bearing in mind the potential complications of the application of TNF-α inhibitors, as well as the financial factor (price of drug production), analogues of TNF-α inhibitors were designed, which have shown similar positive effects, without toxicity [14,15]. In patients in whom the application of TNF-α inhibitors is contraindicated or in whom satisfactory therapeutic response is not achieved, rituximab may be used as the appropriate substitute [16,17,18].

In everyday clinical practice, individual forms of neurosarcoidosis are particularly challenging to treat.

PARENCHYMAL BRAIN DISEASE AND HYDROCEPHALUS

A relatively common form of neurosarcoidosis is characterized by granulomas in the white matter of the brain, which, depending on the size, may imitate sclerotic plaques, zones of micro-ischemia or tumors. If the granulomas are located on the borders of the ventricular systems, within the chambers themselves, or if they involve the leptomeninges, hydrocephalus may develop [19]. The localization and the size of these granulomas may lead to different sensory, motor, and/or cognitive disturbances, as well as to an increase in intracranial pressure. The occurrence of epileptic seizures, which indicate a fulminating course of the disease, is also possible, which is why, in addition to the administration of antiepileptic drugs, it is also necessary to start systemic treatment. The presence of the blood–brain barrier, whose permeability many drugs cannot easily penetrate, presents a particular challenge in treating this form of sarcoidosis. If medicamentous therapy does not lead to a favorable therapeutic response, radiotherapy may be applied in low doses (up to 20 Gy) [20]. Surgical treatment is possible if acute hydrocephalus develops, or if neurosarcoidosis is refractory to medicamentous therapy [19,21].

HYPOTHALAMO-HYPOPHYSEAL INVOLVEMENT

The presence of granulomas in the hypothalamo-hypophyseal region results in a clinical presentation that is similar to non-secreting tumors of this region. Granulomas perform compression and destruction of the surrounding nervous and glandular tissue, and they lead to secondary hypothyroidism, hypogonadotropic hypogonadism, panhypopituitarism, and the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH). Secondary hypothyroidism develops as the result of basophilic thyrotropic cell destruction, due to inflammation, consequently leading to the decrease in thyroid-stimulating hormone (TSH) production and to the reduction of thyroid gland stimulation [22]. The de-

Panhipopituitarizam se češće javlja kod makrogranuloma, i neophodna je hitna supstitucija, pre svega adrenokortikotropnog hormona (engl. *adrenocorticotropic hormone – ACTH*). Kako se u lečenju panhipopituitarizma nastalog usled sarkoidoze koriste i kortikosteroidi, rizik od nastanka Adisonove krize je relativno niži, u odnosu na drugu etiologiju panhipopituitarizma [24,25]. Sindrom neadekvatne sekrecije antidiuretskog hormona (engl. *syndrome of inappropriate antidiuretic hormone secretion – SIADH*) nastaje usled prisustva granuloma u neurohipofizi, i posledičnog smanjenja sekrecije vazopresina. *SIADH* dovodi do poliurije i razvoja insipidnog dijabetesa, kao i pojačanog gubitka natrijuma putem urina; hiponatrijemija često može da bude jedini simptom u neurosarkoidozi [26,27,28].

Svakako je naše mišljenje da, s obzirom na kompleksnost neuroendokrine osovine, u lečenju ove forme neurosarkoidoze uvek treba da učestvuju lekari više specijalizacija, kako bi se mogla paralelno vršiti adekvatna supstitucija hormona i supresija inflamacije, koja je u osnovi sarkoidoze.

NEUROPATIJA MALIH VLAKANA U SARKOIDOZI

Posebna forma neurosarkoidoze jeste neuropatija malih vlakana (engl. *small fiber neuropathy – SFN*), koja se manifestuje u vidu bolnih senzacija i parestezija. Važno je napomenuti da je dosadašnje lečenje *SFN*-a bazirano na primeni analgetika, s obzirom da kortikosteroidna terapija nije pokazala značajnije poboljšanje. Poslednjih nekoliko godina otkriven je efekat eritropoetina na zajedničke β receptore i receptore za reparaciju, a posebno na oporavak nervnih vlakana. ARA 290 je novi polipeptid koji predstavlja modifikovani eritropoetin sa izolovanim dejstvom antiinflamacije i reparacije tkiva, bez stimulacije hematopoeze. U toku su ispitivanja bezbednosti kod zdravih pojedinaca, pacijenata sa bubrežnom insuficijencijom, sarkoidozom i *diabetes mellitus*-om. Do sada, nisu pokazani značajniji neželjeni efekti. Studija sprovedena u Holandiji je, i pored značajnih ograničenja (mali uzorak, odsustvo patohistološke potvrde neuropatije malih vlakana, varijacije u kliničkoj prezentaciji), dala ohrabrujuće rezultate [29].

PSIHOLOŠKE PROMENE I ZAMOR U NEUROSARKOIDOZI

Psihološke promene, od kojih su najčešće depresija, anksioznost i poremećaj koncentracije, često se javljaju u svim oblicima sarkoidoze. U slučaju neurosarkoidoze, promene mogu biti posledica prisustva granuloma u sivoj masi prefrontalnog korteksa, dok se ne sme zaboraviti ni stres, koji prisustvo hronične bolesti izaziva [30,31]. Zamor predstavlja poseban problem, ne samo u neurosarkoidozi, već i u drugim formama bolesti,

struction of basophilic gonadotropic cells leads to the reduction of gonadotropin-releasing hormone (GnRH) secretion, if the damage is at the level of the hypothalamus, or to the reduction of the secretion of the luteinizing hormone (LH) and the follicle-stimulating hormone (FSH), if the lesion is in the adenohypophysis. Bearing in mind that sarcoidosis seldom occurs in the prepubescent or pubescent period, deficits in these hormones primarily lead to infertility [23]. Panhypopituitarism more frequently occurs in macro-granulomas and emergency substitution is necessary, primarily of the adrenocorticotropic hormone (ACTH). As corticosteroids are also used in the treatment of panhypopituitarism resulting from sarcoidosis, the risk of the development of an Addisonian crisis is relatively low, as compared to other etiology of panhypopituitarism [24,25]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) occurs as the result of the presence of granulomas in the neurohypophysis, and of the consequential reduction in vasopressin secretion. SIADH leads to polyuria and to the development of diabetes insipidus, as well as to increased sodium loss via urine; hyponatremia can be the only symptom of neurosarcoidosis [26,27,28].

It is quite definitely our opinion that, bearing in mind the complexity of the neuroendocrine axis, doctors of different specialties need to be involved in treating this form of neurosarcoidosis, so that parallel appropriate hormone substitution and inflammation suppression, which is at the heart of sarcoidosis, could be performed.

SMALL FIBER NEUROPATHY IN NEUROSARCOIDOSIS

Small fiber neuropathy (SFN) is a special form of neurosarcoidosis, which manifests in the form of painful sensations and paresthesia. It is important to note that treatment of SFN so far has been based on the application of analgesics, since corticosteroid therapy has not brough about significant improvement. In the past several years, the effect of erythropoietin on common β receptors and receptors for reparation, and particularly on the regeneration of nerve fibers, has been confirmed. ARA 290 is a new polypeptide, which represents modified erythropoietin with an isolated antiinflammation and tissue regeneration effect, without hematopoiesis stimulation. Testing of its safety in healthy individuals, patients with renal insufficiency, sarcoidosis, and diabetes mellitus is underway. Thus far, significant adverse effects have not emerged. A study carried out in the Netherlands has yielded encouraging results, despite significant limitations (a small sample, absence of pathohistological confirmation of small fiber neuropathy, variations in clinical presentation) [29].

sa visokom prevalencijom [32,33]. U cilju preciznijeg kvantifikovanja, kreirani su različiti upitnici za procenu kvaliteta života [34,35]. Pored samog razgovora sa pacijentom i preciziranjem problema, savetujemo i uključivanje psihologa ili psihijatra u dalje lečenje, kako bi se održao kvalitet života i poboljšala komplijansa pacijenata, s obzirom da lečenje zahteva vreme.

ZAKLJUČAK

Neurosarkoidoza predstavlja formu sarkoidoze koja značajno utiče na kvalitet života i povećava mortalitet kod pacijenata. Iako postoji veliki broj potencijalnih terapijskih protokola, njihova efikasnost i bezbednost je i dalje značajno varijabilna od pacijenta do pacijenta. Razvoj novih lekova (analozi *TNF*-α inhibitora, modifikovani eritropoetin), mogao bi da dovede do standardizacije druge, treće i četvrte linije lečenja neurosarkoidoze, ali je neophodno prethodno sprovesti sistematizovano istraživanje na većem uzorku, kako bi se jasno kvantifikovali pozitivni efekti i rizici. Pored razvoja nove medikamentozne terapije, svakako je neophodno multidisciplinarno lečenje, kako bi se što pre prevazišli defekti nastali usled lezija nervnog sistema.

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PSYCHOLOGICAL CHANGES AND FATIGUE IN NEUROSARCOIDOSIS

Psychological changes, the most common being depression, anxiety, and concentration problems, commonly occur in all forms of sarcoidosis. In the case of neurosarcoidosis, the changes may be the result of the presence of granulomas in the grey matter of the prefrontal cortex. At the same time, stress, caused by the presence of chronic disease, should also be taken into consideration [30,31]. Fatigue is a particular problem, not only in neurosarcoidosis, but in other forms of the disease as well, and it has a high prevalence [32,33]. For more precise quantification, different questionnaires regarding the quality of life have been designed [34,35]. In addition to talking to the patients and defining the problem more precisely, our advice is also involving a psychologist or psychiatrist in further treatment, in order to preserve the quality of life and improve patient compliance, as treatment requires time.

CONCLUSION

Neurosarcoidosis represents a form of sarcoidosis that significantly affects quality of life and increases patient mortality. Although there are numerous potential therapeutic protocols, their efficiency and safety still significantly vary from patient to patient. The development of new drugs (analogues of TNFα inhibitors, modified erythropoietin) may lead to the standardization of second-line, third-line, and fourth-line treatments for neurosarcoidosis, however, it is necessary to previously carry out systematic research on a larger sample, in order to clearly quantify the benefits and risks. In addition to the development of new medicamentous therapy, it is also necessary to apply a multidisciplinary approach to patient treatment, in order to overcome the defects resulting from nervous system lesions, as soon as possible.

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