REVIEW ARTICLES
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TREATMENT OF NEUROSARCOIDOSIS - INNOVATIONS AND CHALLENGES

TERAPIJA NEUROSARKOIDOZE – NOVINE I IZAZOVI

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Summary
Introduction: Sarcoidosis affects the central nervous system more frequently than it used to be believed. While the cranial nerves are most frequently affected, neurosarcoidosis can involve other nervous system tissues as well. **Treatment of Neurosarcoidosis**: Although a lot of drugs have proved useful in treating neurosarcoidosis, corticosteroids are still the gold standard in treatment of these patients. Therapeutic protocols differ regarding the dose of these drugs. Symptomatic neurosarcoidosis should always be treated with pulse corticosteroid therapy. People with diabetes, high blood pressure, osteoporosis and tuberculosis should be carefully monitored, as they are prone to complications associated with treatment with corticosteroids. In cases when treatment with corticosteroids does not show the desired results or therapy is discontinued due to the development of side effects, there are other pharmacologic options, such as methotrexate, mycophenolate mofetil, cyclophosphamide, chloroquine, azathioprine, thalidomide, and infliximab. It should be noted that the treatment response to the above mentioned regimens, except for infliximab, is relatively slow compared to corticosteroids; therefore, corticosteroids should be taken into account in all states and particularly in the acute phase of the disease. **Conclusion**: It is the existence of different forms of the disease, lack of local diagnostic criteria and different and non standardized therapy that makes the treatment of this disease difficult. Despite advances in pharmacotherapy and radiological diagnosis, it is necessary to develop better diagnostic strategies in order to set the optimal therapeutic approach.
Key words: Sarcoidosis; Drug Therapy; Central Nervous System Diseases; Diagnosis; Immunosuppressive Agents; Glucocorticoids + therapeutic use

Sažetak
Uvod. Sarkoidoza zahvata centralni nervi sistem češće nego što se ranije smatralo. Dok su kranijalni nervi najčešće pogođeni, neurosarkoidoza može zahvatiti i druga tkiva nervnog sistema. **Terapija neurosarkoidoze**. Iako se dosta lekova pokazalo korisnim u lečenju neurosarkoidoze, kortikosteroidi i dalje predstavljaju zlatni standard u lečenju ovih bolesnika. Terapijski režimi se razlikuju u pogledu doziranja lekova. Simptomatska neurosarkoidoza uvek se leči pulsnim dozama kortikosteroidne terapije. Osobe sa šećernom bolesti, povišenim krvnim pritiskom, tuberkulozom i osteoporozom treba pažljivo pratiti, pošto su sklone razvoju komplikacija u vezi sa terapijom kortikosteroidima. U slučajevima kada tretman kortikosteroidima ne pokazuje željene rezultate ili je terapija prekinuta zbog razvoja neželjenih efekata, postoje i druge farmakološke opcije, poput metotreksata, mikofenolat-mofetila, ciklofosfamida, hlorokina, azatioprina, talidomida i infliksimaba. Treba napomenuti da je na navedene terapijske režime, izuzev infliksimaba, terapijski odgovor relativno spor u odnosu na kortikosteroide – dakle kortikosteroidi treba da se uzmu o obzir u svim stanjima, naročito u akutnoj fazi bolest. **Zaključak**. Upravo postojanje različitih oblika ovog oboljenja, odsustvo dijagnostičkih kriterijuma i različita i nestandardizovana terapija čine lečenje ove bolesti težim. Uprkos napredovanjima u farmakoterapiji i radiološkoj dijagnostici, potrebno je razviti bolje dijagnostičke strategije kako bi se postavio što optimalniji terapijski pristup.
Ključne reči: Sarkoidoza; Terapija; Oboljenja centralnog nervnog sistema; Dijagnoza; Imunosupresivna terapija; Glukokortikoidi + terapija

Introduction

Sarcoidosis is a systemic granulomatous disease most frequently affecting the lungs and hilar lymph nodes. The lungs are affected in 90-95% of cases, while peripheral lymph nodes are affected

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Abbreviations

CNS	– central nervous system
MR	– magnetic resonance
PET	– positron emission tomography
MTH	– methotrexate
MMF	– mycophenolate mofetil
TNF	– tumor necrosis factor
RT	– radiotherapy

in 50-70% of cases. Nowadays it is known that sarcoidosis can affect any organ. Although the involvement of the nervous system is rather rare, it can lead to serious complications.

According to the literature data, clinically manifested neurosarcoidosis is presented in about 5-15% of patients with systemic sarcoidosis. However, it is difficult to state the exact number because of a large number of subclinical cases, i.e. cases without clearly evident symptoms. Autopsy studies have shown that only half neurosarcoidosis cases are diagnosed during lifetime. Sarcoidosis can affect any part of the nervous system, most frequently displaying symptoms by cranial nerves. Chronic form of neurosarcoidosis is particularly resistant to the applied medicament therapy [1,2,3]. Corticosteroid drugs are the first line therapy, but due to their side-effects and sometimes inadequate therapeutic response, other immunosuppresive drugs have frequently been used lately. This article has been aimed at explaining the choice of drugs, their efficiency and administration at our department.

Neurosarcoidosis Treatment

Both neurosarcoidosis and sarcoidosis are diagnosed according to the clinical and radiological findings (magnetic resonance of endocranium with contrast), laboratory findings (angiotensin-converting enzyme-ACE in liquor), histopathological confirmation, provided that all other possible causes of granulomatous inflammation have been previously excluded. The most reliable diagnostic procedure is certainly the nervous tissue biopsy, showing the presence of non caseating granuloma, although it is rarely applied in clinical practice. Basically there are three clinical forms of neurosarcoidosis where appropriate therapy should be concerned:

1) Patients with neurosarcoidosis confirmed by biopsy should be treated immediately in order to avoid permanent damage of the central nervous system (CNS).

2) Initiation of therapy must be taken into consideration when it is impossible to perform biopsy but the patients have magnetic resonance (MR) and positron emission tomography (PET) scan findings indicating neurosarcoidosis and confirmed systemic sarcoidosis, and particularly in cases when infection, neoplastic and other disorders can be excluded. In these cases the therapy can be 'diagnostic' as well if there is no remission of symptoms under the applied therapy, thus suggesting that neurosarcoidosis is rather improbable.

Immunosuppresive drugs such as corticosteroids can give temporary improvement even though it is not sarcoidosis but tuberculosis or lymphoma, for example. Therapy must be administered with caution and all its risk must be taken into account.

3) An asymptomatic patient with neurosarcoidosis proved by biopsy or some other noninvasive method presents a therapy dilemma. The decision to treat these patients is individual and it is based on the localization of lesion and its evolution during time and the risk from the therapy [3, 4].

Although many drugs have been proved to be useful in neurosarcoidosis treatment, corticosteroids still present the golden standard in treatment of these patients. Therapy regimens differ regarding dosing of these drugs. Symptomatic neurosarcoidosis is always treated with pulse corticosteroid therapy. The patients with diabetes, hypertension, tuberculosis and osteoporosis should be carefully followed since they are prone to complications resulting from corticosteroid therapy. In cases when corticosteroid therapy does not give desired results or the therapy has been discontinued due to the development of side–effects, there are other pharmacological options, such as methotrexate, mycophenolate mofetil, cyclophosphamide, chloroquine, azathioprine, thalidomide and infliximab. It should be noted that the therapeutic response to the above mentioned regimens, except for infliximab, is relatively slow compared to corticosteroids; therefore, corticosteroids should be taken into account in all states and particularly in the acute phase of the disease [5].

Methotrexate (MTH), analogous to folic acid, is most frequently used in neurosarcoidosis therapy. To treat sarcoidosis, MTH can be used independently or as a therapy agent "saving", i.e. reducing the required doses of pronison in treatment of some of its clinical forms. The precise mechanism of MTH effect in sarcoidosis treatment has not been clarified so far. MTH acts as an inhibitor of growth and functions of different cell populations, as well as a specific modulator of cytokines and their production and proliferation of fibroblast. In this way methotrexate shows its anti-inflammatory effect. Lower et al. [6] found that 61% of patients treated by MTH as a replacement for corticosteroid therapy responded adequately to the treatment. When combined with corticosteroids to treat neurosarcoidosis, MTH reduces the necessary dose of prednisone by half, thus reducing the long-term side-effects of corticosteroids. MTH is a well tolerated drug, but it requires regular check-up of complete blood count and liver function before the initiation of therapy and during the treatment in order to avoid blood dyscrasia and hepatotoxicity. It is necessary to point out that the positive effects of MTH can be noticed only with cumulative dose, i.e. after at least six months of

treatment. The positive response to MTH therapy has been described in numerous studies and it varies from 60 to 80% of patients. The most serious complication of MTH therapy is its hepatotoxicity. This complication can sometimes be irreversible. The risk certainly increases with the existence of previous liver damage that a patient may have before MTH therapy. The risk of development of hepatotoxicity effects is increased with the existence of diabetes mellitus, alcohol use and obesity. Hepatotoxic effects of MTH are increased with a cumulative dose exceeding 5 grams or in the presence of a kidney disorder, i.e. renal insufficiency. Serum transaminases (aspartate transaminase – AST and alanine transaminase – ALT) must be checked every 6-8 weeks during the therapy. A moderate increase in serum transaminases can be noticed in 30% of the patients on average.

It is usually not necessary to discontinue MTH therapy in these patients because the increased transaminases get normalized spontaneously. However, some patients still require a MTH dose reduction. In case of elevated serum transaminase values in patients with sarcoidosis, liver sarcoidosis must be excluded as a possible cause of transaminase elavations prior to the initiation of therapy.

It is known that sarcoidosis, being a multisystem disease, can affect liver as well, which is manifested in increase of liver enzymes in serum. Simultaneously, 1 mg dose of folic acid a day is recommended in order to prevent macrocytic anemia and possible abnormalities in the liver function, gastrointestinal intolerance and cardiovascular disorders due to the increase in homocysteine concentration in plasma [7,8].

Mycophenolate mofetil (MMF) is an inhibitor of monophosphate dehydrogenase, the enzyme necessary in purine synthesis and weakening of T and B proliferation. It was used before in cutaneous and gastrointestinal sarcoidosis treatment. Recently MMF has proved to be an efficient and well tolerated drug in neurosarcoidosis treatment [9].

Cyclophosphamide is mainly used in severe forms of neurosarcoidosis. In the study performed in 7 patients with neurosarcoidosis treated by cyclophosphamide, the clinical response was recorded in four patients, which was documented by the improvement on images made by MR or by examination of cerebrospinal liquor [10].

Azathioprine is another cytotoxic agent used in sarciodosis treatment. Although its toxicity is similar to MTH toxicity, azathioprine is considered to be significantly potent immunosuppressive agent in treatment of many disorders caused by immune response disorders. The biggest restriction in azathioprine therapy is its potential carcinogenicity. Azathioprine has strong immunosuppressive effect on inflammatory cells (lymphocytes, neutrophils, macrophages,). Muller- Quernheim et al. [11] have demonstrated supreme effects of azathioprine on the increased values of tumor necrosis factor (TNF) from alveolar macrophages in patients with active sarcoidosis. The recommended dose of azathioprine is 2-3 mg/kg. Patients with methyltransferase deficiency have a significantly increased risk for developing neutropenia during azathioprine therapy. Neutropenia is also the most serious toxic effect of azathioprine and is certainly dependant on the total dose of the applied therapy. Regular checking of complete blood count is recommended, i.e. white blood cells, every two to three months in the patients on regular azathioprine therapy. Feeling of nausea and fatigue frequently appear during azathioprine therapy. In a controlled study aimed at giving comparative effects of azathioprine therapy and MTH in the patients with sarcoidosis, azathioprine was significantly more frequently associated with the side-effects displayed by gastrointestinal system [12]. It is not surprising that the feeling of nausea is dependent on the applied dose of azathioprine. Although the toxic effects related to liver or pancreas are rare in azathioprine therapy, regular check-ups of the liver function are recommended. Since regular blood analyses are necessary in this group of patients, simultaneous checking of liver enzymes is also recommended. Carcinogenic effects of azathioprine therapy remain its biggest problem. Studies dealing with organ transplantation issues showed a significantly increased risk of malignancy in patients on azathioprine therapy. The risk is particularly expressed in patients on triple immunosuppressive therapy. On the other hand, studies performed in order to follow the patients on this therapy, but without previous organ transplantation, showed no increased risk of developing malignancy although these patients had been on azathioprine therapy for several years. The efficiency of azathioprine is different in treatment of sarcoidosis patients. In their study, Müller-Quernheim et al. described 11 patients with sarcoidosis who had positive response to therapy, and only three of them had relapse of disease after discontinuation of therapy [12]. On the other hand, Lewis et al. reported positive response in only two out of nine treated patients [13]. Literature data on the efficiency of azathioprine usually state that two thirds of patients have positive response to this therapy. There are no controlled studies on azathioprine efficiency in relation to methotrexate in patients with chronic sarcoidosis. In one study on uveitis associated with sarcoidosis, MTH was the first cytostatic drug used in therapy. The efficiency of this therapy was observed in 36 out of 53 patients; the patients who did not respond to MTH therapy continued azathioprine treatment (21 patients). Only six patients (29%) from the group without the positive therapy response to MTH, responded favorably to mono azathioprine therapy [14, 15].

Chloroquine and hydroxychlorine, which belong to a group of anti-inflammatory drugs, have also shown the efficiency in sarcoidosis treatment.

In a study [16] performed on 12 treated patients, 10 out of 12 of those who had not responded to corticosteroid therapy showed either improvement or stabilization of symptoms. The biggest problem in using this therapy is its ocular toxicity. The toxicity is cumulative and usually reversible. Routine ophthalmologic check-ups are recommended to all patients on this therapy. Less frequent toxic effects of this therapy are skin changes (rash) as well as hepatotoxicity. The inhibition of cytokine release from the alveolar macrophages underlies the anti-inflammatory effect of this therapy. This includes the release of TNF, although other cytokines can be inhibited by the effect of these drugs. The inhibition effect of cytokine release depends on the dose and, accordingly, the described therapy is more efficient where the accumulation of the drug is more intense, e.g. in the skin. In a randomized study on chronic lung sarcoidosis [17], all patients were initially treated with high doses of chloroquine (750 mg a day), and the resulting clinical response was favorable. After these high doses, the patients were divided into two groups, so the first group received low doses of 250 mg a day or they had no therapy. All the patients with sarcoidosis from the group which had been treated by morbostatic doses of chloroquine, had significantly lower number of clinical relapses of disease, i.e. a low percentage of aggravation at the end of this study. This drug has also proved to be very successful in neurosarcoidosis treatment. Here the percentage of improvement is certainly not so dramatically high. One of the possible explanations is low drug concentration in the brain tissue and the lungs in relation to the skin [18].

The aforementioned statements on sarcoidosis therapy suggest that TNF suppression may have a significant role in sarcoidosis treatment. Three known anti-TNF agents used in treatment of immunologically caused diseases in the United States are: antagonist of TNF receptors–etanercept and monoclonal antibodies such as infliximab and adalimumab. The effect mechanism of anti-TNF agents has been studied in other diseases, not exactly in sarcoidosis. Etanercept, being a soluble TNF receptor, binds from the circulation with free TNF, thus preventing TNF from binding with the cell receptors and their activation as well. Infliximab and adalimumab are monoclonal antibodies binding to free TNF in the circulation. Infliximab and adalimubab have the ability of binding even to the surface of cells releasing TNF. Binding is done via immunoglobulin G (IgG) antibodies and may lead to cell lysa. Infliximab was first used in the therapy of refractory lung and skin sarcoidosis in 2001 [19]. Since then there have been numerous published studies reporting the positive effect of infliximab applied to treat not only lung and skin sarcoidosis, but also chronic eye sarcoidosis, upper respiratory airways and muscle sarcoidosis. Etanercept has not proved so efficient in sarcoidosis treatment.

There are more studies dealing with this subject which show modest results in sarcoidosis treatment achieved by this agent. These studies only confirm the equality of placebo response and this therapy agent [20]. Experience is similar in the therapy of Crohn's disease and other inflammatory diseases. The real reason for achieving high concentrations of this drug in circulation may be its intravenous administration, as is the case with infliximab. Toxic effects of anti-TNF therapy are caused by the reaction on the protein component of therapeutics. Etanercept and adalimumab are applied subcutaneously, so here the reaction is local on the application site. Infliximab is applied intravenously so the reactions such as anaphylaxis may be expected. All the above mentioned therapy agents are associated with the increased risk of infection development. The highest risk is the development of granulomatous infections, especially tuberculosis and histoplasmosis. The risk of developing tuberculosis infection is significantly higher in patients treated by infliximab than in those treated by etanercept [21]. In the last ten years, several studies have been performed on infliximab application in neurosarcoidosis treatment and its efficiency in patients who do not respond to corticosteroid therapy [22, 23]. In the sample of ten patients with sarcoidosis, infliximab alleviated the symptoms in 9, including two patients with neurosarcoidosis [24]. Vital capacities improved significantly in 138 patients with chronic lung sarcoidosis [25]. Other studies have shown clinical efficiency of infliximab in patients with cyclophosphamide refractory neurosarcoidosis [26]. Seven patients with refractory neurosarcoidosis treated by combination of MMF and infliximab had clinical improvement without complications [27]. In addition, infliximab can also be used for urgent stabilization of patients with severe condition or in patients with neurosarcoidosis aggravated due to unsuccessful treatment with high doses of corticosteroids [28]. When pharmacotherapy fails in treatment and/or side-effects cannot be tolerated, the alternative treatment is radiotherapy (RT) of CNS. RT functions on the principle of locating and destroying the cells, such as macrophages and lymphocytes which are directly involved in granuloma forming and which are metabolically active. Recent studies have shown minimal and moderate efficiency of RT in persistent sarcoidosis of CNS. In the biggest study performed so far, researchers treated four patients with neurosarcoidosis resistant to pharmacotherapy by radiotherapy. The complete remission of most of the symptoms was achieved in one patient, and the partial and minimal remission was achieved in two patients and one patient, respectively [29]. In another study, two out of three patients treated by RT had almost complete remission of symptoms [30]. Since the patients in all previous treatments received different doses of gray (Gy) during radiation, the comparison of radiation doses was not possible. Further research is

necessary which would be oriented towards the optimal RT strategy. As mentioned before, the histopathological finding of the involved tissue remains the gold standard in neurosarcoidosis diagnostics. From the therapeutic standpoint, neurosurgery is indicated only when pharmacology is without effect, or in patients with urgent or life threatening conditions. Complications, such as severe hydrocephalus and increased intracranial pressure, can be treated by ventriculoperitoneal shunt. Afterwards, surgical resection of the white mass may be taken into consideration in life threatened patients [31].

Conclusion

It is the variety of forms of this disease, the absence of diagnostic criteria and different and non standardized therapy that make this treatment difficult. In our country, there is a lack of controlled studies on the treatment of these patients, particularly on the application of new immunosuppressive drugs. In spite of advances in pharmacology and radiology, it is necessary to develop better diagnostic strategies in order to set optimal therapeutic approach.

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