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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Neurosarcoidosis – an ever-present clinical challenge

Mihailo Stjepanović[1,2], Ivana Buha[1], Nikola Marić[1], Slobodan Belić[1], Mirjana Stjepanović[3], Sanja Dimić-Janjić[1,2], Marko Baralić[4], Milica Stojković-Lalošević[5], Dragana Bubanja[6], Violeta Mihailović-Vučinić[1,2]

[1]Clinical Center of Serbia, Clinic for Pulmonology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Dr. Laza Lazarević Special Psychiatric Hospital, Belgrade, Serbia;
[4]Clinical Center of Serbia, Clinic for Nephrology, Belgrade, Serbia;
[5]Clinical Center of Serbia, Clinic for Gastroenterology, Belgrade, Serbia;
[6]Clinical Center of Kragujevac, Internal Clinic, Kragujevac, Serbia

SUMMARY
Sarcoidosis afflicts the central nervous system more frequently than previously believed. Neurological symptoms are present in roughly one-half of patients, and depend on the location in the central nervous system. The probability of spontaneous regression is significantly less when compared to other forms of sarcoidosis, which means that the proper diagnosis and treatment is paramount. Even when properly treated, functional defects are not uncommon. Majority of these patients require immunomodulating drugs and continuous follow-up. New immunomodulating drugs, especially biological agents, have shown to be significantly more effective, with fewer side effects, and are important when corticosteroids could not be applied. Less invasive methods, such as cerebrospinal analysis, help greatly in the diagnostics procedure, and require further research and improvement.
Keywords: sarcoidosis; neurosarcoidosis; cerebrospinal liquid; diagnostics; treatment

INTRODUCTION

Even though it has been over a century since sarcoidosis was first discovered, it remains a disease of unknown etiology and course. Sarcoidosis is a systemic granulomatous disease which, most commonly, afflicts the lungs and hilar lymph nodes. The lungs are afflicted in 90–95% of all cases, and peripheral lymph nodes in 50–70%. In patients with systemic sarcoidosis, even though nervous system is rarely afflicted (5–15%), in those cases it can lead to serious complications and even death. The exact percentage is difficult to determine since there is a large number of subclinical cases, which are discovered only on autopsies. Neurological symptoms are present in roughly one-half of the patients. The characteristics vary greatly, depending on the distribution and inflammation of certain parts of the nervous system. The spontaneous regression of the disease is significantly less probable compared to the acute form of sarcoidosis, so the neurological symptoms are something that should always be checked for and treated [1, 2, 3].

WHEN TO SUSPECT NEUROSARCOIDOSIS?

Sarcoidosis granuloma can be present in any part of the nervous system, which leads to a wide array of neurological symptoms. Possible manifestations of neurosarcoidosis are as follows: affliction of the cranial nerves, small fiber neuropathy, seizures, meningitis, lesions of the cranial tissue, tumor-like symptoms, disfunction of the hypothalamus and the pituitary gland, cerebellar ataxia, spinal cord lesions, skeletal muscles diseases, and psychiatric disorders.

The most common manifestation of neurosarcoidosis, present in 50–75% of all cases, is some form of cranial nerve disorder. Depending on which and how many of the cranial nerves are afflicted, the clinical presentation varies. The disfunction of the nerve can be caused by different pathological processes, such as granulomatous infiltration of the nuclei of the specific nerves, the increase of the intracranial pressure or by meningitis (damaging the subarachnoid part of the nerve). Sorting by the frequency of affliction, the unilateral affliction of the facial nerve is the most common presentation, followed by *n. opticus* with scotoma [4, 5]. Approximately 15% of patients with neurosarcoidosis have peripheral neuropathy, caused by the damage of either the large or small neural fibers. If large neural fibers are damaged, the patient will have mononeuritis, polyneuritis, Landry or Guillain–Barré syndrome. However, if small neural fibers are damaged, the patient can have restless legs syndrome or other disorders related to movement of the legs, as well as the loss of sensibility for pain or temperature, and autonomous disfunction [4]. Sudden onset of seizures in patients with sarcoidosis calls for a detailed examination of the central nervous system, and these patients, unfortunately, have

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Correspondence to:
Mihailo STJEPANOVIĆ
Clinical Center of Serbia
Clinic for Pulmonology
Koste Todorovića 26/20
11000 Belgrade, Serbia
mihailostjepanovic@gmail.com

poorer outcome with a fulminant course of the disease. Seizures, present in 5–10% of patients with neurosarcoidosis, show the severity, progression, and the relapses of the disease. Meningeal affliction is, according to the literature, a common location of neurosarcoidosis, and can be present in up to 25% of all the patients. Symptoms are similar to meningitis caused by other agents, and can include fever, headache, and stiffness of the neck. Lymphocytic pleocytosis can be found in cerebrospinal fluid (CSF), and the biochemical analysis shows the elevated values of proteins. Acute meningitis has a good response to corticosteroid treatment, but the chronic form requires a prolonged period of treatment and the outcome is difficult to predict. Roughly 50% of the patients can develop some form of brain lesions, such as encephalopathy, lesions of the gray mass, or lesions of the hypothalamus. The main mechanism of development of these lesions is the presence and fusion of multiple granulomas in the brain. Tumor lesions develop similarly; however, the fused granuloma are bigger, and clinically simulate any other tumor mass in the central nervous system [6]. Neurosarcoidosis has shown to have an affinity for the base of the brain, and 10–15% of all the patients develop neuro-endocrine symptoms due to the lesions of the hypothalamus and the pituitary gland, most commonly as a cause of infiltration in the third brain ventricle. One of the most frequent manifestations are polyuria with polydipsia, due to either diabetes insipidus or dysregulation of antidiuretic hormone. Hypovolemia, chronic hyponatremia, and unregulated thirst can also be present. Dysregulation of prolactin, with its elevation, can also be found in these patients, and can lead to galactorrhea and amenorrhea. Secondary hypogonadotropic amenorrhea with normal levels of prolactin has also been noted [7]. Cerebellum is rarely afflicted with sarcoidosis and, when afflicted, it is difficult to differentiate the symptoms from the symptoms caused by the lesions of the spinal cord. Spinal cord lesions are present in less than 10% of patients with neurosarcoidosis. Depending on the location of the granuloma (extradural, intradural, or intramedullary), the clinical presentation varies. It should be noted that it can be difficult to differentiate the granuloma from leptomeningeal tumors or infections. Cervical and thoracic parts of the spine are most commonly afflicted. The prognosis is unfavorable, and the symptoms at the beginning are muscular weakness and paresthesia. Skeletal muscles are afflicted in 1.4–2.3% of all patients with neurosarcoidosis; however, up to 80% of these patients have no clinical symptoms. The types of afflictions in these patients are acute, nodular, and chronic myopathy, which is the most common [8]. Up to 20% of patients with neurosarcoidosis develop cognitive and behavioral symptoms. The cause can be twofold – either by development of granuloma in the gray matter, or by psychological stress caused by having a chronic, relapsing, or progressive form of the disease. Psychiatric disorders present in these patients are hallucinations, refractory psychosis, paranoid psychosis, and delirium. Aphasia, amnesia, and dementia can also be present. In some rare cases, schizophrenia, depression, and bipolar disorders can develop [9].

HOW TO DIAGNOSE NEUROSARCOIDOSIS

The biopsy of the central nervous system is the most precise, albeit not the most practical, way to definitively confirm the diagnosis. Zajicek has given the diagnostic criteria which are still being used [10]. The criteria are based on the levels of security of diagnosis, and the categories include the clinical presentation of neurosarcoidosis and exclude others. The criteria for definitive diagnosis: a positive biopsy of the nervous system. The criteria for possible neurosarcoidosis: clinical symptoms and diagnosis pointing to neurosarcoidosis; however, infections or malignancies are not excluded and the patient has histological conformation of sarcoidosis of other organ(s). The criteria for probable neurosarcoidosis: clinical symptoms and diagnostical evaluation pointing to neurosarcoidosis. The alternative diagnosis is excluded and there is a histological conformation of systemic sarcoidosis [10, 11].

Nuclear magnetic resonance (MRI) is the preferable method for radiological conformation of the disease. Any patient with a suspicion for neurosarcoidosis is suggested to perform the MRI scan of the endocranium. The normal finding does not exclude the diagnosis, especially if the patient is on corticosteroid treatment. Positron emission tomography (PET) scan can also be performed, although the interpretation is relatively difficult. Elevated metabolism is attributed to the inflammation in sarcoidosis, and the decreased metabolism is caused by the dysfunction of the neurons. Despite the limitations, PET scan can detect lesions in patients with no suspicion for neurosarcoidosis, or can be used to check the treatment response [12, 13].

ANALYSIS OF THE CEREBROSPINAL FLUID

CSF analysis, which is considered a relatively noninvasive method, can provide a great deal of data to confirm the diagnosis. Lymphocytic pleocytosis, elevated protein levels, decreased levels of glucose, and elevated pressure are nonspecific signs of neurosarcoidosis. Elevated immunoglobulins, lysosomes, and β_2 microglobulin, as well as the ratio of CD4+/CD8+ over 5 can also be found in these patients. Elevated values of angiotensin converting enzyme (ACE) is something that can lead to the diagnosis of neurosarcoidosis. The publications so far have shown that over 60% of patients with neurosarcoidosis have elevated levels of ACE. However, it is not enough for a definitive diagnosis. Studies show that the chitotriosidase can be used as a new biomarker [14, 15]. A publication which analyzed the CSF in patients with neurosarcoidosis and multiple sclerosis (MS) has shown that the elevated values of IL-6 and CD4/CD8 ratio were statistically more significant in patients with neurosarcoidosis [16]. It was interesting to find that IL-6 in CSF was higher in patients with the active form of neurosarcoidosis compared with those with the inactive form, and that the patients with concentration of IL-6 above 50 pg/ml in CSF have shown to have a higher probability of reactivation or progression of the disease. The same publication has shown that the

concentration of IL-10 can also be elevated in neurosarcoidosis [16]. Another study tested the levels of IL-2 in CSF as a diagnostic and biomarker of activity in neurosarcoidosis [17]. In this study, the CSF was taken from patients with neurosarcoidosis, MS, neurotuberculosis, viral and bacterial meningitis, cerebral lymphoma, Guillain–Barré syndrome, and 115 patients with non-inflammatory neurological diseases as a control group. IL-2 concentration was related to the clinical activity of the disease, increased uptake of gadolinium, and the number of leucocytes in patients with neurosarcoidosis. It was discovered that IL-2 is elevated in patients with neurosarcoidosis; however, it was not specific enough. IL-2 in CSF can be used in order to differentiate between neurosarcoidosis and MS, and can be used in order to determine the activity of the disease [17].

THE BEST TREATMENT?

Even though a great number of drugs have shown a positive response in treatment of neurosarcoidosis, corticosteroids, administered in a pulse dosage, still remain the golden standard. If remission is not achieved, or the clinical response on corticosteroids is not given, the application of another immunomodulator is the next treatment step – methotrexate, hydroxychloroquine, azathioprine, or cyclophosphamide. In severe forms of neurosarcoidosis, which are resistant to any and all pharmacological treatments, radio treatment, and even surgery, can be performed. Since tumor necrosis factor (TNF) is being produced within granuloma, anti-TNF drugs can be used in the treatment of sarcoidosis. The treatment with infliximab and adalimumab have shown promising results, and there are studies which test other monoclonal antibodies. However, there is still a great need for further clinical trials and experience with these treatments [18, 19].

CONCLUSION

Neurosarcoidosis is an uncommon but significant clinical manifestation of sarcoidosis. There is a significant variation in clinical presentation of this form of the disease, depending on the location of the granuloma in the nervous system. The probability of spontaneous resolution is less than that in other forms of sarcoidosis, with functional deficits remaining long after remission is achieved. Due to previously noted characteristics, patients with neurosarcoidosis require immunosuppressive treatment and long-term follow-up. The variation in presentation, similarity to other diseases, and complexity of treatment are key points that require a multidisciplinary approach in diagnostics and treatment of this disease.

The development of less invasive methods, such as the analysis of CSF, can provide a quicker and easier way to the final diagnosis, and should be further developed.

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Неуросаркоидоза – и даље велики клинички изазов

Михаило Стјепановић[1,2], Ивана Буха[1], Никола Марић[1], Слободан Белић[1], Мирјана Стјепановић[3], Сања Димић-Јањић[1,2], Марко Баралић[4], Милица Стојковић-Лалошевић[5], Драгана Бубања[6], Виолета Михаиловић-Вучинић[1,2]

[1]Клинички центар Србије, Клиника за пулмологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Клиника за психијатрију „Др Лаза Лазаревић", Београд, Србија;
[4]Клинички центар Србије, Клиника за нефрологију, Београд, Србија;
[5]Клинички центар Србије, Клиника за гастроентерологију, Београд, Србија;
[6]Клинички центар Крагујевац, Интерна клиника, Крагујевац, Србија

САЖЕТАК

Саркоидоза захвата централни нерви систем чешће него што се раније сматрало. Неуролошки симптоми се манифестују код отприлике половине оних са неуросаркоидозом. Клиничке и сликовне карактеристике неуросаркоидозе варирају у великој мери, а пре свега зависе од анатомске дистрибуције болести. Сама вероватноћа да се неуросаркоидоза спонтано повуче много је нижа неко код акутних форми саркоидозе. Зато посебно треба обратити пажњу на неуролошке симптоме и по постављању дијагнозе болест одмах лечити. Вероватноћа да се спонтано разреши нижа је него код саркоидозе уопште, а заостали функционални дефицит није реткост. Стога су већини болесника са неуросаркоидозом потребни имуносупресивна терапија и континуирано праћење. Међутим, други имуносупресивни агенси, као и новији биолошки агенси, показали су се као ефикасна, добро подношљива терапија која је нарочито значајна у случајевима кад се кортикостероиди не могу примењивати. Развијање мање инвазивних метода, као што је анализа цереброспиналне течности код оболелих од неуросаркоидозе, свакако је нешто што умногоме може олакшати пут клиничару до дијагнозе, и треба да представља предмет даљих истраживања.

Кључне речи: саркоидоза; неуросаркоидоза; ликвор; дијагностика; лечење