CURRENT TOPIC / АКТУЕЛНА ТЕМА

Neurosarcoidosis – an ever-present clinical challenge

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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, dysfunction 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–Barre 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...
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 diagnosis 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 β2 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 neurosarco-
coidosis [16]. Another study tested the levels of IL-2 in CSF
as a diagnostic and biomarker of activity in neurosarco-
coidosis [17]. In this study, the CSF was taken from patients
with neurosarcooidosis, MS, neotuberculosis, viral and
bacterial meningitis, cerebral lymphoma, Guillain–Barré
syndrome, and 115 patients with non-inflammatory neu-
rological 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 pa-

tients with neurosarcooidosis. It was discovered that IL-2 is
elevated in patients with neurosarcooidosis; however, it was
not specific enough. IL-2 in CSF can be used in order to
differentiate between neurosarcooidosis 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 posi-
tive response in treatment of neurosarcooidosis, cortico-
steroids, administered in a pulse dosage, still remain
the golden standard. If remission is not achieved, or the clini-
cal response on corticosteroids is not given, the applica-
tion of another immunomodulator is the next treatment
step – methotrexate, hydroxychloroquine, azathioprine,
or cyclophosphamide. In severe forms of neurosarcooid-
osis, 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 sarcooidosis. The treatment with infli-
imab 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

Neurosarcooidosis is an uncommon but significant clinical
manifestation of sarcooidosis. There is a significant varia-
tion 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 sarcooidosis, with functional
deficits remaining long after remission is achieved. Due to
previously noted characteristics, patients with neurosar-
coidosis 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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REFERENCES

1. Škodrić-Trifunović V, Vučinić V, Simić-Ogrizović S, Stević R,
štepanović M, ilić K, et al. Mystery called sarcooidosis- forty-four
years follow up of chronic systemic disease. Srp Arh Celok Lek.
2012;140(11–12):768–71.
2. Štjepanović M, Milhailović-Vučinić V, Spasovski V, Milin-Lazovic
J, Škodrić-Trifunović V, Stanković S, et al. Genes and metabolic
pathway of sarcooidosis: identification of key players and risk
modifiers. Arch Med Sci. 2019;15(5):1138–46.
3. Štjepanović M, Milhailović-Vučinić V, Mašković J, Ćolović N,
Gvozdenović B, Stojković-Lalošević M, et al. Alcohol use and
clinical manifestation of tuberculosis. Srp Arh Celok Lek.
2018;146(1–2):110–1.
4. Webb L, Chen J, Aksamit A, Bhattacharyya S, Chwalisz B, Balaban
D, et al. A multi-center case series of sarcoptic optic neuropathy. J
Neurol Sci. 2021;420:117282.
5. Tanyıldız B, Doğan G, Zorlutuna Kaymak N, Tezcan ME, Kılıç AK,
Şenver Comert S, et al. Optic Neuritis and Macular Ischemia
Associated with Neurosarcooidosis: A Case Report. Turk J
Ophthalmol. 2018;48(4):202–5.
6. Crawford F, Alvi SA, Brahmaj B, Byrne R, Kocak M, Wiet RM.
Neurosarcooidosis Presenting as Isolated Bilateral Cerebellopontine
Angle Tumors: Case Report and Review of the Literature. Ear Nose
Throat J. 2019;98(8):NP120–NP124.
7. Crossley J, Aminpour N, Jay A, Harris B, Hoa M.
Neurosarcooidosis Directly Involving the Cervical Vagus Nerve. Ann
Otol Rhinol Laryngol. 2021;130(2):215–8.
8. Lord J, Paz Soldan MM, Galli J, Salzman KL, Kresser J, Bacharach
R, et al. Neurosarcooidosis: Longitudinal experience in a single-
center, academic healthcare system. Neurol Neuroimmunol
eurinflamm. 2020;7(4):e743.
9. Voortman M, De Vries J, Hendriks CMR, Efferich MDP. Wijnen
PAHM, Drent M. Everyday cognitive failure in patients suffering
from neurosarcooidosis. Sarcooidosis Vasc Diffuse Lung Dis.
2019;36(1):2–10.
10. Caçao G, Branco A, Meireles M, Alves JE, Mateus A, Silva AM, et
al. Neurosarcooidosis according to Zajicek and Scolding criteria:
15 probable and definite cases, their treatment and outcomes. J
Neurol Sci. 2017;379:84–8.
11. Stjepanović M, Milhailović-Vučinić V, Jovanović D, Mijailović M,
Škodrić-Trifunović V, Stjepanović M. Diagnosis of neurosarcooidosis-
necessity of biopsy. Med Pregled. 2014;67(3–4):97–9.
12. Stjepanović M, Milhailović-Vučinić V, Jovanović D, Mijailović M,
Škodrić-Trifunović V, Videnović-Ivanov J. Radiological presentation
of neurosarcooidosis. Med Pregled. 2014;67(1–2):24–7.
13. Dorman J, Warrior L, Pandya V, Sun Y, Ninan J, Trick W, et al.
Neurosarcooidosis in a public safety net hospital: a study of 82
cases. Sarcooidosis Vasc Diffuse Lung Dis. 2019;36(1):25–32.
14. Popević S, Šumarac Z, Jovanović D, Babić D, Stjepanović M,
Jovičić S, et al. Verifying sarcooidosis activity: chitotriosidase
versus ace in sarcooidosis – a case-control study. J Med Biochem.
2016;35(4):390–400.
15. Milhailović-Vučinić V, Popević Lj, Popević S, Stjepanović M, Aleksić
A, Stanojević-Paovic A. Utility of angiotensin-converting enzyme
activity in aqueous humor in the diagnosis of ocular sarcooidosis.
Indian J Ophthalmol. 2017;65(10):979–83.
16. Chazal T, Costopoulos M, Mallart E, Pleury C, Psimaras D, Legendre
P, et al. The cerebrospinal fluid CD4/CD8 ratio and interleukin-6

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www.srpskiarhiv.rs
and -10 levels in neurosarcoidosis: a multicenter, pragmatic, comparative study. Eur J Neurol. 2019;26(10):1274–80.

17. Otto C, Wengert O, Unterwalder N, Meisel C, Ruprecht K. Analysis of soluble interleukin-2 receptor as CSF biomarker for neurosarcoidosis. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e725.

18. Arun T, Palace J. Effects of immunotherapies and clinical outcomes in neurosarcoidosis: a retrospective cohort study. J Neurol. 2021. [Online ahead of print] doi: 10.1007/s00415-021-10421-z.

19. Obi O, Lower E, Baughman R. Biologic and advanced immunomodulating therapeutic options for sarcoidosis: a clinical update. Expert Rev Clin Pharmacol. 2021;14(2):179–210.