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Neurosarcoidosis – an ever-present clinical challenge

Неуросаркоидоза, и даље велики клинички изазов

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Neurosarcoidosis – an ever-present clinical challenge

Неуросаркоидоза, и даље велики клинички изазов

SUMMARY
Sarcoidosis afflicts the central nervous system more frequently than previously believed. Neurological symptoms are present in roughly a half of patients, and depend of the location in 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

САЖЕТАК
Саркоидоза захвата централни нерви систем чешће него што се сматрало. Неуролошки симптоми се манифестују код скоро половине оних са неуросаркоидозом. Вероватноћа да се спонтано разреши нижа је него код саркоидозе уопште, а заостали функционални дефицит није реткост. Стога већини пацијената са неуросаркоидозом треба имуносупресивна терапија и континуирано праћење. Међутим, други имуносупресивни агенси, као и новији биолошки агенси су се показали 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 је свакако нешто што у многоме може олакшати пут клиничару до дијагнозе, и свакако треба да представља предмет даљих истраживања.
Кључне речи: саркоидоза, неуросаркоидоза, ликвор, дијагностика, лечење

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 between 90 and 95% of all cases, and peripheral lymph nodes in 50 to 70%. In patients with systemic sarcoidosis, even though nervous system is rarely afflicted, between 5 and 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 a half of patients. The characteristics vary greatly, depending of the distribution and inflammation of certain parts of the nervous system. The spontaneous regression of the disease is significantly

less probable comparing to the acute form of the 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: affliction of cranial nerves, small fiber neuropathy (SFN), seizures, meningitis, lesions of cranial tissue, tumor-like symptoms, disfunction of hypothalamus and pituitary gland, cerebellar ataxia, spinal cord lesions, skeletal muscles diseases and psychiatric disorders. The most common manifestation of neurosarcoidosis, present in 50 to 75% of all cases, is some form of cranial nerve disorder. Depending on which, and how many, 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 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 Gillen-Barre syndrome. However, if small neural fibers are damaged, the patient can have restless leg 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 detail examination of the central nervous system, and these patients, unfortunately, have worse outcome with a fulminant course of the disease. The seizures, present in 5 to 10% of patients with neurosarcoidosis, show the severity, progression and the relapses of the disease.

Meningeal affliction is, if based on literature, common location of neurosarcoidosis, and can be present in up to 25% of all 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 patients can develop some form of brain lesions, such as encephalopathy, lesions of gray mass or lesions of hypothalamus. 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 central nervous system [6]. Neurosarcoidosis has shown to have an affinity for the base of the brain, and 10–15% of all patients develop neuro-endocrine symptoms due to the lesions of 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, whit 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 spinal cord. Spinal cord lesions are present in less than 10% of patients with neurosarcoidosis. Depending of 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 between 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 gray matter, or by psychological stress caused by having chronic, relapsing or progressive form of the disease. Psychiatric disorders present in these patients are hallucinations, refractor 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 et al. have given the diagnostic criteria which are still being used. The criteria are based on the levels of security of diagnosis, and the categories include the clinical presentation of neurosarcoidosis and exclude other. The criteria for definitive diagnosis: require positive biopsy of nervous system. The criteria for possible neurosarcoidosis: clinical symptoms and diagnosis suggest for 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 suggest to neurosarcoidosis. The alternative diagnosis is excluded and there is a histological conformation of systemic sarcoidosis [10, 11].

Nuclear magnetic resonance (MRI) is preferable method for radiological conformation of the disease. Any patient with a suspicion for neurosarcoidosis is suggested to

perform the MRI scan of 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 the 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 treated as 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 beta 2 microglobulins, 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 definitive diagnosis. Studies show that the chitotriosidase can be used as a new biomarker [14, 15]. 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. It was interesting to find that IL-6 in CSF was higher in patients with the active form of neurosarcoidosis compared with those with inactive form, and that the patients with concentration of IL-6 above 50pg/ml in CSF have shown to have a higher probability of reactivation or progression of the disease. The same publication had shown that the concentration of IL-10 can also be elevated in neurosarcoidosis [16]. Another study had

tested the levels of IL-2 in CSF as a diagnostic and biomarker of activity in neurosarcoidosis. In this study, the CSF was taken from patients with neurosarcoidosis, MS, neurotuberculosis, viral and bacterial meningitis, cerebral lymphoma, Gillen-Barre syndrome and 115 patients with noninflammatory 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 pulse dosage, still remain the golden standard. If the remission is not achieved, or the clinical response on corticosteroids is not given, the application of other immunomodulator is the next step in treatment, methotrexate, hydroxychloroquine, azathioprine or cyclophosphamide. In severe forms of neurosarcoidosis, which are resistant to any and all pharmacological treatment, the 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 treatment of sarcoidosis. The treatment whit 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 uncommon, but significant, clinical manifestation of sarcoidosis. There is a significant variation in clinical presentation of this form of disease, depending of the location of the granuloma in nervous system. The probability of spontaneous resolution is less than in other forms of sarcoidosis, with functional deficits remaining long after the 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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