

# Neurosarcoidosis: A Review of the State of Art

Sara Camões\*

*Internal Medicine Service, Hospital Pedro Hispano, Matosinhos, Portugal*

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**\*Corresponding author:** Sara Camões, Internal Medicine Service, 4464-513 Senhora da Hora, Hospital Pedro Hispano, Matosinhos, Portugal

## Abstract

Neurosarcoidosis is a rare disease, difficult to diagnose. A correct diagnostic approach should include a multidisciplinary assessment involving physicians, radiologists and pathologists. Corticosteroids are the first-line treatment for neurosarcoidosis, followed by steroid-sparing immunosuppressants.

**Keywords:** Sarcoidosis; Neurosarcoidosis; Central Nervous System Diseases; Peripheral Nervous System Diseases

## Introduction

Sarcoidosis is a chronic disease with a highest annual incidence among African-American females (39.1/100,000) and males (29.8/100,000), followed by Caucasian females (12.1/100,000) [1]. Although sarcoidosis continues to be considered as an idiopathic disease, there is an increasing evidence of a genetic predisposition that associated with several environmental factors that act as trigger agents (e.g. mycobacteria, viruses, neoplasms and inorganic compounds as aluminum) contributes to the development of the disease [2]. Lungs and intrathoracic lymph nodes are the most frequently affected sites, but sarcoidosis can also involve the heart, skin, joints, gastrointestinal tract and nervous system.

## Neurosarcoidosis

The involvement of the central and peripheral nervous system (neurosarcoidosis) is rare, clinically happening in about 5-10% of patients with sarcoidosis, with an average age of onset around 33-41 years [1]. Because of the rarity of this entity and the non-specificity of its clinical and radiological findings, there is surely a high percentage of poorly diagnosed cases, mainly in an initial approach, as the neurological involvement can be found in up to 25% of autopsies from patients with sarcoidosis [1,2]. Non-specific symptoms such as fatigue, headache, cognitive dysfunction and mood disorders are frequent in cerebral neurosarcoidosis, but the clinical picture is usually dominated by cranial neuropathy or aseptic basilar meningitis. The damage of the optic nerve, the most frequently affected followed by the facial nerve, is associated with a poor prognosis in terms of visual recovery [3].

Spinal neurosarcoidosis can be divided into intramedullary and extramedullary involvement (leptomeningeal, extradural, vertebral and disc involvement); paresthesia and weakness of the lower extremities are the main symptoms, although it often presents as symmetric sensory motor polyneuropathy. Rarely, cases of sudden paraplegia can occur, along with bowel and bladder dysfunction [3].

## Diagnosis

The Zajicek criteria are the mostly adopted classification system for neurosarcoidosis established in 1999 and later revised. The other set of criteria belong to WASOG (World Association of Sarcoidosis and Other Granulomatous Disorders), updated in 2014. The specificity and sensitivity of these two options are unknown [4]. A definite diagnosis of neurosarcoidosis can only be established with a positive biopsy of the affected nervous system, frequently considered impossible or too invasive; for this reason, the biopsy is usually performed outside the central nervous system, in a peripheral nerve or another affected and more accessible organ (as neurosarcoidosis frequently coexists with other organ involvement). None of the serum biomarkers used nowadays have been accepted as the one that establishes the diagnosis, including the angiotensin converting enzyme (ACE) or the serum soluble activity of the interleukin-2 receptor (sIL2 receptor) [1].

Levels of ACE in cerebrospinal fluid (CSF) have a low sensitivity (between 24-55%), but may raise the suspicion of neurosarcoidosis due to its high specificity (around 94%). It seems that there is no correlation between serum and CSF levels of ACE and serum

levels do not correlate with the degree of clinical activity [5]. Image findings should not be considered alone for the diagnosis of neurosarcoidosis, but always included in an appropriate diagnostic algorithm. Magnetic resonance imaging (MRI) is the preferred imaging technique because it provides the best definition for brain and spinal cord disease [3,4]. Meningeal involvement can appear as nodular or diffuse enhancement on contrast-enhanced T1-weighted images, mainly in the basilar meninges, as opposed to intraparenchymal lesions that manifest as multiple small, non-enhancing periventricular or subcortical white matter lesions, with high signal on T2-weighted images [3]. Fluorodeoxyglucose positron emission tomography (FDG-PET) can reveal areas of hypermetabolism that correspond to active lesions in asymptomatic sites, which can be used to identify suitable sites to do a biopsy, although there is a lack of evidence regarding the use of FDG-PET and its usefulness in neurosarcoidosis [4]. Histopathologically, neurosarcoidosis is characterized by the presence of noncaseating epithelioid granulomas, the same lesions as those found elsewhere in the body in systemic disease. These granulomas although not specific for sarcoidosis, are valuable diagnostic clues [1]. The differential diagnosis includes: tuberculosis, especially in endemic areas, other infections like histoplasmosis, aspergillosis and cryptococcosis, but also granulomatosis with polyangiitis [6].

## Treatment

There are no international guidelines to treat neurosarcoidosis and randomized clinical trials are lacking to make treatment recommendations. Taking this into consideration, there is a general consensus that corticosteroids should be the first line of treatment, as the majority of patients improve with only glucocorticoids [1,3,7]. If the symptoms are severe, with involvement of the central nervous system, a short course of intravenous steroids is usually given, up to 1g of methylprednisolone a day for 3-5 days. Subsequently, or if the clinical symptoms are less severe, oral steroids can be administered (e.g. prednisone 40-80mg, around 1mg/kg/day), with gradually descending pattern until the lowest effective or maintenance dose (around 10mg/day). Relapse often occurs after the dose of glucocorticoids is tapered down; if the required maintenance dose is more than 10 mg a day, or if clinical response is insufficient, it is recommended to add a steroid-sparing immunomodulatory agent. The evidence is in favor of methotrexate (between 10-25mg once a week), but other immunosuppressant drugs can be considered, such as azathioprine (at 2mg/kg/day, maximum 200mg/day) [1,3,7]. In severe resistant or refractory cases, cyclophosphamide is classically used (500-1000mg iv every 2-4 weeks, or at a dose of 0.5g/m<sup>2</sup> of body surface area every 4 weeks).

Anti-TNF-alpha agents are becoming strongly recommended because of the increasing evidence of rapid reversal of clinical and radiologic features with these agents, especially infliximab (intravenously at a dose of 3-5mg/kg at weeks 0,2 and 6, with

intervals of 4-6 weeks thereafter); some groups are already considering this treatment option before cyclophosphamide [3,7]. Patients treated with long-term infliximab could develop anti-infliximab antibodies that will lead to treatment failure. To avoid this, concomitant methotrexate is recommended, as an immunomodulatory agent. When to stop the treatment remains controversial [7]. Surgery is generally limited to the diagnostic biopsy rather than to the therapeutic use. Cranial mass lesions could benefit from radiation therapy, although this is not recommended as standard treatment [3].

## Prognosis

There is no cure, but optimal immunosuppressive therapy can achieve clinical remission in approximately two thirds of cases, along with variable improvement in imaging findings. Despite the use of new therapies, close to one third of patients remain stable, deteriorate or die [3,8].

## Conclusion

The optimal diagnostic approach to neurosarcoidosis should include a multidisciplinary team with physicians, radiologists and pathologists. Corticosteroids are the first-line of treatment, followed by steroid-sparing immunomodulatory agents. There is increasingly more evidence considering anti-TNF-alpha agents as the therapeutic of choice for severe resistant or refractory cases. When clinical deterioration progresses despite intensive immunosuppression treatment, an alternative diagnosis should always be ruled out. New therapeutic approaches are expected in the upcoming years.

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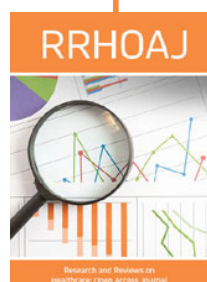
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