

Clinical Note

How to make a decision on the choice of therapy for multiple sclerosis with sarcoidosis comorbidity?

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease. The diagnosis is made on the basis of McDonald's diagnostic criteria, which include clinical manifestations, characteristic lesions registered by magnetic resonance imaging (MRI) and analysis of cerebrospinal fluid, which confirm its dissemination in time and space. Given that MS is an immune-mediated disease from a pathogenesis perspective, many scientific studies have examined the incidence of other autoimmune diseases in patients with MS. These diseases can be inflammatory bowel diseases, diabetes, thyroid disease, psoriasis, rheumatoid arthritis and others.¹ However, sarcoidosis—a multisystem granulomatous disease—is extremely rare in association with MS, and few scientific papers on this topic discuss in favour of it.²

Neurosarcoidosis (NS) in certain clinical forms can mimic the clinical picture of MS. This refers to the possible relapse course of the disease and the appearance of clinical syndromes characteristic of MS (e.g. optic neuritis, brainstem syndromes and acute partial transverse myelitis).² The most common feature of NS and MS is the age at which they most often occur.

Our paper presents the case of a patient diagnosed with systemic sarcoidosis 3 years before the onset of her first neurological symptoms and highlights the need for an adequate diagnostic procedure that can accurately differentiate these types of diseases. The issue of choosing adequate therapy is especially important.

In this paper, we present the case of a 39-year-old woman who suffered from sarcoidosis of the lungs, which was pathohistologically confirmed in April 2016—3 years before the onset of her first MS symptoms. She received corticosteroid therapy on 3 occasions. In March 2019, she noticed worsening vision in her left eye. Visually evoked potentials revealed demyelination of the left optic nerve.

An MRI of the endocranium showed bilateral supratentorial multiple lesions of the periventricular white matter and juxtacortical lesions without active changes when gadolinium was applied.

In May 2019, magnetic resonance spectroscopy (MRS) was performed. The neurobiochemical profile indicated an increased choline/creatinine ratio (Cr) within the frontal right demyelination plaques of 1.48

(normal value below 1.2), while the concentration of n-acetyl aspartate (NAA) was reduced (NAA/Cr was 1.37). These neurobiochemical findings indicated the presence of inflammation with neural dysfunction in the affected area, which evidenced demyelination (Figure 1).

In May 2019, an MRI of the cervical spine was performed, which showed the presence of a focal demyelinating plaque inside the spinal cord on the C5 segment. In May 2019, laboratory analyses included complete peripheral blood counts and detailed biochemical parameters, such as homocysteine, folate, vitamin D and vitamin B12 levels, as well as thyroid hormones (fT3, fT4 and TSH). All were within the reference values. Isoelectric focusing of cerebrospinal fluid revealed the existence of oligoclonal bands of Immunoglobulin G, while blood serum was normal. Proteinuria (0.32g/l), normal glycosuria and normal cytological findings were recorded during biochemical examination of cerebrospinal fluid. *Treponema pallidum* and *Borrelia burgdorferi* were not detected in the serum or cerebrospinal fluid. A diagnosis of MS was considered likely, and further treatment for this disease was recommended.

At the end of July 2019, positron emission tomography/computed tomography of the endocranium was performed, which showed zones of reduced glucose metabolism occipitally and occipitotemporally bilaterally at the level of the brainstem and cerebellum bilaterally, which might correspond to demyelinating lesions.

For this patient without new illness relapses, glatiramer acetate (GA) was added to the therapy. Our case report presented a procedure for diagnostic differentiation and diagnosis of MS based on the evaluation of clinical, radiological and laboratory characteristics.

Based on the fulfilled criteria, MRI findings for MS in the Magnetic Resonance Imaging in MS group, cerebrospinal fluid findings in the absence of leptomeningeal involvement and the absence of nodular lesions in the brain parenchyma, NS was excluded.² This was confirmed by the spectroscopy finding, where the ratio of biomarkers differed from the findings of MS, which is a slight reduction of NAA/Cr, as well as the PET scan finding, where NS is hypermetabolism 18F-FDG-PET. In accordance with the recommendation of Thyskov et al² the paradigm of a 'double diagnosis' is that it is contrary to the 'law of economy', where it is desirable to refer to one

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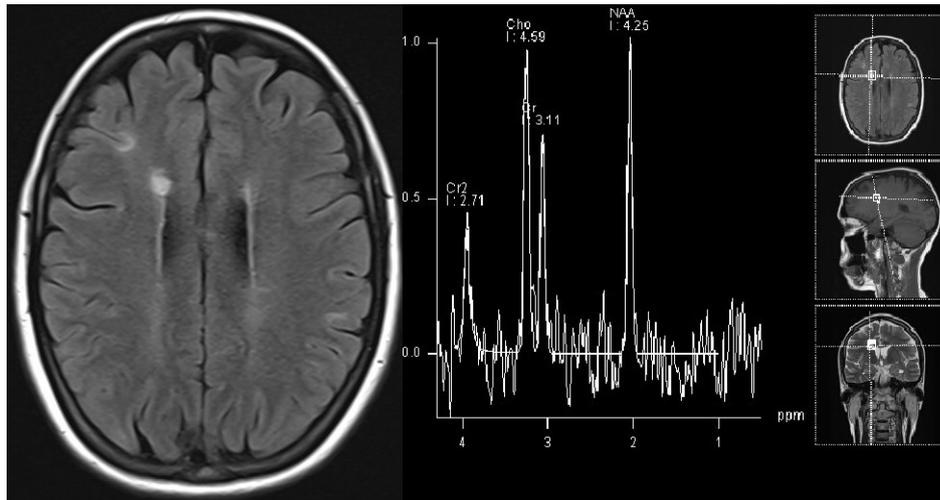


Figure 1 - Findings of magnetic resonance imaging and magnetic resonance spectroscopy.

etiology of the disease to explain the different clinical manifestations. If a patient with sarcoidosis develops symptoms or lesions on MRI that are not consistent with NS, an alternative diagnosis should be sought. CNS lesions are purely due to MS, and no imaging features suggestive of NS.

Another issue we addressed was implementing a suitable therapeutic option for the combined treatment of these diseases. As noted, therapy for MS, primarily the use of interferon-beta (INF- β), may risk worsening sarcoidosis and even induce its occurrence.¹ Drugs such as INF- β and GA reduce the inflammatory process and modulate the activation of immune cells, which, along with the deterioration of the blood–brain barrier, results in demyelination and axonal degeneration.

Binding of INF- β to its receptors reduces the number of antigen-presenting cells and T-cell proliferation. Rare studies on the possible mechanisms of the negative effects of INF- β on sarcoidosis are based on evidence of the proinflammatory role of INF- β , increased production of interleukin-6 (IL-6) in central nervous system astrocytes, the anti-apoptotic effect on T cells and activation of dendritic antigen-presenting cells.¹

Several studies have shown that the effect of GA is based on a switch in the anti-inflammatory secretion of cytokines, with Th1- to Th2-type responses. In addition, it can enhance the suppressor activity of CD8 + T cells. The effect of GA can be manifested in the differentiation and polarisation of T cells. Activation of B cells increases the secretion of anti-inflammatory cytokines (IL-10, IL-4 and transforming growth factor

beta). GA potentiates the natural cytolytic effect of killer cells.¹ As our patient had a milder form of the disease, the use of drugs of low or moderate efficacy was considered. Earlier research confirmed the positive clinical response using GA.

TNF- α blockers are used to treat sarcoidosis. Clinical studies on infliximab and lenercept have been conducted in patients with MS, with surprisingly unsuccessful results. Several patients had a rapid worsening of MS and an increase in the number of lesions on MRI.³ Methotrexate and cyclophosphamide are drugs used in the treatment of systemic sarcoidosis, but are not registered for the treatment of multiple sclerosis.

When considering other drugs used to treat MS and their effects on sarcoidosis, we noted a lack of data on the effect of fingolimod, S1P1 modulator, on the course of sarcoidosis. Moreover, INF- β , natalizumab and alemtuzumab have been shown to induce sarcoidosis.⁴

Rituximab is a drug approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of aggressive forms of NS. It is also a drug used in the treatment of CNS diseases, such as neuromyelitis optica and MS. The mechanism of action of this drug on immune-mediated diseases and sarcoidosis is multi-fold. CD20-targeted B-cell depletion caused by the drug reduces the local Th17 response, which reduces inflammation.⁵ Unfortunately, this medicine is not registered in Serbia. However, ocrelizumab, which has the same mechanism of action, CD20-targeted B-cell depletion, is registered in our

country for treatment of MS, but there is no clinical data on its influence on systemic sarcoidosis.

The patient we presented was introduced to GA therapy, and remission of both diseases was achieved after 3 years of follow-up.

As discussed, the choice of adequate therapy for patients with comorbidity of MS and sarcoidosis has not been the subject of much scientific research. Our study indicates the importance of investigations that would address this issue in the future.

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