Neurologist-in-training

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Case vignette

A 25-year-old woman featured symptoms of increased intracranial pressure such as headache, nausea, and vomiting and presented herself at a neurosurgical department. Initial cerebral MRI showed a pineal cystic lesion and moderate leptomeningeal enhancement (fig. 1A). For symptomatic treatment a ventriculoperitoneal shunt was placed under the suspected diagnosis of a presumably idiopathic pineal cyst. Examination of CSF revealed only a mild pleocytosis (6 cells/µl). Neurological examination three months later showed mild gait instability and palpable cervical lymph nodes in an otherwise asymptomatic patient. Cerebral MRI revealed a slight worsening of leptomeningeal enhancement. Control CSF featured an increase in pleocytosis (303 cells/µl), markedly increased protein (4770 mg/l) and lactate (3.9 mmol/l, normal value 1.1–2.4 mmol/l) levels and intrathecal two-class Ig (IgG 34.7%, IgA 27.5%) synthesis. Laboratory testing including angiotensin converting enzyme (ACE), β2-microglobulin, lysozyme and soluble IL-2-receptor (sIL2R) levels in peripheral blood and CSF was normal. PCR for tuberculosis and routine exams for viral or bacterial infections (e.g., herpes simplex virus, cytomegalovirus, varicella zoster virus, toxoplasmosis, measles virus, Epstein-Barr virus, mycoplasma, treponema pallidum) in CSF were negative. A probatory antiviral and antibacterial therapy was started. The following lumbar puncture showed a decrease in pleocytosis (100 cells/µl), still markedly increased protein (4580 mg/l) and normal lactate levels. Thoraric CT showed hyperplasia of the thymus, but no signs of sarcoidosis. Sonography revealed an enlargement of some cervical lymph nodes with no pathological morphology. Otorhinolaryngology, dermatology and ophthalmology consultations showed no pathologies. Three weeks later cerebral MRI showed a massive increase in leptomeningeal enhancement (fig. 1B). A meningeal biopsy was performed and neuropathological examination proved non-caseating granulomatous inflammation. High-dose intravenous corticosteroids were administered for 5 days and cerebral MRI 1 day after last corticosteroid therapy showed a marked reduction of leptomeningeal enhancement (fig. 1C), whereas the pineal cyst remained unchanged. Under consideration of the biopsy results the diagnosis of isolated, possibly asymptomatic neurosarcoidosis was made. The future course of the disease may clarify whether the pineal cyst is associated with the neurosarcoidosis or not.

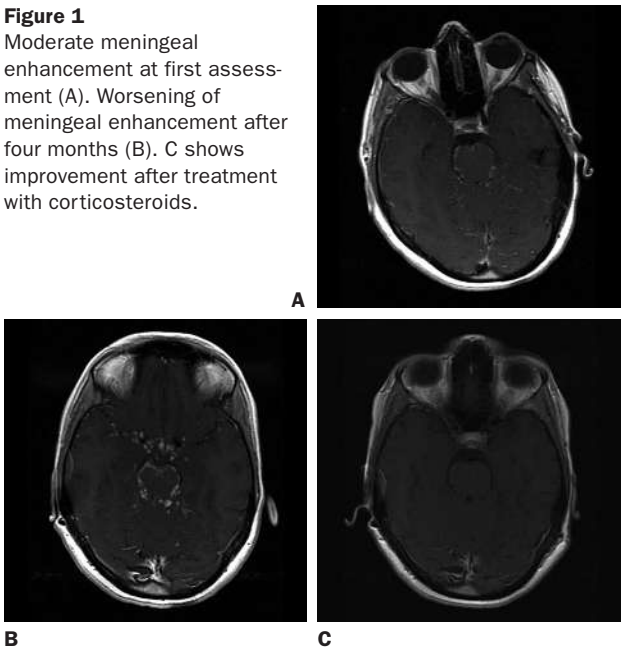

Figure 1
Moderate meningeal enhancement at first assessment (A). Worsening of meningeal enhancement after four months (B). C shows improvement after treatment with corticosteroids.

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Questions

1. What are the diagnostic criteria of neurosarcoidosis?
2. How is neurosarcoidosis characterised by cerebral MRI?
3. Does a standard treatment for neurosarcoidosis exist?

Overview of literature

Sarcoidosis is a systemic disorder which can affect multiple organs [1]. In 1909, Heerfordt first described a neurological manifestation of systemic sarcoidosis. Neurosarcoidosis may occur in up to 25% of patients with systemic disease, but due to an estimated prevalence of 1 per 100,000 there are only a few larger case series on neurosarcoidosis [e.g., 2–4]. Neurosarcoidosis occurs in the absence of systemic disease in 10–17% of patients [5, 6]. Neurological manifestations include cranial neuropathy such as facial nerve palsy or progressive optic neuropathy, aseptic (chronic) meningitis possibly associated with hydrocephalus, parenchymal and/or white matter disease of the CNS, endocrinological disturbances due to the affection of the hypothalamus and/or pituitary gland, myelopathy, (small-fiber) peripheral neuropathy and/or myopathy [7, 8]. The disease is an important differential diagnosis to multiple sclerosis and neurobor-

reliosis and may virtually present with any neurological symptom due to the possible involvement of the central and peripheral nervous system [9]. In 1999, Zajicek and co-workers established criteria for the diagnosis of certain, probable and possible neurosarcoidosis (see table 1) [10].

Table 1 Criteria of neurosarcoidosis, according to [10].

Certain	Clinical presentation suggestive of neurosarcoidosis, exclusion of other diagnoses and positive CNS histology
Probable	Clinical presentation suggestive of neurosarcoidosis, exclusion of other diagnoses, signs of CNS inflammation (MRI and/or CSF) and evidence of systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging and serum ACE)
Possible	Clinical presentation suggestive of neurosarcoidosis and exclusion of other diagnoses in the absence of the above mentioned criteria

CSF analysis in sarcoidosis with CNS involvement often shows inflammatory changes with mild pleocytosis, increased protein levels and oligoclonal bands. Besides ACE, β2-microglobulin, lysozyme and sIL2R levels in the CSF can be measured [11–13]. According to a review by Nowak and Widenka cerebral MRI abnormalities include nodular and/or diffuse meningeal involvement (40%), periventricular and other white matter lesions (40%), multiple supra- and intratentorial parenchymal lesions (35%), a solitary intra-axial mass (10%) and/or a solitary extra-axial mass (5%) [14]. Shah et al. did not find a correlation between clinical symptoms and non-enhancing white matter lesions suggesting that such lesions in patients with systemic sarcoidosis above 50 years do not necessarily indicate neurosarcoidosis [15]. In this series the most frequently observed changes were dural involvement including extra-axial masses (34%), cranial nerve involvement (34%) and meningeal enhancement (31%).

There are no available controlled trials for the treatment of neurosarcoidosis. Although some authors restrict the administration of corticosteroids to patients with significant neurological disease, corticosteroids are in general accepted as first-line therapy of neurosarcoidosis. Other standard immunosuppressive therapies have also been applied successfully [2]. Besides Infliximab has recently been used in several cases of therapy-refractory neurosarcoidosis and should be considered if the standard immunosuppressive therapies are not efficient or feature too many side effects [8]. In patients with neurosarcoidosis and deterioration under immunsuppressive therapy, progressive multifocal leukoencephalopathy and other opportunistic infections should be taken into consideration.

Answers

1. According to Zajicek et al. [10] the minimum diagnostic criteria are a clinical picture suggestive of neurosarcoidosis and the exclusion of other diagnoses. The diagnosis of definite neurosarcoidosis is only possible by positive CNS histology. Probable neurosarcoidosis can be diagnosed in the presence of inflammatory changes according to CSF analysis and/or MRI and evidence of systemic disease. A diagnostic dilemma represents possible neurosarcoidois, e.g., neurological symptoms in patients with systemic sarcoidosis but without evidence of CNS inflammation or patients with neurologic symptoms and evidence of CNS inflammation, but without systemic disease (isolated neurosarcoidosis) [10]. With respect to CSF analysis, elevated protein levels, two-class Ig synthesis and suppression of oligoclonal bands under therapy may be indicative of neurosarcoidosis when compared with multiple sclerosis [8].

2. Cerebral MRI shows a wide variety of pathological changes with dural and meningeal involvement, cranial nerve enhancement and parenchymal lesions arguably being the most eminent alterations. T2-hypointense parenchymal lesions may be associated with the least response to treatment [15].

3. In the absence of evidence-based recommendations, therapy often consists of oral prednisone at a dosage of 1 mg/kg body weight for 3–4 months with subsequent weaning [6]. This therapy can be preceded by the intravenous administration of 1000 mg methylprednisolone/die for 3 days. Alternatively, oral administration of methotrexate, azathioprine or cyclosporine in combination with low-dose prednisone can be considered [2]. This approach should be taken into consideration in cases with severe CNS involvement or in order to avoid using corticosteroids. Especially in therapy-refractory patients infliximab (Remicade®), a monoclonal antibody against TNFα, may be useful [16]. In asymptomatic cases (that do not fulfill the above diagnostic criteria for neurosarcoidosis) it might be justified according to the authors' personal opinion to monitor the course of the disease without initiating an immunosuppressive therapy.

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