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Neurosarcoidosis – a patient series

SHORT REPORT

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BACKGROUND

Neurosarcoidosis is a rare form of sarcoidosis that affects the nervous system. The aim of the study was to survey clinical manifestations, findings from assessments and treatment strategies for patients with neurosarcoidosis.

MATERIAL AND METHOD

The study performed a retrospective assessment of 17 patients with definitive, probable and possible neurosarcoidosis diagnosed in the period 2008–2019 at the Department of Neurology, Haukeland University Hospital.

RESULTS

The average prevalence of definitive, probable or possible neurosarcoidosis in Norway's Vestland county was 2.7 per 100 000 inhabitants in the period in question. Onset took the form of central nervous affection (8 of 17), hydrocephalus (5 of 17) and cranial neuropathy (5 of 17). Sarcoidosis-like findings were made in 14 of 17 patients by means of contrast-enhanced magnetic resonance tomography (MRT) of the central nervous system, in 7 of 8 patients by positron emission tomography (PET), and in 12 of 16 patients by computed tomography (CT) of the thorax. There were cerebrospinal fluid abnormalities in 15 of 15 patients, with biopsy verification for 13 of 15. The symptoms of 16 of 17 patients improved or stabilised with prednisolone and/or other immunotherapy.

INTERPRETATION

Neurosarcoidosis affects both the central and the peripheral nervous system. Cerebrospinal fluid analysis and contrast-enhanced MRT are important means of detecting inflammation. A biopsy is necessary for making a definitive diagnosis, but is not always feasible. PET can be used as a supplement to other examinations to assess various organ manifestations and to pinpoint biopsy sites. Corticosteroid therapy, and in some cases other immunotherapy, elicits a good response.

Main findings

Cranial neuropathy, various types of involvement of the central nervous system and hydrocephalus were frequent findings with neurosarcoidosis. Contrast-enhanced MRT and cerebrospinal fluid analysis were important aids in diagnosing neurosarcoidosis.

Long-term treatment with prednisolone and/or other immunotherapy had a beneficial effect on neurosarcoidosis.

Neurosarcoidosis is a rare, non-necrotising, granulomatous disease which affects both the central and the peripheral nervous system. The condition most frequently manifests as part of systemic sarcoidosis, and is seen in 5–15 % of sarcoidosis patients (1). Sarcoidosis is most frequently seen concurrently in the lungs, eyes and skin (2). The prevalence of neurosarcoidosis is about 1 in 100 000 (3), and the disease occurs most frequently in the age group 40–50 years (4).

A positive neural tissue biopsy is a definitive diagnosis (5). CT thorax and PET coupled with bronchoalveolar lavage (BAL) with measurement of the CD4+/CD8+ ratio can point to extraneural biopsy sites. Contrast-enhanced MRT is the most sensitive non-invasive method of assessing neurosarcoidosis, and a typical finding is leptomeningeal contrast enhancement (2, 6). Analysis of cerebrospinal fluid is important for assessing differential diagnoses. In cases of neurosarcoidosis, the analysis results may be normal or show slight inflammation and elevated angiotensin-converting enzyme (ACE) (1, 7).

Therapy includes corticosteroids and if indicated other immunotherapy, and is personalised to the individual patient. The purpose of our study was to survey clinical manifestations, assessment and treatment of neurosarcoidosis at Haukeland University

Hospital over an eleven-year period.

Material and method

The study was approved by the Data Protection Officer at Haukeland University Hospital

(Project no. 292). In the period 2008–2019, 19 patients were registered with ICD-10 diagnostic code D86.8 (sarcoidosis of other and combined sites). Inclusion status was determined according to the Marangoni-modified Zajicek criteria (5) for definitive, probable or possible neurosarcoidosis (Table 1). This led to the inclusion of 17 patients. The therapeutic response was assessed according to the modified Rankin Scale (mRS) (8). We surveyed demography, onset symptoms, assessment, treatment and follow-up.

Table 1

Inclusion criteria for confirmed, probable and possible neurosarcoidosis.

Classification of neurosarcoidosis	Marangoni-modified Zajicek criteria (5)
Definitive	Positive neural tissue biopsy
Probable	Inflammation in the central nervous system (MRT or cerebrospinal fluid), positive histology from extraneural tissue and/or positive result from two or more of the following: gallium scan 1, CT thorax, bronchoalveolar lavage with CD4+/CD8+ > 3.5 or cerebrospinal fluid with CD4+/CD8+ > 5
Possible	Absence of histological confirmation of sarcoidosis and exclusion of other inflammatory diseases

[1]As PET is a more sensitive method than gallium scan (6), PET was used as one criterion in the study.

Results

Patient demography

The study included nine men and eight women, with an average age at disease onset of 52 years (standard deviation 12). The average prevalence in Norway's Vestland county was 2.7 per 100 000 inhabitants in the period in question. The average follow-up time at the Department of Neurology was 26 months (standard deviation 25).

Types of clinical onset

Affection of the central nervous system with affection of the cerebellum or facial nerve, myelitis, hypopituitarism, vasculitis or neuropsychiatric disease (psychosis or depression) were present in 8 of 17 patients (Table 2). Onset took the form of cranial

neuropathy (facial, vestibulocochlear and optic nerves) in 5 of 17 patients, and 5 of 17 patients first presented with hydrocephalus symptoms. During the course of the disease, 12 of 17 patients displayed multiple neurological manifestations.

Table 2

Types of clinical onset of neurosarcoidosis in patients assessed at the Department of Neurology, Haukeland University Hospital, in the period 2008–2019. The first recorded neurological manifestation due to neurosarcoidosis is regarded as the clinical onset. One patient presented with both cerebellar affection and facial paralysis.

Type of clinical onset	Number of patients (*n* = 17)
Hydrocephalus	5
Cranial neuropathy[1]	5
Central nervous affection[2]	8

[1]Affection of facial, vestibulocochlear or optic nerve.

[2]Affection of cerebellum or facial nerve, myelitis, hypopituitarism, vasculitis or neuropsychiatric disease (psychosis or depression).

Assessment

MRT showed abnormal findings in 14 of 17 patients, with leptomeningeal contrast enhancement in 8 of 14 while 5 were diagnosed with spinal neurosarcoidosis. PET findings were consistent with extraneural sarcoidosis in 6 of 8 patients, and with neurosarcoidosis in 1 of 8. CT thorax showed probable sarcoidosis in 12 of 16 patients. Extraneural organ involvement was found with PET or CT thorax in 15 patients in the form of affection of lymph nodes (11 of 15), lungs (9 of 15), eyes (5 of 15) and spleen, liver and nasal mucosa (4 of 15). There was biopsy verification for 13 of 15 patients, and 1 of 2 had an increased CD4+/CD8+ ratio in BAL fluid.

A lumbar puncture was performed on 15 of 17 patients, and the cerebrospinal fluid revealed one or more abnormal parameters: elevated leukocyte level (13 of 15), elevated protein level (12 of 15), oligoclonal bands (9 of 15), reduced glucose level (3 of 15) and elevated ACE level (4 of 12). Three patients had a definite, 9 a probable and 5 a possible diagnosis of neurosarcoidosis according to the Marangoni criteria (5) (Table 1).

Treatment

All the patients first received prednisolone therapy, which had a beneficial initial effect on 13 of the 17, with an improvement of at least one point on the mRS scale. Six of 17 patients experienced adverse effects such as weight gain, diabetes mellitus and mental symptoms, and two patients experienced progression of the disease despite the therapy. Fifteen patients received other immunotherapy in addition. Eight patients were treated with azathioprine, which had a disease-stabilising effect, while therapy was discontinued for 5 patients because of adverse reactions. Five patients received mycophenolate, and the symptoms of 4 of them improved. Five patients received methotrexate, and the symptoms of 3 of them improved. Three patients received

rituximab, and the symptoms of 2 of them stabilised. Two patients received either cyclosporine or infliximab, but infliximab was discontinued because of adverse reactions. Six patients tried three or more drugs. Twelve of 17 patients were using at least one drug for neurosarcoidosis at the last follow-up. Four patients with hydrocephalus had a ventriculoperitoneal shunt implanted, with beneficial effect. Ten of 17 patients experienced an improvement of at least 1 point in their mRS score between the first and the last entry in the medical records, while 6 experienced no change in mRS score.

Discussion

We found a neurosarcoidosis prevalence of 2.7 per 100 000, which is somewhat higher than previously reported (3). This may be because our study also included patients with possible neurosarcoidosis.

The onset symptoms of neurosarcoidosis in our material varied – there was affection of both the central and the peripheral nervous system, as well as hydrocephalus. Other studies have reported hydrocephalus as being less common (3, 4). We found pathological cerebrospinal fluid more frequently than has previously been reported (6). This may be due to different frequencies of peripheral neuropathies in different studies. Neurosarcoidosis patients with isolated facial paresis often have normal cerebrospinal fluid (2), but the majority in our study had multiple neurological manifestations. Cerebrospinal fluid ACE assay has a low sensitivity, but a higher specificity for neurosarcoidosis (7). Elevated cerebrospinal fluid ACE therefore increases suspicion of neurosarcoidosis, but is of limited usefulness.

Contrast-enhanced MRT is a sensitive method for detecting neurosarcoidosis (6). Only three of our patients had MRT findings showing no signs of neurosarcoidosis. PET is a sensitive method of diagnosing sarcoidosis (9), and PET scans had findings indicating sarcoidosis in 7 of 8 patients. PET findings are not specific for sarcoidosis, and the PET findings of 2 of 7 patients were not verified by biopsies.

Prednisolone monotherapy is often adequate therapy in cases of isolated cranial neuropathies. Slow tapering of steroid treatment should be attempted, with clinical checks and if indicated contrast-enhanced MRT. Patients with multiple and/or more severe neurological manifestations required long-term immunotherapy. In such cases an alternative form of immunotherapy should be administered, to prevent adverse effects of steroids. Azathioprine is a commonly used steroid-sparing drug that can be tried, but several patients in our study had to discontinue the therapy because of adverse reactions. Mycophenolate, methotrexate, infliximab and rituximab may also provide effective immunotherapy (2, 8, 9). There is no consensus on choice of second-line treatment, and this often has to be tested for the individual patient. These therapies were effective in our study, but only one patient tried infliximab. The reason for the different treatment choices was partly contraindications for some of the drugs, and partly lack of efficacy, which led to the drug being changed. Six patients tried three or more drugs before optimal therapy was achieved. A ventriculoperitoneal shunt is indicated for patients with hydrocephalus. Treatment for neuroendocrinal or other

organ manifestation must as a rule be coordinated with other departments. Choice of treatment, duration and follow-up must be personalised for the individual patient, as the disease course and severity of symptoms vary.

The article has been peer-reviewed.

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