Neurosarcoidosis in a Tertiary Referral Center

A Cross-Sectional Cohort Study

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Abstract: The aim of this study was to evaluate clinical characteristics, diagnostic strategy, and treatment in patients with neurosarcoidosis in a tertiary referral centre.

In a cross-sectional study, we included all patients with neurosarcoidosis treated at our tertiary referral center between September 2014 and April 2015.

We identified 52 patients, among them 1 patient was categorized as having definite neurosarcoidosis, 37 probable neurosarcoidosis, and 14 possible neurosarcoidosis. Neurologic symptoms were the first manifestation of sarcoidosis in 37 patients (71%). Chronic aseptic meningitis was the most common presentation (19/52 patients [37%]), followed by cranial neuropathy (16/52 patients [31%]). Serum angiotensin-converting enzyme and lysozyme levels were elevated in 18 of 41 (44%) and 12 of 26 cases (46%). Pulmonary or lymph node sarcoidosis was identified by chest X-ray in 21 of 39 cases (54%) and by computed tomography of the chest in 25 of 31 cases (81%); 18F-fluorodeoxyglucose-positron emission tomography showed signs of sarcoidosis in 15 of 19 cases (79%). Thirty-one of the 46 cases receiving treatment (67%) improved, 13 cases (28%) stabilized, and 2 cases (4%) deteriorated. First-line treatment with corticosteroids resulted in satisfactory reduction of symptoms in 21 of 43 patients (49%). Seventeen patients (33%) needed second-line cytostatic treatment, and 10 patients (19%) were treated with tumor necrosis factor-α inhibitors.

The majority of patients with neurosarcoidosis present with chronic meningitis without a history of systemic sarcoidosis. The diagnosis can be difficult to make because of the poor sensitivity of most diagnostic tests. Half of patients had a satisfactory reduction of symptoms on first-line therapy.

METHODS

In this cross-sectional study, we included all patients with neurosarcoidosis treated at the Academic Medical Center in Amsterdam between September 2014 and April 2015. Ethical approval is not required in the Netherlands for a retrospective observational study.
cross-sectional study with anonymized patient data such as our study. Patients were identified by their treating physician and data were collected in a database. The diagnosis of neurosarco
dosis was categorized according to an acknowledged classi-
fication system in the field of neurosarco
dosis, first formulated by Zajicek et al., later modified by Marangoni et al. The classification system we used categorizes patients into 3 groups according to certainty of the diagnosis: possible, probable, and definite neurosarco
dosis (suppl. Table 1, http://links.lww.com/ MD/A878). Definite neurosarco
dosis is defined as histological confirmation of neuronal tissue, probable and possible neuro-
sarco
dosis are defined as a clinical syndrome suggestive of the disease in combination with histological confirmation of systemic sarco
dosis, laboratory or imaging support. Addi-
tionally, the exclusion of alternative diagnoses, for example, neuro-
ological infection or malignancies, is essential. In this study, we included cases with both central and peripheral nervous system involvement. A positive histology for sarco
dosis was defined as the presence of histological features consistent with sarco
dosis, which include noncaseating granulomas with epithelioid cells and macrophages surrounded by lymphocytes, plasma cells and mast cells. In patients with muscle manifestation of neurosarco
dosis, histological confirmation can be derived from muscle tissue. Although in these cases histological confirmation comes from the tissue that established the diagnosis of neurosarco
dosis, we decided not to regard these cases as having definite neurosarco
dosis, as according to the criteria, only confirmation with central nervous tissue would certify the diagnosis.

For all patients, a case record form was filled in containing baseline demographic features, presenting symptoms, presence of systemic disease prior and subsequent to neurologic disease, results of ancillary investigations, treatment, length of follow-
up, adverse events, and clinical outcome. In scoring patients for a history of autoimmune diseases, we excluded diseases that were later considered to be, or very likely to be, a manifestation of sarco
dosis, such as anterior uveitis. Each case was scored for clinical features and ancillary investigations on presentation contributing to the diagnosis. Complications during follow-up were reported if they were attributable to sarco
dosis or its treatment. Infections were regarded as a side-effect of predni-
solone or other immunosuppressive therapy if they were oppor-
tunistic infections or if the relation with the medication was explicitly noted in the patient records. Clinical outcome was graded into functional disability at the last recorded presentation in in- or outpatient setting. The functional disability in each case was scored as “asymptomatic,” “complaints without functional disability,” “complaints with minor functional disability” (eg, neurological deficits mildly interfering in everyday life, such as inability to cycle owing to motor dysfunction), “complaints with moderate-to-severe functional disability” (eg, neurological deficits interfering everyday life, resulting in failure to return to job or school, requirement of special equipment such as crutches or a wheelchair, or assistance with everyday activi-
ties), and death. The response rate to treatment in each case was scored as “improvement on therapy,” “stable disease” (eg, unchanged compared with clinical situation before treatment), “deterioration,” and “spontaneous improvement” (eg, improvement in patients not treated for neurosarco
dosis or improvement after ceasing treatment in patients).

Statistical analysis was performed to compare differences between groups using the Fisher exact test for dichotomous variables and the Mann-Whitney U test for continuous vari-
ables. A P value <0.05 was considered significant.

RESULTS

We identified a total of 52 patients who met the diagnostic criteria for possible, probable, or definite neurosarco
dosis. One patient (2%) was categorized as having definite neurosarco
dosis, 37 patients (71%) were categorized as having probable, and 14 patients (27%) as having possible neurosarco
dosis. The patient with definite neurosarco
dosis had positive histology for sarco
dosis following a biopsy of dural tissue. Of the patients with probable neurosarco
dosis, 35 patients met the criteria based on signs of inflammation of the nervous system alongside positive histology for a systemic lesion. Two patients met the criteria based on positive results of other ancillary investiga-
tions. One of these patients had a high-resolution CT (HRCT) scan and Gallium-67 scan with abnormalities consistent with the diagnosis, the other patient had a positive HRCT scan and bronchial alveolar lavage with a lymphocytosis and raised CD4/CD8 ratio. Histological confirmation mostly came from lymph nodes (19/34 patients, 56%) and lung tissue (7/34 patients, 21%). In 2 patients with muscle manifestation of neurosarco
dosis, histological confirmation came from muscle tissue. The 14 patients with possible neurosarco
dosis had a clinical syndrome and ancillary investigations suggestive of the disease, but did not fulfill the criteria for probable neurosarco
dosis (eg, no histological evidence of sarco
dosis or 2 positive ancillary investigations as described in suppl. Table 1, http://links.lww.com/ MD/A878).

The median age at the time of diagnosis with neurosar-
dosis was 44 years with a range of 34 to 56 years, and 27 (52%) patients were female (Table 1). Classified by ethnicity, 28 (54%) patients were white, 16 (31%) were of African descent, and 8 (15%) were of Asian descent. Three patients had a positive history of autoimmune diseases, and 7 had a positive family history of autoimmune disease. A positive family history of sarco
dosis was noted in 3 patients.

Of the 15 patients with a prior diagnosis of sarco
dosis outside of the nervous system, pulmonary sarco
dosis was found in 12 cases (80%), ocular sarco
dosis in 2 cases (13%), and liver and skin sarco
dosis were previously diagnosed in 1 patient each. Sarco
dosis of others organs developed during the course of the disease in 25 of 37 patients (68%) presenting with neurosarco
dosis. In 35 patients (67%), lung involvement was reported at any time during disease course. Eye involve-
ment was reported in 17 patients (33%) and consisted of uveitis in 14 cases, sarco
dosis of the skin was reported in 8 cases (15%), and ear-nose and throat pathology was noted in 7 cases (14%).

Neurologic symptoms were the first clinical manifes-
tation of sarco
dosis in 37 of 52 patients (71%). The most common neurological symptom at presentation was limb sensory disturbance in 24 cases (46%), followed by headache in 19 cases (37%). All patients except 2 had >1 neurological symptom at presentation. Neurologic examination at presen-
tation was abnormal in 44 of 52 cases (85%). Frequent findings were cranial nerve pathology (17 cases, 33%) and sensory abnormalities (20 cases, 39%). During the course of the disease, 24 patients (46%) developed additional neurologic symptoms.

During the course of the disease, the most common clinical neurological pathology, based on both clinical signs and results of ancillary investigations, was chronic aseptic meningitis in 19 patients (37%), followed by cranial nerve palsy in 16 patients (31%). Of those 16 patients, 4 exclusively had cranial nerve involvement; the other patients also had other nervous system
Involvement including cerebral and meningeal involvement. Facial nerve palsy was the most frequently reported cranial nerve palsy, occurring unilateral in 6 and bilateral in 2 cases. Peripheral nerve involvement was found in 9 patients (17%), of which 5 had isolated small-fiber neuropathy and 4 had polyneuropathy. Five patients developed hydrocephalus during the course of the disease, which was communicating in 1 and obstructive in 4. Neuroendocrine involvement consisting of hypothalamic-pituitary dysfunction was seen in 3 patients. Neurovascular complications of neurosarcoidosis were seen in 4 cases (8%), and involved brain infarction in 3 and cerebellar hemorrhage in 1 case.

Ancillary investigations on admission are described in Table 2 and suppl. Figure 1, http://links.lww.com/MD/A878. The results of blood chemical tests were available in 49 of 52 cases (94%). The serum angiotensin-converting enzyme (ACE) level was tested in 41 and elevated (>70 units/L) in 18 patients (44%). Lysozyme levels were elevated (>3.5 mg/L) in 12 of the 26 patients tested (46%). Elevated ACE levels were more frequent in patients with pulmonary sarcoidosis than in patients without pulmonary involvement (17/26 [65%] vs 1/15 [1%], \( P < 0.001 \)). CSF analysis was performed in 31 patients and abnormal in 27 (87%). Elevated protein levels were found in 15 of 25 (60%) patients tested. Pleocytosis (defined as >5

### TABLE 1. Baseline Characteristics

| Characteristic | n/N (%) | Characteristic | n/N (%) |
|---------------|---------|---------------|---------|
| Age at baseline assessment, y | 52 (38–59) | Signs on neurologic examination | |
| Age at diagnosis neurosarcoidosis | 44 (34–56) | No abnormalities | 8 (15%) |
| Age at diagnosis sarcoidosis | 43 (31–56) | Cranial nerve palsy | 17 (33%) |
| Male sex | 25/52 (48%) | Sensory abnormalities | 20 (39%) |
| Ethnicity | | Paresis | 16 (31%) |
| White | 28 (54%) | Extensor plantar reflex | 10 (19%) |
| African descent | 16 (31%) | Neurologic pathology | |
| Asian descent | 8 (15%) | Chronic aseptic meningitis | 19 (37%) |
| Patient history | | Cranial nerve palsy | 16 (31%) |
| Sarcoidosis | 15 (29%) | n.VII unilat palsy | 6 (12%) |
| Auto-immune disease | 2 (4%) | n.VII bilat palsy | 2 (4%) |
| Sarcoidosis and autoimmune disease | 1 (2%) | n.V palsy | 4 (8%) |
| Family history | | n.VI palsy | 4 (8%) |
| Sarcoidosis | 3/27 (11%) | n.III palsy | 3 (6%) |
| Autoimmune disease | 7/27 (26%) | n.II palsy | 2 (4%) |
| Presenting symptoms | | n.XII palsy | 1 (2%) |
| Limb sensory disturbance | 24 (46%) | n.X palsy | 1 (2%) |
| Headache | 19 (37%) | Spinal cord | 12 (23%) |
| Abnormal gait | 14 (27%) | Brain parenchymal disease | 11 (21%) |
| Paresis | 14 (27%) | Peripheral nervous system | 9 (17%) |
| Limb pain | 11 (21%) | Small-fibre neuropathy | 5 (10%) |
| Fatigue | 8 (15%) | Hydrocephalus | 5 (10%) |
| Vision loss | 8 (15%) | Muscle | 5 (10%) |
| Diplopia | 8 (15%) | Cerebral infarction | 3 (6%) |
| Myalgia | 8 (15%) | Neuro-endocrine | 3 (6%) |
| Abnormal gait | | Spinal cord | 12 (23%) |
| Lysozyme | | Brain parenchymal disease | 11 (21%) |
| Fatigue | | Peripheral nervous system | 9 (17%) |
| Vision loss | | Small-fibre neuropathy | 5 (10%) |
| Diplopia | | Hydrocephalus | 5 (10%) |
| Myalgia | | Muscle | 5 (10%) |
| Abnormal gait | | Cerebral infarction | 3 (6%) |
| Lysozyme | | Neuro-endocrine | 3 (6%) |
| Fatigue | | Spinal cord | 12 (23%) |
| Vision loss | | Brain parenchymal disease | 11 (21%) |
| Diplopia | | Peripheral nervous system | 9 (17%) |
| Myalgia | | Small-fibre neuropathy | 5 (10%) |
| Abnormal gait | | Hydrocephalus | 5 (10%) |
| Lysozyme | | Muscle | 5 (10%) |
| Fatigue | | Cerebral infarction | 3 (6%) |
| Vision loss | | Neuro-endocrine | 3 (6%) |
| Diplopia | | Spinal cord | 12 (23%) |
| Myalgia | | Brain parenchymal disease | 11 (21%) |
| Abnormal gait | | Peripheral nervous system | 9 (17%) |
| Lysozyme | | Small-fibre neuropathy | 5 (10%) |
| Fatigue | | Hydrocephalus | 5 (10%) |
| Vision loss | | Muscle | 5 (10%) |
| Diplopia | | Cerebral infarction | 3 (6%) |
| Myalgia | | Neuro-endocrine | 3 (6%) |

Data are number/number assessed (%), and median (25th–75th percentile). If the number assessed is not noted, all 52 patients were assessed.

1 Based on both clinical signs and results of ancillary investigation during the complete follow-up period.

1 Membranous glomerulonephritis and psoriasis (n = 1), rheumafactor-negative rheumatoid arthritis (n = 1), primary sclerosing cholangitis (n = 1).

1 Rheumatoid arthritis (n = 5), rheumatoid arthritis and systemic lupus erythematosus (SLE) (n = 1), and Crohn disease (n = 1).

1 Panhypopituitarism (n = 2), diabetes insipidus (n = 1).

1 Systemic involvement during the complete follow-up period: Eye and ENT involvement consisted of uveitis (n = 14), papilledema (n = 1), macular oedema (n = 1), keratoconjunctivitis sicca (n = 1), inflammation of sinus or nasal mucosa (n = 1), parotitis (n = 1), and vocal cord pathology (n = 2).
leukocytes counted per mm³) was found in 18 of the 28 patients tested (64%). Presence of oligoclonal bands was tested in 18 and positive in 4 cases (22%), IgG index was tested in 21 patients and elevated (>0.62) in 8 (38%). Repeated CSF analysis during follow-up showed new abnormalities in 5 cases that had normal initial CSF examination. CSF ACE levels were not determined.

Cranial MRI was performed in 37 patients, and in 27 (73%) patients, there were abnormalities attributed to sarcoidosis (Figure 1). These included signs of inflammation of the meninges (12 cases, 44%), parenchyma (11 cases, 41%), and optic nerve (two cases, 7%). In 2 of these cases, abnormalities consistent with sarcoidosis were only seen in a follow-up cranial MRI. An MRI of the spine was performed in 18 patients, and showed abnormalities consistent with sarcoidosis in 12 (67%) patients. One of these cases initially had a normal spinal MRI scan on presentation, but had spinal cord lesions on a follow-up MRI consistent with sarcoidosis. A chest X-ray was carried out in 39 patients (75%), 21 of which (54%) showed abnormalities consistent with sarcoidosis (Figure 2). A chest CT was done in 31 patients (60%) and consisted of a HRCT in 7 and a regular CT in the other cases. Of the patients tested, 25 (81%) showed abnormalities consistent with sarcoidosis (hilar lymphadenopathy, parenchymal, and pleural abnormalities). In 5 cases with a chest X-ray that was negative or inconclusive for sarcoidosis, a later-performed CT-scan was positive for sarcoidosis. ¹⁸Fluorodeoxyglucose (FDG)-PET CT was done in 19 cases. Fifteen of 19 patients with FDG-PET CT (79%) showed abnormalities consistent with sarcoidosis. In 3 of 9 cases with chest-X-ray, chest CT, and PET-CT, PET-CT was the only imaging test positive for sarcoidosis. Gallium-67 scintigraphy was performed in 5 cases and showed uptake of radioisotope characteristic for sarcoidosis in 3 cases (60%). In one case, both Gallium-67 scintigraphy and FDG-PET CT were done and both showed abnormalities consistent with sarcoidosis.

All except 6 patients (12%) received treatment (Table 3). Of the 46 patients receiving treatment, 43 (93%) were treated with corticosteroids (suppl. Figure 2, http://links.lww.com/MD/A878). Second-line treatment consisted of methotrexate (14 cases), azathioprine (8 cases), cyclophosphamide (1 case), and cyclosporine (1 case). Third-line treatment consisted of monoclonal antibodies against tumor necrosis factor (TNF)-α: infliximab (7 cases), adalimumab (1 case), both infliximab and adalimumab (1 case), and infliximab and mycophenolate mofetil (1 case). All patients were on corticosteroids when second and third treatment were initiated. Corticosteroids could be discontinued in 6 of 17 patients (35%) on second- or third-line

| TABLE 2. Ancillary Investigations on Presentation |
|-------------------------------------------------|
| Characteristic | n/N (%) | Characteristic | n/N (%) | Abnormalities consistent with sarcoidosis | No abnormalities |
| Blood chemical tests | 49/52 (94%) | Imaging | Chest X-ray | 21/39 (54%) | 15/39 (38%) |
| ACE (units/L) serum | 58 (37–90) | Chest CT § | 25/31 (81%) | 6/30 (19%) |
| >70 | 18/41 (44%) | Cranial CT | 7/11 (64%) | 2/10 (18%) |
| Lysozyme (mg/L) serum | 3.5 (2.8–4.8) | Cranial MRI | 27/37 (73%) | 6/37 (16%) |
| >3.5 | 12/26 (46%) | Spine MRI | 12/18 (67%) | 4/18 (22%) |
| Calcium (mmol/L) serum | 2.39 (2.31–2.47) | FDG-PET CT | 15/19 (79%) | 3/19 (16%) |
| >2.6 | 2/35 (6%) | Gallium scintigraphy | 3/5 (60%) | 2/5 (40%) |
| ESR serum | 16.0 (6.0–40.3) | Lymph node | 19/34 (56%) | |
| >20 | 18/46 (39%) | Lung | 7/34 (21%) | |
| Cerebral spinal fluid analysis | 31/52 (60%) | Skin | 4/34 (12%) | |
| Normal | 4/31 (13%) | Muscle | 3/34 (9%) | |
| White cell count, cells/mm³ | 153 (29–553) | Nerve | 1/34 (3%) | |
| >5 cells/mm³ | 18/28 (64%) | Liver | 1/34 (3%) | |
| Lymphocytosis | 6/18 (33%) | Other abnormalities | 5/43 (12%) | |
| Protein (g/L) CSF | 0.55 (0.41–1.08) | Non-caseating granuloma | 34/43 (79%) | |
| >50 | 15/25 (60%) | Glucose ratio (CSF/serum) | 0.48 (0.39–0.71) | 34/43 (79%) |
| <50 | 6/27 (22%) | Non-caseating granuloma | 34/43 (79%) | |
| Glucose, mg/dL | 57.7 (50.5–66.7) | Glucose ratio (CSF/serum) | 0.48 (0.39–0.71) | 34/43 (79%) |
| <0.6 | 6/10 (60%) | Other abnormalities | 5/43 (12%) | |
| IgG-index >0.62 | 8/21 (38%) | No representative tissue | 1/43 (2%) | |
| Oligoclonal bands present | 4/18 (22%) | Tissue analysis | | |

Data are number/number assessed (%) and median (25th–75th percentile).

ACE levels were evaluated in 41 cases (79%), lysozyme levels in 26 cases (50%), calcium in 35 cases (67%), erythrocyte sedimentation rate (ESR) in 46 cases (89%), CSF white cell count in 28 cases (90%), CSF protein in 25 cases (81%), CSF glucose in 27 cases (87%), IgG index in 21 cases (68%), oligoclonal bands in 18 cases (58%), and glucose ratio in 10 cases (32%).

 Imaging and biopsy results presented are results during entire follow-up period.

 This included bilateral hilar lymphadenopathy and typical parenchymal or pleural abnormalities on chest X-ray or chest CT, signs of inflammation on MRI, and isotope uptake characteristic for sarcoidosis on FDG-PET or Gallium scan.

 Including both HRCT and regular CT-scanning.

 Location of histologically proven sarcoidosis.

 * >5 lymphocytes/mm³.
Six patients underwent neurosurgery at some point during the course of the disease. In 3 patients, the operation served diagnostic purposes (peripheral nerve biopsy, spinal cord biopsy, and dural tissue biopsy) and in 3 patients, complications of neurosarcoidosis required neurosurgical intervention (obstructive hydrocephalus in all).

The mean length of follow-up was 42 months and 33 of 52 patients (63%) were followed up >12 months. Complications during follow-up consisted of side-effects of prednisolone use, including weight gain, steroid-induced diabetes, and infection, which were reported in 26 of 30 patients with recorded complications (87%). Other complications during follow-up
The study included 52 patients diagnosed with neurosarcoidosis. Data are number/number assessed (%) and median (25th–75th percentile). TNF = tumor necrosis factor.

| Characteristic | n/N (%) | Characteristic | n/N (%) |
|----------------|---------|----------------|---------|
| Treatment      | 46/52 (88%) | Complications during follow-up | 30/52 (58%) |
| Pharmacological|         | Side-effects prednisolone | 26/30 (87%) |
| Steroids       | 43/52 (83%) | Weight gain | 13 (50%) |
| Prednisolone   | 42/43 (98%) | Diabetes | 10 (38%) |
| Only methylprednisolone | 1/43 (2%) | Infection | 3 (12%) |
| Prednisolone and methylprednisolone | 30/43 (70%) | Pyrosis/stomach ulcer | 2 (8%) |
| Cytoxic pharmaceutics | 17/46 (37%) | Osteoporosis | 2 (8%) |
| Methotrexate   | 14/17 (82%) | Psychiatric | 1 (4%) |
| Azathioprine   | 8/17 (47%) | Avascular necrosis of hip joint | 1 (4%) |
| Cyclophosphamide | 1/17 (6%) | Cardiovascular | 1 (4%) |
| Cyclosporine   | 1/17 (6%) | Other side effects | 8 (31%) |
| TNF-α inhibitors | 10/46 (22%) | Other | 12/30 (43%) |
| Infliximab     | 7 (70%) | Improvement | 31/46 (67%) |
| Adalimumab     | 1 (10%) | Stable disease | 13/46 (28%) |
| Infliximab and Adalimumab | 1 (10%) | Deterioration | 2/46 (4%) |
| Infliximab and Mycophenolate mofetil | 3/46 (7%) | Discharged from follow-up | 14/46 (30%) |
| Other          |         | Outcome |         |
| Neurosurgery   | 6/52 (12%) | Asymptomatic | 15/52 (29%) |
| Follow-up, mo  | 26 (8–70) | Complaints, no disability | 22/52 (42%) |
|                |         | Minor disability | 6/52 (12%) |
|                |         | Moderate-severe disability | 9/52 (17%) |

One patient on prednisone, methotrexate, and infliximab developed recurrent urinary tract infections. We did not encounter other opportunistic infections that could be attributed to second- or third-line immunotherapies.

None of the patients died during follow-up. Thirty-one of the 46 cases receiving treatment (67%) improved upon therapy, 13 cases (28%) stabilized, and 2 cases (4%) deteriorated. Of the 6 patients not receiving therapy, 4 (67%) showed spontaneous improvement. Fourteen of 46 treated patients (30%) were successfully treated (ie, no active inflammation and stable disease or improvement) and discharged from follow-up consultation. Twenty-one of 43 cases (49%) improved after treatment with only corticosteroids. Seventeen of these patients (65%) had no complaints or complaints without functional impairment at their last reported consultation. None of the patients treated with monoclonal TNF-α antibodies deteriorated during therapy. In 4 of the 9 patients (44%) treated with TNF-α inhibitors, improvement was seen and in 5 patients (56%) stable disease was established. In 1 case, treatment was successful and could be discontinued, in 2 cases, treatment was discontinued because it failed to establish improvement, the other cases were still receiving treatment at the last follow-up consultation. Overall, 15 patients (29%) were asymptomatic at their last recorded doctor consultation and 22 patients (42%) still experienced complaints without functional impairment in everyday life. Six patients (12%) experienced symptoms causing minor functional impairment and nine patients (17%) were moderate to severely impaired by their symptoms.

**DISCUSSION**

Diagnostic evaluation of patients with suspected neurosarcoidosis is directed toward detecting disease outside of the nervous system to facilitate tissue diagnosis. The Zajicek criteria focused on central nervous system (CNS) involvement with signs of inflammation on MRI or CSF as a major criterion for “probable neurosarcoidosis.” In our study, we found that limb sensory disturbance is a major symptom at clinical presentation in 46% of patients. Other studies also reported involvement of the peripheral nervous system, ranging from 6% to 69% of reported cases.11–14 ACE and lysozyme analysis were abnormal in about half of our patients, indicating low sensitivity of these investigations in compliance with reported literature.13 A chest CT-scan showed signs of sarcoidosis and a biopsy location in the majority of patients, enabling histological diagnosis. In a minority, FDG-PET or Gallium scintigraphy was needed to secure the diagnosis. Gallium scintigraphy is included in the criteria for diagnosis of probable sarcoidosis owing to high sensitivity of this test in the study of
Marangoni et al. However, Gallium scintigraphy results in CNS uptake in <5% of cases. A recent study suggests that FDG-PET CT could be used as a valid alternative imaging test, for it leads to better uptake in CNS sites. Furthermore, FDG-PET CT is suggested to have a higher sensitivity in detecting lymph node inflammation.

Neurologic symptoms were the first manifestation of neurosarcoidosis in 71% of cases. This is in agreement with previous studies which reported rates between 50% and 70%. Chronic aseptic meningitis was the most frequently found neurologic pathology in 37% of cases. This frequency is relatively high compared with previous studies, which reported between 3% and 40% of cases to present with aseptic meningitis. This could be because of a referral bias, as our center has specific expertise on chronic meningitis.

Forty-four of 46 patients (96%) stabilized or improved upon therapy. Fourteen of 46 patients (30%) were treated successfully and could be discharged from follow-up consultation. About half of the patients had a satisfactory reduction of symptoms on first-line therapy with corticosteroids. Treatment indications of TNF-α inhibitors are not well defined, as available literature on neurosarcoidosis patients treated with TNF-α inhibitors is limited to case reports and case series of patients refractive to other treatment options. In all these cases, response to treatment with few side effects is reported. However, treatment duration is often long and relapse on cessation of the TNF-α inhibitor is reported in several cases. As these case reports have limited follow-up period and are likely to be subject to publication bias, long-term efficacy of TNF-α inhibitors has yet to be established. Neurosarcoidosis is a chronic disease, and 71% of our patient population had residual symptoms at the end of follow-up, leading to functional impairment in 29%.

Our study has several important limitations. First, there are different classification systems for neurosarcoidosis, which all include slightly different populations. We chose to use the modified Zajicek criteria over other available classification systems, such as the more recent WASOG classification systems, which all include slightly different populations. We chose the modified Zajicek criteria as it is the most widely used and acknowledged classification system for neurosarcoidosis, and most fully encompasses the highly variable patient group. For instance, patients with peripheral neuropathy in sarcoidosis are not considered to have neurosarcoidosis according to the WASOG classification. Furthermore, the selection of patients is biased, as we only analyzed patients treated at a tertiary referral center. However, most patients with suspected neurosarcoidosis or a neurological autoimmune disorder of unknown cause are referred to specialized centers because of diagnostic difficulties. We were limited by the observational nature of our analysis, resulting in heterogeneous diagnostic evaluation, no structured follow-up, analysis of cases at different moments of their disease course, and missing data. These limitations caused suboptimal comparison of cases, but could not be overcome as they are inherent to the study design. However, in most patients, a similar course of diagnostic evaluation was followed and most patients were evaluated at a similar stage in their disease course. To overcome the problem of missing data, we gave an overall of n of N (%) in presenting our results. Research of neurosarcoidosis is limited by the observational nature of studies available on this topic. Only a few large cohort studies are available in literature, which are all no longer up-to-date regarding diagnostic or therapeutic possibilities. Future recommendations therefore include research of large patient groups with protocolled ancillary investigations, treatment, and follow-up, allowing for a more comprehensive comparison between patient groups. Furthermore, trials for second and third-line therapy are warranted to evaluate efficacy of different treatment modalities.

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