Medicine®

OBSERVATIONAL STUDY

OPEN

Neurosarcoidosis in a Tertiary Referral Center

A Cross-Sectional Cohort Study

Sonja E. Leonhard, MD, Daan Fritz, MD, Filip Eftimov, MD, PhD, Anneke J. van der Kooi, MD, PhD, Diederik van de Beek, MD, PhD, and Matthijs C. Brouwer, MD, PhD

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%); ^{18}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.

(*Medicine* 95(14):e3277)

Abbreviations: ACE = Serum angiotensin-converting enzyme, CNS = Central nervous system, CSF = Cerebrospinal fluid, CT = Computed tomography, MRI = Magnetic resonance imaging, PET-CT = Positron emission tomography-computed tomography, TNF-α = Tumor necrosis factor α.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology usually diagnosed between 20 and 40 years of age.[1] It can involve virtually any organ, but has a propensity for the lungs, lymph nodes and skin.[1,2] The prevalence of sarcoidosis is estimated at about 5 to 50 per 100,000 with the highest prevalence in Northern Europe.[3]

Nervous system involvement has been reported in 5% to 15% of patients and can involve any part of the nervous system, ranging from brain parenchyma, cranial nerves to peripheral nerves.[3–5] Previous studies reported neurologic symptoms as the presenting manifestation of sarcoidosis in 50% to 70% of neurosarcoidosis patients.[1,2,6,7] The most commonly reported neurological manifestation is cranial neuropathy with the facial and optic nerve being the most frequently affected nerves.[1,2,5,7,8] Other described neurological complications include parenchymal lesions, hydrocephalus, aseptic meningitis, peripheral neuropathy, and myopathy.[1–3,7]

Diagnosing neurosarcoidosis may be difficult because clinical features can be nonspecific. Furthermore, definite neurosarcoidosis requires histological confirmation, which is often not performed in patients with isolated central nervous system localization of sarcoidosis. Typically, extensive ancillary investigations are performed to exclude other causes and identify granulomas outside of the central nervous system for histological confirmation of sarcoidosis. Imaging techniques include cranial and muscle magnetic resonance imaging (MRI), chest X-ray or computed tomography (CT), and positron emission tomography-computed tomography (PET-CT).

If the diagnosis of possible, probable, or definite neurosarcoidosis is made, treatment can consist of corticosteroids (first line), methotrexate or azathioprine (second line) or monoclonal antibodies (third line).[5,9,10] The efficacy of these treatments, however, has not been studied systematically. In our hospital, a national neurosarcoidosis referral center has been established in 2014. In this study, we evaluated the clinical presentation, ancillary investigations, treatment, and disease course of patients with neurosarcoidosis in a tertiary referral center.

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

Editor: Maria Luz Cuadrado.
Received: December 28, 2015; revised: March 8, 2016; accepted: March 9, 2016.
From the Academic Medical Center, Center of Infection and Immunity Amsterdam (CINIMA), Department of Neurology (SEL, DF, FE, AJV, DV, MCB), Amsterdam, the Netherlands.
Correspondence: Matthijs C. Brouwer, Department of Neurology, Academic Medical Center, University of Amsterdam, Meibergdreef 9 Amsterdam 1105AZ, the Netherlands (e-mail: m.c.brouwer@amc.uva.nl).
Financial support and conflict of interest disclosure: MCB is supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw; NWO-Veni grant 2012 [916.13.078]), DvdB is supported by grants from the Netherlands Organization for Health Research and Development (ZonMw; NWO-Vidi grant 2010 [016.116.358]) and the European Research Council (ERC Starting Grant 281156).
All authors report no conflicts of interest.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003277

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 neurosarcoidosis was categorized according to an acknowledged classification system in the field of neurosarcoidosis, first formulated by Zajicek et al,[7] later modified by Marangoni et al.[8] The classification system we used categorizes patients into 3 groups according to certainty of the diagnosis: possible, probable, and definite neurosarcoidosis (suppl. Table 1, http://links.lww.com/MD/A878). Definite neurosarcoidosis is defined as histological confirmation of neuronal tissue, probable and possible neurosarcoidosis are defined as a clinical syndrome suggestive of the disease in combination with histological confirmation of systemic sarcoidosis, laboratory or imaging support. Additionally, the exclusion of alternative diagnoses, for example, neurological infection or malignancies, is essential. In this study, we included cases with both central and peripheral nervous system involvement. A positive histology for sarcoidosis was defined as the presence of histological features consistent with sarcoidosis, which include noncaseating granulomas with epithelioid cells and macrophages surrounded by lymphocytes, plasma cells and mast cells. In patients with muscle manifestation of neurosarcoidosis, histological confirmation can be derived from muscle tissue. Although in these cases histological confirmation comes from the tissue that established the diagnosis of neurosarcoidosis, we decided not to regard these cases as having definite neurosarcoidosis, 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 sarcoidosis, 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 sarcoidosis or its treatment. Infections were regarded as a side-effect of prednisolone or other immunosuppressive therapy if they were opportunistic 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 activities), 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 neurosarcoidosis 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 variables. 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 neurosarcoidosis. One patient (2%) was categorized as having definite neurosarcoidosis, 37 patients (71%) were categorized as having probable, and 14 patients (27%) as having possible neurosarcoidosis. The patient with definite neurosarcoidosis had positive histology for sarcoidosis following a biopsy of dural tissue. Of the patients with probable neurosarcoidosis, 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 investigations. 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 broncheal 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 neurosarcoidosis, histological confirmation came from muscle tissue. The 14 patients with possible neurosarcoidosis had a clinical syndrome and ancillary investigations suggestive of the disease, but did not fulfill the criteria for probable neurosarcoidosis (eg, no histological evidence of sarcoidosis 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 neurosarcoidosis 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 sarcoidosis was noted in 3 patients.

Of the 15 patients with a prior diagnosis of sarcoidosis outside of the nervous system, pulmonary sarcoidosis was found in 12 cases (80%), ocular sarcoidosis in 2 cases (13%), and liver and skin sarcoidosis were previously diagnosed in 1 patient each. Sarcoidosis of others organs developed during the course of the disease in 25 of 37 patients (68%) presenting with neurosarcoidosis. In 35 patients (67%), lung involvement was reported at any time during disease course. Eye involvement was reported in 17 patients (33%) and consisted of uveitis in 14 cases, sarcoidosis 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 manifestation of sarcoidosis 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 presentation 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 neurologic 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

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%)
		n.XII palsy	1 (2%)
Presenting symptoms		n.X palsy	1 (2%)
Limb sensory disturbance	24 (46%)	Spinal cord	12 (23%)
Headache	19 (37%)	Brain parenchymal disease	11 (21%)
Abnormal gait	14 (27%)	Peripheral nervous system	9 (17%)
Paresis	14 (27%)	Small-fibre neuropathy	5 (10%)
Limb pain	11 (21%)	Hydrocephalus	5 (10%)
Fatigue	8 (15%)	Muscle	5 (10%)
Vision loss	8 (15%)	Cerebral infarction	3 (6%)
Diplopia	8 (15%)	Neuro-endocrine[§]	3 (6%)
Myalgia	8 (15%)	Systemic involvement[‖]	41 (79%)
Ataxia	4 (8%)	Lungs	35 (67%)
Dysphagia	4 (8%)	Eye	17 (33%)
Cognitive decline	4 (8%)	Skin	8 (15%)
Speech disorder	4 (8%)	ENT	7 (14%)
Facial paresis	3 (6%)	Liver	3 (6%)
Psychiatric symptoms	3 (6%)	Heart	3 (6%)
Facial sensory loss	2 (4%)	Joints	2 (4%)
Impaired smell	2 (4%)	Diagnostic classification	
Hearing loss	1 (2%)	Definite	1 (2%)
		Probable	37 (71%)
		Possible	14 (27%)

Data are number/number assessed (%), and median (25th–75th percentile). If the number assessed is not noted, all 52 patients were assessed.
[*]Based on both clinical signs and results of ancillary investigation during the complete follow-up period.
[†]Membranous glomerulonephritis and psoriasis (n = 1), rheumafactor-negative rheumatoid arthritis (n = 1), primary sclerosing cholangitis (n = 1).
[‡]Rheumatoid arthritis (n = 5), rheumatoid arthritis and systemic lupus erythematosus (SLE) (n = 1), and Crohn disease (n = 1).
[§]Panhypopituitarism (n = 2), diabetes insipidus (n = 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 = 4), parotitis (n = 1), and vocal cord pathology (n = 2).

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 2. Ancillary Investigations on Presentation

Characteristic	n/N (%)	Characteristic	n/N (%)	
Ancillary investigations*		Imaging†	Abnormalities consistent with sarcoidosis‡	No abnormalities
Blood chemical tests	49/52 (94%)			
ACE (units/L) serum	58 (37–90)	Chest X-ray	21/39 (54%)	15/39 (38%)
>70	18/41 (44%)	Chest CT§	25/31 (81%)	6/30 (19%)
Lysozyme (mg/L) serum	3.5 (2.8–4.8)	Cranial CT	7/11 (64%)	2/10 (18%)
>3.5	12/26 (46%)	Cranial MRI	27/37 (73%)	6/37 (16%)
Calcium (mmol/L) serum	2.39 (2.31–2.47)	Spine MRI	12/18 (67%)	4/18 (22%)
>2.6	2/35 (6%)	FDG-PET CT	15/19 (79%)	3/19 (16%)
ESR serum	16.0 (6.0–40.3)	Gallium scintigraphy	3/5 (60%)	2/5 (40%)
>20	18/46 (39%)			
Cerebral spinal fluid analysis	31/52 (60%)	Location biopsy‖		
Normal	4/31 (13%)	Lymph node	19/34 (56%)	
White cell count, cells/mm^3	153 (29–553)	Lung	7/34 (21%)	
>5 cells/mm^3	18/28 (64%)	Skin	4/34 (12%)	
Lymphocytosis¶	6/18 (33%)	Muscle	3/34 (9%)	
Protein (g/L) CSF	0,55 (0,41–1,08)	Nerve	1/34 (3%)	
>50	15/25 (60%)	Liver	1/34 (3%)	
Glucose, mg/dL	57.7 (50.5–66.7)			
<50	6/27 (22%)	Tissue analysis		
Glucose ratio (CSF/serum)	0.48 (0.39–0.71)	Non-caseating granuloma	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%)			

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/mm^3.

leukocytes counted per mm^3) 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. ^{18}Fluorodeoxyglucose (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

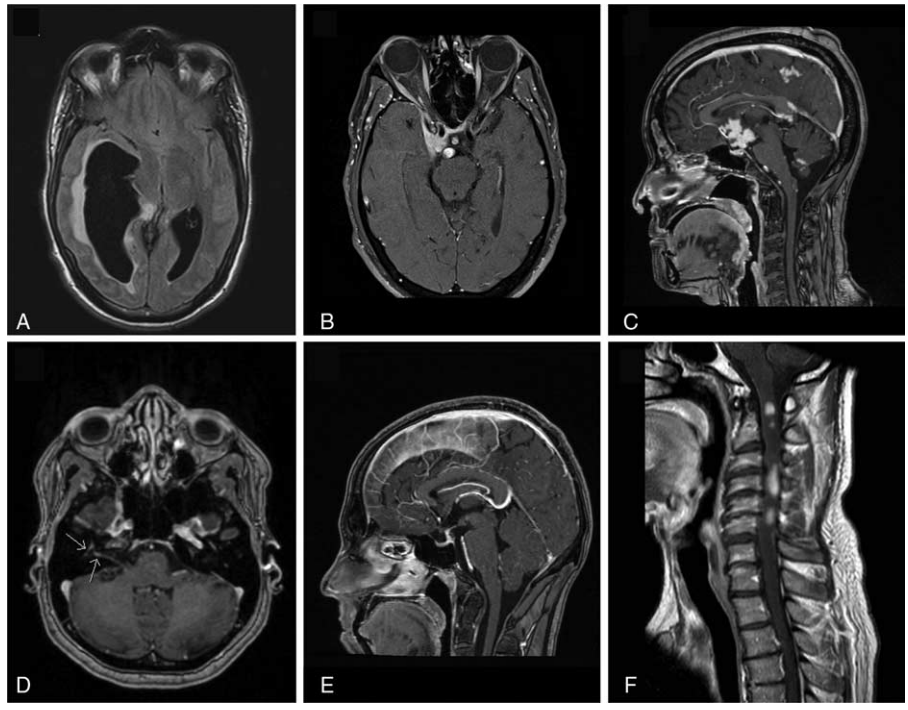

FIGURE 1. MRI results of patients with neurosarcoidosis. (A) Hydrocephalus because of an obstructive multicystic mass. (B) Meningeal enhancement and thickening of the right cavernous sinus in a patient with a third nerve palsy. (C) Leptomeningeal nodular enhancing lesions in a patient with cognitive decline and an abnormal gait. (D) Enhancement and thickening of the facial nerve (arrow) in a patient with facial nerve palsy. (E) Leptomeningeal and dural enhancement in a patient with chronic meningitis. (F) Enhancing lesions of the spinal cord in a patient with sensory loss and paresis of the left arm and leg.

treatment. 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

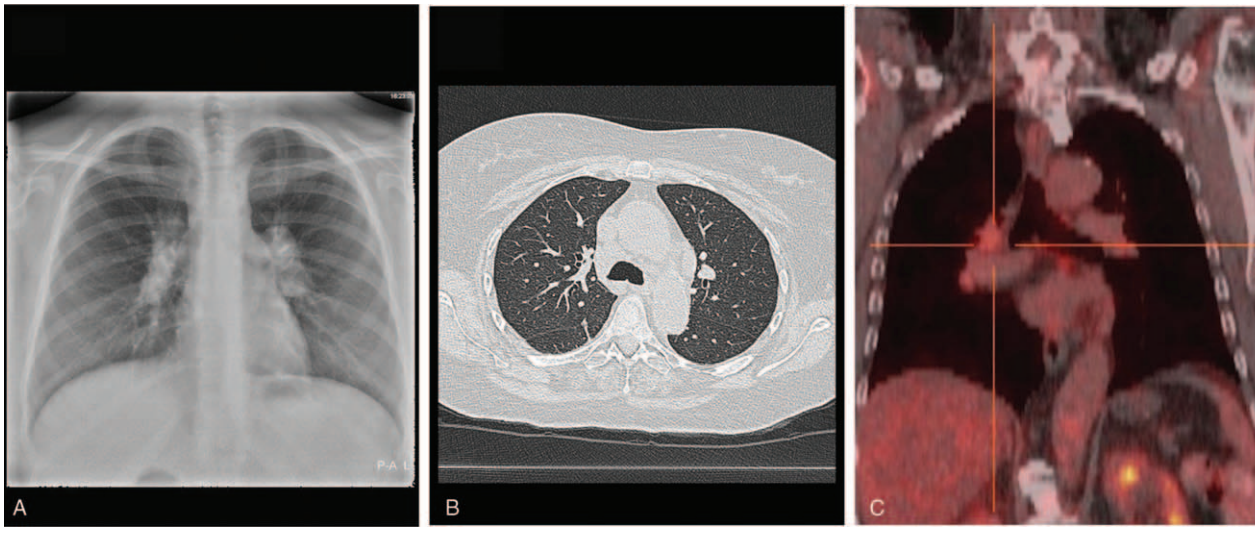

FIGURE 2. Systemic imaging in neurosarcoidosis patients. Chest X-ray showing substantial bilateral hilar lymphadenopathy. (B) Chest CT showing mediastinal and hilar lymphadenopathy. (C) Fluorodeoxyglucose-positron emission tomography-computed tomography showing pathological uptake in mediastinal and hilar lymph nodes.

TABLE 3. Treatment and Outcome Characteristic

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%)
Cytotoxic 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%)		
Adalimumab	1 (10%)	Response rate	
Infliximab and Adalimumab	1 (10%)	Improvement	31/46 (67%)
Infliximab and Mycophenolate mofetil	1 (10%)	Stable disease	13/46 (28%)
Other	3/46 (7%)	Deterioration	2/46 (4%)
		Discharged from follow-up	14/46 (30%)
Neurosurgery	6/52 (12%)		
		Outcome	
Follow-up, mo	26 (8–70)	Asymptomatic	15/52 (29%)
		Complaints, no disability	22/52 (42%)
		Minor disability‡	6/52 (12%)
		Moderate-severe disability§	9/52 (17%)

The study included 52 patients diagnosed with neurosarcoidosis. Data are number/number assessed (%) and median (25th–75th percentile). TNF = tumor necrosis fator.

*Intravenous pulsed methylprednisolone.

†Other complications during follow-up included pulmonary embolism (n = 4), pneumonia (n = 2), cryptococcal meningitis (n = 1), immunocompromised status contributed to sarcoidosis (n = 1), osteomyelitis owing to polyneuropathy (n = 1) and side effects of other used medication (n = 3).

‡Neurological deficits mildly interfering in everyday life, such as inability to cycle because of motor dysfunction.

§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 activities.

included pulmonary embolism (4 cases), pneumonia (2 cases), cryptococcal meningitis (1 case), and side effects of other used medication (3 cases). 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 and/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.[15] 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.[8] However, Gallium scintigraphy results in CNS uptake in <5% of cases.[16] 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.[16] Furthermore, FDG-PET CT is suggested to have a higher sensitivity in detecting lymph node inflammation.[5,17]

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%.[14] 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.[1,2,7,18–21] 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.[22–29] 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.[25,29] 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 sarcoidosis organ assessment instrument,''[30] 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.

REFERENCES

1. Joseph FG, Scolding NJ. Neurosarcoidosis: a study of 30 new cases. *J Neurol Neurosurg Psychiatry.* 2009;80:297–304.
2. Stern BJ, Krumholz A, Johns C, et al. Sarcoidosis and its neurological manifestations. *Arch Neurol.* 1985;42:909–917.
3. Hoitsma E, Faber CG, Drent M, et al. Neurosarcoidosis: a clinical dilemma. *Lancet Neurol.* 2004;3:397–407.
4. James DG, Sharma OP. Neurosarcoidosis. In *Proceedings of the Royal Society of Medicine.* 1967;60(11 Part 1):1169–1170.
5. Hoitsma E, Drent M, Sharma OP. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. *Curr Opin Pulm Med.* 2010;16:472–479.
6. Shah R, Roberson GH, Cure JK. Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. *AJNR Am J Neuroradiol.* 2009;30:953–961.
7. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis–diagnosis and management. *QJM.* 1999;92:103–117.
8. Marangoni S, Argentiero V, Tavolato B. Neurosarcoidosis. Clinical description of 7 cases with a proposal for a new diagnostic strategy. *J Neurol.* 2006;253:488–495.
9. Dutra LA, Braga-Neto P, Oliveira RA, et al. Neurosarcoidosis: guidance for the general neurologist. *Arq Neuropsiquiatr.* 2012;70:293–299.
10. Hebel R, Dubaniewicz-Wybieralska M, Dubaniewicz A. Overview of neurosarcoidosis: recent advances. *J Neurol.* 2015;262:258–267.
11. Wegener S, Linnebank M, Martin R, et al. Clinically isolated neurosarcoidosis: a recommended diagnostic path. *Eur Neurol.* 2015;73:71–77.
12. Nozaki K, Scott TF, Sohn M, et al. Isolated neurosarcoidosis: case series in 2 sarcoidosis centers. *Neurologist.* 2012;18:373–377.
13. Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. *QJM.* 2009;102:449–460.
14. Allen RK, Sellars RE, Sandstrom PA. A prospective study of 32 patients with neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2003;20:118–125.
15. Carlson ML, White JR Jr, Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: a review of 305 patients. *Otol Neurotol.* 2015;36:156–166.
16. Nishiyama Y, Yamamoto Y, Fukunaga K, et al. Comparative evaluation of 18F-FDG PET and 67Ga scintigraphy in patients with sarcoidosis, Journal of nuclear medicine: official publication. *Soc Nucl Med.* 2006;47:1571–1576.
17. Bolat S, Berding G, Dengler R, et al. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis. *J Neurol Sci.* 2009;287:257–259.
18. Hoyle JC, Jablonski C, Newton HB. Neurosarcoidosis: clinical review of a disorder with challenging inpatient presentations and diagnostic considerations. *Neurohospitalist.* 2014;4:94–101.
19. Lower EE, Broderick JP, Brott TG, et al. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med.* 1997;157:1864–1868.
20. Delaney P. Neurologic manifestations in sarcoidosis: review of the literature, with a report of 23 cases. *Ann Intern Med.* 1977;87:336–345.
21. Nozaki K, Judson MA. Neurosarcoidosis. *Curr Treat Options Neurol.* 2013;15:492–504.

22. Pettersen JA, Zochodne DW, Bell RB, et al. Refractory neurosarcoidosis responding to infliximab. *Neurology.* 2002;59:1660–1661.
23. Carter JD, Valeriano J, Vasey FB, et al. Refractory neurosarcoidosis: a dramatic response to infliximab. *Am J Med.* 2004;117:277–279.
24. Kobylecki C, Shaunak S. Refractory neurosarcoidosis responsive to infliximab. *Pract Neurol.* 2007;7:112–115.
25. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology.* 2009;72: 337–340.
26. Sodhi M, Pearson K, White ES, et al. Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. *Respir Med.* 2009;103:268–273.
27. Chintamaneni S, Patel AM, Pegram SB, et al. Dramatic response to infliximab in refractory neurosarcoidosis. *Ann Indian Acad Neurol.* 2010;13:207–210.
28. Santos E, Shaunak S, Renowden S, et al. Treatment of refractory neurosarcoidosis with Infliximab. *J Neurol Neurosurg Psychiatry.* 2010;81:241–246.
29. Riancho-Zarrabeitia L, Delgado-Alvarado M, Riancho J, et al. Anti-TNF-alpha therapy in the management of severe neurosarcoidosis: a report of five cases from a single centre and literature review. *Clin Exp Rheumatol.* 2014;32:275–284.
30. Judson MA, Costabel U, Drent M, et al. The WASOG Sarcoidosis Organ Assessment Instrument: an update of a previous clinical tool. *Sarcoidosis Vasc Diffuse Lung Dis.* 2014;31:19–27.