Characteristics and Long-Term Outcome of Neurosarcoidosis: A Population-Based Study from 1976–2013

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Keywords

Sarcoidosis · Neurosarcoidosis · Epidemiology · Outcome

Abstract

Background/Aims: Neurosarcoidosis is a rare condition with serious health consequences. However, little is known about clinical characteristics and outcome of neurosarcoidosis in the community setting. **Methods:** Patients with neurosarcoidosis were identified from a previously described cohort of patients with incident sarcoidosis from Olmsted County, Minnesota, United States from 1976 to 2013 using individual medical record review. Data on clinical characteristics, treatment, and outcome were collected. **Results:** Neurological involvement by sarcoidosis occurred in 11 patients (3% of all patients with sarcoidosis). Cranial neuropathy was the most common type of neurological disease (5 patients; 45%) followed by peripheral neuropathy (3 patients; 27%), and meningitis (3 patients; 27%). Cerebrospinal fluid (CSF) pleocytosis and elevated CSF protein levels were observed in patients with meningitis, intramedullary spinal cord sarcoidosis, intracranial mass lesion and some patients with cranial neuropathy but were normal in patients with peripheral neuropathy. All patients received high-dose glucocorticoids as initial treatment and almost all responded to this therapy.

Relapse after glucocorticoid dose reduction necessitated subsequent treatment with steroid-sparing agents in 4 patients. **Conclusion:** Neurosarcoidosis is an uncommon manifestation of sarcoidosis. Neurosarcoidosis manifestations generally responded well to high-dose glucocorticoids in the majority of patients, but relapse was common.

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Introduction

Sarcoidosis is an immune-mediated disorder characterized by the presence of noncaseating granuloma. The exact pathogenesis of sarcoidosis is not known but is believed to be a dysregulated immunologic response to environmental trigger(s) [1, 2]. The reported incidence of sarcoidosis ranges from 1 to 70 new cases per 100,000 person-years, depending on the ethnic background of the population [3–5]. Sarcoidosis can affect any organ, with the lung and mediastinal lymph node being the most frequently affected sites. Involvement of the nervous system by sarcoidosis is relatively uncommon with a reported prevalence of 4–9% [3, 6–8] but is associated with high morbidity and mortality. The current study used a previously identified cohort of patients with sarcoidosis from

Olmsted County, MN, United States, to characterize the epidemiology, clinical characteristics, and outcome of patients with neurosarcoidosis [9].

Methods

This is a retrospective cohort study that identified potential cases of incident sarcoidosis from 1976 to 2013 from the medical record-linkage system of the Rochester Epidemiology Project (REP) using the diagnosis codes related to sarcoid, sarcoidosis, and non-caseating granuloma. The REP medical record-linkage system collects diagnostic codes of all clinical encounters (hospitalization, outpatient visit, and emergency room visit) of Olmsted County, Minnesota residents with local providers (the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes and few private practitioners). Thus, virtually all clinically recognized cases of sarcoidosis in the community can be identified from the database. History, methodology, and clinical application of the REP medical record-linkage system have been described in detail elsewhere [10].

Medical records of the identified cases were individually reviewed to confirm the diagnosis of pulmonary sarcoidosis, which required the presence of noncaseating granuloma on histopathology, radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other possible causes of granulomatous inflammation such as tuberculosis and fungal infection. The only exception to the histopathology requirement was stage I pulmonary sarcoidosis that required only the presence of symmetric bilateral hilar adenopathy on thoracic imaging studies after excluding other alternative diagnoses. Isolated extrathoracic sarcoidosis (including isolated neurosarcoidosis) without pulmonary sarcoidosis was diagnosed by the presence of noncaseating granuloma, compatible clinical presentation, and exclusion of other granulomatous diseases, similar to the diagnosis of pulmonary sarcoidosis. However, diagnosis of all cases of extrathoracic sarcoidosis required histopathologic confirmation. Patients who were diagnosed with sarcoidosis prior to residency in Olmsted County (i.e., prevalent cases) were not included.

Confirmed cases of sarcoidosis were then reviewed for assessing neurologic involvement. Data on demographic characteristics, neurological manifestations, imaging study of the brain/spinal cord, cerebrospinal fluid (CSF) analysis, laboratory investigations, treatment, and outcome were collected. Follow-up was continued until death, migration out of system, or April 1, 2017. Descriptive statistics were used to summarize the data. This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards and the need for informed consent was waived.

Result

Between 1976 and 2013, 345 residents of Olmsted County, MN were diagnosed with sarcoidosis. Demographics and clinical characteristics of this cohort were previously described in detail [9]. Neurological involve-

ment was observed in 11 patients (3% of all patients with sarcoidosis; 95% CI 2–6%). Among these 11 patients, 55% were female, 73% Caucasian, 18% African-American, and 9% Asian with an average age of 44.8 years (SD 10.7 years at diagnosis; Table 1). Most patients fulfilled the criteria for probable neurosarcoidosis as proposed by Zajicek et al. [11]. A total of 3 patients fulfilled the criteria for definite neurosarcoidosis and 1 patient fulfilled the criteria for possible neurosarcoidosis. Cranial neuropathy was the most common type of neurological disease (5 patients; 45%) followed by peripheral neuropathy (3 patients; 27%) and meningitis (3 patients; 27%). Intramedullary spinal cord sarcoidosis and intracranial mass lesion were present in 1 patient. Extraneurologic involvement by sarcoidosis was also seen in all but 1 patient. Lung was by far the most commonly affected extraneurologic site (73%) followed by skin (18%). Involvement of skin, joint, lacrimal gland, and extrathoracic lymph node was seen in 1 patient.

Neurological abnormalities were part of the presenting symptoms that led to the diagnosis of sarcoidosis in 7 of the 11 patients (64%). The median time from onset of neurological symptoms to diagnosis of sarcoidosis was 1 month (range 2 weeks to 4 months). Neurosarcoidosis occurred after the diagnosis of sarcoidosis was established in the other 4 patients. In 1 patient, neurosarcoidosis developed 22 years after the initial diagnosis of systemic sarcoidosis.

CSF analysis was performed in all but 1 patient. All of those with meningitis had CSF pleocytosis (cell count ranged from 37 to 107 cell/mm³, predominately lymphocytes; normal range 0–5 cells/mm³) and elevated CSF protein level (range 47–206 mg/dL; normal range 14–45 mg/dL), but hypoglycorrhachia was seen only in 1 patient. CSF pleocytosis and high CSF protein level were also observed in the patient with intramedullary spinal cord sarcoidosis, the patient with intracranial mass lesion, and in some patients with cranial neuropathy but not in patients with peripheral neuropathy. Oligoclonal bands were present in the CSF of only 1 patient (14% of tested patients). The angiotensin-converting enzyme level was obtained in 10 patients and was elevated in 2 patients (20%).

All patients, except for 1 with isolated cranial nerve VII neuropathy, were treated with prolonged courses of glucocorticoids of 1 year or more. Almost all patients had a good response to initial treatment with high-dose glucocorticoids, often initially 1 g methylprednisolone daily for 3–5 days, or prednisone, 1 mg/kg body weight as initial dose. However, relapse of neurosarcoidosis was

Table 1. Demographics, clinical characteristics, treatment, and outcome of patients with neurosarcoidosis in this study

Case	Gender and age, years	Duration of follow-up, years	Neurological manifestations	Neurological diagnosis	Onset of neurological symptoms	Other involved organs	Imaging study at diagnosis	CSF analysis at diagnosis				Serum ACE level	Biopsy	Level of diagnosis*	Treatment	Outcome
								cells (per mm ³)	protein, mg/dL	glucose	oligo-clonal bands					
1	M, 44	7.3	Facial palsy	Cranial nerve VII	6 years after the diagnosis of sarcoidosis	Lung	Not done	Not done	Not done	Not done	Not done	Not done	Lung: noncaseating granulomas	Possible	Prednisone (60 mg/day; tapered a course of 1 week)	Good response, No recurrence after stopping prednisone. No residual neurological deficit.
2	F, 41	35.8	Facial palsy and paresthesia in all 4 extremities	Cranial nerve VII neuropathy and peripheral neuropathy	2 weeks before the diagnosis of sarcoidosis	Lung	Not done	Normal (2)	High (62)	Normal (52)	Not done	High	Lung: noncaseating granulomas	Probable	Prednisone (60 mg/day; tapered a course of 1.5 years)	Good response, No recurrence after stopping prednisone. No residual neurological deficit
3	F, 55	14.3	Facial palsy, ataxia and dysphonia	Cranial nerve VII neuropathy and intra-cerebellar mass	2 weeks before the diagnosis of sarcoidosis	None	MRI brain: Large solitary enhancing intra-cerebellar mass lesion	High (13; 99% L)	High (57)	Normal (79)	No	Normal	Intracerebellar mass lesion: noncaseating granulomas	Definite	Prednisone (60 mg/day; tapered a course of a year) after stopping prednisone. Good response. Able to taper off with AZA but developed hepatitis. HCQ 400 mg daily was later added	Good but the mass recurred 6 months after stopping prednisone. Good response. Able to taper off prednisone in 9 months. No recurrence. Remained on HCQ until death from lymphoma. No residual neurological deficit
4	M, 51	13.0	Subacute painless visual loss left eye (VA 20/25)	Optic neuritis of left eye	3 months before the diagnosis of sarcoidosis	Lung and extra-thoracic lymph node	MRI brain: Nonspecific white matter lesions	High (11; 70% L)	High (65)	Normal (60)	No	Normal	Extra-thoracic lymph node: noncaseating granulomas	Probable	Prednisone (40 mg/day; tapered a course of a year)	Good response. No recurrence after stopping prednisone. Last eye exam showed VA of 20/20 both eyes

Table 1. (continued)

Case	Gender	Age, years	Duration of follow-up, years	Neurological manifestations	Neurological diagnosis	Onset of neurological symptoms	Other involved organs	Imaging study at diagnosis	CSF analysis at diagnosis			Serum ACE level	Biopsy	Level of diagnosis*	Treatment	Outcome
									cells (per mm ³)	protein, mg/dL	glucose (mg/dL)	oligo-clonal bands				
5	F	42	7.5	Subacute painless visual loss both eyes (VA 20/40 right eye and 20/25 left eye)	Optic neuritis of both eyes	8 years after the diagnosis of sarcoidosis	Lung and skin	MRI brain: Enhancement and swelling of both optic nerves	Normal (1)	Normal (24)	Normal (53)	No	Normal	Probable	IV methylprednisolone 1,000 mg IV for 5 days and prednisone at 60 mg/day were initiated. Infliximab 5 mg/kg IV monthly and HCQ at 400 mg/day were added.	No response. VA continued to decline to decline
6	M	48	7.4	Headache	Meningitis	4 months before the diagnosis of sarcoidosis	Eye	MRI brain: Diffuse leptomeningeal enhancement	High (107; 91% L)	High (206)	Low (30)	Yes	Normal	Lepto-meninges: Definite noncaseating granulomas	Prednisone (60 mg/day; tapered over 2 years)	Good response but meningitis recurred when prednisone tapered to 15–20 mg/day. Still unable to taper prednisone lower than 15–20 mg/day. Prednisone taper is underway
7	M	47	28.2	Headache and ataxia	Meningitis with communicating hydrocephalus	1 month before the diagnosis of sarcoidosis	Lung	CT brain: communicating hydrocephalus	High (37; 89% L)	High (130)	Normal (61)	No	High	Mediastinal lymph node: noncaseating granulomas	Prednisone (60 mg/day; tapered over 1 year)	Headache decreased but ataxia persisted
8	F	26	15.5	Headache and fever	Meningitis	1 month before the diagnosis of sarcoidosis	Lung and lacrimal gland	CT brain: normal	High (39; 85% L)	High (47)	Normal (49)	Not done	Normal	Probable	Prednisone (40 mg/day; tapered over 10 months).	Good response but meningitis recurred 5 months after stopping prednisone. Good response. Able to taper off prednisone in 9 months. No recurrence. No residual neurological deficit

Table 1. (continued)

Case	Gender, and age, years	Duration of follow-up, years	Neurological manifestations	Neurological diagnosis	Onset of neurological symptoms	Other involved organs	Imaging study at diagnosis	CSF analysis at diagnosis			Serum ACE level	Biopsy	Level of diagnosis*	Treatment	Outcome
								cells (per mm ³)	protein, mg/dL	glucose (mg/dL)					
9	F, 44	5.3	Mid-back pain and paresthesia around chest wall	Spinal cord sarcoidosis	1 month before the diagnosis of sarcoidosis	Lung	MRI spinal cord: normal PET scan: moderate FDG avid activity within the spinal canal from T9-T12	High (26; 89% L)	High (41)	Normal (52)	Normal	Lung: noncaseating granulomas	Probable	Prednisone (60 mg/day; tapered over 1.5 years)	Good response, No recurrence after stopping prednisone. No residual neurological deficit.
10	F, 65	4.1	Weakness of all 4 extremities	Peripheral neuropathy	22 years after the diagnosis of sarcoidosis	Lung and joint	MRI brain and spinal cord: normal	Normal (1)	Normal (35)	Normal (47)	Not done	Lung: noncaseating granulomas	Probable	Prednisone (60 mg/day; tapered over 1 years) Prednisone was reinitiated at 20 mg/day along with MMF 2 g/day	Good response but the weakness recurred 1 month after stopping prednisone. Good response the weakness still recurred after stopping prednisone. Patient thereafter maintained on prednisone 10 mg/day and MMF 2 g/day until her death from MDS.
11	M, 30	1.5 months	Decreased sensation of lateral aspect of left foot	Peripheral neuropathy	4 years before the diagnosis of sarcoidosis	Skin	Not done	Normal (1)	Normal (29)	Normal (60)	No	Sural nerve: granulomatous endoneurial inflammation Skin: non-caseating granulomas	Definite	Prednisone was initiated at 60 mg/day, the patient then migrated out of the country. No further follow-up information was available.	NA

AZA, azathioprine; HCQ, hydroxychloroquine; MTX, methotrexate; MMF, mycophenolate mofetil; NA, not available; MDS, myelodysplastic syndrome; VA, visual acuity.

* Level of diagnosis per Zajicek et al. [11].

common (4 patients) after the treatment was discontinued or the glucocorticoid dose was reduced. Several disease-modifying anti-rheumatic disease drugs (DMARDs), including methotrexate, mycophenolate mofetil, hydroxychloroquine, and azathioprine were used in this cohort as glucocorticoid-sparing agents after failure of glucocorticoids taper. The disease progressed in 1 patient despite high-dose glucocorticoids. Infliximab was added as rescue therapy with good response.

Discussion

Similar to previous studies, the prevalence of neurosarcoidosis was low in the current cohort (3% of all patients with sarcoidosis). However, the prevalence observed in this study is slightly lower than the reported prevalence of 4–9% from previous referral-based cohorts [3, 6–8]. The difference in methodology is possibly responsible for the lower prevalence, as the current study utilized a population-based cohort of patients with sarcoidosis, which may be able to capture a more complete spectrum of sarcoidosis in the community, unlike referral-based studies that may have selection bias and include more severe cases. The frequency of specific types of neurological abnormalities in this cohort was similar to previous studies with cranial neuropathy being the most common neurological abnormality, present in almost half of patients, followed by meningitis and peripheral neuropathy [12, 13].

The diagnosis of neurosarcoidosis is often challenging as the neurologic abnormalities due to neurosarcoidosis can be seen in a myriad of neurologic disorders. Demonstration of noncaseating granuloma in neural tissue remains the gold standard for the diagnosis. However, biopsy of the nervous system is often prohibitively invasive [13]. In addition, false negative results are common, with up to 30–40% of brain parenchymal and meningeal biopsies failing to demonstrate the presence of noncaseating granuloma [14]. Zajicek et al. [11] proposed a set of criteria for diagnosing neurosarcoidosis that allows a “probable” diagnosis to be made by biopsy of an extraneurologic organ and evidence of inflammation in the central nervous system (from CSF analysis and/or MRI) without the requirement of nervous system histopathology. None of the patients in this cohort had isolated neurosarcoidosis. Sarcoidosis affected at least 1 additional organ in all patients in this cohort, with the lung being the most commonly affected organ.

The high frequency of extraneurologic sarcoidosis among patients with neurosarcoidosis has been consistently demonstrated in several cohorts [11, 13, 15]. Thus, careful physical examination and imaging study of the thorax should be performed to identify affected organs that may be eligible as alternative sites for biopsy. Histopathological confirmation of the diagnosis was available in all patients, including the biopsy of nervous system tissues in 3 patients. Identification of the extent of sarcoidosis is also important for monitoring the progression and response to treatment of the disease in each organ.

CSF analysis can be helpful to identify the central nervous system inflammation, as most patients with neurosarcoidosis involving the central nervous system in this cohort had CSF pleocytosis and elevated CSF protein level. However, the degree of CSF abnormality was generally mild (highest protein level in this cohort was 206 mg/dL; highest cell count was 107 cell/mm³). In general, more profound CSF abnormalities including neutrophil-predominant pleocytosis and hypoglycorrhachia are not characteristics of neurosarcoidosis and are more suggestive of bacterial infection. Oligoclonal bands were detected in CSF only in 1 patient in this cohort. This observation is in line with the low prevalence of oligoclonal bands in other neurosarcoidosis cohorts [11, 16]. CSF analysis for oligoclonal bands may have a diagnostic value for differentiating neurosarcoidosis from multiple sclerosis with their presence being suggestive of multiple sclerosis; their absence, on the other hand, is suggestive of neurosarcoidosis.

A high rate of relapse after initial response to high-dose glucocorticoids was observed in this cohort despite prolonged duration (1–2 years) of glucocorticoids treatment in almost all patients. A high recurrence rate was described in previous studies as well [16, 17]. Several DMARDs were used as steroid-sparing agents in this study, but only 2 patients were able to discontinue glucocorticoids and both received hydroxychloroquine. Another study reported the stabilization and/or improvement of neurological symptoms in 10 out of 12 patients who could not tolerate or who were elected not to take glucocorticoids and were treated with hydroxychloroquine mono-therapy [18]. Given the significant morbidity associated with relapse, the use of concomitant DMARD therapy could be considered from the outset of treatment along with glucocorticoids, similar to the treatment of other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [19, 20]. The potential benefits of DMARD therapy must be weighed against their potential risks. Controlled studies are required to establish the role of combination therapy in neurosarcoidosis.

The efficacy of infliximab, a chimeric monoclonal antibody against tumor-necrosis factor alpha, for pulmonary sarcoidosis has been demonstrated in randomized, controlled clinical trials [21, 22]. In this cohort, infliximab was successfully used in 1 patient as a rescue therapy after glucocorticoids failure. The efficacy of infliximab as a rescue therapy for neurosarcoidosis was previously described in a few case reports and case series [23, 24], but no controlled study is available.

This study has some limitations related to its retrospective nature, as patients were not systematically evaluated for neurologic involvement of sarcoidosis. Therefore, the burden of unrecognized disease is not known. In addition, some recognized cases may not have been captured in this cohort if they were not correctly coded as sarcoidosis in the medical-linkage system. There was no standard follow-up or documentation protocol and, thus, some of the pertinent data were not available. Generalizability of the observations is another limitation, as the clinical characteristics and outcome of sarcoidosis vary considerably between ethnic groups [5]. The population of Olmsted County, MN as well as the patients in this cohort, is predominately of northern European ancestry.

Conclusion

Neurosarcoidosis is an uncommon manifestation of sarcoidosis that was seen in only 3% of patients in this cohort. Cranial neuropathy, meningitis, and peripheral neuropathy were the most common types of neurological

diseases. Neurosarcoidosis manifestations generally responded well to high-dose glucocorticoids in the majority of patients, but relapse was common.

Disclosure Statement

The authors have no financial or nonfinancial potential conflicts of interest to declare.

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Author Contribution

P.U. was responsible for conception and design, acquisition, and interpretation of data, drafting of the manuscript, statistical analysis. E.L.M. was responsible for conception and design, acquisition, and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis, and supervision. C.S.C. was responsible for conception and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis.

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