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Neurosarcoidosis in a public safety net hospital: a study of 82 cases

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Abstract. *Objective:* To characterize clinical presentation, laboratory and imaging data, and treatment outcomes for neurosarcoidosis in an urban safety net hospital. *Methods:* The research database of Cook County Health and Hospitals system was queried for all cases of sarcoidosis from 2006 to 2013. These cases plus those identified through a survey of neurology faculty were reviewed and flagged if suspected to be neurosarcoidosis. Data were extracted in a standardized fashion, upon review by two experienced neurologists; patients were classified as definite, probable or possible neurosarcoidosis. Disagreements on classification were resolved by consensus conference. *Results:* 1706 cases of sarcoidosis were identified, with 82 (4.8%) classified as neurosarcoidosis. The cohort was predominantly African American (89%). Six were classified as definite, 34 as probable, and 42 as possible neurosarcoidosis. Neurosarcoidosis was the presenting symptom of sarcoidosis in 74% of cases. The most common presenting phenotype was myelopathy (21.7%), followed by optic nerve/chiasm involvement (16.0%) and epilepsy (11.3%). The facial nerve was involved in only 2% of cases. Chest x-ray showed abnormalities of sarcoidosis in 43.3% of cases, while chest CT did so in 78.6%. Corticosteroids were the initial treatment in 91% of cases, and outcomes were good in 53% of cases. *Conclusion:* Neurosarcoidosis remains a challenging diagnosis with the majority of patients without a previous diagnosis of systemic sarcoidosis. Chest imaging was supportive of the diagnosis in a majority of patients. Our cohort differs from others in the literature due to a low prevalence of facial nerve involvement. Prospective registry studies are needed. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 25-32)*

Key words: neurosarcoidosis, sarcoidosis, inflammatory diseases

Introduction

Sarcoidosis is an inflammatory multisystem disease of unknown etiology, histologically characterized by noncaseating granulomas. Sir Jonathan Hutchinson first described sarcoidosis in 1877, while Heerfordt's description of uveoparotid fever in 1917 is thought of as the first description of neurosarcoidosis (1). While the lungs and thorax are involved in 90% of cases of sarcoidosis, nervous system involvement in sarcoidosis is rare, occurring in 5-15% of clinical cases, and up to 25% of cases at autopsy (2-5). Despite 140 years of advances in medicine, the cause and optimal treatment of this disorder remain elusive.

The worldwide prevalence of sarcoidosis is 60 per 100,000, with age of onset typically between

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20-40 years (1). The incidence has been noted to vary among different ethnic groups, with European Americans having an incidence of 3-10 per 100,000 and an African American incidence of 35-80 per 100,000 (6). Racial and ethnic differences have been noted for age of onset of disease, clinical presentation, and putative susceptibility genes (6, 7).

Neurosarcoidosis remains a challenging diagnosis, and is another "great imitator" in modern medicine. It can involve any area of the neuraxis and can have a monophasic, relapsing, or chronic progressive course. Data on neurosarcoidosis have largely been limited to small case series, with varying frequencies of common clinical presentations having been described in various centers. African Americans have a higher incidence of sarcoidosis than other populations, and are more likely to have extrathoracic involvement (8-11). Case series of neurosarcoidosis to date have often failed to enumerate demographic data in their patients. We aimed to contribute to the existing literature by examining the clinical presentation, laboratory and imaging data, and treatment outcomes of neurosarcoidosis patients in an urban, public safety-net hospital system.

Methods

The research database of Cook County Health and Hospitals System (CCHHS) was queried for all cases of sarcoidosis from 2006 to 2013, identified by ICD 9 codes. We supplemented the potential cases with patients identified as having neurosarcoidosis through a survey of neurology faculty. Local IRB approval was obtained for this protocol, and individual patient data were de-identified after initial data extraction. Data were extracted in a standardized fashion, with initial training and audits of results during the data extraction process. Upon review by two experienced neurologists; (LW and JD) patients were classified as definite, probable or possible neurosarcoidosis according to a modified version of the criteria proposed by Zajicek, et al (4).

All diagnostic categories required a clinical syndrome compatible with neurosarcoidosis and exclusion of other potential diagnoses (Table 1). Definite neurosarcoidosis required a tissue biopsy of nervous system tissue demonstrating non-caseating granulomas. Probable neurosarcoidosis was defined as a compatible syndrome combined with a biopsy showing non-caseating granulomas in non-nervous system tissue. This category differed from the Zajicek (4) criteria in that indirect indicators such as chest imaging combined with evidence of CNS inflammation via MRI or CSF were not allowed. Possible neurosarcoidosis patients either did not have a tissue biopsy performed, or had non-diagnostic biopsies. Disagreements on classification were resolved by consensus conference (LW and JD).

Table 1. Diagnostic criteria for neurosarcoidosis

Definite	Compatible clinical syndrome, exclusion of other etiologies, nervous system tissue biopsy showing non-caseating granulomas
Probable	Compatible clinical syndrome, exclusion of other etiologies, non-nervous system tissue biopsy showing non-caseating granulomas
Possible	Compatible clinical syndrome, exclusion of other etiologies, no tissue biopsy or non-diagnostic biopsy

Statistical comparisons were made for gender, and in the comparison of neurosarcoidosis and non-neurosarcoidosis patients. Chi squared and Fisher's exact tests were used for categorical variables, while the t-test was used for continuous variables.

Results

The initial search yielded 1706 cases of sarcoidosis, of which 82 were classified as definite, probable or possible neurosarcoidosis. There were 6 definite cases (7.3% of the cohort), 34 probable cases (41.5%) and 42 possible cases (51.2%) of neurosarcoidosis identified.

Demographic data (Table 2) were available in 1702 of the sarcoidosis cases and all of the neuro-

Table 2. Demographics

	All Sarcoidosis (N=1702)	Neurosarcoidosis (N=82)
Gender	59.4% Female	47.6% Female
Race	N (%)	N (%)
Black	1467 (86.2)	73 (89.0)
Hispanic	89 (5.2)	4 (4.9)
White	65 (3.8)	3 (3.7)
Other	81 (4.8)	2 (2.4)

sarcoidosis cases. The sarcoidosis patient population was 60% female, while that of the neurosarcoidosis cohort was 48% female (p=.03). Both groups showed an African American predominance. During the time of the study, CCHHS overall patient population was 53% African American. Neurosarcoidosis was the presenting symptom of sarcoidosis in 74% of cases. The median age at time of first diagnosis was 45±11.4 years (range 21-76 years) in the neurosarcoidosis group, and 49±10.8 years (range 16-82 years) in the sarcoidosis group. For neurosarcoidosis patients, men tended to be diagnosed at a younger mean age than women, 40 vs. 52 years (P<0.0001).

Neurosarcoidosis was the presenting phenotype in 74% of cases. The most common clinical syndrome encountered was myelopathy (22%), followed by optic nerve/chiasm involvement (16%), epilepsy(12%) and both meningeal (11%) and parenchymal brain lesion (11%) (Table 3). Multiple different clinical syndromes would often affect an individual patient. Peripheral nervous system manifestations of sarcoidosis were rare, occurring in 4.8% of patients. Hypothalamic and/or pituitary lesions were counted in a category distinct from parenchymal brain lesions due to the unique implications of neuroendocrine dysfunction.

Chest X-ray data was available in 82% of the neurosarcoidosis cohort, of which 43% had abnormalities consistent with a diagnosis of sarcoidosis. Chest CT data was available in 69% of the patients, of which 79% had abnormalities consistent with sarcoidosis. Gallium scan was abnormal in 6 of 9 cases. No patients underwent whole body FDG-PET, as this imaging modality was not routinely available in our health system during the time of the study. Systemic imaging results are summarized in Table 4.

Table 3. Clinical syndromes

Syndrome (N=106)	n (%)
Myelopathy	23 (21.7)
Optic Nerve/Chiasm	17 (16.0)
Parenchymal brain lesion	11 (10.4)
Epilepsy	12 (11.3)
Meninges	11 (10.4)
Pituitary/Hypothalamic	9 (8.5)
CN lesion other than 2 or 7	7 (6.6)
Hydrocephalus	6 (5.7)
Brainstem/Cerebellar	2 (1.9)
CN 7 lesion	2 (1.9)
Headache	2 (1.9)
Peripheral Neuropathy	2 (1.9)
Myopathy	1 (0.9)
Radiculopathy	1 (0.9)

Table 4. Systemic imaging

	N (%)
CXR (N=63)	
Normal	34 (54)
Abnormal - hilar LAD	20 (32)
Abnormal - other sarcoidosis	7 (11)
Abnormal - non-sarcoidosis	2 (3)
Chest CT (N=56)	
Normal	12 (21)
Abnormal - hilar LAD	38 (68)
Abnormal - other sarcoidosis	6 (11)
Gallium scan (N=9)	
Abnormal	6 (67)
Normal	3 (33)

Brain MRI was performed in 52 patients. The most common areas of abnormality were optic nerve/chiasm (23%), followed by meninges (21%), and combined involvement of both parenchyma and meninges (17%). Spine MRI was performed in 19 patients, with abnormalities most often found involving both spinal cord parenchyma and meninges (68%) followed by isolated meningeal involvement (21%). The region of spinal cord involvement was cervical in 8 cases (42%), thoracic in 6 cases (32%) and both cervical and thoracic in 5 cases (26%). Neuroimaging is summarized in Table 5. Representative examples of MRI findings are in Figure 1.

Laboratory data are shown in Table 6. Serum ACE level was abnormal in 30% of cases. CSF leukocytosis was noted in 51% of cases, while CSF protein was elevated in 64% of cases. CSF glucose was abnormal in 2.6% of cases. Oligoclonal bands were noted 2 of 13 (15%) of tested samples. CSF ACE level was not tested. CSF was normal in 23% of patients.

Biopsies were performed 56 times in 54 patients. Results are shown in Table 7. Lung was the most common organ biopsied (most often via transbronchial lung biopsy), comprising 50% of the biopsies performed. Non-caseating granulomas were found in 79% of lung biopsies, while the remainder were non-diagnostic. Brain biopsy was performed in 6 patients, 11% of the biopsy cohort, and had abnormalities consistent with sarcoidosis in 5 patients, while

Table 5. Neuroimaging

	N (%)
CT Head (N=52)	
Normal	16 (31)
Atrophy	8 (15)
Hydrocephalus	7 (13)
Parenchymal lesion	5 (10)
Ischemic white matter	3 (6)
Meninges	3 (6)
Cavernous Sinus	2 (4)
Infarct	2 (4)
Parenchyma and Meninges	2 (4)
Pituitary lesion	2 (4)
Encephalomalacia	1 (2)
Meningioma mimic	1 (2)
MRI Brain (N=52)	
Optic Nerve/Chiasm	12 (23)
Meninges	11 (21)
Parenchyma and Meninges	9 (17)
Hydrocephalus	5 (10)
High T2 signal	4 (8)
Cavernous Sinus	3 (6)
Pituitary	3 (6)
Meningioma mimic	3 (6)
Encephalomalacia	1 (2)
Normal	1 (2)
Parenchyma only	2 (4)
Spine MRI Regions (N=19)	
Cervical	8 (42)
Thoracic	6 (32)
Cervical and Thoracic	5 (26)
Spine MRI abnormalities (N=19)	
Cord parenchyma and meninges	13 (68)
Cord parenchyma only	4 (21)
Cord atrophy	1 (5)
Meninges only	1 (5)

* Two patients had Brain MRI abnormalities fitting in more than one of the chosen categories

one brain biopsy was nondiagnostic. Skin and lymph node were the next most common biopsy sites (9% and 7% of the cases, respectively), and were abnormal in all cases. Two spinal cord biopsies were performed, both of which yielded a tissue diagnosis of neurosarcoidosis. Isolated dural biopsies were performed in 3 cases, 1 of which showed noncaseating granulomas, while the other two were nondiagnostic. Other biopsy sites included nose, parotid gland, kidney, liver, conjunctiva, and testicle.

Corticosteroids were used as initial treatment in 91% of cases. Long-term steroid use was observed in 51% of all patients, and in 83% of patients in which any chronic immunotherapy was used. Some form of chronic immunosuppression, including corticosteroids and other immunosuppressants, was used in 59% of the cases.

Steroid sparing agents consisted of methotrexate, azathioprine, infliximab, hydroxychloroquine and mycophenolate mofetil. Methotrexate was the most commonly used steroid sparing agent, but no single agent was predominant.

Data on outcomes were available in 59 patients, 72% of the cohort. Patient functional status was assessed via chart review on the last available visit. The classification was as follows:

Good: Asymptomatic, minor complaints, minor functional disability but still able to do ADLs (activities of daily living)

Fair: Moderate functional disability, unable to work, still able to do ADLs

Poor: Severe functional disability, impaired ambulation, unable to do ADLs, or dead

Based on this schema, 53% of patients had a good outcome, 20% had a fair outcome, and 27% had poor outcomes. There were two deaths in the cohort, one from gastric cancer and one due to neurosarcoidosis. The neurosarcoidosis death was in a patient who had acute decompensation of a chronic hydrocephalus, and who had refused ventriculoperitoneal shunting on multiple occasions.

Discussion

This case series of neurosarcoidosis patients is one of the largest case series published to date. Many of our findings approximate those of previously reported case series. For example, neurosarcoidosis affected 5% of the sarcoidosis cohort., and was the presenting symptom in 74% of the cases. Both of these observations fall within the range of previously reported data (3, 4, 12). The demographics of this cohort are predominantly African-American. Prior studies often omit demographics, or have lower percentages of African-American patients. African-Americans with sarcoidosis have been noted to have a higher incidence of systemic involvement, and a more aggressive course (8, 9). The age range of patients in this study was slightly higher than previously reported peak incidence of 20-40 years, but largely overlapped with prior published data. This may relate to our patient population who are largely uninsured or underinsured, presenting later in the course of disease.

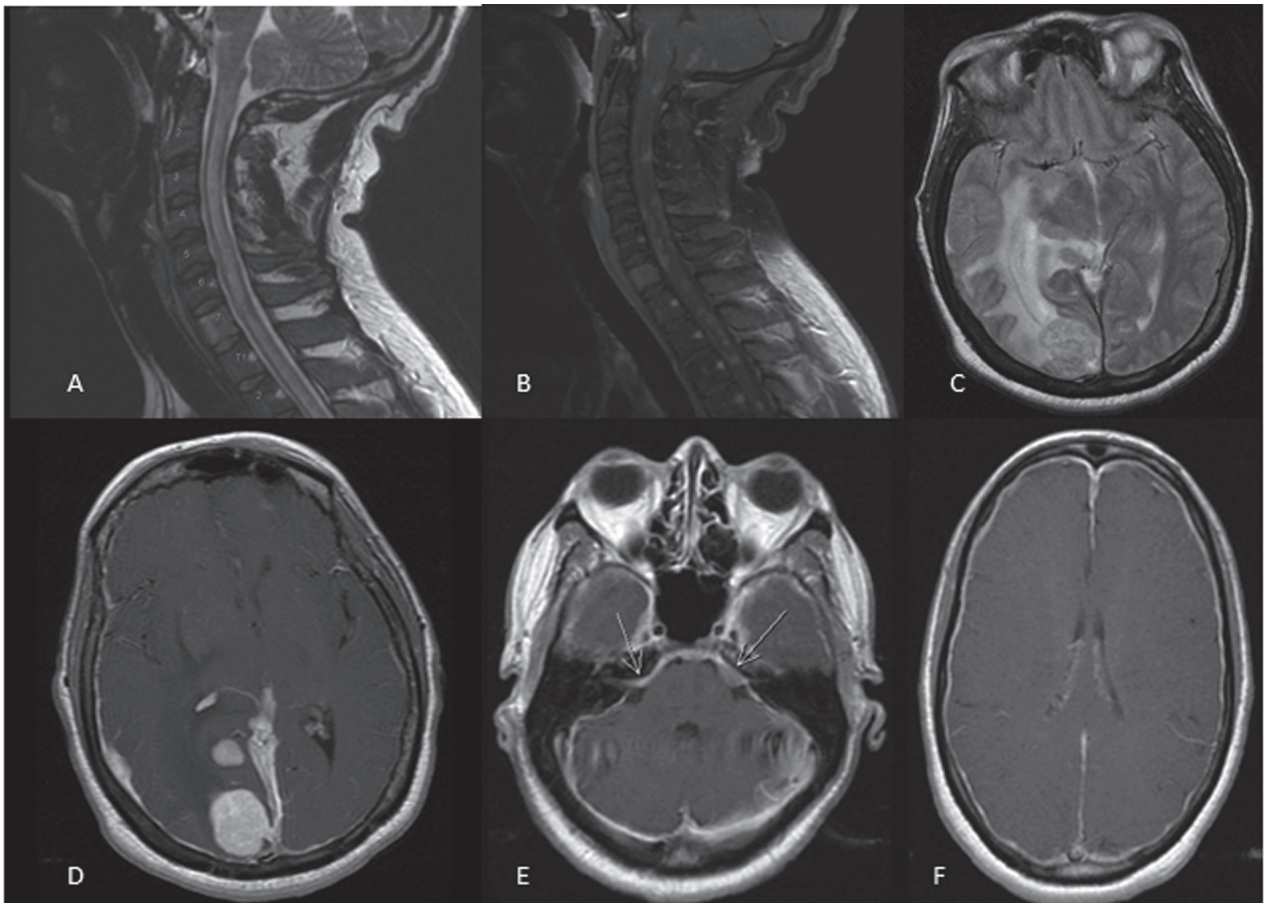

Fig. 1. MRI Images from 3 patients with neurosarcoidosis. Patient 1 had a spinal cord MRI showing T2 parenchymal hyperintensity (A) and post contrast T1 images (B) showing nodular contrast enhancement. Patient 2 had images initially concerning for a neoplastic mass lesion in (C), showing a T2 lesion with surrounding edema and (D) avid T1 homogenous enhancement of the lesion and nearby meninges. Patient 3 (E,F) had T1 enhancement of cranial nerve structures and smooth enhancement of the pachymeninges. All images are from patients with either definite or probable neurosarcoidosis

Table 6. CSF data and Serum ACE levels

	Mean	Median	St. Dev	Range	%abnormal
Serum ACE (u/L) (N=58)	45.4	33	36.7	2-193	30.1
CSF WBC (cells/uL) (N=39)	21	6	26	0-80	51.3
CSF protein (mg/dL) (N=39)	193	92	424	11-2659	64.1
CSF glucose (mg/dL) (N=39)	64.7	60	29.3	16-121	2.6

The clinical presentation of neurosarcoidosis most commonly involves the facial nerve in most case series, followed by optic neuropathy and other cranial neuropathies. Our series differed from the literature due to a low prevalence of facial nerve involvement (13, 14). This may be due to under-reporting of mild cases, but screening of all sarcoidosis cases was meant to avoid this problem. In addition, aseptic meningitis was rare in this cohort, with only 4 patients (5%) of the cohort, and typically did not occur in isolation. Peripheral nervous system sarcoidosis was also rare in this cohort, occurring in 4.8% of patients. Case series with a Caucasian predominance have reported peripheral neuropathy in 2-40% of cases, with

Table 7. Biopsy results

Total biopsies (N=56)	n (%)
Lung - abnormal	22 (39.3)
Lung - nondiagnostic	6 (10.7)
Brain - abnormal	5 (8.9)
Lymph node - abnormal	5 (8.9)
Skin - abnormal	4 (7.1)
Dura - nondiagnostic	2 (3.6)
Lung - normal	2 (3.6)
Spinal cord - abnormal	2 (3.6)
Brain - nondiagnostic	1 (1.8)
Conjuctiva - normal	1 (1.8)
Dura - abnormal	1 (1.8)
Kidney - abnormal	1 (1.8)
Liver - abnormal	1 (1.8)
Nose - abnormal	1 (1.8)
Parotid - normal	1 (1.8)
Testicle - abnormal	1 (1.8)

*56 biopsies performed in 54 patients

some authors reporting a lower frequency in African Americans (15), which may explain this finding. In addition, patients with confounding factors and peripheral neuropathy, such as diabetes mellitus, were excluded from the cohort, which could have resulted in false negative exclusions. Myelopathy was a frequent phenotype, in similar frequency to other cohorts.

Some of these findings may be due to the aforementioned tendency towards more aggressive disease in the African American population. In addition, case series differ in classification schema and reporting. For example, in this series we elected to separate out pituitary/hypothalamic lesions from parenchymal lesions due to the unique manifestations and management implications of endocrine dysfunction. As an additional example, several patients with communicating hydrocephalus in this series certainly must have had meningeal disease at some point, but could not be classified as such based on available data.

The diagnosis of neurosarcoidosis remains challenging. Neurosarcoidosis can affect both central and peripheral nervous system structures and thus present in myriad different phenotypes. Often there is a wide differential diagnosis including demyelinating diseases, infectious granulomatous diseases, neoplasms, fungal infections, vasculitis or neurosyphilis. However, there is no universally agreed upon diagnostic protocol for patients with neurosarcoidosis. A general diagnostic approach is to perform a serologic and microbiologic evaluation to exclude infectious and vasculitic processes. This is followed by imaging of the chest via CT or x-ray and imaging affected nervous system structures with MRI in order to delineate a biopsy site as well as to rule out other diseases. In lieu of a superficial biopsy site such as skin or lymph node, biopsy of a non-CNS organ such as lung or mediastinal lymph nodes may be performed to avoid the potential morbidity of biopsy of brain or spinal cord. If standard imaging techniques fail to find such a site, Gallium scintigraphy or PET-CT may be useful adjuncts.

This case series confirms that imaging studies remain an essential part of the diagnostic evaluation of neurosarcoidosis. Chest X-ray was a useful but insensitive diagnostic tool, as abnormalities in our cohort were slightly lower than other reported studies. Chest CT remained as the non-CNS imaging modality of choice, with diagnostic yield similar to other reported series (3, 4, 12, 13). Gallium scintigraphy was an infrequently used modality in our cohort. FDG-PET CT has shown promise as a diagnostic modality in the evaluation of suspected neurosarcoidosis patients for whom an amenable biopsy site is not readily apparent. This imaging modality, however, was not readily available at our institution during the time of the study and no patients in the cohort had FDG-PET CT performed.

Brain imaging included a high incidence of normal brain CT (31%), with a low incidence of normal brain MRI (2%). A reasonable approach in diagnosis would be the preferred use of MRI in non-emergent settings, with continued use of brain CT as the initial imaging modality in urgent or emergent settings, where stroke, hydrocephalus or mass lesions leading to increased intracranial pressure are suspected. Our series is notably different than others in that the percent of white matter lesions is much lower; ours was 7.7%, while other case series have reported 43% (4) and 30% (3). This may be due to referral bias, as several such studies have originated from multiple sclerosis centers. In addition, this series captures the frequent occurrence of concomitant parenchymal and meningeal disease on MRI (17%), a finding that is well known but often not captured in studies. Isolated brain parenchymal lesions lacking concomitant meningeal involvement were relatively rare in this series. Another radiologic finding of interest were 3 patients (6% of the cohort), in whom the initial radiologic impression was that of meningioma, demon-

strating yet another disorder which can be mimicked by neurosarcoidosis.

Spinal MRI was abnormal in all patients in whom it was performed. No particular predilection was noted for cervical or thoracic regions for myelopathic patients. As in the brain studies, concomitant parenchymal and meningeal disease was a common finding.

No lumbar spine MRI scans were obtained, likely due to the low incidence of radiculopathy in this case series. This differs from the case series of Sohn et al (14), wherein the lumbosacral level was involved in 37% of the patients.

Laboratory parameters in our cohort were similar to those reported in the literature. Serum ACE level was unhelpful in diagnosing sarcoidosis. CSF findings are nonspecific, but helpful in confirming CNS inflammation. CSF oligoclonal bands are helpful when present, but were noted in a minority of patients. Normal CSF was encountered in a significant (23%) proportion of cases, and thus should not be used to rule out neurosarcoidosis. CSF hypoglycorachia was rare in our study. However, this finding is at odds with other series (12, 16) and thus is not a reliable exclusionary tool. The most common phenotypes with abnormal CSF were meningitic syndromes, with or without hydrocephalus, and myelopathy. However, no clear relationship was noted between clinical syndrome and abnormal CSF. Interestingly, several cases of pachymeningitis were noted to have normal spinal fluid findings. These observations may reflect the lack of a standardized diagnostic workup in this retrospective study.

Tissue biopsy is essential for a diagnosis of sarcoidosis, with lung being the most common site as expected. The high rate of positive brain biopsy in our series likely speaks to the procedure being reserved for those patients with a high pre-test probability. Conjuctival biopsy, which has had conflicting data on utility in the literature, was only performed once in our cohort, and was normal. Some of the variance in our biopsy data compared to other series likely results from differing local practice patterns and areas of surgical expertise.

Inferring the optimal treatment course remains difficult. Two-thirds of neurosarcoidosis cases are monophasic, typically those with facial palsy or aseptic meningitis. Corticosteroids are the mainstay of treatment, but choice of second line treatment for refractory, steroid unresponsive or steroid intolerant cases remains unclear. Recent literature has generated enthusiasm for TNF alpha-blockers such as infliximab (12, 19) or adalimumab (12, 17, 18) for refractory disease, but the rarity of the disease has made study of efficacy challenging. Sarcoidosis has an inflammatory/granulomatous aspect to its pathophysiology that could reasonably be expected to respond to anti-inflammatory or immunomodulatory treatments. However, a subset of neurosarcoidosis patients remain medically refractory despite treatment with multiple immunomodulatory agents. Future research into medication efficacy will require careful patient selection and novel clinical trial designs.

Symptomatic treatment is of paramount importance to patients and their families, but receives little attention in the neurosarcoidosis literature. As in other neurologic illness, treatment of spasticity, mood disorder, epilepsy, cognitive deficits, fatigue and pain must not be neglected. The importance of a caring, knowledgeable physician maintaining a compassionate, therapeutic physician patient relationship cannot be overstated.

Our patient population was homogenous, with a predominant African American race, and tended to be patients of low socioeconomic status; two categories which tend to be underrepresented in the medical literature (20). Thus the information presented in this series represents a valuable addition to the limited available literature about neurosarcoidosis, as many published case series have failed to specify demographic information, or have a documented Caucasian predominance (3,4,21).

We acknowledge the methodological limitations of case series. The retrospective nature of our case series places limits on case ascertainment, particularly in the possible neurosarcoidosis category. Diagnostic evaluations were variable, and at the discretion of the treating physician. Similarly, treatment was also not per any prespecified protocol, thus introducing confounding factors and bias into treatment choices. Outcome assessment similarly was approximate and one must factor this in to any conclusions on prognosis.

Given the rarity of neurosarcoidosis, prospective controlled trials remain unlikely. Prospectively collected registry data is a promising next step. Examples of current registries include a sarcoidosis registry

at www.stopsarcoidosis.org. and a different registry specific to neurosarcoidosis at www.neurosarcoidosis.org . Such data should include detailed collection of demographic data, well-defined consensus phenotype classification, and a standardized minimum diagnostic evaluation, including serology, spinal fluid analysis, systemic imaging, and neuroimaging. Analysis of treatment and outcomes would need outcome assessment appropriate to phenotype (e.g. visual acuity for optic neuropathy, or functional outcome assessment for those with weakness). Treatment assessment will need to focus on steroid unresponsive patients, and stratification of patients according to phenotype, race, ethnicity or other factors may reveal the next best path forward. Neurosarcoidosis remains a challenging entity which demands further attention, particularly in defining optimal evaluation and treatment.

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