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Central Nervous System Sarcoidosis: A National-Based registry study

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Abstract. *Background and aim:* Sarcoidosis of the central nervous system (CNS) often presents deleterious effects on affected patients. Data and available literature discussing the diagnosis and treatment of this condition are scarce and inconsistent. In this study, we aim to shed light on demographics, management, diagnostics, and clinical complications of CNS sarcoidosis patients within the United States (US) based on a nation-wide registry questionnaire. *Methods:* Our retrospective study was conducted based on a national registry investigating 3,835 respondents to the Foundation for Sarcoidosis Research Sarcoidosis Advanced Registry for Cures Questionnaire (FSR-SARC). This national registry data was collected during the period of June 2014 to August 2019. We performed propensity score matching, summary, univariate, and multivariate analyses to establish a comparison between the presence and absence of central nervous system sarcoidosis. *Results:* We identified a total of 420/3634 (11.55%) patients having CNS sarcoidosis; 296 (70.5%) were females, 307 (73.1%) were Caucasian and 81 (19.3%) were African American. The mean (±SD) age at diagnosis of CNS sarcoidosis was 43.3 (±12) years old. Multiorgan involvement (≥3 organs) was present in 318/420 (75.7%) patients. Brain magnetic resonance imaging was the most common ancillary diagnostic modality used and reported to be abnormal 251/328 (76.5%). Corticosteroids were the most used treatment by CNS sarcoidosis patients 206/420 (49.0%) followed by cytotoxic agents 180/420 (42.9%). *Conclusions:* CNS sarcoidosis prevalence in our cohort was similar to what has been described previously. The most prevalent imaging modality used was cranial MRI. Corticosteroids were the most used medications. Lastly, CNS sarcoidosis showed a propensity to cause several clinical complications such as chronic pain syndrome and disability.

Key words: sarcoidosis, neuro-sarcoidosis, central nervous system, registry

Introduction

Sarcoidosis is a multi-systemic granulomatous inflammatory disease that is thought to be a consequence of exposure to specific environmental agents in a genetically susceptible patient (1). Incidence for sarcoidosis is estimated to be in the range of 10 to 20 cases per 100,000 (2). Although sarcoidosis more commonly affects organs such as the lungs, skin, and eyes, previous literature suggests sarcoidosis involves the nervous system in 5% to 20% of cases (3,4).

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Sarcoidosis can affect many areas of the nervous system including the brain parenchyma, spinal cord, cranial nerves, and peripheral nerves (5-7). Neurological manifestations of sarcoidosis include aseptic meningitis, cranial nerve palsies, peripheral neuropathy, myelopathy, intraparenchymal lesions, and hydrocephalus (5). Moreover, due to its likely autoimmune nature, sarcoidosis is frequently associated with several neurologically-adjacent manifestations such as depression, chronic pain, and fibromyalgia (8,9).

The diagnosis of neurological involvement of sarcoidosis is often challenging due to the nonspecific nature of the clinical presentations and the sensitivity for the suspected lesions loci in an anatomical sense. Furthermore, a definite diagnosis of these patients requires histological confirmation and ruling out alternative etiologies (10,14). Typically, cases are diagnosed with the aid of extensive ancillary investigations and imaging modalities such as electroencephalography (EEG), computed tomography (CT), magnetic resonance imaging (MRI) of the cranium or spinal cord, lumbar puncture, and positron emission tomography (PET scan), yet there is little information regarding the modality of choice (11-13).

Once sufficient diagnostic certainty is achieved for a definite, probable, or possible case of neurosarcoidosis, treatment is usually administered in a stepwise manner (14). One suggested course of treatment involves corticosteroids as the first-line intervention, cytotoxic agents as the second line, and monoclonal antibodies such as infliximab as third-line therapy (7,15,16). Treatment regimen for neurosarcoidosis is also highly dependent on the lesion's location and disease severity, for instance, treatment for facial nerve involvement might be treated with the mere usage of prednisone, while involvement of the spinal cord might elicit the need for stronger regimens i.e. infliximab and methylprednisolone due to the severity of the disease manifestations (7,15,16). However, the practice is not universal and varies between different centers. Despite treatment, most patients frequently relapse with progression (17). Patients with central nervous system (CNS) sarcoidosis are often refractory to treatment, relapse is often common in patients even those treated with drugs such as methotrexate (MTX) or infliximab and patients usually require chronic use of corticosteroids combined with these drugs resulting in a considerable increase in morbidity (7,15,17,18,19). Evidence on the optimal therapeutics for CNS sarcoidosis is thus far scarce.

Given the paucity of data related to CNS sarcoidosis, in this study, we aim to describe demographics, diagnostics used, management strategies and complications of CNS sarcoidosis based on data from a survey-based national registry.

Methods

Our study population was acquired through a national registry investigating 3835 adult respondents to the Foundation for Sarcoidosis Research (FSR)-Sarcoidosis Advanced Registry for Cures (SARC) questionnaire (1,20,21). This registry was open to all patients self-identifying as having sarcoidosis via a 72-question web-based questionnaire. Respondents were recruited through their treating physicians, the FSR, or national and international organizations. The 72-question questionnaire was written in English and included a glossary in case patients encountered a term with which they were unfamiliar. The registry provides an observational cohort platform for collecting cross-sectional and longitudinal self-reported data on demographics, organ involvement, diagnostics, treatment, and the physical and psychosocial impact of sarcoidosis on patients. We included all United States sarcoidosis patient surveys completed between June 2014 and August 2019. Respondents were able to update their surveys longitudinally over time. Analysis of data was based on the most recent survey.

We excluded 201 respondents from the final cohort; thirteen were excluded due to being reported as deceased or having missing information for the question "is the patient living" and their surveys were completed by their loved ones, and another 188 respondents because more than 75% of survey questions lacked responses. The study was approved by the University of Florida Institutional Review Board (no. 201902211).

We aimed to compare differences in patient characteristics, sarcoidosis organ involvement, diagnostic modalities utilized, management strategies, and complications of the disease between two groups: patients with and without CNS sarcoidosis.

We divided patients into two groups based on the presence or absence of CNS sarcoidosis. Central nervous system sarcoidosis was defined as sarcoidosis involvement in one or more of the following: I) Brain, II) cranial nerves, and/or III) spinal cord. Answers for sarcoidosis organ involvement were considered

positive for involvement if patients answered with "diagnosed;" and negative when patients answered, "not involved." To avoid overestimation of organ involvement, we grouped the answer "suspected" for organ involvement with "not involved" as it may represent a source of confusion for patients. Multiorgan sarcoidosis was defined as sarcoidosis involvement of three or more organs (22,23). Questions with a tick-box fill-in format, such as those reporting clinical complications of sarcoidosis, were regarded to be negative if the box was left empty by the respondents. We divided systemic medications used to treat sarcoidosis into the following categories: I) corticosteroids, II) cytotoxic agents, III) tumor necrosis factors (TNF) inhibitors and IV) other systemic therapies. Corticosteroids encompass prednisone, methylprednisolone, and dexamethasone. Cytotoxic agents encompass methotrexate, azathioprine, leflunomide, mycophenolate, and cyclophosphamide. TNF inhibitors encompass infliximab, adalimumab, certolizumab, golimumab, and etanercept. Other systemic therapies included drugs such as rituximab, pentoxifylline, intravenous immunoglobulin (IVIG), thalidomide, or adrenocorticotropic hormone.

Descriptive measures included mean ± standard deviations (SD), median, and 95% confidence interval (CI) for quantitative variables. Categorical variables were presented using frequencies and percentages (%). Associations between CNS involvement and quantitative variables were determined using student's t-test if the normality assumption was not violated. Data normality testing was conducted using Shapiro-Wilk test, and when this assumption was violated, we used Mann-Whitney U test instead. Chi-square test, or Fisher's exact test when >20% of cells had counts less than five, were used to assess the relationship between categorical variables. 1:1 propensity-score matching between CNS sarcoidosis and non-CNS sarcoidosis was conducted using age at diagnosis, gender, race, and multiorgan involvement. 1:1 matching was then performed using the nearest neighbor algorithm with a 0.1 caliper width of pooled standard deviation. The order of rows was randomized to eliminate bias resulting from nearest neighbor algorithms. A binary logistic regression analysis was done to identify the association between CNS involvement and different clinical and demographic features across the cohort using the Enter method. Variables included in the model were selected based on separate univariate analysis, including all variables yielding a < 0.1 p-value. The clinical and demographic variables included in the analysis included chronic fatigue syndrome, chronic pain syndrome, depression, sleep apnea, sleep disorders, use of mobility devices, and disability status. Goodness-of-fit was measured using Nagelkerke's r-squared. The variables in the model were checked for multicollinearity using variance inflation factor (VIF). Statistical significance was defined as a two-sided p-value of ≤ 0.05. All data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software for Windows, version 26.0.

Results

A total of 3634 self-reported sarcoidosis cases had been identified. Overall, patients had a mean age (± SD) of 44.0 (± 11.8) and 40.7 (± 12.8) upon diagnosis and onset of first symptoms, respectively. Most of the cases were of Caucasian ancestry (76.3%) and women (73.4%).

Among the CNS group, the patients experienced their first symptoms at a significantly older age compared to the non-CNS group (43.3 ± 11.8 years vs 40.9 ± 12.7 years; p = 0.026). Furthermore, the CNS group were more likely to be unemployed compared to the non-CNS group (61.0% vs 48.6%). The most common therapeutic modality reported was corticosteroids in both the CNS (n=206/420; 49.0%) and non-CNS group (n=1167/3214; 36.3%). CNS sarcoidosis patients reported a higher rate of treatment use across all treatment modalities (Table 1).

After propensity analysis, a significant association has been identified between CNS sarcoidosis involvement and age at diagnosis, age at onset of first symptoms, gender, race, family history, consultation with neurologists, insurance status, annual income, and treatment modalities. The CNS group were significantly older than the non-CNS group at diagnosis (43.3 ± 12.0 vs 40.79 ± 11.2; p = 0.002) and at onset of first symptoms (39.2 ± 12.8 vs 37.0 ± 12.3; p = 0.013), and they were more likely to be men compared to the non-CNS group (29.5% vs 13.3%; p < 0.001). The CNS group had a higher proportion of Caucasians (73.1% vs 68.1%). However, the non-CNS group was more likely to be associated with a positive family history of sarcoidosis (26.7% vs 17.9%; p = 0.002). The CNS group were more likely to be insured (84.8% vs 77.9%; p = 0.01). Corticosteroids

Table 1. Demographical characteristics and treatment modalities reported. (pre- and post- propensity score matching)

Participants Demographics	All Patients N=3634	Sarcoidosis Involvement (Pre-propensity)			Sarcoidosis Involvement (Post-propensity)		
		Non-CNS Sarcoidosis (N=3214)	CNS Sarcoidosis (N=420)		Non-CNS Sarcoidosis (N=420)	CNS Sarcoidosis (N=420)	
	N (%)	N (%)	N (%)	P-value	N (%)	N (%)	P-value
Age at Diagnosis							
Mean ± SD	44.0 ± 11.8	44.1 ± 11.9	43.3 ± 12.0	0.304	40.79 ± 11.2	43.3 ± 12.0	0.002
Age at Onset of First Symptoms							
Mean ± SD	40.7 ± 12.8	40.9 ± 12.7	43.3 ± 11.8	0.026	37.0 ± 12.3	39.2 ± 12.8	0.013
Number of Hospital Admissions							
Mean ± SD	0.78 ± 1.7	0.77 ± 1.7	0.86 ± 2.11	0.386	0.77 ± 1.9	0.86 ± 2.11	0.749
Gender							
Male	968 (26.6)	884 (27.5)	124 (29.5)	0.155	56 (13.3)	124 (29.5)	<0.001
Race							
Caucasian	2774 (76.3)	2467 (76.8)	307 (73.1)		286 (68.1)	307 (73.1)	
African American	625 (17.2)	544 (16.9)	81 (19.3)		85 (20.2)	81 (19.3)	
American Indian	112 (3.1)	93 (2.9)	19 (4.5)		17 (4.0)	19 (4.5)	
Asian	28 (0.8)	27 (0.8)	1 (0.2)		5 (1.2)	1 (0.2)	
Native Hawaiian	8 (0.2)	8 (0.2)	0 (0.0)	0.142	7 (1.7)	0 (0.0)	
Other	87 (2.4)	75 (2.3)	12 (2.9)		20 (4.8)	12 (2.9)	<0.01
Family History							
Positive	538 (14.8)	463 (14.4)	75 (17.9)	0.061	112 (26.7)	75 (17.9)	0.002
Consultation with neurologist							
Yes	1491 (44.4)	1129 (38.1)	362 (91.9)	<0.001	151 (39.2)	362 (91.9)	<0.001
Employment Status							
Unemployed	1817 (50.0)	1561 (48.6)	256 (61.0)		243 (57.9)	256 (61.0)	
Employed	1772 (48.8)	1615 (50.2)	157 (37.4)		168 (40.0)	157 (37.4)	
Student	45 (1.2)	38 (1.2)	7 (1.7)	<0.001	9 (2.1)	7 (1.7)	0.618
Insurance Status							
Insured	3064 (84.3)	2708 (84.3)	356 (84.8)	0.790	327 (77.9)	356 (84.8)	0.010
Annual Income							
<$35,000	762 (26.3)	652 (25.5)	110 (32.4)		129 (40.4)	110 (32.4)	
$35,000-99,999	1340 (46.2)	1191 (46.5)	149 (43.8)		134 (42.0)	149 (43.8)	
>$100,000	798 (27.5)	717 (28.0)	81 (23.8)	0.020	56 (17.6)	81 (23.8)	0.045
Treatment Modalities							
Corticosteroids							
Yes	1373 (37.8)	1167 (36.3)	206 (49.0)	<0.001	152 (36.2)	206 (49.0)	<0.001
Cytotoxic agents							
Yes	965 (26.6)	785 (24.4)	180 (42.9)	<0.001	129 (30.7)	180 (42.9)	<0.001
TNF alpha inhibitors							
Yes	240 (6.6)	159 (4.9)	81 (19.3)	<0.001	22 (5.2)	81 (19.3)	<0.001
Other Systemic Therapy							
Yes	240 (6.6)	159 (4.9)	81 (19.3)	<0.001	129 (30.7)	81 (19.3)	0.003

remained the most reported intervention across both CNS (n=206/420; 49.0%) and non-CNS groups (n=152/420; 36.3%). However, the CNS group had a significantly higher rate of corticosteroids (49.0% vs 36.2%, p <0.001), cytotoxic agents (42.9% vs 30.7%; p < 0.001), and TNF alpha inhibitors use (19.3% vs 5.2%; p < 0.001), while other systemic therapies were more likely to be used in the non-CNS group (30.7% vs 19.3%; p = 0.003) (Table 1).

CNS involvement was identified in 11.6% (420/3634) of the patients. The mean number ± SD of organs involved was higher in the CNS vs non-CNS group both before and after propensity analysis (5.15 ± 3.25 vs 2.74 ± 2.20 & 5.15 ± 3.25 vs.68 ± 2.60; p < 0.001), respectively. The CNS group had a higher proportion of multiorgan involvement (at least 3 organs involved) when compared to the non-CNS group (75.7% vs 42.8%; p < 0.001). Among the CNS group, brain involvement (n=319/420; 76.0%) was more common compared to spinal cord involvement (n=101/420; 24.0%). Pulmonary involvement was the most frequent and the second most frequent organ involved in the non-CNS (n=2282/3214; 71.0%) and CNS group (n= 252/420; 60.0%), respectively. Prior to propensity score matching between the CNS and Non-CNS cohorts, we found a significant difference in the proportions for the number of organs with sarcoidosis involvement with sole exception for hepatic sarcoidosis. Nonetheless, post-propensity score matching, central lymph nodes, pulmonary and peripheral nerves were the only organs maintaining statistical significance (Table 2).

The most-reported investigation used to diagnose CNS sarcoidosis was a combination of cranial computed tomography (CT), cranial magnetic resonance imaging (MRI), and lumbar puncture. The sole use of lumbar puncture was the least commonly used diagnostic modality among CNS patients with only a minuet number of patients reporting its use. Cranial MRI was the most common ancillary investigation conducted and had the highest proportion of abnormal results (Table 3).

A binary logistic regression was performed to detect the effect of chronic fatigue syndrome, chronic pain syndrome, depression, sleep apnea, sleep disorder, use of mobility devices, and disability status in predicting the likelihood of CNS sarcoidosis involvement. This model explained 10.0% (Nagelkerke R2) of the variance in the involvement of the CNS by sarcoidosis, and correctly classified 88.4% of the cases. After propensity analysis, the model explained 5.2% (Nagelkerke R2) of the variance in the involvement of the CNS by sarcoidosis, and correctly classified 50% of the cases.

The multivariate analysis showed that CNS sarcoidosis patients were more likely to have chronic pain syndrome (OR = 1.447, 95% confidence interval [CI] = 1.102-1.979; P=0.009), use mobility devices (OR: 2.822; 95% CI: 2.194-3.631; P < 0.001), and have disabilities (OR: 1.544; 95% CI: 1.210-1.971; P <0.001) prior to propensity matching. However, CNS sarcoidosis patients did not impact the likelihood of having clinical complications such as chronic fatigue syndrome, depression, sleep apnea, and sleep disorders. After propensity matching, CNS involvement patients were also more likely to have chronic pain syndrome, use mobility devices, and have disabilities (Table 4).

Discussion

This manuscript serves as a comparison for sarcoidosis involvement within the central nervous system and other organs. Our study found out that CNS sarcoidosis was reported by 11.6% of patients. Our CNS sarcoidosis patients' cohort was mostly white women who were diagnosed later than non-CNS sarcoidosis patients. Utilization of corticosteroids alongside immuno-suppressive drugs represented the mainstay intervention for treatment of our CNS sarcoidosis patients. CNS sarcoidosis was associated with a higher number of multiple sarcoidosis organ involvement. Furthermore, patients were more likely to develop concomitant clinical complications such as chronic pain syndrome, disability, and more likely to use mobility devices.

A meta-analysis conducted by Fritz et al, reported a mean age at diagnosis of CNS sarcoidosis similar to results in our study, around 43 years; nonetheless, we observed an overall higher proportion of women in our cohort compared to their data (73.4% vs. 55%) (24). Our cohort is primarily composed of cases from the Caucasian race (73.1%) followed by the African American race (19.3%). A similar representation was observed in cohorts of the aforementioned meta-analysis which revealed Caucasian female predominance (24). In our cohort, patients with CNS sarcoidosis were more likely to have multi-organ involvement (>=3); especially in the lungs, central lymph nodes, and peripheral nerves

Table 2. Organ involvement reported for sarcoidosis (pre- and post- propensity score matching)

Total Number of participants	All Patients N=3634	Sarcoidosis Involvement (Pre-propensity)			Sarcoidosis Involvement (Post-propensity)		
		Non-CNS Sarcoidosis (N=3214)	CNS Sarcoidosis (N=420)		Non-CNS Sarcoidosis (N=420)	CNS Sarcoidosis (N=420)	
	N (%)	N (%)	N (%)	P-value	N (%)	N (%)	P-value
Number of Involved Organs Reported.							
Mean ± SD	3.02 ± 2.47	2.74 ± 2.20	5.15 ± 3.25	<0.001	3.68 ± 2.60	5.15 ± 3.25	<0.001
Multi-organ Involvement (≥3)							
Yes	1684 (46.7)	1366 (42.8)	318 (75.7)	<0.001	278 (66.2)	318 (75.7)	0.002
Organs Involved							
Bone and/or vertebrae	271 (7.5)	195 (6.1)	76 (18.1)	<0.001	37 (8.8)	76 (18.1)	0.008
Brain	319 (8.7)	N/A	319 (76.0)	N/A	N/A	319 (76.0)	N/A
Spinal cord	101 (2.8)	N/A	101 (24.0)	N/A	N/A	101 (24.0)	N/A
Central Lymph Nodes	1685 (46.4)	1456 (45.3)	229 (54.5)	<0.004	175 (41.7)	229 (54.5)	<0.001
Eyes	720 (19.8)	552 (17.2)	168 (40.0)	<0.001	136 (32.4)	168 (40.0)	0.022
Heart	386 (10.6)	322 (10.0)	64 (15.2)	<0.001	42 (10.0)	64 (15.2)	0.022
Joints (Arthritis)	748 (20.6)	589 (18.3)	159 (37.9)	<0.001	149 (35.5)	159 (37.9)	0.474
Kidney	194 (5.3)	156 (4.9)	38 (9.0)	<0.001	23 (5.5)	38 (9.0)	0.046
Parotid or Lacrimal Glands	162 (4.5)	118 (3.7)	44 (10.4)	<0.001	23 (5.5)	44 (10.4)	0.007
Liver	377 (10.4)	326 (10.1)	51 (12.1)	0.206	57 (13.6)	51 (12.1)	0.536
Pulmonary	2534 (69.7)	2282 (71.0)	252 (60.0)	<0.001	316 (75.2)	252 (60.0)	<0.001
Muscles	239 (6.6)	173 (5.4)	66 (15.7)	<0.001	47 (11.1)	66 (15.7)	0.055
Peripheral Lymph Nodes	732 (20.1)	624 (19.4)	108 (25.7)	0.002	114 (27.1)	108 (25.7)	0.639
Peripheral Nerves	604 (16.6)	396 (12.3)	208 (49.5)	<0.001	98 (23.3)	208 (49.5)	<0.001
Sinuses	252 (6.9)	190 (5.9)	62 (14.8)	<0.001	63 (15.0)	62 (14.8)	0.923
Skin	893 (24.6)	756 (23.5)	137 (32.6)	<0.001	160 (38.1)	137 (32.6)	0.097
Spleen	331 (9.1)	281 (8.7)	50 (11.9)	0.034	45 (10.7)	50 (11.9)	0.586
Stomach/Intestine	182 (5.0)	136 (4.2)	46 (10.9)	<0.001	29 (6.9)	46 (10.9)	0.040
Other	259 (7.1)	175 (5.4)	84 (20.0)	<0.001	30 (7.1)	84 (20.0)	<0.001

which is coherent with findings from the University of Minnesota and the ACCESS study cohorts (25).

Confidence in reaching a diagnosis of CNS sarcoidosis in patients who present with isolated CNS symptoms without systemic sarcoid is a challenge. The latter is due to the fact that the CNS is a relatively uncommon site for the manifestation of the disease unless it is present in other organs (26). Many diseases present in a manner indistinguishable from CNS sarcoidosis and thus should be investigated thoroughly to differentiate them apart. Additionally, there are no well-studied neuro-diagnostic tests that are highly specific for CNS sarcoidosis (26-28). Acquiring a definite diagnosis requires invasive techniques, i.e., a biopsy, which could explain the lower prevalence of definite diagnosis (24).

Cranial MRI has proven to be the most reported ancillary imaging modality in the present study. Abnormal results were detected in 76.5% of CNS sarcoidosis patients using cranial MRI. Body PET scan was performed on 90 CNS sarcoidosis patients of which 70.0% had abnormal results. Other modalities including cranial CT, lumbar puncture, and electroencephalogram detected abnormal results in CNS

Table 3. Diagnostic imaging and Ancillary imaging reported for CNS sarcoidosis

Initial diagnostic imaging for CNS sarcoidosis	**n/N**	**(%)***
Cranial CT, Cranial MRI & Lumbar Puncture	106/420	(25.2)
Cranial CT & Cranial MRI	76/420	(18.1)
Cranial MRI (Magnetic Resonance Imaging)	57/420	(13.6)
Cranial MRI & Lumbar Puncture	44/420	(10.5)
Cranial CT (Computed Tomography)	14/420	(3.3)
Cranial CT & Lumbar Puncture	13/420	(3.1)
Lumbar Puncture	7/420	(1.7)
Others	103/420	(24.5)
Abnormal ancillary imaging in CNS patients	n/N (%)**	
Cranial MRI	251/328	(76.5)
Body PET (Positron Emission Tomography) Scan	63/90	(70.0)
Cranial CT	139/225	(61.8)
Lumbar-Puncture	141/240	(58.8)
Electro-Encephalogram	60/144	(41.7)

*n: Number of test modality used for CNS sarcoidosis initial diagnosis; N: Total number of CNS sarcoidosis patients. **n: number of abnormal results in the ancillary imaging conducted; N: Total number of investigations conducted.

sarcoidosis patients at lower rates in comparison to Cranial MRI and body PET scan. In a study on 9 patients with hypothalamic-pituitary involvement of sarcoidosis, MRI detected abnormalities in all the cases (27). Contrast-enhanced MRI is the neuroimaging modality of choice for CNS sarcoidosis (27-29).

Guidelines on the treatment and management of CNS sarcoidosis are lacking; partially due to the rarity of the disease and thus the difficulty of conducting randomized controlled trials. The ultimate target of therapy for CNS sarcoidosis is to either stabilize the disease or achieve clinical improvement (30). In the present study, patients with CNS sarcoidosis reported a higher rate of treatment use across all treatment modalities including corticosteroids, cytotoxic agents, and TNF-α inhibitors. This is attributed to the fact that CNS sarcoidosis almost always requires a certain kind of intervention when compared to non-CNS sarcoidosis which is not always the case.

From this cohort, 49.0% of CNS sarcoidosis patients reported receiving corticosteroids in comparison to 36.2% of patients with non-CNS sarcoidosis. In a large series of 85 patients with neurosarcoidosis, almost 96.0% of CNS sarcoidosis patients presented with a higher frequency of corticosteroid use in comparison to 47.0% of those with PNS sarcoidosis (31). In the Fritz et al meta-analysis, 83.0% of CNS sarcoidosis patients were treated with corticosteroids of which 227 patients received corticosteroids as monotherapy. While 71.0% (161/227) of the cases achieved favourable outcomes, 24.0% of those initially treated with corticosteroids were switched to other lines of therapy (24).

Despite the high rate of corticosteroid use in the management of CNS sarcoidosis, complete response remains low as the significant side effects, high dosages, and prolonged use of corticosteroids compromise patients' clinical status (32-34). As a result of corticosteroid toxicity and failure to respond in some cases, steroid-sparing immunosuppressive therapies have been investigated with variable outcomes of success (26,30,35,36).

In our cohort, 42.9% and 19.3% of CNS sarcoidosis and non-CNS sarcoidosis respectively, reported using TNF-α inhibitors and cytotoxic agents to manage their disease. In a small cohort study on 6 biopsy-proven CNS sarcoidosis patients, the use of infliximab, a TNF-α inhibitor, in combination with mycophenolate mofetil, a cytotoxic immunosuppressant, achieved a remarkable reduction in lesion size, improvement of symptoms including seizures,

Table 4. Clinical Complications reported by CNS and Non-CNS participants

Variables	CNS Sarcoidosis	Non-CNS Sarcoidosis	Adjusted OR (95% CI) (Before propensity)	P-value	Non-CNS Sarcoidosis	Adjusted OR (95% CI) (After propensity)		P-value
Chronic Fatigue Syndrome								
Yes	142 (33.8)	565 (17.6)	1.330 (0.995-1.778	0.054	299 (71.2)	-	-	-
No	278 (66.2)	2649 (82.4)	1 (Reference)	Reference	121 (28.8)	-	-	-
Chronic Pain Syndrome								
Yes	286 (68.1)	2747 (85.5)	1.477 (1.102-1.979)	0.009	100 (23.8)	1.051 (0.741-1.491)		0.009
No	134 (31.9)	467 (14.5)	1 (Reference)	Reference	320 (76.2)	1 (Reference)		Reference
Depression								
Yes	142 (33.8)	720 (22.4)	0.935 (0.715-1.223)	0.626	148 (35.2)	-	-	-
No	278 (66.2)	2494 (77.6)	1 (Reference)	Reference	272 (64.8)	-	-	-
Sleep Apnea								
Yes	105 (25.0)	575 (17.9)	0.982 (0.755-1.279)	0.895	105 (25.0)	-	-	-
No	315 (75.0)	2639 (82.1)	1 (Reference)	Reference	315 (75.0)	-	-	-
Sleep Disorder								
Yes	121 (28.8)	499 (15.5)	1.276 (0.968-1.682)	0.084	92 (21.9)	1.140 (0.807-1.609)		0.084
No	299 (71.1)	2715 (84.5)	1 (Reference)	Reference	328 (78.1)	1 (Reference)		Reference
Use of Mobility Device								
Yes	156 (37.1)	403 (12.5)	2.822 (2.194-3.631)	<0.001	85 (20.2)	2.021 (1.440-2.836)		<0.001
No	264 (62.9)	2811 (87.5)	1 (Reference)	Reference	335 (79.8)	1 (Reference)		Reference
Disability								
Disabled	180 (42.9)	705 (21.9)	1.544 (1.210-1.971)	<0.001	129 (30.7)	1.315 (0.963-1.796)		<0.001
Not Disabled	240 (57.1)	2509 (78.1)	1 (Reference)	Reference	291 (69.3)	1 (Reference)		Reference

neuropathic pain, and headaches, and no serious adverse effects during the follow-up period that extended up to 18 months in all patients (37).

Using infliximab, a multi-institutional series conducted on 66 patients diagnosed with CNS sarcoidosis observed an improvement clinically in 77.3% of patients and radiological evidence of favourable response to administered treatment was noted in 82.1% of patients. After 16 patients achieved clinical and imaging remission, infliximab was discontinued. Upon discontinuation, CNS sarcoidosis relapsed in 9 patients. Relapse after discontinuation of infliximab could require using a more intensive regimen or combination therapy (38).

Given that CNS sarcoidosis is associated with poor prognosis; monotherapy of corticosteroids, due to its high rate of relapse, adverse effects, and morbidity profile has fallen out of favour compared to the usage of corticosteroids in combination with other immunosuppressive medications which represent the current mainstay therapy (26,30,35,36-38).

Although sarcoidosis could be clinically in remission, pain and fatigue are symptoms that may persist longer than the disease course. The exact pathophysiology behind chronic fatigue and pain is yet to be solved (39). In the current study, 68.1% of CNS sarcoidosis patients and 23.8% of non-CNS sarcoidosis patients reported chronic pain syndrome.

Peripheral nerve involvement, particularly small fibre neuropathy, might explain the higher rates of chronic pain syndrome as it affects 49.5% of CNS sarcoidosis patients and 12.3% of non-CNS sarcoidosis patients.

Given that multi-organ involvement (>=3) was reported to affect over three-quarters of CNS sarcoidosis patients in contrast to 42.8% of non-CNS sarcoidosis, it might explain the significantly higher rates of disability and use of mobility devices in 42.9% and 37.1% of CNS sarcoidosis patients in comparison to 20.2% and 30.7% of non-CNS sarcoidosis patients. We, however, also believe that disability is innately higher within the CNS sarcoidosis group due to the inherent neurological damage implicated by lesions' location.

We argue that early initiation of treatment might delay the onset of disability in patients with CNS sarcoidosis. However, randomized controlled trials are needed to provide firm evidence on disease control with regard to timing of treatment.

It is important to take into consideration the limitations of our study when interpreting the results discussed above. Such limitations include the self-reported nature of the questionnaire we used which could be a source of introducing recall bias and non-differential misclassification of our variables, most importantly the diagnosis of neurosarcoidosis including differentiating both its peripheral and central subtypes. Nonetheless, it is important to note the questionnaire included separate questions for the involvement of both the central and peripheral nervous system. Unfortunately, this bias is commonly expressed in self-reported registry studies; however, the relatively large number of participants within our paper in comparison to those within existing pool of literature might play a role in mitigating this bias. The process of electrical recruitment for participants of the registry may also have led to the introduction of referral bias explaining a plausible over-representation of Caucasian women in the paper, thus limiting the generalizability of our data. Moreover, chronic and severe cases of sarcoidosis are more likely to be included in this registry in comparison with self-limiting sarcoidosis. This could lead to selection bias given these patients are at an increased risk for developing neurosarcoidosis.

To conclude, our study showed that self-reported central nervous system involvement is widespread among sarcoidosis patients and is a potential treatable etiology for several clinical complications and disabilities, the generalizability and interpretation for these findings however must be taken with caution given the higher degree severity of CNS sarcoidosis manifestations makes it more likely to be reported when compared to other organ involvement within our cohort. Nonetheless, propensity matching done in synthesis of the results helps alleviate such bias to some extent and gives us a higher degree of confidence in interpreting our findings. CNS sarcoidosis patients reported a higher overall intake for medications. CNS sarcoidosis was also associated with multi-organ sarcoidosis involvement. Given our findings, referral to neurology for assessment of CNS sarcoidosis is suggested in patients with symptoms consistent with central nervous system sarcoidosis, especially those with other several organs involvement and concomitant clinical complications. Future studies are needed to improve diagnostic certainty and treatment protocols.

Data Availability: Data is available upon request through the FSR S.A.R.C. Registry Committee. You can contact the committee at datarequests@stopsarcoidosis.org. Restrictions on access to data are to ensure patient privacy for all persons in the FSR S.A.R.C. Registry.

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