

Clinical Manifestations of Neurosarcoidosis in the Netherlands

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Abstract

Background: Neurosarcoidosis is a rare disease. We investigated the prevalence of different manifestations of neurosarcoidosis and the influence of race or gender in the Netherlands, as well as the treatment strategies for neurosarcoidosis patients.

Methods: Multicentre observational cohort study of patients with neurosarcoidosis in two tertiary referral centres; the ILD Center of Excellence of the St. Antonius Hospital, Nieuwegein and the Amsterdam University Medical Centre (UMC), the Netherlands, from 2015 till 2017, as well as participants of the Dutch Neurosarcoidosis Registry between June 2014 and December 2017.

Results: A total of 194 patients were included, 27 of whom were in the Dutch Neurosarcoidosis Registry, 70 treated at the ILD Center of Excellence and 97 treated at the Amsterdam UMC. Of the 194 patients included, 54% were female. The most common neurosarcoidosis manifestations were chronic meningitis (41%), cranial nerve dysfunction (39%), myelopathy (28%) and cerebral parenchymal disease (26%). Age, gender and race did not differ for the various manifestations, except for peripheral polyneuropathy, which was more prevalent in men than in women (21% versus 10%). Most neurosarcoidosis patients were treated with prednisone (89%), methotrexate (46%) or infliximab (21%). A total of 102 patients (53%) received second- or third-line treatment.

Conclusion: In a large cohort of neurosarcoidosis patients, chronic meningitis, cranial nerve dysfunction, spinal cord involvement and cerebral parenchymal disease were the most common manifestations. Age, race and gender did not influence the clinical presentation, except for peripheral polyneuropathy (men>women). Over half of the patients required multiple immunosuppressive treatments.

Keywords: Neurosarcoidosis; Manifestations; Gender; Race; Treatment

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Introduction

Sarcoidosis is a multisystem inflammatory disorder of unknown aetiology in genetically predisposed individuals [1-3]. The hallmark of sarcoidosis is granulomatous inflammation in the organs involved [4]. The natural history and prognosis of sarcoidosis are highly variable, and its course is often unpredictable [5-7]. Sarcoidosis most often affects the lungs and lymph nodes, though any other organ system can be involved [8].

Involvement of the nervous system, or neurosarcoidosis, is

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detected in 5% of cases during life, [9-12] although autopsy studies have shown neurologic involvement in 25-50% [13,14]. Currently, the classification by Marangoni et al.[15], including definite, probable and possible neurosarcoidosis is used. Neurosarcoidosis can involve any part of the nervous system, causing a variety of neurological symptoms. A meta-analysis showed that the most common manifestations of neurosarcoidosis were cranial nerve dysfunctions and myelopathy [16,17]. Since neurologic involvement is the first presenting symptom in 50-70% of the neurosarcoidosis patients, and 52% of the patients have isolated neurosarcoidosis without systemic involvement [18-22], it can be difficult to diagnose. This might explain why previous studies reported variable prevalence of different manifestations [3,19,23-26].

The influence of race on the epidemiology of sarcoidosis is generally recognized. The incidence of sarcoidosis in patients of African descent is high compared to that in Caucasians [27]. Moreover, they often present with more severe organ involvement, a worse prognosis and higher mortality rates than Caucasians [27-29]. It has also been acknowledged that the prevalence of various organ manifestations differs between different ethnic subgroups, e.g. cutaneous and ocular sarcoidosis is more common in patients of African descent than in Caucasians, while hypercalcemia is more common in Caucasians [10]. In terms of gender differences, pulmonary and cardiac sarcoidosis is more common in men, whereas more peripheral lymph node involvement, cutaneous, ocular and liver sarcoidosis are seen more often in women [10,30]. To the best of our knowledge, racial and gender differences have so far not been studied specifically in neurosarcoidosis.

The aim of this study was to assess the prevalence of different manifestations of neurosarcoidosis and examine whether they vary with race and/or gender. In addition, the treatment strategies used for neurosarcoidosis patients were studied.

Materials and Methods

Study design

In this multicentre study, all neurosarcoidosis patients evaluated and/or treated between 2015 and 2018 were included. Furthermore, patients participating in the Dutch Neurosarcoidosis Registry between June 2014 and 2018 were included. All patients with neurosarcoidosis in the Netherlands had been invited to join the Dutch Neurosarcoidosis Registry, an online registration study [31]. Curavista (a certified eHealth platform) provided the online platform for this study and maintained the website. The present study was performed in accordance with the Declaration of Helsinki and its amendments. The patient registry and study protocol have been approved by the Medical Ethical Committee of the St. Antonius Hospital Nieuwegein. Digital or written informed consent was obtained from all patients.

Study sample

The overall study sample was comprised of patients from the ILD Center of Excellence of the St. Antonius Hospital Nieuwegein, and the Amsterdam University Medical Centre (UMC), the Netherlands, and the online Dutch Neurosarcoidosis Registry.

We carefully checked for overlap in registrations between the different sources.

At the ILD Center of Excellence and the Amsterdam UMC, patients were identified by their treating physician and data were extracted from medical records, de-identified and collected in a database. Patients in the Dutch Neurosarcoidosis Registry had either been identified and entered by their physician with their consent or joined the online registry of their own accord. Data in the registry were self-reported by patients. Additional medical data were requested from their treating physician(s) and data were checked to see if the diagnosis of neurosarcoidosis had been confirmed. Curavista (a certified eHealth platform) collected the data online and exported de-identified data to a database. All patients participating in the Dutch Neurosarcoidosis Registry had sufficient command of Dutch and had access to the internet.

Multiple diagnostic criteria have been proposed for neurosarcoidosis. In this population, neurosarcoidosis was diagnosed according to the classification system by Zajicek, later modified by Marangoni, which labels patients as definite, probable or possible neurosarcoidosis [15,22]. Definite neurosarcoidosis was diagnosed in case of a clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology. Probable neurosarcoidosis was diagnosed in case of a clinical presentation suggestive of neurosarcoidosis with MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system and after rigorous exclusion of other causes and evidence for systemic sarcoidosis. Possible neurosarcoidosis was diagnosed in case of a clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnosis where the above criteria are not met.

Patients with solely small fiber neuropathy (SFN) without granuloma formation in the affected tissue due to sarcoidosis were not considered to have neurosarcoidosis [32] and were excluded from this study (N=50, Dutch neurosarcoidosis registry). Myopathy was also excluded from this analysis.

Data collection and definition of phenotypes

Demographic and clinical data were extracted from medical records. Onset of sarcoidosis and neurosarcoidosis and their various manifestations were also recorded.

In order to determine associations between the various manifestations (systemic and neurosarcoidosis manifestations), we categorized neurosarcoidosis manifestations into 3 subgroups depending on anatomic location and severity.

Group 1: Peripheral polyneuropathy;

Group 2: Spinal cord manifestations (myelitis and polyradiculitis); and

Group 3: Cerebral parenchymal lesions, neuro-endocrine, and brainstem involvement, cerebral infarction, chronic aseptic meningitis, hydrocephalus and cranial nerve manifestations.

Statistical analysis

All statistical analyses were performed using SPSS version 24.

Table 1 Summary of the overall characteristics of the Dutch neurosarcoidosis sample studied, subdivided by gender.

Characteristics	Female (N=104)	Male (N=90)	Total Sample (N=194)	p-value*
Age at diagnosis of sarcoidosis (mean; range)	44.5 (13-80)	43.1 (20-79)	43.8 (13-80)	0.443
Age at diagnosis of neurosarcoidosis (mean; range)	45.9 (15-80)	46.1 (20-79)	46 (15-80)	0.939
Race				
Caucasian	72 (69.2)	58 (64.4)	130 (67)	0.846
African descent	22 (21.2)	19 (21.1)	41 (21.1)	
Diagnostic classification of neurosarcoidosis[#]				
Definite	9 (8.7)	3 (3.3)	12 (6.2)	0.277
Probable	81 (77.9)	72 (80)	153 (78.9)	
Possible	14 (13.5)	15 (16.7)	29 (14.9)	
Neurosarcoidosis Manifestations				
Cranial Nerve Dysfunction	46 (44.2)	30 (33.3)	76 (39.2)	0.121
NI/NII/NIII/NIV/NV/NVI	2/12/1/0/9/3	0/7/4/1/7/5	2/19/5/1/16/8	
NVII/NVIII/NIX/NX/NXI/NXII	27/7/4/1/0/0	14/9/1/1/0/1	41/16/5/2/0/1	
Chronic Aseptic Meningitis	43 (41.3)	38 (42.2)	80 (41.2)	0.894
Spinal Cord Disease / Myelitis	27 (26)	28 (31.1)	55 (28.4)	0.427
Polyradiculitis	1 (0.5)	0 (0)	1 (0.5)	0.351
Cerebral Parenchymal Disease	31 (29.8)	19 (21.1)	50 (25.8)	0.168
Neuro-Endocrine	13 (12.5)	8 (8.9)	21 (10.8)	0.421
Brain Stem	6 (5.8)	5 (5.6)	11 (5.7)	0.951
Hydrocephalus	12 (11.5)	8 (8.9)	20 (10.3)	0.547
Cerebral Infarction	5 (4.8)	9 (10)	14 (7.2)	0.162
Peripheral Polyneuropathy	10 (9.6)	19 (21.1)	29 (14.9)	0.025

*p-value for difference between men and women
[#]Diagnostic classification according to Zajicek, as modified by Marangoni [15,22]
 Data are expressed as number with percentage in parenthesis or mean with range in parenthesis if appropriate.

Data are presented as the means and range for continuous variables and as the number and percentage for categorical variables. In the analysis concerning race, we only compared Caucasians and patients of African descent, since other races were underrepresented, and groups were therefore too small to analyse.

Differences between genders and races were analysed using the Chi-square test for dichotomous variables and the Mann-Whitney-U test for continuous variables. Differences between the various neurosarcoidosis groups were analysed using the Chi-square test for dichotomous variables and Kruskal-Wallis tests for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

From the data sources 194 patients with neurosarcoidosis were identified: 27 participated in the Dutch Neurosarcoidosis Registry, 70 were recruited by the ILD Center of Excellence and 97 patients by the Amsterdam UMC. Demographic data are summarized in **Table 1**. Twelve patients (6%) were classified as definite neurosarcoidosis, 153 patients (79%) as probable neurosarcoidosis and 29 patients (15%) as possible neurosarcoidosis. Ten patients (5%) had an isolated neurosarcoidosis without systemic manifestations.

The most common manifestations of neurosarcoidosis were chronic meningitis (41%), cranial nerve dysfunction (39%), spinal cord involvement (28%) and cerebral parenchymal disease (26%)

(Table 1). Cerebral parenchymal disease varied from white matter lesions (48%) to intracerebral lesions with mass effect (30%) and intracerebral nodules (24%). Multiple neurosarcoidosis manifestations occurred simultaneously in 109 patients (56%).

Treatment for neurosarcoidosis had been initiated in 181 patients (93%), of whom 173 patients (89%) with prednisone. Second-line treatment had been given to 121 patients (62%), 89 of whom had been treated with methotrexate (46%), 24 patients with azathioprine (12%), five patients with mycophenolate mofetil (3%), two patients with cyclophosphamide (1%) and one patient with cyclosporine (0.5%). Third-line treatment had been started in 44 patients (23%), 40 of whom had been treated with infliximab (21%) and four with adalimumab (2%). Of the 13 patients (7%) for whom no treatment had been initiated, six had shown spontaneous regression, while one had stable disease for years, three had no symptoms and three refused treatments. Patients with a facial nerve palsy as the only manifestation of neurosarcoidosis had mostly received prednisone (6 out of 7 cases). In 11 out of 20 cases with a hydrocephalus neurosurgical intervention was necessary (55%).

A mortality rate of 2.1% was found in this cohort (four patients). The cause of death was neurosarcoidosis in two patients (hydrocephalus and cerebral lesions, respectively), infection due to immunosuppression in one patient and unknown cause in one patient.

No gender differences were found for the various neurosarcoidosis manifestations, except for peripheral polyneuropathy, which appeared to be more prevalent in men than in women (21.1% versus 9.6%, $p=0.025$; **Table 1**). We found no significant differences

Table 2 Various neurosarcoidosis manifestations subdivided by race.

Neurosarcoidosis manifestation	Caucasian (N=130)	African descent (N=41)	p-value*
Cranial nerve dysfunction	51 (39.2)	18 (43.9)	0.595
NI/NII/NIII/NIV/NV/NVI	2/13/4/1/8/6	0/4/1/0/3/1	
NVII/NVIII/NIX/NX/NXI/NXII	26/13/3/2/0/1	9/1/1/0/0/0	
Chronic aseptic meningitis	50 (38.4)	20 (48.8)	0.241
Spinal cord disease / myelitis	39 (30)	10 (24.4)	0.489
Cerebral parenchymal disease	35 (26.9)	11 (26.8)	0.991
Neuro-endocrine	12 (9.2)	5 (12.2)	0.580
Brain stem	7 (5.4)	2 (4.9)	0.899
Hydrocephalus	14 (10.8)	5 (12.2)	0.800
Cerebral infarction	9 (6.9)	4 (9.8)	0.551
Peripheral neuropathy	21 (16.2)	6 (14.6)	0.816

*p-value for difference between neurosarcoidosis patients of Caucasian and African descent
Data are expressed as number with percentage in parenthesis.

Table 3 Treatment for different groups of neurosarcoidosis manifestations.

	Group 1 (N=29)	Group 2 (N=56)	Group 3 (N=155)
Prednisone	26 (90)	51 (91)	140 (90)
Methotrexate	20 (69)	30 (54)	65 (42)
Azathioprine	4 (14)	5 (9)	21 (14)
Mycophenolate mofetil	0 (0)	3 (5)	4 (3)
Cyclosporine	0 (0)	0 (0)	1 (0.6)
Cyclophosphamide	0 (0)	1 (2)	1 (0.6)
Infliximab	7 (24)	16 (29)	32 (21)
Adalimumab	0 (0)	0 (0)	4 (3)

Data are expressed as number with percentage in parenthesis.

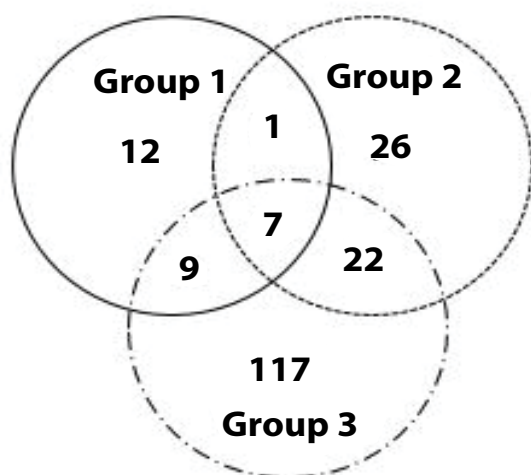


Figure 1 Venn diagram of manifestations from different neurosarcoidosis categories (Group 1: Polyneuropathy, Group 2: Spinal cord involvement and Group 3: Cerebral involvement).

between the two races regarding the various neurosarcoidosis manifestations (**Table 2**).

Various categories of neurosarcoidosis

The total neurosarcoidosis sample was subdivided according to

the various manifestations. Group 1 (peripheral polyneuropathy) comprised of 29 patients, 10 women and 19 men ($p=0.025$). Group 2 (spinal cord manifestations [myelitis and polyradiculitis]) comprised of 56 patients, 28 women and 28 men (not significant). Group 3 (cerebral parenchymal lesions, neuro-endocrine, cerebral infarction and brainstem involvement, chronic aseptic meningitis, hydrocephalus and cranial nerve manifestations) comprised of 155 patients, 90 women and 65 men ($p=0.012$). No significant differences between these groups were found regarding age at time of diagnosis of sarcoidosis. Age at time of diagnosis of neurosarcoidosis was significantly different ($p=0.001$); patients in group 3 were younger than patients in group 1 and 2 (44 years versus 51 and 48 years, respectively).

Thirty-nine patients presented with neurosarcoidosis manifestations from more than one category (**Figure 1**). There were seven patients with neurosarcoidosis manifestations from all three categories.

Group 1: Polyneuropathy

Hypercalcaemia was seen more frequently in patients with group 1 manifestations than in the other two groups (14% vs 2%, $p=0.006$). Patients with polyneuropathy had less cerebral involvement (7% vs 29%, $p=0.01$). Regarding treatment, patients with polyneuropathy were more often treated with methotrexate than patients in groups 2 and 3 (69% vs 42%, $p=0.007$) (**Table 3**).

Group 2: Spinal cord disease

Peripheral lymph node involvement was observed more frequently (93% vs 79%, $p=0.02$) in this subgroup compared to group 1 and 3. No neuro-endocrine or cerebrovascular involvement was observed in patients with spinal cord manifestations ($p=0.002$ and $p=0.015$, respectively). Cranial nerve dysfunction and chronic aseptic meningitis were also less common among patients with manifestations in this group (19.6% vs 47.1%, $p<0.001$ and 27.7% vs 47.8%, $p=0.011$, respectively). By contrast, there was more brainstem involvement (11.1% vs 3.6%, $p=0.045$). Infliximab had been started in a relatively high proportion of patients with manifestations in this group compared to the other categories, although this difference was not significant (29% vs 17%, $p=0.07$) (Table 3).

Group 3: Cerebral parenchymal lesions, neuro-endocrine, and brainstem involvement, cerebral infarction, chronic aseptic meningitis, hydrocephalus and cranial nerve manifestations

No differences in systemic manifestations were observed between group 3 patients and the rest (Group 1 and 2). Patients with manifestations in this group had less frequently received treatment with methotrexate (42% vs. 62%, $p=0.03$) compared to the other groups (Table 3). Adalimumab was only given to patients in this group ($N=4$).

Discussion

This study has been one of the few neurosarcoidosis cohort studies so far and was performed in two Dutch national expertise centres and a national neurosarcoidosis database. Both expertise centres showed similar results in terms of prevalence of the manifestations. The most common neurosarcoidosis manifestations were chronic aseptic meningitis (42%), cranial nerve dysfunction (39%), spinal cord involvement (28%) and cerebral parenchymal disease (26%). Strikingly, much overlap was found in manifestations, with 56% of patients having two or more manifestations simultaneously. Over 90% of patients needed treatment.

The clinical presentation of neurosarcoidosis is known to be heterogeneous [18]. The disorder is hard to recognize due to its heterogeneity and rarity. We also found this diversity of clinical presentations in our Dutch cohort of neurosarcoidosis patients. We report a higher prevalence of meningitis, viz. 41%, versus 16% reported in a meta-analysis [9]. This could probably be explained by the fact that both centres in our study are tertiary referral centres (inclusion bias). The Amsterdam UMC is also a referral centre for inflammatory and infectious meningitis. We also found more spinal cord involvement (28% versus 18%) [9]. These manifestations are found in severely affected neurosarcoidosis patients, which is the main reason for referral. By contrast, we found less cranial nerve involvement (39% versus 55%) [9], with the facial, optic, trigeminal and vestibulocochlear nerves as the most commonly involved nerves. It is highly likely that these differences can be explained by the small sample sizes and mainly retrospective design of these previous studies [9], and by the tertiary setting of our neurosarcoidosis population. A comparison between our results and those reported from other referral centres showed that results were similar [16,24,33]. The prevalence of peripheral polyneuropathy in our study was comparable to that reported in a large meta-analysis [9]. Race

and gender distributions in our total cohort of neurosarcoidosis patients were also similar to those found in previous studies [9].

Manifestations of sarcoidosis are known to differ between races and genders [10,27-30,34-40]. Men with sarcoidosis tend to have higher rates of cardiac and pulmonary involvement, whereas women have a higher prevalence of peripheral lymph node involvement, cutaneous, musculoskeletal, liver, spleen and ocular involvement [10,30,34-38]. Furthermore, hypercalcaemia tends to be more prevalent in men [38]. In the Dutch neurosarcoidosis sample studied, the prevalence of various neurosarcoidosis manifestations did not differ between genders, except for peripheral polyneuropathy which was more common in men than in women (21.1% versus 9.6%). This finding is in line with other auto-immune polyneuropathies [41-45], in contrast to diabetic polyneuropathy, where no gender differences were found [46]. The explanation for this finding remains unclear.

As regards race, the ACCESS study, a large case-control study of sarcoidosis, found that patients of African descent were more likely to have cutaneous involvement, as well as erythema nodosum, extrathoracic lymph node, ocular, liver and bone marrow involvement, while Caucasians were more likely to develop hypercalcemia and spleen involvement [10,39]. In a self-reported organ involvement registry, Baughman et al. did not find differences in the prevalence of neurosarcoidosis in general between genders or races [11]. In our neurosarcoidosis sample patients of African descent appeared to be overrepresented (21%) in comparison with the general Dutch population (4%) This might be explained by the fact that the population in urban areas of the Netherlands (the west of the country [including Amsterdam]) and to a lesser extent the centre (e.g. Nieuwegein) includes more people of non-Dutch origin, causing bias in the racial distribution in our cohort. Moreover, patients of African descent have a higher risk of developing a more chronic severe course of sarcoidosis. However, no differences between races were found in our neurosarcoidosis sample regarding the prevalence of the various neurosarcoidosis manifestations.

Differences between races and genders regarding the various manifestations of sarcoidosis need to be considered in the management of this disorder. One of the main difficulties in accurately identifying patients at risk of progressive major organ damage and death is the heterogeneity of its presentation. Thus, the optimal risk stratification strategy in the general sarcoidosis population continues to be unclear [47]. The identification of patients at higher risk of eventual major organ involvement, in order to initiate timely treatment to prevent progression, remains a clinical challenge. The integration of clinical symptoms, results of functional and imaging examinations, and observed disease behaviour in the definition of severe sarcoidosis seems to be the most comprehensive approach suggested to date [48]. Studies in the United States found sarcoidosis mortality to be related to both race and gender, perhaps reflecting genetic factors. African-American individuals and women had a worse prognosis, with a higher prevalence of extra-pulmonary organ involvement and prolonged disease duration, and a higher rate of sarcoidosis-related hospitalizations [27-29,49]. Sarcoidosis patients of African descent also had a higher mortality rate than Caucasians and were treated more often [10,29]. In a large neurosarcoidosis study by

Joubert et al. (n=234), no differences in mortality rates were found between various ethnicities [16]. The mortality difference between Caucasians and patients of African descent with sarcoidosis is thus explained by other sarcoidosis manifestations than neurosarcoidosis, for instance pulmonary hypertension and cardiac and more advanced pulmonary sarcoidosis [10,29,47].

The majority of patients in the studied Dutch neurosarcoidosis sample needed treatment (93%). This underlines that treatment is mandatory for neurosarcoidosis, and in many cases second- or third-line treatment is required (53%). Considering this, plus the high relapse rate necessitating long-term treatment for neurosarcoidosis and the many side-effects of corticosteroids [16,33,50,51], second- or third-line agents (methotrexate, azathioprine, or TNF-alpha inhibitors) are preferable as the first-choice treatment in selected neurosarcoidosis cases, especially in patients with comorbidities such as obesity or diabetes. Based on clinical experience with other sarcoidosis manifestations and previous studies, second-line treatment with azathioprine and methotrexate can be regarded as safe and effective [52]. TNF-alpha inhibitors have shown efficacy and safety for both sarcoidosis in general and neurosarcoidosis [23,53-60]. Moreover, lower relapse rates of neurosarcoidosis have been described with infliximab and methotrexate [16,33], as well as high relapse rates of sarcoidosis and neurosarcoidosis after discontinuation of infliximab. Thus, the decision to discontinue should be made very carefully and long-term continuation should be considered [23,53,54,61,62]. Previously, treatment with TNF-alpha inhibitors led to high health care costs. The expiring of the patent of Remicade® (Infliximab) and the availability of biosimilars (Inflectra®) with similar efficacy have now reduced the costs [63].

Our study had several limitations. Despite significant advances in diagnostics of neurosarcoidosis made in the last two decades, no consensus has been achieved about its classification. We used the most widely used modified Zajicek criteria. Follow-up of neurosarcoidosis is difficult, since no sensitive and specific biomarker is available so far. Disease assessment is often based on symptoms and neurologic examination, sometimes combined with follow-up cerebral or spinal CTs (when applicable), making it hard to assess whether the disease is truly in remission. Another limitation could be a selection bias, since most of our patients were diagnosed and treated in tertiary expertise centres. However, patients with suspected neurosarcoidosis are usually

referred to such expertise centres because of the complexity of diagnosing and treating this rare disease entity. Another limitation is the observational nature of our study, with some missing values and no structured monitoring and follow-up. Since neurosarcoidosis is a rare sarcoidosis manifestation, however, it is difficult to perform studies with another study design.

Conclusion

In conclusion, chronic aseptic meningitis, cranial nerve dysfunction, spinal cord involvement and cerebral parenchymal disease appeared to be the most common neurosarcoidosis manifestations, without racial or gender differences. Treatment was mandatory in the majority of patients, >50% of whom required second- or third-line treatment. The current risk stratification strategy to identify severe neurosarcoidosis patients involves a multidisciplinary approach integrating symptoms, functional tests and imaging findings. Future studies are warranted to enhance our understanding of the diversity of neurosarcoidosis, the determinants of morbidity, severity and mortality, as well as optimal treatment regimens, in order to determine the best treatment to improve the quality of life of patients suffering from this rare form of sarcoidosis.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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