Clinical characteristics and outcome of neurosarcoidosis-associated myelitis: A retrospective cohort study and review of the literature

Jessica Y. C. Nolte | Leroy ten Dam | Diederik van de Beek | Matthijs C. Brouwer

Abstract

Background and purpose: Neurosarcoidosis can affect all parts of the nervous system of which myelitis is relatively frequent. The aim of this study was to describe clinical characteristics, treatment and prognosis of patients with myelitis attributable to neurosarcoidosis.

Methods: We performed a retrospective cohort study and a systematic review and meta-analysis of neurosarcoidosis-associated myelitis.

Results: Myelitis was identified in 41 of 153 (27%) neurosarcoidosis patients seen at our clinic from 2015 to 2020. Classification of neurosarcoidosis was definite in three (7%), probable in 29 (71%) and possible in nine patients (22%). The median (interquartile range) age at onset was 49 (41–53) years and 20 of the patients were female (49%). The presenting symptoms included muscle weakness in 31 of 41 patients (78%), sensory loss in 35 (88%) and micturition abnormalities in 30 (75%). Spinal magnetic resonance imaging showed longitudinally extensive myelitis in 27 of 36 patients (75%) and cerebrospinal fluid examination showed an elevated leukocyte count in 21 patients (81%). Initial treatment consisted of glucocorticoids in 38 of 41 patients (93%), with additional methotrexate or azathioprine in 21 of 41 patients (51%) and infliximab in 10 of 41 patients (24%). Treatment led to remission, improvement or stabilization of disease in 37 of 39 patients (95%). Despite treatment, 18 of 30 patients (60%) could not walk independently at the end of follow-up (median 36 months). A review of the literature published between 2000 and 2020 identified 215 patients with comparable clinical characteristics and results of ancillary investigations.

Conclusion: Sarcoidosis-associated myelitis is observed in 27% of neurosarcoidosis patients. Although treatment often led to a decrease in disease activity, residual neurological deficits leading to loss of ambulation occurred frequently.

KEYWORDS
autoimmune disease, neurosarcoidosis, spinal cord, transverse myelitis
INTRODUCTION

Sarcoidosis is a multi-system disorder, characterized by the accumulation of non-caseating granulomata, which can involve every organ system. The incidence is estimated to be between 1.0 and 35.5 per 100,000 people worldwide, with variations among populations and ethnicities [1]. Involvement of the nervous system, or neurosarcoidosis, has been reported in 5%–20% of patients with sarcoidosis, and in approximately half of the neurosarcoidosis patients it is the presenting feature of sarcoidosis [2]. Neurosarcoidosis is a clinically heterogeneous disorder, as it can involve all parts of the central and peripheral nervous system [2]. Spinal cord involvement in sarcoidosis has previously been reported in 18% of patients in a meta-analysis of studies on neurosarcoidosis [2]. In this retrospective single-center cohort study we evaluate clinical features and treatment response in patients diagnosed with sarcoidosis-associated myelitis. We also performed a systematic review and meta-analysis of the literature on sarcoidosis-associated myelitis.

METHODS

We retrospectively reviewed all case records from adult patients who were seen between June 2015 and November 2020 at the Neurology Department at the Amsterdam University Medical Centers, a tertiary referral center for neurosarcoidosis. We included patients with (1) neurosarcoidosis (either definite, probable or possible according to the criteria from the Neurosarcoidosis Consortium Consensus Group [3]) and (2) a clinical diagnosis of myelopathy with evidence of myelitis on neuroimaging or in cerebrospinal fluid (CSF) analysis.

Clinical data and ancillary investigations

Detailed history and neurological examination data were retrieved from patient files in an electronic database including presenting symptoms, age of onset of symptoms, results of ancillary investigations and data on treatment and treatment response and outcome of hydrocephalus in neurosarcoidosis. Spinal cord magnetic resonance imaging (MRI) was re-evaluated for myelopathy and pattern of contrast enhancement. The study conforms to the World Medical Association Declaration of Helsinki, 7th revision 2013 Fortaleza. Ethical approval is not required in the Netherlands for a retrospective study with anonymized patient data such as used in our study.

Review of the literature

A literature search was performed in PubMed using the following terms: (“sarcoidosis” [MeSH Terms] OR sarcoid [tiab] OR “Neurosarcoidosis” [Supplementary Concept] OR neurosarcoid [tiab]) AND (“myelitis” [MeSH Terms] OR myelitis [tiab] OR myelopathy [tiab] OR spinal cord [MeSH Terms] OR spinal cord [tiab]). We included articles written in English, describing more than five adult patients, that were published in the last 20 years. The search was followed by a manual search in the reference lists of the publications found.

RESULTS

Between June 2015 and November 2020, a total of 358 patients were evaluated for suspected neurological involvement of sarcoidosis at our outpatient department or clinical department. Of these, 153 patients were diagnosed with neurosarcoidosis (either definite, probable or possible according to the criteria from the Neurosarcoidosis Consortium Consensus Group [3]). Sarcoidosis-associated myelitis was present in 41 neurosarcoidosis patients (27%; Table 1) of whom 20 were female (49%). The median (interquartile range [IQR]) age at onset was 49 (41–53) years.

Seven patients (17%) had a previous diagnosis of sarcoidosis, of whom three developed myelitis while receiving immunosuppressive therapy. Presenting symptoms were sensory abnormalities in 35 (85%), loss of strength in 31 (76%) and micturition abnormalities in 30 patients (73%). The median (range) time from symptom onset to first neurological evaluation was 13 (0–163) weeks. A subacute onset of symptoms (<6 weeks) was present in 12 patients (36%). Frequent findings on neurological examination included abnormal reflexes in 29 patients (71%), sensory abnormalities in 29 patients (71%), as well as paresis of the legs in 20 (49%) and arms in seven patients (18%). Neurological examination showed normal strength, reflexes and sensory function in four patients (10%), who presented with either micturition abnormalities, subjective gait abnormalities or transitory sensory abnormalities (Lhermite’s signs) consistent with myelopathy. On presentation, 26 of 40 patients (65%) could walk independently, 10 (25%) walked with a walking aid and four (10%) were unable to walk. The median (IQR) time of onset of symptoms to diagnosis of neurosarcoidosis was 7 (4–17) months. Causes of prolonged time to diagnosis were diverse and included, among others, an initial diagnosis of compressive myelopathy, primary progressive multiple sclerosis or transversa myelitis, followed by detection of granulomata in lymph nodes during follow-up, after which neurosarcoidosis was diagnosed. Eight patients had another site of neurological involvement besides myelitis (20%), which consisted of chronic meningitis in three patients and brain parenchymal involvement, cranial neuropathy, hydrocephalus, peripheral neuropathy and myopathy in one patient each. Involved organ systems besides the nervous system included lymph nodes in 36 (88%), lungs in 17 (41%), eyes in three (7%) and the heart in two patients (5%). Skin, joint, liver and sinus involvement were present in one patient each.

Serum angiotensin-converting enzyme (ACE) level was analysed in 30 patients (73%) and was elevated in 20 (67%), soluble interleukin-2 receptor (sIL-2R) was evaluated in five patients (12%) and was found to be elevated in four (80%). In 26 patients, CSF analysis was performed (63%), which showed a leukocyte count >5/mm³ in 21 patients (81%), elevated total protein concentration (>0.6 g/L) in 15
1765

CLINICAL CHARACTERISTICS AND OUTCOME OF NEUROSARCOIDOSIS-ASSOCIATED MYELITIS

TABLE 1 Clinical characteristics and results of ancillary investigations in sarcoidosis-associated myelitis

| Characteristics                                      | Median (IQR)        |
|-------------------------------------------------------|---------------------|
| Median (IQR) age at onset, years                      | 49 (41–53)          |
| Sex: female, n/N (%)                                  | 20/41 (49)          |
| History of sarcoidosis, n/N (%)                       | 7 (17)              |
| Time to neurological evaluation, n/N (%)              |                     |
| <6 weeks                                              | 12/33 (36)          |
| ≥6 weeks                                              | 21/33 (64)          |
| Clinical symptoms at onset, n/N (%)                   |                     |
| Loss of strength                                      | 31/41 (76)          |
| Sensory abnormalities                                 | 35/41 (85)          |
| Micturition abnormalities                             | 30/41 (73)          |
| Gait abnormalities                                    | 22/41 (54)          |
| Ambulation at first evaluation, n/N (%)               |                     |
| Walks independently                                   | 26/40 (65)          |
| Walks with walking aids                               | 10/40 (25)          |
| Unable to walk                                        | 4/40 (10)           |
| Sarcoïdosis localization, n/N (%)                    |                     |
| Lung                                                  | 17/41 (41)          |
| Lymph nodes                                           | 36/41 (88)          |
| Eye                                                   | 3/41 (7)            |
| Other                                                 | 4/41 (10)           |
| Ancillary investigations, n/N (%)                     |                     |
| Elevated ACE                                          | 20/30 (67)          |
| Elevated sIL-2R                                       | 4/5 (80)            |
| Abnormal ^18 FDG-PET                                  | 19/20 (95)          |
| Cerebrospinal fluid analysis, n/N (%)                 |                     |
| Elevated leukocyte count                              | 21/26 (81)          |
| Elevated total protein                                | 15/26 (58)          |
| Decreased glucose                                     | 6/26 (23)           |
| Abnormal spinal cord MRI, n/N (%)                     | 40/41 (98)          |
| Lesion length: 1–2 segments, n/N (%)                  | 11/40 (28)          |
| Lesion length: ≥3 segments, n/N (%)                   | 29/40 (73)          |
| Lesion location: cervical spine, n/N (%)              | 28/40 (70)          |
| Lesion location: thoracic spine, n/N (%)              | 30/40 (75)          |
| Contrast enhancement, n/N (%)                        |                     |
| Intramedullary enhancement                            | 23/35 (66)          |
| (Lepto)meningeal enhancement                          | 12/35 (34)          |
| No enhancement                                        | 11/35 (31)          |
| Biopsy, n/N (%)                                       | 25/28 (89)          |
| Non-caseating granulomas                              |                     |
| Classification, n/N (%)                               |                     |
| Definite                                              | 3/41 (7)            |
| Probable                                              | 29/41 (71)          |
| Possible                                              | 9/41 (22)           |
| Immunosuppressive treatment, n/N (%)                  | 38/41 (93)          |
| (Continues)                                           |                     |

| TABLE 1 (Continued) | Characteristics                                      |
|----------------------|-------------------------------------------------------|
|                       | Corticosteroid pulse                                  |
|                       | 32/41 (78)                                           |
|                       | Corticosteroid maintenance                           |
|                       | 37/41 (90)                                           |
|                       | Second-line therapy                                   |
|                       | 1/41 (2)                                              |
|                       | Third-line therapy                                    |
|                       | 1/41 (2)                                              |
|                       | Medication changes, n/N (%)                           |
|                       | 21/41 (51)                                           |
|                       | Corticosteroid therapy                                |
|                       | 17/21 (86)                                           |
|                       | Second-line therapy                                   |
|                       | 21/21 (43)                                           |
|                       | Third-line therapy                                    |
|                       | 10/21 (48)                                           |
| Follow-up             |                                                       |
|                       | Median (IQR) duration, months                         |
|                       | 36 (12–72)                                           |
|                       | Median (range) mRS score                              |
|                       | 2 (0–6)                                               |
| Outcome of neurosarcoidosis, n/N (%)                  |                                                       |
|                       | Remission                                             |
|                       | 15/39 (39)                                           |
|                       | Improvement                                           |
|                       | 4/39 (10)                                             |
|                       | Stable disease                                        |
|                       | 18/39 (46)                                            |
|                       | Deterioration                                         |
|                       | 2/39 (5)                                              |
| Ambulation at last evaluation, n/N (%)                |                                                       |
|                       | Walks independently                                   |
|                       | 12/30 (40)                                            |
|                       | Walks with walking aids                               |
|                       | 12/30 (40)                                            |
|                       | Unable to walk                                        |
|                       | 6/30 (20)                                             |

Abbreviations: ^18 FDG-PET, fluor-18-deoxyglucose positron emission tomography; ACE, angiotensin-converting enzyme; IQR, interquartile range; mRS, modified Rankin scale; sIL2-R, soluble interleukin-2 receptor.

patients (58%) and CSF glucose < 2.5 mmol/L in six patients (23%). Oligoclonal bands were tested in 18 patients (44%) and were present in seven (39%).

Results of spinal MRI were available for all patients and were abnormal in 40 (98%). Fluor-18-deoxyglucose positron emission tomography (^18 FDG-PET) showed focal uptake in the cervical spinal cord in the absence of abnormalities on MRI of the spine in one patient. Myelitis often affected multiple segments (median 5, range 1–20). In 29 patients (73%) longitudinally extensive myelitis was present (≥3 segments affected; Figure 1). The cervical and thoracic regions were affected in 28 (75%) and 30 patients (75%), respectively. In nine patients (23%) multiple separate spinal cord lesions were found. Contrast-enhanced MRI of the spine was performed in 35 patients (85%) and showed intramedullary enhancement in 23 (66%) and (lepto)meningeal enhancement in 12 (34%; Figure 2). Of the patients with intramedullary contrast enhancement there was dorsal enhancement in four patients (17%), both central and ventral enhancement in one patient (4%) and diffuse enhancement in the remaining 17 patients (74%). Post hoc analysis of neurological examination in these patients showed neuroanatomical correlates in most; three of the four patients with dorsal enhancement had isolated sensory abnormalities, the other had both sensory abnormalities and paresis, the patient with ventral enhancement had isolated paresis and the patient with central enhancement had both paresis.
and sensory abnormalities. A trident sign (combined dorsal and central intramedullary enhancement [4]) was not present in any of the patients. In 11 patients there was no gadolinium enhancement (31%). In 20 of 34 patients (59%), $^{18}$FDG-PET was performed without a previous diagnosis of sarcoidosis, and showed abnormalities suggestive of sarcoidosis (e.g., lymphadenopathy, pulmonary or regional FDG uptake elsewhere in the body) in 19 patients (95%) and spinal cord hypermetabolism in nine patients (45%; Figure 3). In the 28 patients without a medical history of sarcoidosis, biopsy was performed of lymphoid tissue in 24 (86%), pulmonary tissue in three (11%), the spinal cord in two (7%) and the brain in one (4%). Biopsy results showed non-caseating granulomas in 25 of 28 patients (89%).

Of the 41 patients three were diagnosed with definite neurosarcoidosis (7%), 29 with probable neurosarcoidosis (71%) and nine with possible neurosarcoidosis (22%). Of the patients classified as having possible neurosarcoidosis there was no suitable biopsy site outside of the CNS in two patients, the biopsy was inconclusive in three, and biopsy was refrained from in four patients. In all patients classified as having possible neurosarcoidosis extensive ancillary investigations were performed to exclude alternative causes of myelitis such as infectious diseases (e.g., HIV, borrelia, lues, tuberculosis, neurotropic viruses), other systemic autoimmune disorders or anti-neuronal antibody-associated myelitis, demyelinating disorders (neuromyelitis optica, multiple sclerosis), deficiencies (e.g., vitamin B12) and malignancy.

The median (IQR) follow-up was 36 (12–72) months. Thirty-eight patients (93%) received immunosuppressive medication. Initial therapy consisted of corticosteroid pulse therapy in 32 patients (78%), corticosteroid maintenance therapy in 37 patients (90%), methotrexate in one patient (2%) and infliximab in one patient (2%). Medication was changed a total of 22 times in 19 out of 41 patients (46%) due to insufficient response to initial therapy (17 of 22; 77%) or side effects (5 of 22; 23%). Fourteen out of 41 patients (34%) had a relapse of neurosarcoidosis after an episode of sarcoidosis-associated myelitis. The mean (range) total number of relapses of symptoms per patient was 2 (1–4). The site of relapse of neurosarcoidosis was myelopathy in 30 out of 32 relapses (94%). Other sites of relapses included cranial neuropathy and radiculopathy in three patients (9%) and chronic meningitis, brain parenchymal lesions and hydrocephalus in one patient (3%). We could not detect specific features that were related to the occurrence of a relapse. Medication changes included corticosteroid pulse or maintenance therapy in 17 (81%), methotrexate in 18 (86%), azathioprine in nine (43%) or infliximab in 10 (48%) out of 21 patients. Three patients were not treated with immunosuppressive medication as the symptoms spontaneously improved.

Neurological examination at the end of follow-up was available in 31 patients and was abnormal in 28 (90%). At end of follow-up only 12 patients (40%) could walk independently, 12 (40%) required a walking aid and six out of 30 (20%) were unable to walk. Outcome of neurosarcoidosis at last follow-up was classified as remission in 15 (39%), improvement in four (10%), stable disease in 18 (46%) and deterioration in two patients (5%). The median (range) modified Rankin scale (mRS) score at last follow-up was 2 (0–6).

**Literature review**

Our literature review yielded 419 articles which were assessed for eligibility based on the title and abstract. Twelve articles describing a total of 215 cases met our inclusion criteria. A summary of these...
FIGURE 2 Different patterns of sarcoidosis-associated myelitis on magnetic resonance imaging (MRI) of the spine. The left column (a, c) shows sagittal contrast enhanced T1-weighted images and the right column shows sagittal T2-weighted images (b, d). The top row (a, b) shows longitudinally extensive myelitis of the cervical spine with intramedullary and leptomeningeal contrast enhancement. The bottom row (c, d) shows myelitis of the lower spinal cord and cauda equina with intramedullary and leptomeningeal contrast enhancement.
studies is presented in Table 2 [5–16] and Supplementary Table 1. The median (range) age was 47 (30–62) years and 77 of 169 patients were female (46%). Twenty-two of 116 patients (17%) had a previous diagnosis of sarcoidosis.

Elevated CSF leukocyte count was found in 107 of 143 patients (75%) and CSF protein concentration was elevated in 117 of 144 patients (81%). Spinal imaging found longitudinally extensive myelitis (≥3 spinal segments) in 69 of 89 cases (78%). Location of the lesion was the cervical spinal cord in 116 of 174 (67%) and the thoracic spinal cord in 110 of 174 patients (63%). Neurosarcoidosis was classified as definite in 34 (16%), probable in 174 (81%) and possible in six (4%) out of 215 patients. Glucocorticoids were started in 120 of 122 patients (98%). Other frequently used immunosuppressive therapies included methotrexate in 67 of 128 (51%), azathioprine in 11 of 122 (9%) and infliximab in 33 of 108 patients (31%). Other immunosuppressive therapies used included cyclophosphamide, mycophenolate mofetil, leflunomide, cyclosporine and (hydroxy)chloroquine. A relapse of neurosarcoidosis-associated symptoms occurred in 25 of 86 patients (29%).

**DISCUSSION**

In this retrospective single-center study we found sarcoidosis-associated myelitis occurs in 27% of neurosarcoidosis patients. This presents with a subacute or chronic myelopathy and is often longitudinally extensive on imaging. Sarcoidosis-associated myelitis is a disabling chronic disease with relapses in approximately a third of the patients requiring prolonged immunosuppressive treatment. Diagnosis is often delayed due to low clinical suspicion as relatively few patients with sarcoidosis-associated myelitis had a medical history of sarcoidosis. In the absence of a positive history of (neuro)sarcoidosis the differential diagnosis of acute transverse myelitis is diverse and includes other inflammatory, (post-)infectious, (para) neoplastic, vascular and metabolic causes [17]. A Finnish series of 63 patients with acute transverse myelitis showed neurosarcoidosis was the cause in three (5%) [18]. Although neurosarcoidosis is an uncommon cause of myelitis it should be included in the differential diagnosis of patients with a myelitis of unknown etiology. Several ancillary investigations are used in the diagnosis. The sensitivity of serum biomarkers for detecting sarcoidosis is low, at 62% for ACE and 88% for sIL2-R in patients with suspected systemic sarcoidosis [19]. In our series, 33% of patients with sarcoidosis-associated myelitis had normal ACE and 20% normal sIL2-R levels. Therefore, these cannot be used to screen for sarcoidosis or to exclude the diagnosis. CSF analysis was abnormal in the majority of patients in our study (85%) but disease-specific markers for sarcoidosis are not available. A recent study showed that the value of sIL2-R in CSF is limited in the diagnosis of neurosarcoidosis, as it can be elevated in a range of infectious and autoimmune diseases included in the differential diagnosis [20]. In myelitis patients with unknown cause, chest CT and, if normal, whole-body 18FDG-PET should be performed to identify characteristic abnormalities suggestive of sarcoidosis. Biopsy of lymph nodes in suspected neurosarcoidosis often leads to histopathological confirmation of the disease, and a diagnostic classification of probable neurosarcoidosis [21]. Whole-body 18FDG-PET showed abnormalities suggestive of sarcoidosis in all but one patient (95%) in whom it was performed.
outcomes of myelitis was associated with older age and more extensive neurological deficits but not with time to admission, number of contrast-enhancing lesions or recurrence of symptoms [23,24]. Data are inconsistent about the association between number of spinal cord segments involved and outcome. Potentially, long diagnostic uncertainty and associated delay in immunosuppressive treatment contributes to the poor prognosis. However, post hoc analysis did not show an association using the chi-squared test between diagnosis <1 year from onset of symptoms and mRS score at last follow-up (p = 0.148). Furthermore, the currently available disability scales are insufficient to accurately quantify disability in myelopathy patients; therefore, it is important to develop tools that better reflect disability in the myelopathy population.

This study has several limitations. First, patients evaluated were referred to our tertiary center. This may introduce selection bias leading to overestimation of the impact of sarcoidosis-associated myelitis. Second, the retrospective design of our study resulted in heterogeneous assessment of disease activity as well as missing data in some patients. This prohibits drawing firm conclusions regarding outcome and treatment effect. Third, there might be publication bias regarding sarcoidosis-associated myelitis as the patients in the review more often had a diagnosis of definite neurosarcoidosis. Nevertheless, our retrospective single-center cohort study and systematic review provides valuable information on sarcoidosis-associated myelitis.

In conclusion, myelitis is found in a significant minority of neurosarcoidosis patients and has a poor prognosis. Diagnosis relies on MRI of the spinal cord and chest CT or 18FDG-PET to identify CNS and extra-CNS disease activity of sarcoidosis, especially in patients with myelitis of unknown cause. Since most data on sarcoidosis-associated myelitis is from retrospective case series, future research should focus on prospective studies that compare different or novel treatment strategies, such as top-down treatment (i.e., early initiation of anti-TNF-α therapy) or novel immunosuppressive agents.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Jessica Y. C. Nolte: Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). Leroy...
ten Dam: Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). Diederik van de Beek: Conceptualization (equal); Writing – original draft (equal); Writing – review and editing (equal). Matthijs C. Brouwer: Conceptualization (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal).

ETHICAL APPROVAL
The study conforms with the World Medical Association Declaration of Helsinki, 7th revision 2013, Fortaleza. Ethical approval is not required in the Netherlands for a retrospective study with anonymized patient data such as used in our study.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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