Chapter 2

Many faces of neurosarcoidosis: from chronic meningitis to myelopathy

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Abstract

Purpose of review

Neurosarcoidosis occurs in 5% of patients with sarcoidosis and can be difficult to diagnose. In this review we discuss the most recent advances in our understanding of the disease, describing clinical characteristics, the diagnostic process, treatment and prognosis.

Recent findings

Clinical presentation is heterogeneous with most patients presenting with cranial nerve palsy, headache and sensory abnormalities. Patients are classified according to probability of the diagnosis according to the Zajicek criteria. In these criteria histopathological confirmation of non-caseating granulomas in affected tissue outside the nervous system is key. Radiological abnormalities on neuroimaging are non-specific. No biomarkers have been described that adequately identify patients with sarcoidosis. However, soluble interleukin-2 receptor is a relatively novel biomarker and may be useful. In addition to HRCT scan, ^{18}F-FDG PET-CT scanning can identify occult locations of disease activity and aid in obtaining histological evidence of the disease. Despite the use of new therapies, still a third of the patients remain stable, deteriorate or die.

Summary

Diagnosing and treating patients with neurosarcoidosis remains a challenge. Long-term prospective studies evaluating patients suspected of neurosarcoidosis are needed to assess sensitivity and specificity of ancillary investigations and the diagnostic criteria. Furthermore, future studies are needed to evaluate the prognosis and the optimal treatment strategy.

Introduction

Sarcoidosis is a multisystem disorder, caused by an exaggerated immune response to an unknown antigen in genetic predisposed individuals.[1] It is characterized by granulomatous inflammation that can affect every organ system. Involvement of the nervous system is called neurosarcoidosis. Because of the heterogeneous clinical presentation and low sensitivity of ancillary investigations, the diagnosis of neurosarcoidosis can be difficult.

International literature concerning neurosarcoidosis predominantly consists of retrospective studies and no randomized controlled trials have been performed to assess treatment strategies.[2**] In this review we give an overview of the most recent advances in our understanding of the disease, clinical characteristics, the diagnostic process, treatment and prognosis.

Epidemiology and risk factors

Sarcoidosis is estimated to occur in 10–65 per 100 000 persons in whom the nervous system is involved in approximately 5%.[1,2**,3] However, in autopsy studies granulomatous inflammation of the nervous system is seen in up to 25% of patients.[4] Neurosarcoidosis affects women slightly more frequently than men (55% vs. 45%) as was reported in a recent meta-analysis including 1088 patients with neurosarcoidosis, with a mean age at presentation of 43 years.[2**] The cause of sarcoidosis has not yet been elucidated. Studies show that sarcoidosis occurs in families, with an increased risk of first-degree and second-degree relatives.[5] Several alleles in the human leukocyte antigen (HLA) region are associated with sarcoidosis, supporting the hypothesis that sarcoidosis manifests after exposure to so-far unidentified antigens.[6] In addition, HLA typing of patients with sarcoidosis may identify patients with an increased risk for extra-pulmonary manifestations, but the clinical utility remains unknown.[7] Only one study reported specific genetic risk factors for neurosarcoidosis.[8] In this imputation-based fine-mapping study of the chromosomal region 15q25 in African-Americans with neurosarcoidosis, the investigators found ZNF592 to be highly associated in patients with neurosarcoidosis compared to healthy controls. However, when comparing neurosarcoidosis cases against sarcoidosis cases without neurological involvement, they found no association.

Clinical characteristics

In 69% of patients with neurosarcoidosis, neurological involvement is the first presenting symptom. A neurological presentation without systemic involvement is seen in 52% of patients.[2**] During the disease course, systemic involvement consists of pulmonary sarcoidosis in 67%, ophthalmological sarcoidosis in 25% and skin and joint involvement both in 21%.[2**] Sarcoidosis stays confined to the nervous system in 22% of the cases.[2**] Most patients present with more than one neurological symptom and up to half develop additional neurological symptoms during the disease course.[9*]
The clinical presentation is heterogeneous and the three most frequently described presenting symptoms in a meta-analysis including 1088 patients were cranial nerve palsy (55%), headache (32%), and sensory abnormalities (29%). Neurological symptoms consistent with spinal cord involvement were found in 18%, peripheral neuropathy in 17%, aseptic meningitis in 16%, myopathy in 15%, and neuro-endocrine involvement in 9%.

Cranial neuropathy

Cranial neuropathy can be caused by direct granulomatous infiltration, increased intracranial pressure, or basilar aseptic meningitis.[10] In one study evaluating cranial nerve involvement in 305 patients, 44% of patients had involvement of more than one cranial nerve.[11*] Cranial nerve palsy mainly consisted of facial nerve (24%) and optical nerve palsy (21%). It tends to be unilateral, but especially optical, vestibulocochlear, facial, and trigeminal nerve palsy can manifest bilaterally.[11*]

Aseptic meningitis

Neurosarcoidosis is an important cause of non-infectious meningitis and can manifest with sub-acute or chronic symptoms.[10,12] Symptoms include headache, nuchal rigidity, or cranial nerve palsy. Hydrocephalus occurs in 9% of patients and is a life-threatening complication.[2**] It can be communicating or noncommunicating, resulting from either abnormal arachnoid villi absorption, subependymal inflammation, or granulomatous obstruction.[13-15]

Cerebral involvement and mass lesions

A variety of cerebral lesions can be observed in patients with neurosarcoidosis, varying from dural mass lesions mimicking meningioma's to multiple or singular parenchymal nodular lesions.[16,17] Symptoms include focal symptoms and seizures. Seizures are described in 14% of 965 patients.[2**] Hypothalamic-pituitary involvement was found in

9% of 1034 patients.[2**] In a multicenter study of 24 patients with neurosarcoidosis with pituitary involvement, the most common hormonal abnormalities were gonadotropin deficiency (88%), TSH deficiency (63%), and hyperprolactinemia (50%).[18]

Spinal cord involvement

Common presenting symptoms of spinal cord sarcoidosis are paraparesis, paresthesia, and bowel, bladder, and sexual dysfunction.[19,20*] The majority of patients with spinal cord involvement present with insidious chronic symptoms for more than 2 months.[20*]

Peripheral neuropathy

Peripheral nerve involvement in neurosarcoidosis is heterogeneous. It includes mononeuropathy, multiple mononeuropathy and sensory, sensorimotor, or motor polyneuropathies.[21,22] In addition, radiculopathy and polyradiculopathy have been described.[23] It is hypothesized that peripheral neuropathy may occur because of granulomatous involvement of the nerve directly or in close proximity of blood vessels, ultimately leading to localized vasculitis and epineurium and/or perineurinum involvement.[21] Small fiber neuropathy is rather common in sarcoidosis as well and is considered an epiphenomenon as there is no granulomatous inflammation of the small fibers. This syndrome is not specific for sarcoidosis and is observed in multiple disorders.

Diagnosis

Two sets of diagnostic criteria have been established: the Zajicek criteria and the WASOG criteria.[17,24-26] The Zajicek criteria were established in 1999 and modified by Marangoni et al. and Tavee et al. (Table 2.1). The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) updated their criteria in 2014 (Table 2.2). A certain (or 'definite') diagnosis can only be established by biopsy of affected nervous system tissue. Frequently, this is either not possible or considered too invasive as for instance stereotactic brain biopsy has been associated with morbidity in 3.5% and mortality in 0.7% of patients.[17,27,28] Therefore, the diagnostic process is commonly steered towards performing biopsy outside the central nervous system.[24,25]
The essence of both sets of criteria is a clinical presentation suggestive for neurosarcoidosis, characteristic abnormalities in cerebrospinal fluid (CSF), or on MRI, evidence of noncaseating granulomas, and no evidence of alternative diagnoses. Sensitivity and specificity of both criteria are unknown. Recent published articles mostly

use the Zajicek criteria[9*,17] The main disadvantage of the WASOG criteria is the exclusion of peripheral nerve involvement.

Table 2.1 Modified Zajicek criteria.

A clinical presentation suggestive of neurosarcoidosis in which all other diagnoses have been excluded	
definite neurosarcoidosis	positive nervous system histology
probable neurosarcoidosis	signs of inflammation in the central or peripheral nervous system on MRI or CSF (elevated protein, cells, immunoglobulin G indices, or the presence of oligoclonal bands) compatible with neurosarcoidosis; and positive histology for a systemic lesion or positive results for at least two of the following tests: ^{18}F-FDG PET, gallium scan, chest HRCT, serum ACE
possible neurosarcoidosis	above criteria are not met

ACE=angiotensin-converting enzyme; CSF=cerebrospinal fluid; FDG-PET=fluordoexyglucose positron emission tomography; HRCT=high resolution computed tomography. Data from Tavee et al. and Zajicek et al.[17,24]

Table 2.2 WASOG criteria.

highly probable neurosarcoidosis: at least 90% likelihood	when clinical signs consistent with granulomatous inflammation of the meninges, brain, ventricular (CSF) system, cranial nerves, pituitary gland, spinal cord, cerebral vasculature or nerve routs alongside imaging characteristics of disease (predominantly MRI gadolineum enhancement) or a cerebrospinal fluid exam demonstrating inflammation
probable neurosarcoidosis: a 50-89% likelihood	isolated facial palsy with negative MRI-brain or clinical syndrome consistent with granulomatous inflammation of meninges, brain, ventricular (CSF) system, cranial nerves, pituitary gland, spinal cord, cerebral vasculature or nerve routs but without characteristic MRI or CSF findings
possible neurosarcoidosis: less then 50% likelihood	seizure or cognitive decline with negative MRI.

CSF=cerebrospinal fluid. Biopsy of that organ demonstrating granulomatous inflammation of no alternate cause implies highly probable involvement; another organ has demonstrated granulomatous inflammation of no alternate cause; alternative causes for the clinical manifestation have been reasonable excluded. Based on Judson et al.[25]

Ancillary investigations

Various serological biomarkers, predominantly ACE and soluble interleukin-2 receptor (sIL2r), are associated with sarcoidosis, but none have been established to be sufficiently accurate to diagnose patients with neurosarcoidosis, although some might have a role in following disease activity.[1] In the meta-analysis, serum ACE was elevated in only 35% of 674 patients neurosarcoidosis.[2**] The value of genotype-corrected ACE has not been evaluated in neurosarcoidosis, but in systemic sarcoidosis it does not improve the diagnostic accuracy considerably.[1,29] Serum sIL2r has been considered a

promising biomarker in sarcoidosis.[1] Serum sIL2r was more frequently elevated in patients with sarcoidosis and extra-pulmonary involvement compared to healthy controls and has been shown to predict ^{18}F-FDG avidity.[30,31] However, a study evaluating serum sIL2r in neurosarcoidosis showed no differences between patients with neurosarcoidosis and those with tuberculous, bacterial or viral meningitis, multiple sclerosis, cerebral vasculitis, and healthy controls.[32] CSF examination can be useful to exclude infections and carcinomatous meningitis. Pleiocytosis was found in 58% of 730, elevated CSF protein in 63% of 729, and normal CSF in 27% of 332 patients.[2**] CSF ACE is considered to have a too low sensitivity for the diagnosis of neurosarcoidosis and not to be associated with disease activity.[17,33*] Recently, a study was published evaluating the value of CSF sIL2r and showed that levels above 150 pg/ml identified patients with untreated neurosarcoidosis with a sensitivity of 63% and a specificity of 93% compared to non-infectious neurological diseases.[32] However, in another study with patients with clinically isolated neurosarcoidosis CSF sIL2r was elevated in only 46%.[34]

Gadolineum enhanced MRI is the first choice imaging modality to assess central nervous system involvement of sarcoidosis and evaluate disease activity.[17] Abnormalities suggestive for neurosarcoidosis includes leptomeningeal enhancement, tumour-like lesions, cranial nerve enhancement, and hydrocephalus (Figure 2.1).[35*] Spinal cord lesions are most frequently localized intramedullary in 81% of the cases and the majority extends over three or more spinal segments.[19] In the meta-analysis, abnormalities suggestive for neurosarcoidosis on cranial MRI were seen in 78% of 362 patients and on spinal MRI in 48% of 185 patients.[2**]

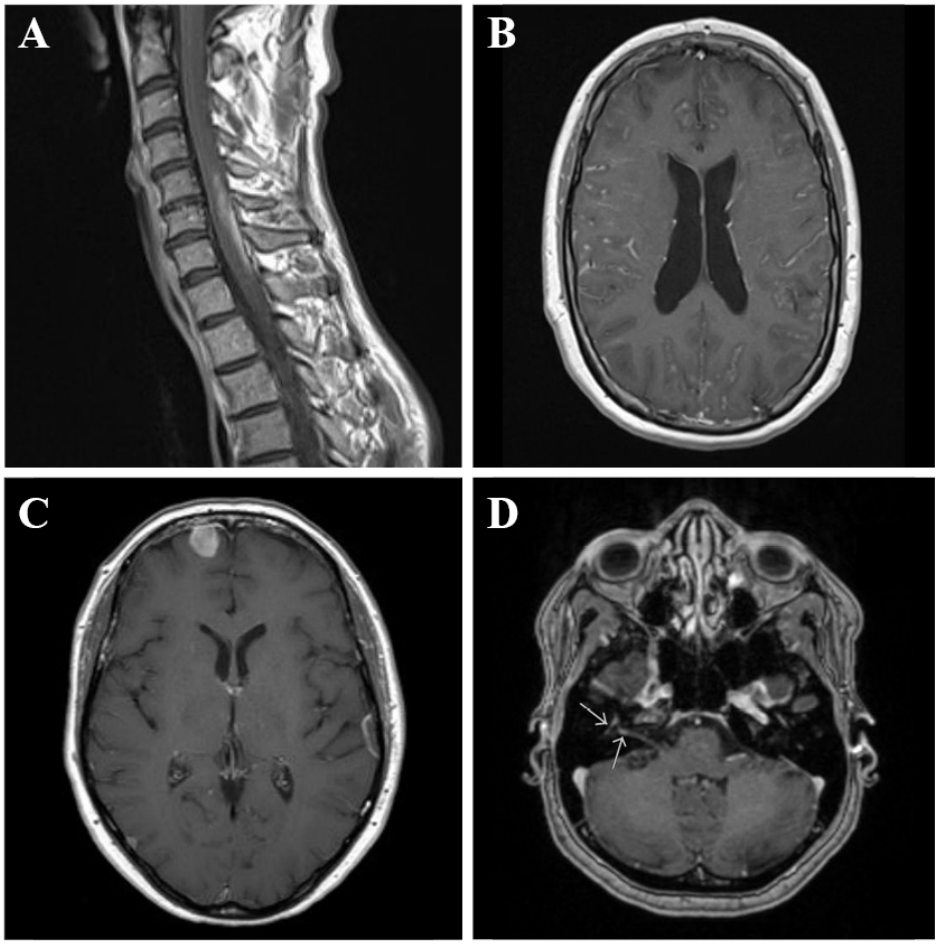

Figure 2.1 Abnormalities suggestive of neurosarcoidosis on neuroimaging. Abnormalities on magnetic resonance imaging (MRI) brain and spinal cord in patients with neurosarcoidosis consisting of gadolineum enhancement of a spinal cord lesion (**A**), leptomeningeal enhancement (**B**), gadolineum enhancement of dural lesions (**C**), and gadolineum enhancement of the right facial nerve (**D**).

In patients suspected of neurosarcoidosis and no prior history of sarcoidosis, an extensive systemic work-up should be performed to obtain a biopsy location outside the nervous system to achieve histopathological confirmation (Figure 2.2).[17,36] The systemic work-up should include a high-resolution CT-scan (HRCT) and if negative or when biopsy is negative, a ^{18}F-FDG PET-CT should be considered. ^{18}F-FDG PET-CT can reveal occult sites of disease activity outside the central nervous system, even when serological markers are normal or when other imaging modalities are normal.[37] In our

tertiary referral center, we have evaluated the clinical utility of ^{18}F-FDG PET-CT in patients suspected of neurosarcoidosis and 24 of 110 patients (22%) showed abnormalities suggestive for sarcoidosis and this led to a biopsy confirmation in 12 of 20 patients (59%; data not yet published). ^{18}F-FDG PET-CT should preferably be performed before treatment with immunosuppressive therapy as this can lower the sensitivity.[38,39]

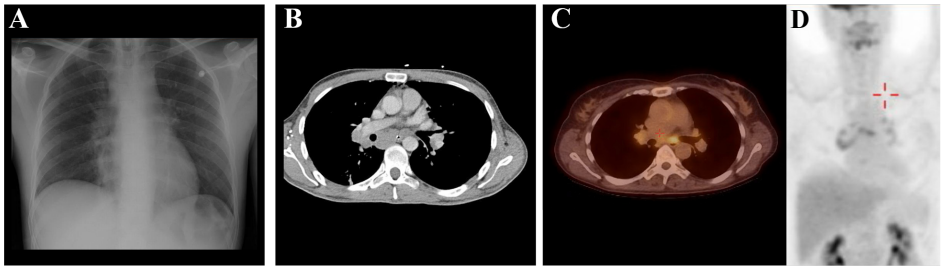

Figure 2.2 Abnormalities suggestive of neurosarcoidosis on systemic imaging. Abnormalities suggestive of sarcoidosis on systemic imaging consisting of hilar lymphadenopathy on chest X-ray (**A**), hilar and mediastinal lymphadenopathy on chest CT-scan (**B**), and hilar and mediastinal FDG activity on ^{18}F-FDG PET-CT (**C** and **D**).

Differential diagnosis and mimics

The exclusion of other differential diagnoses is essential. Diagnoses to consider are tuberculosis, Behcet's disease, Sjögren's disease, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis, central nervous system vasculitis, multiple sclerosis, neuromyelitis optica and malignancies, among others.[17,36]

As patients are being diagnosed according to probability and confidence of the diagnosis can be strengthened over time, they may initially be diagnosed with diseases mimicking neurosarcoidosis, which can present with similar histopathological findings.[40] Examples include IgG4-related disease and a sarcoid-like reaction due to malignancies or medication use. IgG4-related disease can present with a chronic meningitis, cranial nerve palsy, or pituitary involvement.[41] In 2012, consensus was reached that granulomatous inflammation excluded IgG4-related disease.[42,43] However, recently two patients presenting with IgG4-related lymphadenopathy together with granulomas were described, underlining that in the appropriate clinical context granulomas should not exclude IgG4-related disease.[44] Sarcoid-like reactions are described as a noncaseating granulomatous inflammation, without further evidence for sarcoidosis, in association with malignancies – most notably a lymphoma or malignancy of the breast

– or certain medication.[45] Tumour necrosis factor alpha (TNF-α) antagonists can paradoxically cause a sarcoid-like reaction, as well as a variety of neurological symptoms, mimicking neurosarcoidosis.[46-49]

Treatment

Since neurosarcoidosis is a rare disease, no randomized, double-blind, placebo-controlled trials have been performed. Treatment options are based on expert opinion and are derived from evidence in the treatment of pulmonary sarcoidosis.[50-52] Corticosteroids are the mainstay of treatment in neurosarcoidosis. In a meta-analysis, 83% of 655 patients were treated with corticosteroids during the course of the disease, although spontaneous remissions do occur and 15% of 655 patients did not receive any treatment.[2**] The optimal initial dose of corticosteroids in neurosarcoidosis varies and depends on disease severity with more aggressive therapy in patients with more severe disease.[17,19,53] In patients with diabetes or obesitas, the dosage of prednisone should be low and tapered as soon as possible. In these patients second-line treatment should be considered early as steroid sparing agent. Prednisolone side-effects can be significant and are undesirable.[54] Corticosteroid tapering is essential, even though symptoms may reoccur at lower dosages.[24,55,56**] Reported treatment response to corticosteroids varies widely with progression of disease ranging from 24 to 71%.[2**] Although the short-term effect of corticosteroids has been well established, there are limited data beyond 2 years to indicate whether oral steroids have a disease modifying effect on the long-term.[57] Second-line treatment is recommended in case of severe disease at presentation, refractory, or relapsing disease during corticosteroid treatment, when prolonged treatment with corticosteroids is expected or a primary contra-indication for corticosteroids exists.[51,53,58,59] Most second-line therapies (most importantly methotrexate and azathioprine) need 3-6 months before a clinical response might be expected.[52] In the meta-analysis, methotrexate was reported as the most frequently used second-line treatment (16% of 655 cases), followed by azathioprine in 8%.[2**] Overall, second-line therapy was used in 27% of 539 patients.[2**] One study reported a response rate of 61% in patients treated with methotrexate and corticosteroids, after corticosteroids monotherapy failed.[58] Moreover, the side effects of methotrexate are less severe compared to other second-line treatments.[60] In pulmonary sarcoidosis, in addition to methotrexate, azathioprine is commonly used and is reported to have a similar treatment response and adverse events, except for a higher rate of infection compared to methotrexate.[61] In a recent retrospective study comparing the efficacy of methotrexate and mycophenolate mofetil (MMF) in neurosarcoidosis, a higher relapse

rate was observed in patients receiving MMF (11/14 [79%]) compared to methotrexate (15/32 [47%]). Furthermore, the authors reported a significantly shorter time to relapse in the MMF group (11 months MMF versus 28 months methotrexate treatment).[56**]
Third-line treatment consists of TNF-α antagonists and cyclophosphamide. In the meta-analysis, third-line treatment was started in 9% of 539 patients.[2**] Increasingly, patients are being treated with TNF-α antagonists.[2**] A randomized controlled trial conducted in patients with chronic steroid-resistant pulmonary sarcoidosis showed a decrease in extra-pulmonary involvement after 24-weeks of treatment.[62] In a retrospective study 18 patients with biopsy proven neurosarcoidosis were treated with infliximab, of whom 16 patients did not respond to at least one immunosuppressant drug in addition to corticosteroids (including 11 patients after cyclophosphamide treatment). At 6 months after initiation of infliximab treatment, 33% had a complete remission, 56% a partial remission, and stable disease was observed in 11%.[63**] Other case reports and case series also reported beneficial effects of TNF-α antagonists in refractory neurosarcoidosis, not responding to other agents.[64-78] When treating patients with long-term infliximab, anti-infliximab antibodies formation can lead to treatment failure.[79] Therefore, concomitant methotrexate treatment is strongly recommended as this has been shown to be efficient in reducing immunogenicity in a dose-dependent manner.[80,81] Recently, responsiveness to TNF-α antagonists has been associated with the TNF-α G-308A polymorphism.[82] Cyclophosphamide is recommended as a third-line treatment option in severe disease, refractory to other cytotoxic agents because of a similar reported treatment response and its high toxicity.[58,83] There is widespread recognition that new therapeutic options should be developed for sarcoidosis. A better insight into the advantages and disadvantages of second-line and third-line treatment is important. The long-term effects of immunosuppressive agents, the optimal starting and maintenance dosages, and the best interval and discontinuation regimens should be elucidated. Identified associations of polymorphisms with treatment response suggest a step towards personalized medicine.[82] Future research should focus on the role for pharmacogenetics and phenotypic predictors of treatment response and toxicity.[84] Neurosurgical intervention may be needed for obstructive hydrocephalus.[14,85] In our cohort study we described this treatment in 3 of 52 patients (6%).[9*] Furthermore, especially in extramedullary involvement spinal decompressive surgery can be indicated.[86] Cranial mass lesions have been described to respond to radiation therapy, although this is not recommended as standard treatment.[50] Symptomatic treatment consists of anti-epileptic medication and hormonal substitution among others.[2**]

Prognosis

In the meta-analysis outcome could be assessed in 415 patients and showed complete remission in 27%, incomplete remission in 32%, stable disease in 24%, and deterioration in 6%.[2**] Mortality was reported in 42 of 826 patients (5%). Despite the increased usage of second-line and third-line therapy, still a third of the patients remain stable, deteriorate or die.[2**] Our experience suggests that neurosarcoidosis is a chronic disease with 71% of 52 patients having residual symptoms at the end of follow-up, leading to functional impairment in 29%.[9*] Neurological involvement in conjunction with lung involvement is associated with an increased mortality (hazard ratio=4.18; 95% confidence interval 1.44-12.1).[3] Patients with neurosarcoidosis more often have a chronic disease course compared to other forms of sarcoidosis (odds ratio=19.24).[87]

Conclusion

Diagnosing and treating patients with neurosarcoidosis remains a challenge. Recent advances have mainly been made by combining all the available data to shed light on the prevalence of neurosarcoidosis and its manifestations. Currently, a national neurosarcoidosis registry in the Netherlands is being conducted to prospectively describe the various manifestations of neurosarcoidosis. Furthermore, recent studies have described the use of CSF sIL2r and ^{18}F-FDG PET-CT, which may be useful in the diagnostic process. Long-term prospective studies evaluating patients suspected of neurosarcoidosis are needed to assess sensitivity and specificity of ancillary investigations and the diagnostic criteria. Furthermore, future studies are needed to evaluate the prognosis and the optimal treatment strategy.

References

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

1. Valeyre D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet 2014;383(9923):1155-67.
2. Fritz D, van de Beek D, Brouwer MC. Clinical features, treatment and outcome in neurosarcoidosis: systematic review and meta-analysis. BMC Neurol 2016;16(1):220.
   ** A meta-analysis combining all the available data published between 1980 and 2016, including 1088 patients as decribed in 29 articles. This meta-analysis sheds light on clinical characteristics, diagnostic modalities, treatment and outcome. Furthermore, it describes temporal trends in treatment strategies and outcome over time.
3. Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946-2013: a population-based study. Mayo Clin Proc 2016;91(2):183-8.
4. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357(21):2153-65.
5. Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med 2001;164(11):2085-91.
6. Fingerlin TE, Hamzeh N, Maier LA. Genetics of sarcoidosis. Clin Chest Med 2015;36(4):569-84.
7. Darlington P, Gabrielsen A, Sorensson P, et al. HLA-alleles associated with increased risk for extra-pulmonary involvement in sarcoidosis. Tissue Antigens 2014;83(4):267-72.
8. Lareau CA, Adrianto I, Levin AM, et al. Fine mapping of chromosome 15q25 implicates ZNF592 in neurosarcoidosis patients. Ann Clin Transl Neurol 2015;2(10):972-7.
9. Leonhard SE, Fritz D, Eftimov F, et al. Neurosarcoidosis in a tertiary referral center: a cross-sectional cohort study. Medicine (Baltimore) 2016;95(14):e3277.
   * In this retrospective observational study 52 patients diagnosed with neurosarcoidosis are described, focussing on clinical characteristics, diagnosis, treatment and outcome.
10. Zunt JR, Baldwin KJ. Chronic and subacute meningitis. Continuum (Minneap Minn) 2012;18(6 Infectious Disease):1290-318.
11. Carlson ML, White JR, Jr., Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: a review of 305 patients. Otol Neurotol 2015;36(1):156-66.
    * In this retrospective study, 305 patients with cranial base manifestations have been described, foccusing on cranial nerve palsy. This is one of the largest retrospective cohorts of neurosarcoidosis patients.
12. Hahn LD, Fulbright R, Baehring JM. Hypertrophic pachymeningitis. J Neurol Sci 2016;367:278-83.
13. Yoshitomi M, Uchikado H, Hattori G, et al. Endoscopic biopsy for the diagnosis of neurosarcoidosis at the fourth ventricle outlet with hydrocephalus. Surg Neurol Int 2015;6(Suppl 25):S633-6.
14. Benzagmout M, Boujraf S, Gongora-Rivera F, et al. Neurosarcoidosis which manifested as acute hydrocephalus: diagnosis and treatment. Intern Med 2007;46(18):1601-4.
15. Tabuchi S, Uno T. Hydrocephalus with panventricular enlargement as the primary manifestation of neurosarcoidosis: a case report. J Med Case Rep 2013;7:240.
16. Rodriguez F, Link MJ, Driscoll CL, Giannini C. Neurosarcoidosis mimicking meningioma. Arch Neurol 2005;62(1):148-9.
17. Tavee JO, Stern BJ. Neurosarcoidosis. Continuum (Minneap Minn) 2014;20(3 Neurology of Systemic Disease):545-59.
    ** In this review article, the most recent update of the Zajicek criteria was proposed.
18. Langrand C, Bihan H, Raverot G, et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM 2012;105(10):981-95.
19. Sohn M, Culver DA, Judson MA, et al. Spinal cord neurosarcoidosis. Am J Med Sci 2014;347(3):195-8.
20. Durel CA, Marignier R, Maucort-Boulch D, et al. Clinical features and prognostic factors of spinal cord sarcoidosis: a multicenter observational study of 20 BIOPSY-PROVEN patients. J Neurol 2016;263(5):981-90.

* A retrospective cohort describing the clinical characteristics and prognostic factors of spinal cord sarcoidosis.
21. Said G, Lacroix C, Plante-Bordeneuve V, et al. Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. Brain 2002;125(Pt 2):264-75.
22. Scott TS, Brillman J, Gross JA. Sarcoidosis of the peripheral nervous system. Neurol Res 1993;15(6):389-90.
23. Fahoum F, Drory VE, Issakov J, Neufeld MY. Neurosarcoidosis presenting as Guillain-Barre-like syndrome. A case report and review of the literature. J Clin Neuromuscul Dis 2009;11(1):35-43.
24. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis-diagnosis and management. QJM 1999;92(2):103-17.
25. Judson MA, Costabel U, Drent M, et al. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis 2014;31(1):19-27.
* In this delphi concensus study an update of the WASOG criteria was proposed.
26. Marangoni S, Argentiero V, Tavolato B. Neurosarcoidosis. Clinical description of 7 cases with a proposal for a new diagnostic strategy. J Neurol 2006;253(4):488-95.
27. Hall WA. The safety and efficacy of stereotactic biopsy for intracranial lesions. Cancer 1998;82(9):1749-55.
28. McGirt MJ, Woodworth GF, Coon AL, et al. Independent predictors of morbidity after image-guided stereotactic brain biopsy: a risk assessment of 270 cases. J Neurosurg 2005;102(5):897-901.
29. Biller H, Zissel G, Ruprecht B, et al. Genotype-corrected reference values for serum angiotensin-converting enzyme. Eur Respir J 2006;28(6):1085-90.
30. Mostard RL, Van Kuijk SM, Verschakelen JA, et al. A predictive tool for an effective use of (18)F-FDG PET in assessing activity of sarcoidosis. BMC Pulm Med 2012;12:57.
31. Gungor S, Ozseker F, Yalcinsoy M, et al. Conventional markers in determination of activity of sarcoidosis. Int Immunopharmacol 2015;25(1):174-9.
32. Petereit HF, Reske D, Tumani H, et al. Soluble CSF interleukin 2 receptor as indicator of neurosarcoidosis. J Neurol 2010;257(11):1855-63.
** In this study 139 paired CSF and serum samples from 11 patients with neurosarcoidosis, 21 with multiple sclerosis, 10 with central nervous system vasculitis, 22 with bacterial meningitis, 17 with viral meningitis/encefalitis, 7 with tuberculosis and 18 healthy doners were assessed for sIL2-R. They found that sIL2-R levens in CSF above 150pg/ml identified NS patients a sensitivity of 63% and a specificity of 93% compared to non-infectious neurological diseases.
33. Bridel C, Courvoisier DS, Vuilleumier N, Lalive PH. Cerebrospinal fluid angiotensin-converting enzyme for diagnosis of neurosarcoidosis. J Neuroimmunol 2015;285:1-3.
34. Wegener S, Linnebank M, Martin R, et al. Clinically isolated neurosarcoidosis: a recommended diagnostic path. Eur Neurol 2015;73(1-2):71-7.
35. Bathla G, Singh AK, Policeni B, et al. Imaging of neurosarcoidosis: common, uncommon, and rare. Clin Radiol 2016;71(1):96-106.
* A review describing the imaging spectrum of neurosarcoidosis, including follow-up imaging.
36. Hoitsma E, Drent M, Sharma OP. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. Curr Opin Pulm Med 2010;16(5):472-9.
37. Teirstein AS, Machac J, Almeida O, et al. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007;132(6):1949-53.
38. Mostard RL, van Kroonenburgh MJ, Drent M. The role of the PET scan in the management of sarcoidosis. Curr Opin Pulm Med 2013;19(5):538-44.
39. Keijsers RG, Verzijlbergen JF, van Diepen DM, et al. 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. Sarcoidosis Vasc Diffuse Lung Dis 2008;25(2):143-9.
40. James DG. A clinicopathological classification of granulomatous disorders. Postgrad Med J 2000;76(898):457-65.
41. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366(6):539-51.
42. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25(9):1181-92.

43. Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 2015;67(7):1688-99.
44. Bateman AC, Ashton-Key MR, Jogai S. Lymph node granulomas in immunoglobulin G4-related disease. Histopathology 2015;67(4):557-61.
45. Ravaglia C, Gurioli C, Casoni GL, et al. Sarcoid-like lesion is a frequent benign cause of lymphadenopathy in neoplastic patients. Eur Respir J 2013;41(3):754-5.
46. Tong D, Manolios N, Howe G, Spencer D. New onset sarcoid-like granulomatosis developing during anti-TNF therapy: an under-recognised complication. Intern Med J 2012;42(1):89-94.
47. Booker MJ, Flint J, Saravana S. Aseptic meningitis in a patient taking etanercept for rheumatoid arthritis: a case report. Cases J 2008;1(1):364.
48. Berrios I, Jun-O'Connell A, Ghiran S, Ionete C. A case of neurosarcoidosis secondary to treatment of etanercept and review of the literature. BMJ Case Rep 2015;2015.
49. Hunter JB, Rivas A. Multiple cranial neuropathies following etanercept administration. Am J Otolaryngol 2016;37(3):259-62.
50. Nozaki K, Judson MA. Neurosarcoidosis: clinical manifestations, diagnosis and treatment. Presse Med 2012;41(6 Pt 2):e331-48.
51. Saketkoo LA, Baughman RP. Biologic therapies in the treatment of sarcoidosis. Expert Rev Clin Immunol 2016;12(8):817-25.
52. Baughman RP, Grutters JC. New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches. Lancet Respir Med 2015;3(10):813-22.
53. Scott TF, Yandora K, Valeri A, et al. Aggressive therapy for neurosarcoidosis: long-term follow-up of 48 treated patients. Arch Neurol 2007;64(5):691-6.
54. Hoes JN, Jacobs JW, Verstappen SM, et al. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Annals of the rheumatic diseases 2009;68(12):1833-8.
55. Sharma OP. Pulmonary sarcoidosis and corticosteroids. The American review of respiratory disease 1993;147(6 Pt 1):1598-600.
56. Bitoun S, Bouvry D, Borie R, et al. Treatment of neurosarcoidosis: a comparative study of methotrexate and mycophenolate mofetil. Neurology 2016;87(24):2517-21.
** This is a retrospective multicenter comparative study describing 40 patients with a diagnosis of neurosarcoidosis based on a definite or probable diagnosis according to the Zajicek criteria receiving at least 3 months of either MTX (26 patients) and MMF (8 patients). MTX significantly increased survival time without relapse compared to MMF.
57. Paramothayan NS, Lasserson TJ, Jones PW. Corticosteroids for pulmonary sarcoidosis. Cochrane Database Syst Rev 2005(2):CD001114.
58. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. Arch Intern Med 1997;157(16):1864-8.
59. Agbogu BN, Stern BJ, Sewell C, Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. Arch Neurol 1995;52(9):875-9.
60. Cremers JP, Drent M, Baughman RP, et al. Therapeutic approach of hepatic sarcoidosis. Curr Opin Pulm Med 2012;18(5):472-82.
61. Vorselaars AD, Wuyts WA, Vorselaars VM, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest 2013;144(3):805-12.
62. Judson MA, Baughman RP, Costabel U, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J 2008;31(6):1189-96.
63. Cohen Aubart F, Bouvry D, Galanaud D, et al. Long-term outcomes of refractory neurosarcoidosis treated with infliximab. J Neurol 2017; 264(5):891-7.
** A retrospective cohort study describing the long-term outcomes of treatment with infliximab in biopsy proven neurosarcoidosis patients. They included 18 patients with biopsy proven neurosarcoidosis of whom 16 patients did not respond to at least 1 immunosuppressant drug in addition to corticosteroids (including 11 patients after cyclophosphamide treatment). At 6 months after initiation of infliximab treatment, 33% had a complete remission, 56% a partial remission and stable disease was observed in 11%. After a median follow-up of 20 months 50% of patients had a relaps. Furthermore in 8 patients side effects were observed, 7 of which were infections.

64. Pettersen JA, Zochodne DW, Bell RB, et al. Refractory neurosarcoidosis responding to infliximab. Neurology 2002;59(10):1660-1.
65. Carter JD, Valeriano J, Vasey FB, Bognar B. Refractory neurosarcoidosis: a dramatic response to infliximab. Am J Med 2004;117(4):277-9.
66. Kobylecki C, Shaunak S. Refractory neurosarcoidosis responsive to infliximab. Pract Neurol 2007;7(2):112-5.
67. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. Neurology 2009;72(4):337-40.
68. Sodhi M, Pearson K, White ES, Culver DA. Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. Respir Med 2009;103(2):268-73.
69. Chintamaneni S, Patel AM, Pegram SB, et al. Dramatic response to infliximab in refractory neurosarcoidosis. Ann Indian Acad Neurol 2010;13(3):207-10.
70. Santos E, Shaunak S, Renowden S, Scolding NJ. Treatment of refractory neurosarcoidosis with Infliximab. J Neurol Neurosurg Psychiatry 2010;81(3):241-6.
71. Riancho-Zarrabeitia L, Delgado-Alvarado M, Riancho J, et al. Anti-TNF-alpha therapy in the management of severe neurosarcoidosis: a report of five cases from a single centre and literature review. Clin Exp Rheumatol 2014;32(2):275-84.
72. Lorentzen AO, Sveberg L, Midtvedt O, et al. Overnight response to infliximab in neurosarcoidosis: a case report and review of infliximab treatment practice. Clin Neuropharmacol 2014;37(5):142-8.
73. Srivastava S, Rajakariar R, Ashman N, et al. Infliximab as long-term maintenance in steroid-resistant and recurrent sarcoidosis in a renal transplant with central nervous system involvement. Clin Kidney J 2012;5(1):53-5.
74. Lahmer T, Knopf A, Lanzl I, et al. Using TNF-alpha antagonist adalimumab for treatment for multisystem sarcoidosis: a case study. Rheumatology International 2012;32(8):2367-70.
75. Pereira J, Anderson NE, McAuley D, et al. Medically refractory neurosarcoidosis treated with infliximab. Intern Med J 2011;41(4):354-7.
76. Bomprezzi R, Pati S, Chansakul C, Vollmer T. A case of neurosarcoidosis successfully treated with rituximab. Neurology 2010;75(6):568-70.
77. Toth C, Martin L, Morrish W, et al. Dramatic MRI improvement with refractory neurosarcoidosis treated with infliximab. Acta Neurol Scand 2007;116(4):259-62.
78. Sollberger M, Fluri F, Baumann T, et al. Successful treatment of steroid-refractory neurosarcoidosis with infliximab. J Neurol 2004;251(6):760-1.
79. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348(7):601-8.
80. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Annals of the rheumatic diseases 2013;72(12):1947-55.
81. Drent M, Cremers JP, Jansen TL, Baughman RP. Practical eminence and experience-based recommendations for use of TNF-alpha inhibitors in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31(2):91-107.
82. Wijnen PA, Cremers JP, Nelemans PJ, et al. Association of the TNF-alpha G-308A polymorphism with TNF-inhibitor response in sarcoidosis. Eur Respir J 2014;43(6):1730-9.
83. Doty JD, Mazur JE, Judson MA. Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. Chest 2003;124(5):2023-6.
84. Vorselaars AD, Cremers JP, Grutters JC, Drent M. Cytotoxic agents in sarcoidosis: which one should we choose? Curr Opin Pulm Med 2014;20(5):479-87.
85. Scott TF, Brillman J. Shunt-responsive dementia in sarcoid meningitis: role of magnetic resonance imaging and cisternography. J Neuroimaging 2000;10(3):185-6.
86. Schaller B, Kruschat T, Schmidt H, et al. Intradural, extramedullary spinal sarcoidosis: report of a rare case and review of the literature. Spine J 2006;6(2):204-10.
87. Baughman RP, Lower EE. Features of sarcoidosis associated with chronic disease. Sarcoidosis Vasc Diffuse Lung Dis 2015;31(4):275-81.