Chapter 2

Neurosarcoidosis: a clinical dilemma

E Hoitsma, CG Faber, M Drent, OP Sharma

Lancet Neurol 2004;3:397-407

Abstract

Sarcoidosis is an inflammatory multisystem disorder of unknown cause. Practically no organ is immune to sarcoidosis; most commonly, in up to 90% of patients, it affects the lungs. The nervous system is involved in 5-15% of patients. Neurosarcoidosis is a serious and commonly devastating complication of sarcoidosis. Clinical diagnosis of neurosarcoidosis depends on the finding of neurological disease in multisystem sarcoidosis. As the disease can present in many different ways without biopsy evidence, solitary nervous-system sarcoidosis is difficult to diagnose. Cortico-steroids are the drug of first choice. In addition, several cytotoxic dugs, including methotrexate, have been used to treat sarcoidosis. The value of new drugs such as anti-tumour necrosis factor-α will be assessed. In this review we describe the clinical manifestations of neurosarcoidosis, diagnostic dilemmas and considerations, and therapy.

Introduction

Sarcoidosis is an inflammatory multisystem disorder of unknown cause that can affect any part of the nervous system. The prevalence of clinical involvement of the nervous system is estimated to be about 5-15%.[1,2] However, the prevalence of subclinical neurosarcoidosis may be much higher.[3,4] Post-mortem studies suggest that ante-mortem diagnosis is only made in 50% of patients with sarcoidosis with nervous-system involvement.[5] Because neurosarcoidosis may manifest in many different ways, diagnosis may be complicated.[2,3,6–10] Neurosarcoidosis can appear in an acute explosive fashion or as a slow, chronic illness. Furthermore, any part of the nervous system can be attacked by sarcoidosis but cranial nerves, the hypothalamus, and the pituitary gland are most commonly involved.[1] Sarcoid granulomas can affect the meninges, parenchyma of the brain, hypothalamus, brainstem, subependymal layer of the ventricular system, choroid plexuses, peripheral nerves, and blood vessels supplying the nervous structures.[11,12] A third of patients with neurosarcoidosis have multiple neurological lesions. If neurological syndromes develop in a patient with active systemic sarcoidosis (proven by biopsy), the diagnosis is generally easy. However, without biopsy evidence of sarcoidosis at other sites, nervous-system sarcoidosis is difficult to diagnose.[13] Neurological symptoms may also arise in the patients with inactive sarcoidosis. In such situations neurosarcoidosis may occupy a high place in the list of differential diagnoses, but histological evidence of granulomatous involvement of the nervous system is still needed in these cases. Furthermore, in a few patients sarcoidosis may selectively involve the nervous system.[14,15] In such cases it is important not to confuse the non-specific local sarcoid reaction with multisystem sarcoidosis.[16] Neurosarcoidosis is rare; most research reports small numbers of patients or case reports and prospective studies of neurosarcoidosis are scarce.[17] Evidence-based recommendations consequently are lacking.

Epidemiology and pathogenesis

Sarcoidosis occurs worldwide, affecting people of all races, both sexes, and all ages; it is the second most common respiratory disease in young adults after asthma. The disease typically affects adults age between 20 years and 40 years. In Scandinavian countries and Japan there is a second peak incidence in women age more than 50 years. Estimates of prevalence range from one to 50 per 100 000 individuals, and this varies among ethnic and racial groups. Sarcoidosis is most common among North Americans of African heritage and north European white people.[18]

Noncaseating epithelioid granulomas are the pathological hallmarks of sarcoidosis and reveal the inflammatory character of the disease. Granulomas are structured masses of activated macrophages and their derivatives (i.e., epitheloid and giant cells). Although the cause of sarcoidosis is unknown, there is evidence that sarcoidosis results from exposure of genetically susceptible hosts with increased Th1-immune response to specific environmental factors.[18] The most compelling argument for a genetic mechanism is that there is occasional familial clustering of cases. Environmental factors involved in sarcoidosis can be grouped under infection (such as *Mycobacterium tuberculosis* and *Propionibacterium acnes* or *P granulosum*) and non-infectious environmental exposures (such as pesticides and insecticides, pine pollen, silica or talc, metal dusts, and man-made mineral fibers).[18,19] Exposure to these factors can cause diseases that are histologically and clinically indistinguishable from sarcoidosis. This association supports environmental hypotheses as do reports of community outbreaks, a work-related risk of sarcoidosis for nurses, and an important study tracing case contacts on the Isle of Man.[19] Further evidence is found in the inflammatory response in sarcoidosis, which is characterised by large numbers of activated macrophages and T lymphocytes bearing the CD4-helper phenotype, with a pattern of cytokine production that is most consistent with a Th1-type immune response triggered by an antigen.[18]

Neurological manifestations of sarcoidosis

Cranial neuropathy

Cranial neuropathy seems to be the most common neurological complication of sarcoidosis.[1] Cranial-nerve palsy may be caused by nerve granulomas, increased intracranial pressure or granulomatous basal meningitis. A peripheral seventh nerve palsy (Bell's palsy) is the most common cranial-nerve lesion,[1] and is in fact the most common neurological manifestation of sarcoidosis overall.[2,3,9,20-22] Bilateral dysfunction occurs both simultaneously and sequentially.

The optic nerve seems to be the second most commonly affected cranial nerve.[20] Although sarcoid granulomas of the optic nerve are generally unilateral, they may involve both nerves.[23] Sarcoidosis of the optic nerve may occur without systemic involvement.[24] When optic neuropathy occurs, especially in young patients, multiple sclerosis is considered a likely cause. In these cases, chest radiograph with evidence of sarcoidosis makes multiple sclerosis highly unlikely. Optic nerve involvement in sarcoidosis can be divided into a chronic progressive type that responds poorly to corticosteroids[25] and an acute type that responds to prednisone.[2,25,26]

Other cranial nerves may be affected as well. Cranial neuropathies may be single or multiple.[27,28] Heerfordt's syndrome is a cranial neuropathy (mostly the facial nerve) with uveitis, parotid-gland enlargement, and fever. The syndrome is highly suggestive of sarcoidosis.

Horner syndrome (caused by disruption of the cervical sympathetic nerves[1] as well as pupillary abnormalities, including internal ophthalmoplegia), Argyll-Robertson pupil, and Adie's pupil have been described in sarcoidosis.[21,29-32]

Papilledema

The diagnosis of neurosarcoidosis should be considered in young adults, particularly women of childbearing age, with rapidly developing papilloedema, especially associated with the seventh or other nerve palsies. In patients with sarcoidosis, fundoscopy should be done; in those with papilloedema, imaging of the brain is indicated.

Aseptic meningitis

Meningeal symptoms may be acute or chronic. Symptoms and signs include fever, headache, neck rigidity, and sterile cerebrospinal fluid (CSF) with pleocytosis (particularly lymphocytes).[33]

Concentration of glucose in the CSF may be low in about a fifth of patients.[34] Sometimes mental status changes and polyradiculopathy are present.[35,36] The basal meninges may be affected, resulting in cranial neuropathy. Chronic meningitis is commonly recurrent and requires long-term therapy, whereas acute meningitis responds favourably to corticosteroids. Cerebral herniation after lumbar puncture in sarcoid meningitis has been described in one patient.[37] Arachnoid villi dysfunction may have contributed to very high intracranial pressures in this patient and lumbar puncture may have caused an acute pressure differential.

Hydrocephalus

Hydrocephalus is rare and may occur because of absorption disturbances[12,14,38] or obstruction.[39,40] As well as headache and somnolence, hydrocephalus can cause amnesia, dementia, urinary incontinence, and gait disturbances.[41,42]

Cerebral sarcoid lesions

Granulomas may remain small or form large intracranial tumours and may be single or multiple. They can occupy extradural, subdural, and parenchymatous locations.[43-46] Furthermore, periventricular white-matter lesions are observed. These lesions may resemble those seen in multiple sclerosis or as a result of vascular changes. Asympto-

matic periventricular white-matter lesions without meningeal enhancement in patients with sarcoidosis age over 50 years are most likely not caused by sarcoidosis and can be thought of as age-related small-vessel disease.

The clinical features of mass lesions are similar to any space occupying intracranial mass. Granulomatous lesions are commonly found in the hypothalamus or pituitary gland.[47-51] This may cause endocrine manifestations, such as diabetes insipidus,[52] adenopituitary failure,[53,54] amenorrhoea-galactorrhoea syndrome,[50] isolated or in various combinations. Infratentorial granulomas are less common than supratentorial but cerebellar masses also occur (figure 2.1).[22] When no evidence of systemic sarcoidosis is found, differential diagnosis of pituitary lesions consists of pituitary adenoma and lymphocytic adenohypophysitis.[55] Because some physicians treat lymphocytic hypophysitis empirically based on MRI findings and overall diagnostic assessment, the need for biopsy is not clear.

Granulomatous cerebral angiitis also occurs in sarcoidosis.[14,56] Ophthalmological screening can identify angiitis. Diffuse cerebral vasculopathy may cause psychosis, dementia, and epileptic seizures.[38,57-61] Pseudotumour cerebri, caused by dural sinus thrombosis, has also been reported as a presenting symptom of neurosarcoidosis.[62,63]

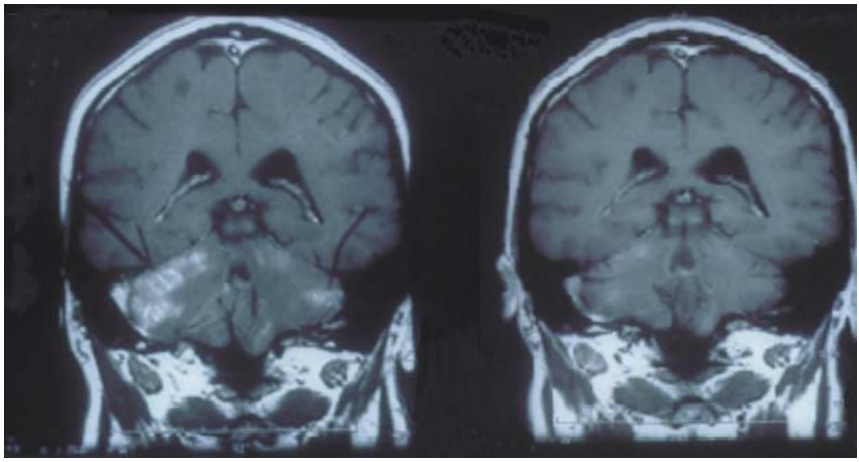

Figure 2.1 Left enhanced lesion in a middle aged, white male with multisystem sarcoidosis. A biopsy of the cerebellum showed noncaseating granuloma. Right: resolution of the lesion after combined prednisone and hydroxychloroquine therapy.

Seizures

Seizure may be the first consequence of neurosarcoidosis to appear. Any type of seizure may appear. In neurosarcoidosis seizures indicate chronicity and poor prognosis.[64]

Psychiatric symptoms

Granulomatous infiltration of the central nervous system (CNS) may produce various mental symptoms. In a patient with multisystem sarcoidosis and unexplained mental deterioration, aggressive assessment of the CNS is indicated. Symptoms may respond to corticoid therapy.[38,60] A subset of patients with sarcoidosis present with mild amnesic problems, without objective deterioration or neurological deficit. This might be related to fatigue. However, further study with neuropsychological testing is needed to explore this hypothesis.

Spinal sarcoidosis

Spinal sarcoidosis encompasses a range of intraspinal diseases, including arachnoiditis, extradural and intradural extramedullary lesions, and intramedullary lesions.[1,65,66] Intramedullary spinal involvement is one of the rarest neurological manifestations of the disease (figure 2.2). Granulomas are commonly clinically and radiologically indistinguishable from a malignant tumour of the spinal cord.[67,68] Patients may present with transverse myelopathy with paraparesis or tetraparesis,[65,69-71] autonomic dysreflexia,[72] radicular syndrome,[65] and cauda equina syndrome.[73–78]

Peripheral neuropathy

Peripheral neuropathy is thought to be rare in sarcoidosis.[79,80] The pattern of large fiber neuropathy reported in sarcoidosis includes multiple mono-neuropathies, poly-radiculopathy, Guillain-Barré syndrome, and symmetric distal polyneuropathy, which may be sensorimotor, mostly sensory, or mostly motor.[14,80-92] Epineural and perineural granulomas and granulomatous vasculitis can cause ischaemic axonal degeneration and demyelination owing to local pressure.[79,83,84] Nerve biopsy may be helpful in the diagnosis of problems. In most patients the clinical course of sarcoid neuropathy is subacute[83] and many patients seem to respond to corticosteroid therapy.[17]

Small fiber neuropathy

Small fiber neuropathy has been found in sarcoidosis[93,94] and seems to be quite common.[94] However, as standard nerve conduction tests measure only large-nerve fiber

function, and because quantitative techniques for the assessment of small nerve fibers are not routinely applied, the diagnosis of small fiber neuropathy can easily be missed. If the neuropathy is unrecognised, the symptoms may be enigmas to both patient and doctor. Recognition of small fiber neuropathy is important as it may cause disabling symptoms. Small fiber neuropathy may also involve autonomic nerve fibers. Whether life-threatening symptoms, such as cardiac arrhythmias, occur in sarcoidosis when cardiac autonomic denervation is involved needs further study. Small fiber neuropathy may also cause restless legs syndrome,[95] which, like periodic leg-movement disorder, is associated with, and related to, sleep disturbances. Periodic leg-movement disorder and restlesslegs syndrome have been found in patients with sarcoidosis.[96] The pathophysiology and treatment of small fiber neuropathy in sarcoidosis are unknown and need further study.

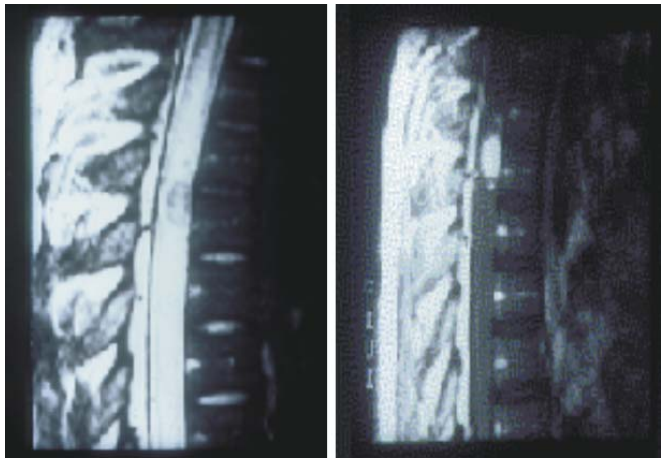

Figure 2.2 Left: unenhanced spinal cord lesion in a patient with sarcoidosis who developed marked weakness of the lower extremities. Right: gadolinium-enhanced image. The patient responded to coricosteroid treatment.

Skeletal muscle involvement

Muscle involvement may be symptomatic or asymptomatic.[97,98] Asymptomatic granulomatous muscle involvement in sarcoidosis has been reported with a prevalence of 50-80%[99] whereas symptomatic muscle involvement is much less common (1.4-2.3%).[100] Most patients present with pain, weakness, and tenderness of the

involved muscles, and muscle atrophy; some have muscle cramps and contractures.[100] Symptomatic involvement may be divided into the following types: a palpable nodular type, which is seen less frequently; an acute myositis, which is rare and seen more commonly in women; and a chronic myopathic type, which is more common, is slower in onset, and occurs later in life.[98,100-102]

Because most granulomatous infiltration is in connective tissue structures and necrosis of muscle fibers is uncommon, electromyography findings can be quite normal.[97] However, electromyography can show myopathic changes. It may be difficult to distinguish myopathy caused by sarcoidosis from that caused by steroids, especially in chronic myopathy. In the first case steroids are indicated, whereas in the second case steroids should be tapered. Steroid myopathy is mostly seen in fluorinated corticosteroids (dexamethasone, triamcinolone, betamethasone; table 2.1). Muscle biopsy is most helpful here. In sarcoid myopathy lesions take the form of granulomata in connective tissue, particularly in a perivascular distribution. The lesions are quite focal and serial sections increase the chances of establishing diagnosis.[98] In steroid myopathy typically type-2 fiber atrophy is found.

Table 2.1 Differences between myopathy caused by sarcoidosis and myopathy caused by steroids

Feature	Steroid-induced myopathy	Sarcoid myopathy
Clinical features	Myalgia, proximal weakness, especially legs	Myalgia; weakness: proximal>distal; Sometimes palpable nodules, contractures or cramp
CK	Mostly normal	Sometimes high
Frequency	2-21% in all patients receiving steroids	50% of patients have granulomas in their muscles, which are commonly asymptomatic
EMG	Low amplitude MUPs of short duration	Fibrillations and positive sharp waves Low amplitude MUPs of short duration
Biopsy	Type-2 fiber atrophy	Myositis, nodular myositis

CK=creatin kinase; EMG=electromyography; MUP=motor unit potential

Diagnosis

Nearly every neurological symptom could be caused by neurosarcoidosis. However, as the disease is rare, most physicians have little experience with it. The diagnosis of neurosarcoidosis requires a compatible clinical or radiological picture of sarcoidosis and histological confirmation of noncaseating granulomas.[103,104] One can distinguish definite, probable, and possible neurosarcoidosis (table 2.2).[105]

Three different situations of patients presenting with neurological symptoms can be distinguished: a patient with histologically confirmed active systemic sarcoidosis; a

patient with a history of sarcoidosis but with no evidence of disease activity; and a patient not known with sarcoidosis. In the first situation, neurological symptoms are most likely due to the confirmed systemic sarcoidosis and one is justified in starting therapy (figure 2.3).

Table 2.2 Criteria for the diagnosis of neurosarcoidosis, according to Zajieck et al.[105]

Definite	Clinical presentation compatible with neurosarcoidosis Exclusion of other possible causes Positive nervous system histology
Probable	Clinical presentation compatible with neurosarcoidosis Laboratory support of central nervous system inflammation* Exclusion of other possible causes Evidence of systemic sarcoidosis**
Possible	Clinical presentation compatible with neurosarcoidosis Exclusion of other possible causes

* High concentrations of cerebrospinal fluid (CSF) protein and high numbers of cells, the presence of oligoclonal bands, or magnetic resonance imaging (MRI) evidence compatible with neurosarcoidosis

** Positive histology or at least two indirect indicators from gallium scan, chest imaging, and serum angiotensin converting enzyme. Reproduced with permission from Oxford University Press.[105]

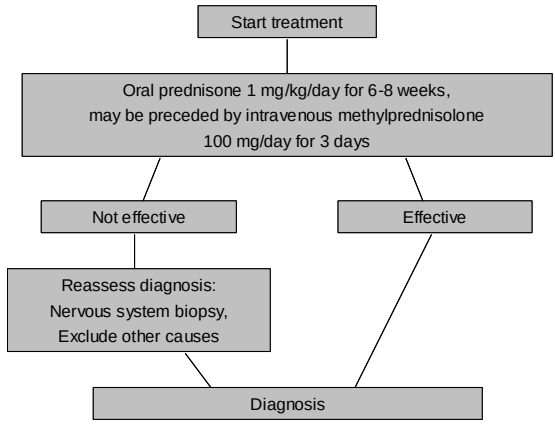

Figure 2.3 Diagnostic flow chart for patients with active systemic sarcoidosis and presentation of neurological symptoms.

However, when treatment fails in these cases, diagnosis should be reassessed, other causes should be excluded and an attempt should be made to obtain biopsy at the appropriate site. In patients with a history of sarcoidosis who present with neurological

symptoms, neurosarcoidosis will be considered early in the differential diagnosis. On the other hand, in the third situation neurosarcoidosis will rarely be considered at an early stage. Thus, neurosarcoidosis remains one of the more challenging diagnostic problems.[106,107] The diagnostic approach in the second and third situation should be the same (figure 2.4). In cases with previous sarcoidosis new evidence of active sarcoidosis should be assessed, other causes need to be excluded, and an effort should be made to obtain biopsy before treatment is started.[104] Whole-body gallium scanning[108,109] or fluorodeoxyglucose-PETscanning[110] can be used to find other suitable sites for biopsy. The importance of histological verification in patients with previous sarcoidosis will be underlined in case reports 1 and 2. The important lesson from the case reports is that a history of sarcoidosis does not necessarily mean that any new problem of the patient is automatically attributable to sarcoidosis. In our opinion the approach in such a patient should be the same as in a patient without a history of sarcoidosis (figure 2.4). While excluding other causes, the differential diagnosis of sarcoidosis should be taken into account (table 2.3). If no evidence of systemic sarcoidosis is found but a CNS biopsy reveals a sarcoid-like granulomatous reaction, one should be aware of the distinction between systemic neurosarcoidosis and a local (neurological) sarcoid-like reaction, particularly related to an old scar[111] or a helminthic reaction (table 2.4).[16,112]

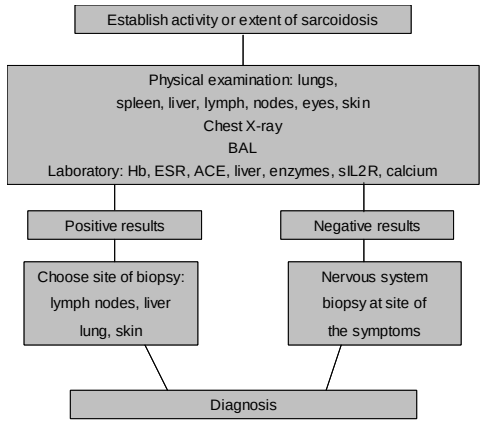

Figure 2.4 Diagnostic flow chart for patients with neurological symptoms with and without a history of sarcoidosis but without signs of active disease. BAL = bronchoalveolar lavage; Hb = Haemoglobin; ESR = erythrocyte sedimentation rate; ACE = angiotensin converting enzyme; sIL2R = soluble interleukin-2 receptor.

Table 2.3 Differential diagnosis of neurosarcoidosis

Infectious diseases	Leprosy Tuberculosis Whipple`s disease Toxoplasmosis Mycosis Helminthic infections Treponemal infections Lyme disease
Granulomatous diseases	Wegener`s granulomatosis ChurgStrauss syndrome Lymphomatoid granulomatosis
Tumors	Neurolymphomas Gliomas Meningeomas (leptomeningeal) metastases
Vasculopathies	Vasculitis Behçet`s disease
Systemic diseases	Amyloidosis
Lymphocytic adenohypophysitis	
Neurological diseases	Multiple sclerosis Acute demyelinating encephalomyelitis

Table 2.4 Differences between a non-specific local cerebral sarcoid-like granulomatous reaction and multi-system sarcoidosis

Features	**Local cerebral sarcoid reaction**	**Multisystem sarcoidosis**
Multiple organs involved	No, usually one	Yes
Age, years	Any	20-50
Chest radiograph	Normal	Abnormal in 90%
Delayed hypersensitivity	Normal	Depressed
Elevated serum ACE	<5%	>60%
BAL lymphocytosis	Absent	Present
Slit lamp examination	Normal	Positive 15-20%
Hypercalcemia	Absent	Present in 13%
Gallium body scan	Localized uptake	Multisystem uptake

BAL=bronchoalveolar lavage; ACE=angiotensin converting enzyme

Case 1

A 55-year-old male with cough and fatigue had pulmonary sarcoidosis. His clinical presentation justified a wait-and-see policy and his symptoms gradually disappeared. After he had been asymptomatic for 8 months, he presented at the neurology depart-

ment with headaches, diplopia, dysarthria, a painful right leg, and weakness of the right leg. Physical examination revealed L5 radicular syndrome on the right leg, abducens paresis of the left eye, tongue paresis on the left side, facial paresis on the left side, and dysarthria. No signs of active sarcoidosis were found. Chest radiograph showed no abnormalities and serum angiotensin converting enzyme (ACE) was within normal limits. Gadolinium enhanced MRI showed multifocal leptomeningeal lesions (a focal enhancing lesion intradurally at the level of the fifth root, intracranial enhancing lesions located ventrally of the medulla oblongata on the left side, at the left cerebellopontine angle, and left parasellar region). As the patient had a history of sarcoidosis and the clinical picture and imaging studies were compatible, he was thought to have neurosarcoidosis. Corticosteroid treatment was started. However, symptoms were progressive despite adequate dosage (1 mg/kg). The patient was referred to our clinic for a second opinion. Biopsy samples of the fifth lumbar root lesion were taken and revealed metastasis of anaplastic seminoma.

Case 2

A 40-year-old male had hilar adenopathy and pulmonary infiltrate on a routine chest radiograph. Mediastinal-lymph-node biopsy samples showed noncaseating granulomas consistent with the diagnosis of sarcoidosis. He was treated with prednisone for 3 years. He remained asymptomatic for almost 20 years. Then the patient developed multiple neurological symptoms including poor memory, inability to concentrate, tremors, insomnia, loss of balance, transient paraesthesias, and skin sensitivity. However, the patient had no fever, weight loss, anorexia, night sweats, chest pain, dyspnoea or cutaneous lesions. Because of his past history of sarcoidosis, the diagnosis of neurosarcoidosis was suspected. CSF sampling showed normal opening pressure and 26 white blood cells per min_3, mostly lymphocytes. A MRI of the brain revealed multiple foci of abnormal enhancement with associated whitematter oedema in both cerebral hemispheres. There was a large enhancing lesion near the posterior horn of the left lateral ventricle. These lesions were consistent with intraparenchymal neurosarcoidosis. Intravenous methylprednisolone was given and the patient was put on prednisone 90 mg/day. Over the next few days, his condition improved somewhat: he was able to do a few routine activities and his ataxia also improved. His prednisone was then gradually tapered to 40 mg/day. At this point his symptoms reappeared. Methotrexate was added, but the patient continued to deteriorate. Cyclophosphamide was tried without any success. A brain biopsy sample was taken that showed B-cell lymphoma.

Systemic sarcoidosis and its diagnosis

A patient's clinical presentation may be suggestive of systemic sarcoidosis (*e.g.*, the presence of fatigue, weight loss, fever, and the presence of features of sarcoidosis on chest radiography). Intrathoracic involvement is found in up to 90% of patients. Chest radiograph abnormalities can vary from sole bilateral hilar lymphadenopathy to extensive parenchymal disease and fibrosis. In general, chest radiographic appearances have been divided into five stages or types according to the modified Scadding criteria: stage 0, no lung involvement; stage I, bilateral hilar enlargement alone; stage II, hilar enlargement in association with interstitial lung disease; stage III, interstitial lung disease alone; and stage IV, (a more recent addition to the original classification) requires radiographic evidence of lung fibrosis.[113]

There are no definite diagnostic blood, skin, or radiological imaging tests specific for the disorder. Serum concentrations of ACE have poor predictive value in sarcoidosis.[114] Sensitivity of an increase in serum concentrations of ACE in neurosarcoidosis varies from 24% to 76%.[103] Serum interleukin-2-receptor (IL2R) is better than the more commonly used ACE for the monitoring of disease activity.[114,115] Despite these limitations, serum concentration of ACE is still the only serological marker recommended by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) in sarcoidosis.[18] Analyses of fluid and cells retrieved by bronchoalveolar lavage have improved our understanding of the immunopathogenesis of sarcoidosis, but none of these findings are specific for sarcoidosis, including the CD4/CD8 lymphocyte ratio.[19] The Kveim-Silzbach skin test, in which spleen or lymph node homogenate from a patient with sarcoidosis is injected intradermally and later a biopsy sample is taken, is not widely available, not well standardised, and not approved for general use by the Food and Drug Administration.

According to the latest recommendations as published by Baughman and colleagues,[116] diagnosis of sarcoidosis can be established by means of the following criteria: (1) the presence of granulomas in biopsy specimen without evidence of tuberculosis, fungus, malignancy, or other causes of granuloma, together with clinical features of sarcoidosis, support the diagnosis; (2) in the absence of biopsy material, clinical features such as bilateral hilar adenopathy on chest radiograph, erythema nodosum, uveitis, and macular papular skin lesions are suggestive of sarcoidosis. If there is no evidence of an alternative diagnosis and additional features highly suggestive of sarcoidosis are present, such as raised concentration of ACE, bronchoalveolar lavage fluid lymphocytosis. or lupus pernio, the diagnosis can also be confirmed.[116]

Neuroimaging

Neuroimaging studies, especially MRI, are the most sensitive diagnostic tools for the detection and localisation of neurological lesions. However, they are not specific as their appearences on radiography are highly variabale.[117]

CSF analysis

CSF abnormalities in neurosarcoidosis are usually nonspecific and include mild pleocytosis, high protein content, and, sometimes, slightly low glucose concentrations. Furthermore, increases in the concentration of ACE,[118-124] IgG-index,[125-127] oligoclonal bands,[9,125,126] CD4/CD8 lymphocyte ratios,[128] and lysosyme and β2-microglobulin concentrations[129] in CSF have been reported. About a third of patients with neurosarcoidosis have normal CSF.[11,21,103] Moreover, in disorders such as multiple sclerosis and systemic lupus erythematosus similar CSF abnormalities may be found.

The concentration of ACE in the CSF seems to be high in more than half of the patients with neurosarcoidosis.[119] It must be emphasised, however, that high concentrations are not specific to neurosarcoidosis and have also been reported in CNS infections and malignant tumours.[119,124] Several studies found significantly high concentrations of ACE in CSF in patients with active neurosarcoidosis compared with those in controls and patients with sarcoidosis without nervous-system involvement.[118-124] Furthermore, serial measurements of the concentration of ACE in the CSF change with disease activity.[122,123,130] However, neither was there relation found between serum and CSF concentrations of ACE in patients with neurosarcoidosis, nor was there any relation between serum concentrations and the clinical picture and CSF-total protein or CSF-albumin (increase of albumin concentration in the CSF is an indicator of functioning of the blood–brain barrier). Thus, ACE in the CSF is most probably synthesised in the nervous system and released by sarcoid granulomas in the CNS. In conclusion, determination of ACE concentration in the CSF is not specific for neurosarcoidosis but seems to be especially useful in the monitoring of disease activity and treatment response.

Neurophysiological studies

EEG may detect an early stage of acute encephalomeningitis and epileptic discharges caused by the neurosarcoidosis. Visual evoked potentials, brainstem evoked potentials and trigeminofacial reflexes can be useful in the detection of cranial neuropathy.

Electromyography (EMG) and nerve-conduction studies can show large fiber neuropathy and myopathy, whereas temperature threshold testing or skin biopsy are needed to assess small fiber neuropathy. The latter techniques are not yet routinely available.

Assessment of autonomic dysfunction, which may be present in small fiber neuropathy, requires special equipment, such as quantitative sudomotor axon reflex testing. Cardiovascular autonomic function testing with the Ewing tests have a low sensitivity for autonomic dysfunction in small fiber neuropathy.[94,131] Testing of the sympathetic skin response is widely available but seems to be neither specific nor sensitive.[94,132]
Polysomnography with EMG monitoring can be helpful in revealing periodic leg-movement disorder and sleep disturbances.

Therapy

Drug therapy

Given the morbidity and mortality of neurosarcoidosis, most authors recommend early treatment. However, clear guidelines and indications as well as prospective controlled studies are not available in neurosarcoidosis and prospective multicenter studies are needed. As a result, recommendations about treatment are based on experience rather than evidence.
Therapeutic medical options (figure 2.5) for neurosarcoidosis are similar to that in sarcoidosis at other locations and corticosteroids represent the drugs of first choice.[133] Doses in neurosarcoidosis are higher than those advised for the treatment of other localisations of sarcoidosis, including pulmonary. In general, the initial recommended dose is 40 mg daily, whereas in neurosarcoidosis an initial dose of 1 mg/kg/day is typically recommended. In severe cases high doses of intravenous methylprednisolone may be used for a few days to obtain a high initial loading dose. Some may use bolus pulsed methylprednisolone once a week, eventually along with daily low doses of oral prednisone, or alternate day treatment to avoid the side-effects associated with long-term, high-dose oral treatment.[105] However, at present there is not enough evidence to recommend this. Although corticosteroids suppress inflammation in many patients, symptoms tend to recur in a subset of patients at doses of prednisone less than 10-25 mg/day or the equivalent in other corticoid types, making cessation of corticoids difficult. Furthermore, the incidence of steroid-related side-effects is extremely high with such long treatment.

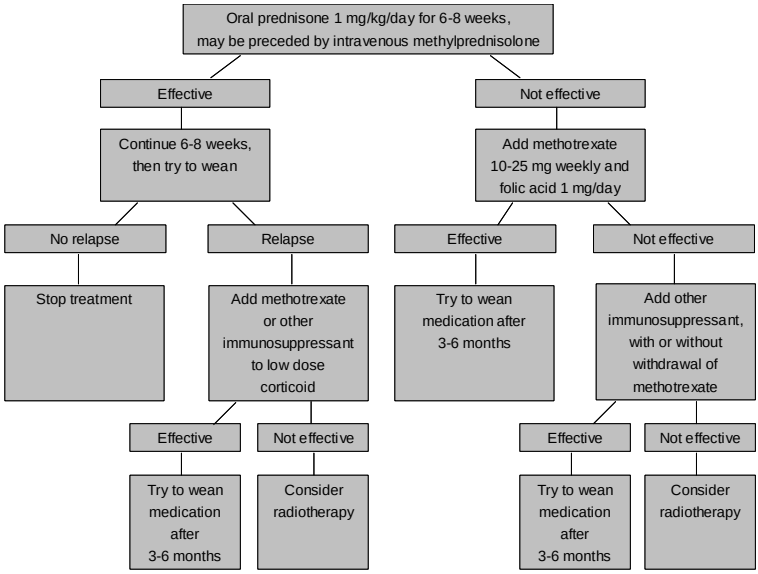

Figure 2.5 Therapeutic flow-chart for patients diagnosed with neurosarcoidosis.*
* Recommendations are based on experience rather than evidence.

In patients where corticosteroids may be contraindicated, cytotoxic drugs, such as methotrexate, azathioprine, ciclosporin, and cyclophosphamide, have been used.[105,134137] The choice for one or the other is more a matter of experience than of double-blind studies. On the basis of safety and efficacy, methotrexate and azathioprine may be preferred. Methotrexate has been the most widely reported drug for sarcoidosis and its use for sarcoidosis has been reviewed.[138] It seems to be well tolerated and associated with minimal toxic effects. The major problem is liver toxicity for which regular blood tests are needed. Response rate of methotrexate in neurosarcoidosis is about 60%, which is similar to that in chronic sarcoidosis.[136] Azathioprine is useful in chronic sarcoidosis, although others have been disappointed in its efficacy in patients with refractory sarcoidosis.[139] Treatment with ciclosporin has also resulted in variable outcomes.[136] About 75% of neurosarcoidosis patients respond to ciclosporin.[134,135] Response rates of intravenously given cyclophosphamide seems to be about 60-80% in patients with corticosteroid resistant neurosarcoidosis.[136,137] A short course pulsed regimen seemed to minimise cumulative toxicity.[137] The role of newer immunosuppressive drugs, such as mycophenolate mofetil, is unknown.

Drugs that change the immune system or block cytokine effect, have also been used for the treatment of patients with sarcoidosis. The antimalarial drugs chloroquine and hydroxychloroquine are useful in the treatment of some patients with neurological

sarcoidosis.[140] Tumour necrosis factor α is released at high concentrations by alveolar macrophages from patients with active sarcoidosis and the concentrations go down with corticosteroid or methotrexate therapy.[139] These observations have led to studies of substances that suppress tumour-necrosis-factor release or block its effect on the cell. Immunomodulators known to suppress the release of tumour necrosis factor are thalidomide and infliximab. Infliximab has been shown effective in few cases with refractory sarcoidosis. In refractory neurosarcoidosis it may also be effective.[141] The toxicity of treatment for up to 1 year is low. However, the effect of long-term treatment is still unknown.[139] An important complication associated with infliximab has been the increased rate of tuberculosis.[142] Side-effects and experience with certain drugs may play a part in drug choice (table 2.5).

Table 2.5 Treatment of neurosarcoidosis

Medication	Starting dose	Side effects*	Remarks
Corticosteroids			
Prednison	1 mg/kg/day orally	Osteoporosis, cushing syndrome, hypertension, diabetes mellitus, ulcus pepticum, pseudotumour cerebri, glaucoma, cataract, euphoria, psychosis	
Methylprednisolon	1000 mg/day for 3 days, intravenous	Very rare	
Cytotoxic agents**			
Methotrexate	10-25 mg/once weekly orally or subcutaneously	Anemia, neutropenia, hepatic dysfunction, pneumonitis	Should be combined with folic acid (1mg/day orally)
Cyclosporine	5 mg/kg/day, divided in 2 doses orally	Renal insufficiency, hypertension	Expensive
Azathioprine	50 mg three times daily orally	Anemia, neutropenia, hepatic dysfunction	Cheap
Cyclophosphamide	50-200 daily orally 500 mg once every 2-3 weeks, intravenous	Cystitis, neutropenia	Monthly urinanalysis to monitor for microscopic hematuria
Immunomodulators**			
Hydroxychloroquine	200 mg/day orally	Retinopathy, ototoxic, myopathy, cardiomyopathy, neuropathy, neuropsychiatric	Routine eye examinations every 3-6 months
Infliximab	3 mg/kg once in week 1, week 3, and week 5, than once every 6 weeks, intravenous	Fever, headache, dizziness, flushes, nausea, abdominal pain, dyspepsia, fatigue, myalgia, arthralgia, polyneuropathy	Tuberculosis screening is indicated before treatment is started Contra-indicated in patients with heart failure Should be combined with methotrexate

* All can cause infection because of immunosuppression; ** these drugs are generally used as adjuncts to low dose steroids, or as steroid sparing agents when long-term treatment is necessary. In refractory patients, these drugs may be used in combination with high-dose steroids.

Radiation

There are several reports on radiation therapy in refractory neurosarcoidosis.[143-146] Although evidenced based recommendations cannot be provided, radiation therapy may be given in patients who do not respond to drug therapy.

Neurosurgical treatment

Neurosurgical resection of intracranial and spinal granulomas is only indicated in life-threatening situations or when medical treatment is insufficient. However, extramedullary spinal lesions may be amenable to surgical resection with postoperative steroid therapy.[147] Hydrocephalus typically needs ventriculo-peritoneal shunting.[148,149]

Conclusions

Neurosarcoidosis is a rare disease with many presentations. Although sporadic reports of small numbers of patients with neurosarcoidosis are published, little progress has been made in defining this condition in detail. Therefore, most clinicians are not confident in its diagnosis or treatment. There is a need for a multinational prospective study in order to develop diagnostic and therapeutic standards to bring this severe illness under control.

References

1. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985;42:909-17.
2. James DG, Sharma OP. Neurosarcoidosis. *Proc R Soc Med* 1967;60:1169-70.
3. Sharma OP, Sharma AM. Sarcoidosis of the nervous system. A clinical approach. *Arch Intern Med* 1991;151:1317-21.
4. Manz HJ. Pathobiology of neurosarcoidosis and clinicopathologic correlation. *Can J Neurol Sci* 1983;10:50-5.
5. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. *Acta Pathol Jpn* 1993;43:372-6.
6. Burns TM. Neurosarcoidosis. *Arch Neurol* 2003;60:1166-8.
7. Minagar A, Hardjasudarma M, Kelley RE. Neurosarcoidosis. *Neurology* 2002;59:477.
8. Oksanen V. Neurosarcoidosis. *Sarcoidosis* 1994;11:76-9.
9. Scott TF. Neurosarcoidosis: progress and clinical aspects. *Neurology* 1993;43:8-12.
10. Chan Seem CP, Spokes EG. Neurosarcoidosis. *Lancet* 1985;2:1363.
11. Sharma OP. Neurosarcoidosis. *Chest* 1991;100:301-2.
12. Strefling AM, Summerville JW, Urich H. Involvement of choroid plexuses in neurosarcoidosis. *Acta Neuropathol (Berl)* 1987;74:402-4.
13. Kidd D, Beynon HL. The neurological complications of systemic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:85-94.
14. Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. *Acta Neurol Scand* 1986;73:283-90.
15. Pentland B, Mitchell JD, Cull RE, Ford MJ. Central nervous system sarcoidosis. *Q J Med* 1985;56:457-65.
16. Sharma OP, Lamb C. Cancer in interstitial pulmonary fibrosis and sarcoidosis. *Curr Opin Pulm Med* 2003;9:398-401.
17. Allen RK, Sellars RE, Sandstrom PA. A prospective study of 32 patients with neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:118-25.
18. Hunninghake GW, Costabel U, Ando M, Baughman RP, Cordier JF, du Bois RM, Eklund A, Kitaichi M, Lynch J, Rizzato G, Rose C, Selroos O, Semenzato G, Sharma OP. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:149-73.
19. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336:1224-34.
20. Colover J. Sarcoidosis with involvement of the nervous system. *Brain* 1948;71:451-75.
21. Delaney P. Neurologic manifestations in sarcoidosis: review of the literature, with a report of 23 cases. *Ann Intern Med* 1977;87:336-45.
22. Sharma OP. Cardiac and neurologic dysfunction in sarcoidosis. *Sarcoidosis* 1997;18:813-25.
23. Blain JG, Riley W, Logothetis J. Optic nerve manifestations of sarcoidosis. *Arch Neurol* 1965;13:307-9.
24. Wachtel AS, Saunders M. Optic nerve sarcoidosis. *Mayo Clin Proc* 1997;72:791.
25. Graham EM, Ellis CJ, Sanders MD, McDonald WI. Optic neuropathy in sarcoidosis. *J Neurol Neurosurg Psychiatry* 1986;49:756-63.
26. Gelwan MJ, Kellen RI, Burde RM, Kupersmith MJ. Sarcoidosis of the anterior visual pathway: successes and failures. *J Neurol Neurosurg Psychiatry* 1988;51:1473-80.
27. Bandyopadhyay T, Das D, Das SK, Ghosh A. A case of neurosarcoidosis presenting with multiple cranial nerve palsy. *J Assoc Physicians India* 2003;51:328-9.
28. Palacios E, Rigby PL, Smith DL. Cranial neuropathy in neurosarcoidosis. *Ear Nose Throat J* 2003;82:251-2.
29. De Broff B, Donahue S. Bilateral optic neuropathy as the initial manifestation of systemic sarcoidosis. *Am J Ophthalmol* 1993;116:108-11.

30. James DG, Zatouroff MA, Trowell J, Rose FC. Papilledema in sarcoidosis. *Br J Ophtalmol* 1967;51:526-30.
31. Karma A. Ocular sarcoidosis. *Semin Respir Med* 1992;131:425-31.
32. Westlake J, Heath JD, Spalton DJ. Sarcoidosis involving the optic nerve and hypothalamus. *Arch Ophthalmol* 1995;113:669-70.
33. Plotkin GR, Patel BR. Neurosarcoidosis presenting as chronic lymphocytic meningitis. *Pa Med* 1986;89:36-7.
34. Powers WJ, Miller FM. Sarcoidosis mimicking glioma: Case report and review of of intracranial sarcoidosis like mass lesions. *Neurology* 1981;31:907-10.
35. Mayer SA, Yim GK, Onesti ST, Lynch T, Faust PL, Marder K. Biopsy-proven isolated sarcoid meningitis. Case report. *J Neurosurg* 1993;78:994-6.
36. Jensen S, Jensen IW. Bilateral papilledema with normal CT-scan in neurosarcoidosis. *Acta Med Scand* 1987;222:381-3.
37. Scott TF. Cerebral herniation after lumbar puncture in sarcoid meningitis. *Clin Neurol Neurosurg* 2000;102:26-8.
38. Willigers H, Koehler PJ. Amnesic syndrome caused by neurosarcoidosis. *Clin Neurol Neurosurg* 1993;95:131-5.
39. Kumpe DA, Rao CV, Garcia JH, Heck AF. Intracranial neurosarcoidosis. *J Comput Assist Tomogr* 1979;3:324-30.
40. Cahill DW, Salcman M. Neurosarcoidosis: a review of the rarer manifestations. *Surg Neurol* 1981;15:204-11.
41. Akhondi H, Barochia S, Holmstrom B, Williams MJ. Hydrocephalus as a presenting manifestation of neurosarcoidosis. *South Med J* 2003;96:403-6.
42. Maniker AH, Cho ES, Schulder M. Neurosarcoid infiltration of the ventricular catheter causing shunt failure: a case report. *Surg Neurol* 1997;48:527-9.
43. Veres L, Utz JP, Houser OW. Sarcoidosis presenting as a central nervous system mass lesion. *Chest* 1997;111:518-21.
44. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestation. *J Neurol* 2001;248:363-72.
45. Stubgen JP. Neurosarcoidosis presenting as a retroclival mass. *Surg Neurol* 1995;43:85-7.
46. Gizzi MS, Lidov M, Rosenbaum D. Neurosarcoidosis presenting as a tumour of the basal ganglia and brainstem: sequential MRI. *Neurol Res* 1993;15:93-6.
47. Randeva HS, Davison R, Chamoun V, Bouloux PM. Isolated neurosarcoidosis - a diagnostic enigma: case report and discussion. *Endocrine* 2002;17:241-7.
48. Murialdo G, Tamagno G. Endocrine aspects of neurosarcoidosis. *J Endocrinol Invest* 2002;25:650-62.
49. Gleckman AM, Patalas ED, Joseph JT. Sudden unexpected death resulting from hypothalamic sarcoidosis. *Am J Forensic Med Pathol* 2002;23:48-51.
50. Tamagno G, Murialdo G. Amenorrhea-galactorrhea syndrome as an uncommon manifestation of isolated neurosarcoidosis. *Ann Ital Med Int* 2001;16:260-6.
51. Sato N, Sze G, Kim JH. Cystic pituitary mass in neurosarcoidosis. *Am J Neuroradiol* 1997;18:1182-5.
52. Konrad D, Gartenmann M, Martin E, Schoenle EJ. Central diabetes insipidus as the first manifestation of neurosarcoidosis in a 10-year-old girl. *Horm Res* 2000;54:98-100.
53. Bullmann C, Faust M, Hoffmann A, Heppner C, Jockenhovel F, Muller-Wieland D, Krone W. Five cases with central diabetes insipidus and hypogonadism as first presentation of neurosarcoidosis. *Eur J Endocrinol* 2000;142:365-72.
54. Guoth MS, Kim J, de Lotbiniere AC, Brines ML. Neurosarcoidosis presenting as hypopituitarism and a cystic pituitary mass. *Am J Med Sci* 1998;315:220-4.
55. Ahmadi J, Meyers GS, Segall HD, Sharma OP, Hinton DR. Lymphocytic adenohypophysitis: contrast-enhanced MR imaging in five cases. *Radiology* 1995;195:30-4.
56. Urich H. Neurosarcoidosis or granulomatous angiitis: a problem of definition. *Mt Sinai J Med* 1977;44:718-25.
57. Friedman SH, Gould DJ. Neurosarcoidosis presenting as psychosis and dementia: a case report. *Int J Psychiatry Med* 2002;32:401-3.

58. Popli AP. Risperidone for the treatment of psychosis associated with neurosarcoidosis. *J Clin Psychopharmacol* 1997;17:132-3.
59. Bona JR, Fackler SM, Fendley MJ, Nemeroff CB. Neurosarcoidosis as a cause of refractory psychosis: a complicated case report. *Am J Psychiatry* 1998;155:1106-8.
60. Sabaawi M, Gutierrez-Nunez J, Fragala MR. Neurosarcoidosis presenting as schizophreniform disorder. *Int J Psychiatry Med* 1992;22:269-74.
61. Caplan L, Corbett J, Goodwin J, Thomas C, Shenker D, Schatz N. Neuro-ophthalmologic signs in the angiitic form of neurosarcoidosis. *Neurology* 1983;33:1130-5.
62. Akova YA, Kansu T, Duman S. Pseudotumor cerebri secondary to dural sinus thrombosis in neurosarcoidosis. *J Clin Neuroophthalmol* 1993;13:188-9.
63. Redwood MD, Winer JB, Rossor M. Neurosarcoidosis presenting as benign intracranial hypertension. *Eur Neurol* 1990;30:282-3.
64. Krumholz A, Stern BJ, Stern EG. Clinical implications of seizures in neurosarcoidosis. *Arch Neurol* 1991;48:842-4.
65. Junger SS, Stern BJ, Levine SR, Sipos E, Marti-Masso JF. Intramedullary spinal sarcoidosis: clinical and magnetic resonance imaging characteristics. *Neurology* 1993;43:333-7.
66. Day AL, Sypert GW. Spinal cord sarcoidosis. *Ann Neurol* 1977;1:79-85.
67. Vinas FC, Rengachary S, Kupsky WJ. Spinal cord sarcoidosis: a diagnostic dilemma. *Neurol Res* 2001;23:347-52.
68. Rieger J, Hosten N. Spinal cord sarcoidosis. *Neuroradiology* 1994;36:627-8.
69. Sauter MK, Panitch HS, Kristt DA. Myelopathic neurosarcoidosis: diagnostic value of enhanced MRI. *Neurology* 1991;41:150-1.
70. Castellano-Sanchez AA. Extensive leptomeningeal and intraparenchymatous spinal cord neurosarcoidosis. *South Med J* 2000;93:815-7.
71. Hayat GR, Walton TP, Smith KR Jr, Martin DS, Manepalli AN. Solitary intramedullary neurosarcoidosis: role of MRI in early detection. *J Neuroimaging* 2001;11:66-70.
72. Sakakibara R, Uchimaya T, Kuwubara S, Kawaguchi N, Nemoto I, Nakata M, Hattori T. Autonomic dysreflexia due toneurogenic bladder dysfunction; an unusual presentation of spinal cord sarcoidosis. *J Neurol Neurosurg Psychiatry* 2001;71:819-20.
73. Prelog K, Blome S, Dennis C. Neurosarcoidosis of the conus medullaris and cauda equina. *Australas Radiol* 2003;47:295-7.
74. Shah JR, Lewis RA. Sarcoidosis of the cauda equina mimicking Guillain-Barre syndrome. *J Neurol Sci* 2003;208:113-7.
75. Abrey LE, Rosenblum MK, DeAngelis LM. Sarcoidosis of the cauda equina mimicking leptomeningeal malignancy. *J Neurooncol* 1998;39:261-5.
76. Ku A, Lachmann E, Tunkel R, Nagler W. Neurosarcoidosis of the conus medullaris and cauda equina presenting as paraparesis: case report and literature review. *Paraplegia* 1996;34: 116-20.
77. Verma KK, Forman AD, Fuller GN, Dimachkie MM, Vriesendorp FJ. Cauda equina syndrome as the isolated presentation of sarcoidosis. *J Neurology* 2000;247:573-4.
78. Fitzpatrick KJ, Chancellor MB, Rivas DA, Kumon H, Mandel S, Manon-Espaillat R. Urologic manifestation of spinal cord sarcoidosis. *J Spinal Cord Med* 1996;19:201-3.
79. Gainsborough N, Hall SM, Hughes RA, Leibowitz S. Sarcoid neuropathy. *J Neurol* 1991;238:177-80.
80. Miller R, Sheron N, Semple S. Sarcoidosis presenting with an acute Guillain-Barre syndrome. *Postgrad Med J* 1989;65:765-7.
81. Strickland-Marmol LB, Fessler RG, Rojiani AM. Necrotizing sarcoid granulomatosis mimicking an intracranial neoplasm: clinicopathologic features and review of the literature. *Mod Pathol* 2000;13:909-13.
82. Oh SJ. Sarcoid polyneuropathy: a histologically proved case. *Ann Neurol* 1980;7:178-81.
83. Said G, Lacroix C, Plante-Bordeneuve V, Le Page L, Pico F, Presles O, Senant J, Remy P, Rondepierre P, Mallecourt J. Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. *Brain* 2002;125:264-75.

84. Nemni R, Galassi G, Cohen M, Hays AP, Gould R, Singh N, Bressman S, Gamboa ET. Symmetric sarcoid polyneuropathy: analysis of a sural nerve biopsy. *Neurology* 1981;31:1217-23.
85. Vital C, Aubertin J, Ragnault JM, Amigues H, Mouton L, Bellance R. Sarcoidosis of the peripheral nerve: a histological and ultrastructural study of two cases. *Acta Neuropathol* 1982;58:111-4.
86. Challenor YB, Felton CP, Brust JC. Peripheral nerve involvement in sarcoidosis: an electrodiagnostic study. *J Neurol Neurosurg Psychiatry* 1984;47:1219-22.
87. Galassi G, Gibertoni M, Mancini A, Nemni R, Volpi G, Merelli E, Vacca G. Sarcoidosis of the peripheral nerve: clinical, electrophysiological and histological study of two cases. *Eur Neurol* 1984;23:459-65.
88. Elkin R, Willcox PA. Neurosarcoidosis. A report of 5 cases. *S Afr Med J* 1985;67:943-6.
89. Baron B, Goldberg AL, Rothfus WE, Sherman RL. CT features of sarcoid infiltration of a lumbosacral nerve root. *J Comput Assist Tomogr* 1989;13:364-5.
90. Matthews WB. sarcoid neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, editors. *Peripheral neuropathy. 2nd ed*. Philadelphia: W.B. Saunders 1984:2018-26.
91. Scott TS, Brillman J, Gross JA. Sarcoidosis of the peripheral nervous system. *Neurol Res* 1993;15:389-90.
92. Koffman B, Junck L, Elias SB, Feit HW, Levine SR. Polyradiculopathy in sarcoidosis. *Muscle Nerve* 1999;22:608-13.
93. Hoitsma E, Marziniak M, Faber CG, Reulen JPH, Sommer C, De Baets M, Drent M. Small Fiber Neuropathy in Sarcoidosis. *Lancet* 2002;359:2085-6.
94. Hoitsma E, Drent M, Verstraete E, Faber CG, Troost J, Spaans F, Reulen JPH. Abnormal warm and cold sensation thresholds suggestive of small-fibre neuropathy in sarcoidosis. *Clin Neurophysiol* 2003;114:2326-33.
95. Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology* 2000;55:1115-21.
96. Verbraecken J, Hoitsma E, van der Grinten CPM, Cobben NAM, Wouters EFM, Drent M. Sleep disturbance associated with periodic leg movements in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:137-46.
97. Alpert JN, Groff AE, Bastion FO, Blum MA. Acute polymyositis caused by sarcoidosis, report of a case and review of the literature. *Mt Sinai J Med* 1979;46:486-8.
98. Stjernberg N, Cajander S, Truedsson H, Uddenfeldt P. Muscle involvement in sarcoidosis. *Acta Med Scand* 1981;209:212-6.
99. Silverstein A, Siltzbach LE. Muscle involvement in sarcoidosis. Asymptomatic, myositis, and myopathy. *Arch Neurol* 1969;21: 235-41.
100. Jamal MM, Cilursu AM, Hoffman EL. Sarcoidosis presenting as acute myositis. Report and review of the literature. *J Rheumatol* 1988;15:1868-71.
101. Nidiry JJ, Mines S, Hackney R, Nabhani H. Sarcoidosis: a unique presentation of dysphagia, myopathy, and photophobia. *Am J Gastroenterol* 1991;86:1679-82.
102. Fonseca GA, Baca S, Altman RD. Acute myositis and dermatitis as the initial presentation of sarcoidosis. *Clin Exp Rheumatol* 1993;11:553-6.
103. Lynch JP, 3rd. Neurosarcoidosis: how good are the diagnostic tests? *J Neuroophthalmol* 2003;23:187-9.
104. Moore FG, Andermann F, Richardson J, Tampieri D, Giaccone R. The role of MRI and nerve root biopsy in the diagnosis of neurosarcoidosis. *Can J Neurol Sci* 2001;28:349-53.
105. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, Scadding JW, Thompson EJ, Chamoun V, Miller DH, McDonald WI, Mitchell D. Central nervous system sarcoidosis--diagnosis and management. *Qjm* 1999;92:103-17.
106. Uchino M, Nagao T, Harada N, Shibata I, Hamatani S, Mutou H. Neurosarcoidosis without systemic sarcoidosis - case report. *Neurol Med Chir (Tokyo)* 2001;41:48-51.
107. Cipri S, Gambardella G, Campolo C, Mannino R, Consoli D. Unusual clincal presentation of cerebral-isolated sarcoidosis. Case report and review of the literature. *J Neurosurg Sci* 2000;44:140-4.

108. Israel HL, Albertine KH, Park CH, Patrick H. Whole-body gallium 67 scans. Role in diagnosis of sarcoidosis. *Am Rev Respir Dis* 1991;144:1182-6.
109. Jarman PR, Whyte MK, Glass DM, Peters AM. Case report: imaging of central nervous system sarcoidosis with gallium-67 single photon emission computed tomography. *Br J Radiol* 1996;69:192-4.
110. Dubey N, Miletich RS, Wasay M, Mechtler LL, Bakshi R. Role of fluorodeoxyglucose positron emission tomography in the diagnosis of neurosarcoidosis. *J Neurol Sci* 2002;205:77-81.
111. Williams JW. The identification of sarcoid granulomas in the nervous system. *Proc Roy Soc Med* 1967;60:38-40.
112. Davis LE, Kornfeld M. Neurocysticercosis: neurologic, pathogenetic, diagnostic and therapeutic aspects. *European Neurology* 1991;31:229-40.
113. DeRemee RA. The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. *Chest* 1983;83:128-33.
114. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PGH, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003;49:1510-7.
115. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JMM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. *Chest* 2003;124:186-95.
116. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. *Lancet* 2003;361:1111-8.
117. Pickuth D, Spielmann RP, Heywang-Kobrunner SH. Role of radiology in the diagnosis of neurosarcoidosis. *Eur Radiol* 2000;10:941-4.
118. Tahmoush AJ, Amir MS, Connor WW, Farry JK, Didato S, Ulhoa-Cintra A, Vasas JM, Schwartzman RJ, Israel HL, Patrick H. CSF-ACE activity in probable CNS neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;19:191-7.
119. Oksanen V, Fyhrquist F, Somer H, Gronhagen-Riska C. Angiotensin converting enzyme in cerebrospinal fluid: a new assay. *Neurology* 1985;35:1220-3.
120. Jones DB, Mitchell D, Horn DB, Edwards CR. Cerebrospinal fluid angiotensin converting enzyme levels in the diagnosis of neurosarcoidosis. *Scott Med J* 1991;36:144-5.
121. Rubinstein I, Hoffstein V. Angiotensin-converting enzyme in neurosarcoidosis. *Arch Neurol* 1987;44:249-50.
122. Oksanen V, Fyhrquist F, Gronhagen-Riska C, Somer H. CSF angiotensin-converting enzyme in neurosarcoidosis. *Lancet* 1985;1:1050-1.
123. Chan Seem CP, Norfolk G, Spokes EG. CSF angiotensin-converting enzyme in neurosarcoidosis. *Lancet* 1985;1:456-7.
124. Schweisfurth H, Schioberg-Schiegnitz S, Kuhn W, Parusel B. Angiotensin I converting enzyme in cerebrospinal fluid of patients with neurological diseases. *Klin Wochenschr* 1987;65:955-8.
125. Borucki SJ, Nguyen BV, Ladoulis CT, McKendall RR. Cerebrospinal fluid immunoglobulin abnormalities in neurosarcoidosis. *Arch Neurol* 1989;46:270-3.
126. McLean BN, Mitchell DN, Thompson EJ. Local synthesis of specific IgG in the cerebrospinal fluid of patients with neurosarcoidosis detected by antigen immunoblotting using Kveim material. *J Neurol Sci* 1990;99:165-75.
127. Scott TF, Seay AR, Goust JM. Pattern and concentration of IgG in cerebrospinal fluid in neurosarcoidosis. *Neurology* 1989;39:1637-9.
128. Juozevicius JL, Rynes RI. Increased helper/suppressor T-lymphocyte ratio in the cerebrospinal fluid of a patient with neurosarcoidosis. *Ann Intern Med* 1986;104:807-8.
129. Oksanen V, Gronhagen-Riska C, Tikanoja S, Somer H, Fyhrquist F. Cerebrospinal fluid lysozyme and beta 2-microglobulin in neurosarcoidosis. *J Neurol Sci* 1986;73:79-87.
130. Oksanen V. New cerebrospinal fluid, neurophysiological and neuroradiological examinations in the diagnosis and follow-up of neurosarcoidosis. *Sarcoidosis* 1987;4:105-10.
131. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve* 1992;15:661-5.
132. Lacomis D. Small-fiber neuropathy. *Muscle Nerve* 2002;26:173-88.
133. Selroos O. Treatment of sarcoidosis. *Sarcoidosis* 1994;11:80-3.

134. Agbogu BN, Stern BJ, Sewell C, Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. *Arch Neurol* 1995;52:875-9.
135. Stern BJ, Schonfeld SA, Sewell C, Krumholz A, Scott P, Belendiuk G. The treatment of neurosarcoidosis with cyclosporine. *Arch Neurol* 1992;49:1065-72.
136. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med* 1997;157:1864-8.
137. Doty JD, Mazur JE, Judson MA. Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. *Chest* 2003;124:2023-6.
138. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999;54:742-6.
139. Baughman RP. Therapeutic options for sarcoidosis: new and old. *Curr Opin Pulm Med* 2002;8:464-9.
140. Sharma OP. Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement. *Arch Neurol* 1998;55:1248-54.
141. Pettersen JA, Zochodne DW, Bell RB, Martin L, Hill MD. Refractory neurosarcoidosis responding to infliximab. *Neurology* 2002;59:1660-1.
142. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098-104.
143. Menninger MD, Amdur RJ, Marcus RB Jr. Role of radiotherapy in the treatment of neurosarcoidosis. *Am J Clin Oncol* 2003;26:E115-8.
144. Kang S, Suh JH. Radiation therapy for neurosarcoidosis: report of three cases from a single institution. *Radiat Oncol Investig* 1999;7:309-12.
145. Rubinstein I, Gray TA, Moldofsky H, Hoffstein V. Neurosarcoidosis associated with hypersomnolence treated with corticosteroids and brain irradiation. *Chest* 1988;94:205-6.
146. Bejar JM, Kerby GR, Ziegler DK, Festoff BW. Treatment of central nervous system sarcoidosis with radiotherapy. *Ann Neurol* 1985;18:258-60.
147. Fried ED, Landau AJ, Sher JH, Rao C. Spinal cord sarcoidosis: a case report and review of the literature. *J Assoc Acad Minor Phys* 1993;4:132-7.
148. Hesselmann V, Wedekind C, Terstegge K, Schulte O, Voges J, Krug B, Lackner K. An isolated fourth ventricle in neurosarcoidosis: MRI findings. *Eur Radiol* 2002;12 Suppl 3:S1-3.
149. Foley KT, Howell JD, Junck L. Progression of hydrocephalus during corticosteroid therapy for neurosarcoidosis. *Postgrad Med J* 1989;65:481-4.