Neurosarcoidosis: Clinical Features, Pathogenesis, and Management

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Introduction

Sarcoidosis is an idiopathic, multi-organ, immune-mediated, inflammatory disorder of unrecognized cure characterized by the development of non-caseating epithelioid granulomas. As a systemic disorder, it heavily involves the respiratory and lymphatic systems (particularly intrathoracic lymph nodes) as well as the skin. Nervous system involvement in the course of sarcoidosis (neurosarcoidosis) is uncommon and occurs only in 5–10 % of cases. Interestingly, neurologic symptoms can be the only presentation of sarcoidosis in 10–17 % of individuals [1]. Despite these figures, the exact prevalence of nervous system involvement in the course of sarcoidosis is believed to be higher since subclinical involvement of the nervous system has been reported in up to 27 % of patients with sarcoidosis on autopsy [2]. Neurosarcoidosis comprises a wide gamut of clinical presentations which stem from involvement of both central and peripheral components of the human nervous system; therefore, it can imitate many other neuropathologies. Clinically, neurosarcoidosis presents with cranial nerve(s) involvement (facial nerve palsy is particularly common), aseptic meningitis, diencephalic syndromes (particularly hypopituitarism), epilepsy, cognitive decline, myelopathy, and peripheral neuropathy.

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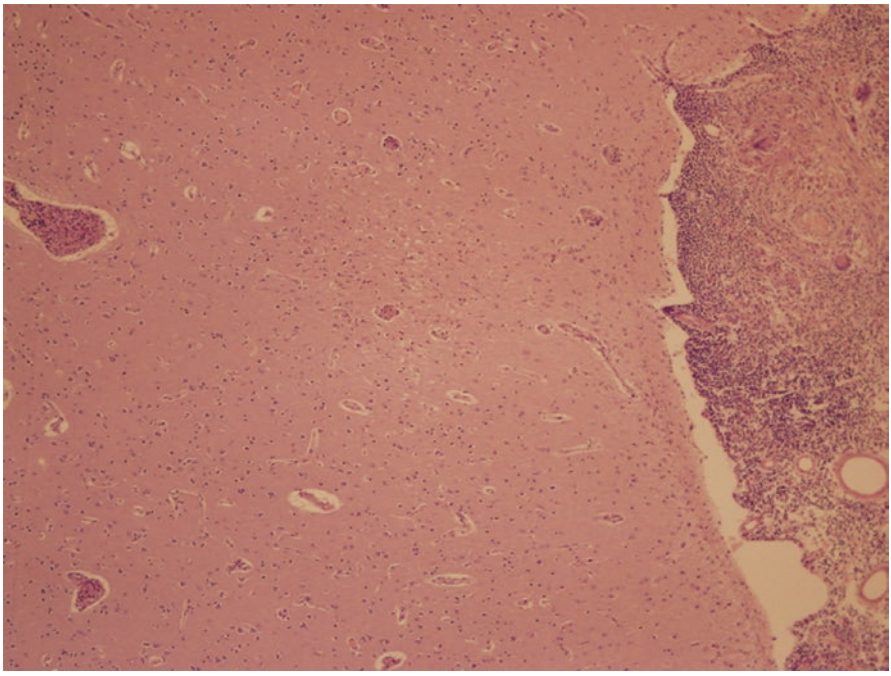

Fig. 5.1 10×4XX: Low-power photomicrograph showing granulomas within the meninges. A small granuloma is seen in the parenchyma of the brain (H&E, original magnification × 40)

Neuropathologically, sarcoidosis is characterized by the presence of epithelioid, non-caseating granulomas, including clusters of activated and highly differentiated macrophages and other epithelioid cells surrounded by T lymphocytes (Figs. 5.1 and 5.2). Langerhans-type multinucleated giant cells are commonly present, and further examination of the granulomas reveal that the center consists mainly of $CD4^+$ lymphocytes, while the $CD8^+$ lymphocytes exist in the periphery (Figs. 5.1, 5.2, and 5.3). Also, tumor necrosis factor-α (TNFα) is implicated in the pathogenesis of nervous system inflammation [3].

Epidemiology

Sarcoidosis, more frequently, affects African-Americans as well as individuals of Scandinavian origin. The estimated incidence of neurosarcoidosis in these ethnic groups is 15–20 and 35–80 cases per 100,000, correspondingly. However, a review of a number of retrospective case series reports indicates that 5–10 % of patients with sarcoidosis suffer from neurological complications and in 50–70 % of these individuals neurologic abnormalities are the initial clinical presentations**.** These neurologic abnormalities commonly develop during the first 2 years of systemic involvement. Isolated neurosarcoidosis, which means exclusive involvement of the

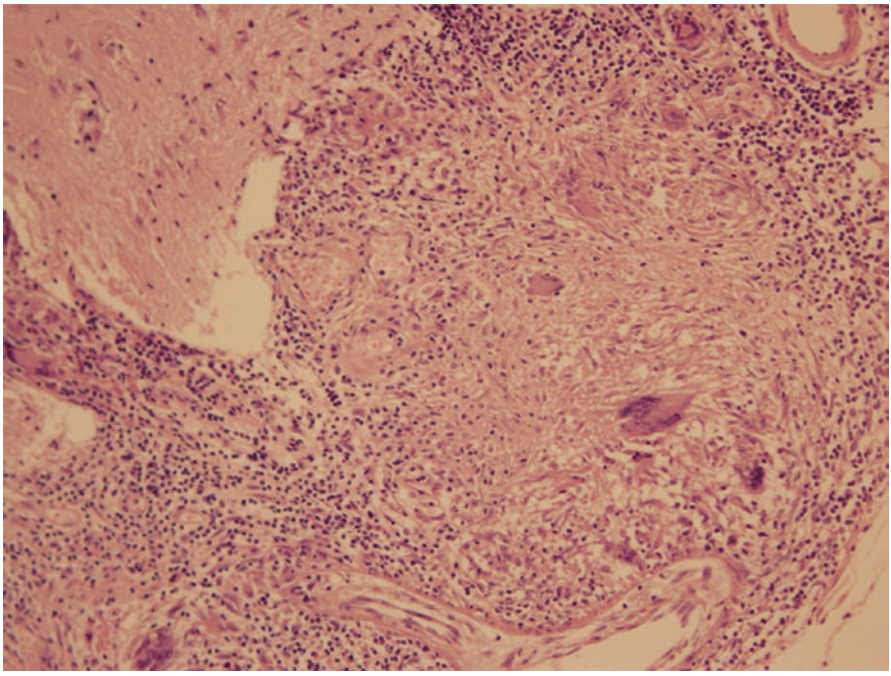

Fig. 5.2 0×10XX: Medium-power photomicrograph showing meningeal granulomas containing a few giant cells and a surrounding lymphocytic infiltrate (H&E, original magnification × 100)

nervous system without systemic involvement, is uncommon and its prevalence differs among various studies between 1–3 % and 10–17 % [4, 5]. Usually, sarcoidosis peaks in the third to fifth decades for most individuals, and neurologic symptoms commonly manifest during the first 2 years of disease. Women often have been reported to have a later age of onset and are more frequently affected compared to men. Various genetic, infectious, and environmental causes have been associated with sarcoidosis but without any proven cause and effect relationship.

Clinical Manifestations

Sarcoidosis is a great masquerader of other systemic diseases (particularly tuberculosis) and in a large number of patients with neurosarcoidosis presents with non-neurologic issues. Neurologists should always be aware of certain clues such as pulmonary involvement, eye disease (especially uveitis), dermatologic manifestations such as erythema nodosum, lymphadenopathy, joint pain, and other systemic symptoms (such as unexplained fever), which can eventually guide them to a correct diagnosis.

As a complicated multisystemic disease, sarcoidosis affects various parts of human nervous system and such widespread process leads to a wide range of

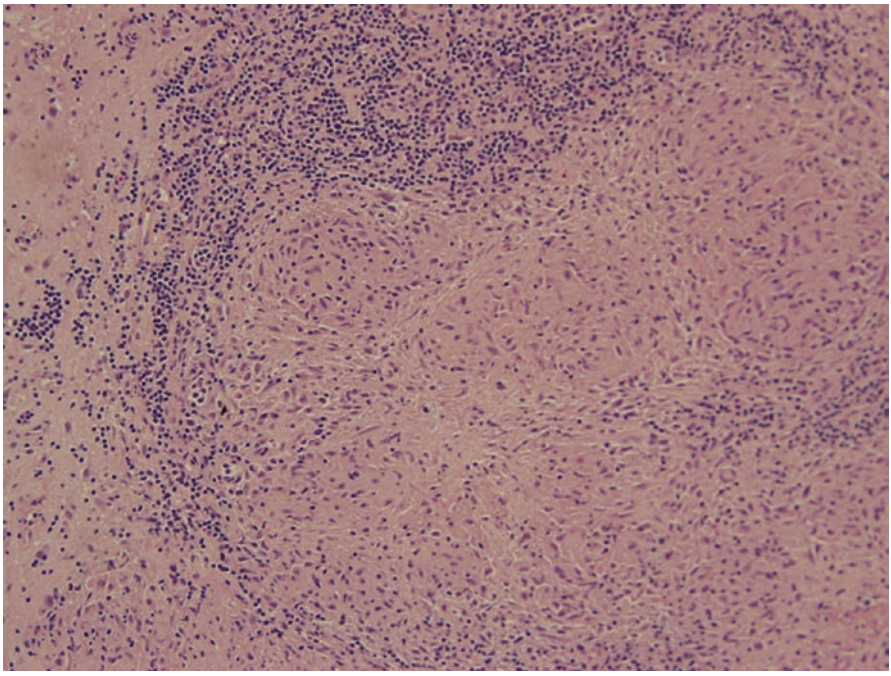

Fig. 5.3 ×10: Medium-power photomicrograph showing a parenchymal granuloma with central epithelioid cells and surrounding lymphocytic infiltrate (H&E, original magnification × 100)

neurological manifestations. Cranial nerve palsy and neuropathy, either due to granuloma, elevated intracranial pressure, or granulomatous basal meningitis, is the most common neurological presentation of neurosarcoidosis. Among the cranial nerves, the facial and the optic nerves are the most commonly affected. Bilateral facial nerve palsy due to neurosarcoidosis may occur, or the seventh cranial nerve may be affected sequentially.

While patients with neurosarcoidosis may present with rapidly progressing papilledema, other cranial nerves including olfactory, optic, oculomotor, vestibulocochlear, and uncommonly trigeminal, may be affected either alone or in combination. The pathologic process of the sarcoidosis can affect the cranial nerve nucleus or at any point within their anatomic pathway. Patients with Heerfordt's syndrome present with cranial neuropathy (most commonly facial nerve palsy), uveitis, fever, and enlargement of parotid gland. Such a unique combination is highly suggestive of neurosarcoidosis. Also, Horner's syndrome which develops from the disruption of cervical sympathetic fibers could be a manifestation of neurosarcoidosis. Pupillary abnormalities including Argyll-Robertson pupil and Adie's pupil have also been described in sarcoidosis.

Leptomeningeal involvement due to widespread meningeal infiltration of brain occurs in the presence or absence of parenchymal brain lesions and clinically may be symptomatic or may manifest as subacute or chronic aseptic meningitis, basilar

polycranial neuropathy, and neuroendocrine abnormalities. Clinicians who manage these patients should bear in mind that headache and seizures may stem from meningitis, hydrocephalus, space-occupying lesions, or opportunistic infections (particularly in immunocompromised patients). Headache in these patients less often originates from trigeminal neuropathy or worsening of coexisting migraines [6]. In patients with neurosarcoidosis, seizures may be the initial presentation of the underlying disease process, and they may experience any type of seizures. Manifestation of the seizure in these patients may designate chronicity and an unfavorable prognosis [7].

Rarely, neurosarcoidosis may result in stroke due to penetration of the endothelial layers of small or large blood vessels, with disruption of the media and internal elastic lamina, resulting in obstruction of the vessel and ischemic cerebral infarct [8]. Other possible stroke pathology suggested includes sarcoidosis-associated mass lesion compression of an intracranial artery, necrotizing arteritis with fibrinoid necrosis of the media and massive leukocyte invasion [9], and cardiac granulomatous inflammation resulting in cardiogenic emboli. Cerebral and dural venous sinus thrombosis is also a potential, however, rare complication of this inflammatory process [5, 10].

With more diffuse leptomeningeal disease, headache may be accompanied by gait dysfunction, cognitive changes, and/or seizures, suggesting involvement of the brain parenchyma. Patients presenting acutely with this complex of symptoms should be evaluated urgently for hydrocephalus, which can often complicate severe cases of leptomeningeal inflammation and is considered a neurologic emergency. Hydrocephalus is another interesting clinical feature of neurosarcoidosis, which may be due to meningeal infiltration of the arachnoid granulations or cerebral aqueduct. Patients with neurosarcoidosis may develop cauda equina syndrome due to meningeal infiltration of the lumbosacral nerve roots.

Myelopathy in the context of neurosarcoidosis occurs as a result of spinal leptomeningeal infiltration, extensive myelitis, or both. Cases of neurosarcoidosis with longitudinally extensive myelitis which span an average of 3.9 segments (a significant differentiating feature from multiple sclerosis with smaller and patch cord lesions) have been reported. The most significant differential diagnoses of neurosarcoidosis patients with such extensive myelitis include multiple sclerosis, neuromyelitis optica, lupus myelitis, Sjogren's syndrome, and infectious diseases.

Neuroendocrine abnormalities of neurosarcoidosis, which stem from hypothalamic and pituitary involvement by the subependymal granulomatous invasion of the third ventricle region, includes hypothalamic hypothyroidism, hypogonadotropism, SIADH, diabetes insipidus, growth hormone deficiency, and hyperprolactinemia [11].

Neurosarcoidosis may be associated with various nonspecific neuropsychiatric symptoms such as memory loss, fatigue, mood disturbances, and other behavioral issues, without evidence of a CNS lesion. These are attributed primarily to underlying systemic disease, medication side effects, depression, and sleep disorders such as sleep apnea syndrome and primary hypersomnia.

Peripheral nervous system involvement in the process of neurosarcoidosis includes asymmetric polyradiculoneuropathy, mononeuritis multiplex, small fiber sensory neuropathy with autonomic dysfunction, AIDP, CIDP, and subacute length-dependent axonal polyneuropathy. Mononeuropathy is another manifestation of neurosarcoidosis and the ulnar and peroneal nerves are the most frequently affected. Autonomic dysfunction symptoms include orthostatic hypotension, gastrointestinal dysmotility, and disorders of sweating. Small fiber neuropathy of neurosarcoidosis can involve autonomic nerve fibers and cause cardiac sympathetic denervation with cardiac arrhythmias and may cause restless leg syndrome [12]. Patients with neurosarcoidosis may develop myopathy with granulomatous muscle involvement, and this may be clinically symptomatic or remain asymptomatic. In symptomatic cases, patients complain of myalgia, weakness, and muscle tenderness and suffer from cramps and muscle atrophy. Acute myositis in the context of neurosarcoidosis is uncommon and the myopathy more often takes a chronic course.

Sleep Disorders in Neurosarcoidosis Patients

The exact incidence of sleep disorders in patients with neurosarcoidosis remains unrecognized, and the only diagnostic polysomnographic studies in these patients include cases of narcolepsy with cataplexy [13–15]. Recently, May et al. had reported the HLA DQB1*0602-negative case of hypocretin deficiency and respiratory dysfunction (hypoventilation and hypercapnia) from extensive destruction of hypocretin neurons and key diencephalic structures secondary to the underlying sarcoidosis [13–15]. In another HLA DR2/DQ1-positive case of neurosarcoidosis, patients presented with hypothalamic lesion, excessive daytime sleepiness, sleep attacks, and cataplexy, and multiple sleep latency tests (MSLT) were characteristic of narcolepsy [14]. Anecdotally, low-dose, whole-brain irradiation, but not high dose of corticosteroids, led to complete resolution of the narcoleptic features in patients with structural neurosarcoidosis lesion in the hypothalamus [15]. Even though sleep-disordered breathing (SDB) is very prevalent in sarcoidosis patients ranging from 17 to 67 % [16–18], overall prevalence of SDB and obstructive sleep apnea in neurosarcoidosis population is unknown. Epidemiologic distribution of other primary and secondary sleep disorders in neurosarcoidosis remains largely unknown.

Neuropathology

On growth appearance, neurosarcoidosis most frequently involves the meninges at the base of the brain, particularly in the area of the infundibulum and optic chiasm, although it may involve other meningeal areas including the brain stem, convexities, cerebellum, and spinal cord. It may involve both cranial and spinal nerves where they traverse the meningeal space. The involved meninges are thickened, gray yellow, and frequently gelatinous (Fig. 5.1). Long-standing sarcoidosis results in progressively more fibrosis resulting in a tough fibrous-thickened membrane.

Occasional cases also exhibit involvement of the choroid plexus and/or ependymal lining of the ventricular system. Dural involvement is unusual but would have similar gross features.

Although less common, the granulomas of sarcoidosis may be seen within the parenchyma of the brain where they are usually small, discrete, gray, firm nodular lesions that may be solitary or multifocal. The infundibulum and hypothalamus are the favored parenchymal areas of involvement followed by the brain stem.

Microscopic Appearance

The granulomas are composed of numerous central epithelioid macrophages with abundant eosinophilic cytoplasm and vesicular nuclei. Multinucleated giant cells representing a fusion of these macrophages may be seen, but are not always present (Figs. 5.2 and 5.3). Although not common, giant cells may contain asteroid bodies or calcified nodular Schaumann bodies. The central cluster of epithelioid macrophages is surrounded by a cuff of benign lymphocytes and plasma cells. Necrosis is uncommon but rarely may be seen. Although blood vessels may be seen within rare granulomas, this is not common. With age progressively more fibrosis is seen in the meninges.

The tissue surrounding parenchymal granulomas contains gemistocytic astrocytes and may exhibit edema or loss of neuropil. Small perivascular cuffs of benign lymphocytes are frequently seen in the tissue surrounding the parenchymal granulomas. Microglial nodules are usually absent. Special stains for mycobacteria, fungi, and amyloid are negative.

Differential Diagnosis

The histologic differential diagnosis includes fungal and mycobacterial infections. These can usually be excluded using special stains. Special stains are also useful in excluding amyloid angiopathy with a granulomatous response. The presence of granulomas within the parenchyma and the rarity of blood vessels within the granulomas help distinguish sarcoidosis from primary angiitis of the CNS. As in all cases, the clinical history and presence of disease elsewhere are essential for making the correct diagnosis. Clinically, the most significant differential diagnoses of neurosarcoidosis include multiple sclerosis, CNS tuberculosis, neuromyelitis optica, transverse myelitis, HIV infection, and neuro-Behcet's disease.

Diagnosis

Neuroimaging plays a crucial role in diagnosing of neurosarcoidosis, and all suspected patients should undergo magnetic resonance imaging of the brain and spinal cord with and without gadolinium contrast. Interestingly, many of neuroimaging abnormalities of neurosarcoidosis mimic other inflammatory, neoplastic, demyelinating, and

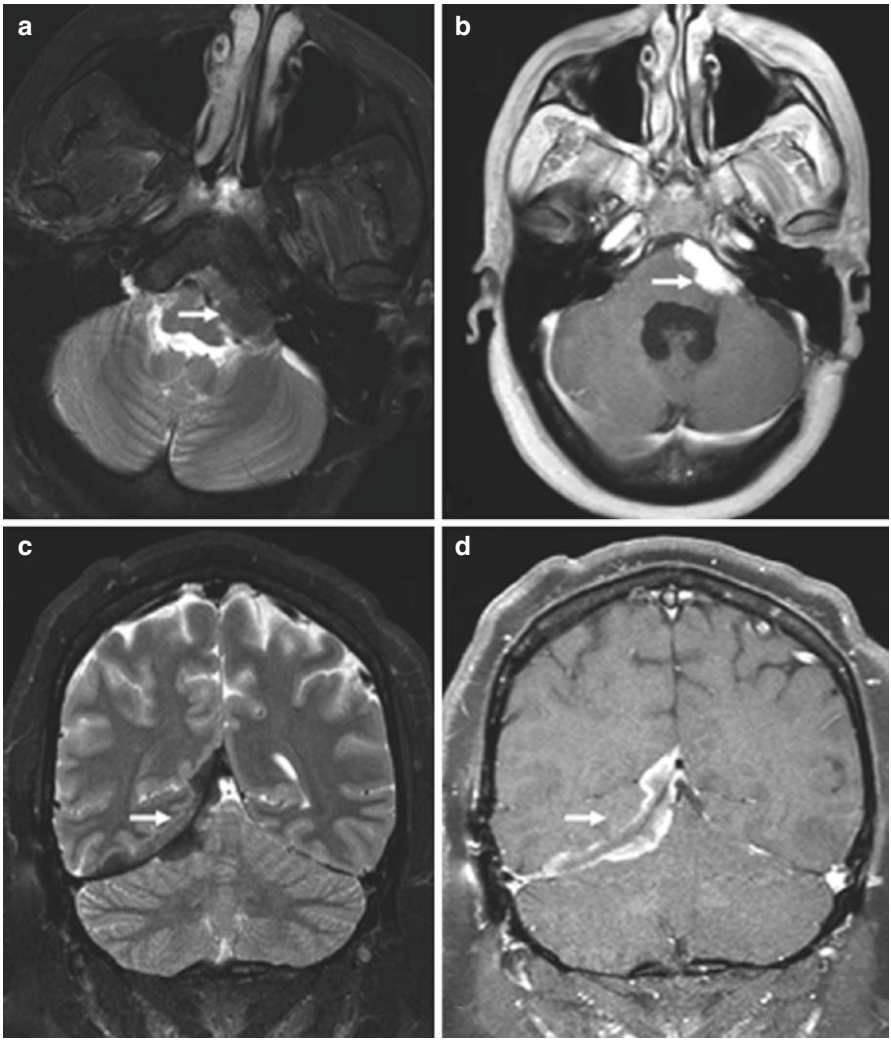

Fig. 5.4 Extra-axial masses in sarcoidosis. (**a**, **b**) Axial T2- and enhanced axial T1-weighted images demonstrate an enhancing T2-hypointense extra-axial mass in the left cerebellopontine angle cistern (*arrow*). (**c**, **d**) Coronal T2 and enhanced coronal T1 images from a different patient show a T2-hypointense enhancing right tentorial mass (*arrow*). Noncontrast CT (not shown) did not demonstrate any calcification. Biopsy (not shown) revealed granulomatous inflammation (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

infectious neurological diseases. Also, the disease may manifest as meningeal involvement either as a focal thickening concerning for meningioma or diffuse pachymeningeal involvement as seen in intracranial hypotension or leptomeningeal disease. Hydrocephalus, either communicating or noncommunicating, may develop as a result of severe meningeal inflammation. Various neuroimaging abnormalities of the neurosarcoidosis are presented in Figs. 5.4, 5.5, 5.6, 5.7, 5.8, and 5.9 [19].

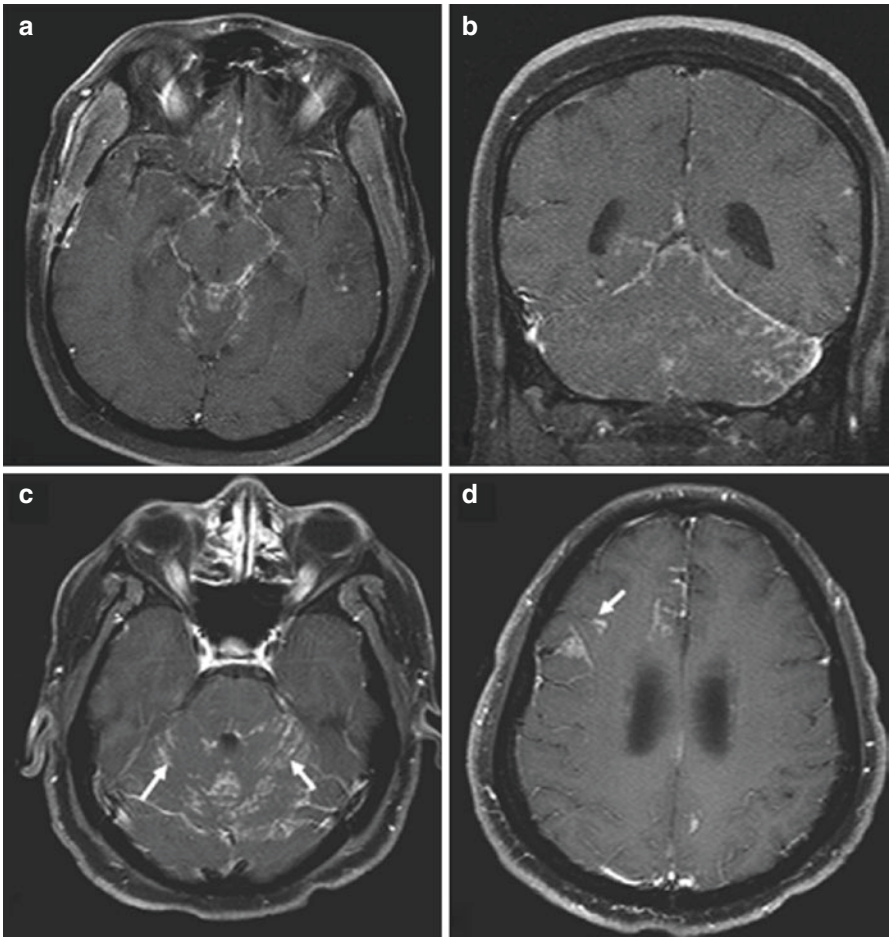

Fig. 5.5 Leptomeningeal involvement in sarcoidosis. (**a**, **b**) Enhanced axial and coronal T1-weighted images demonstrate nodular leptomeningeal enhancement in the basilar cisterns and posterior fossa. (**c**, **d**) Enhanced axial T1-weighted images in a different patient demonstrate nodular leptomeningeal enhancement along the cerebellar folia (*arrows*). Involvement of perivascular spaces is seen at a higher level in **d** (*arrow*) (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

The classification by Zajicek and colleagues [20] is by far the most acceptable and utilized diagnostic criteria for neurosarcoidosis (Table 5.1). As per them the disease process can be categorized as definite (direct neural tissue confirmation), probable (neurologic inflammation along with evidence of systemic sarcoidosis), and possible (typical clinical presentation but no other criteria met except for the exclusion of other potential etiologies).

In almost half of patients with neurosarcoidosis, intramedullary spinal cord lesions are present with involvement of ≥3 segments with a patchy and noncontiguous dissemination which may or may not enhance and is usually accompanied by

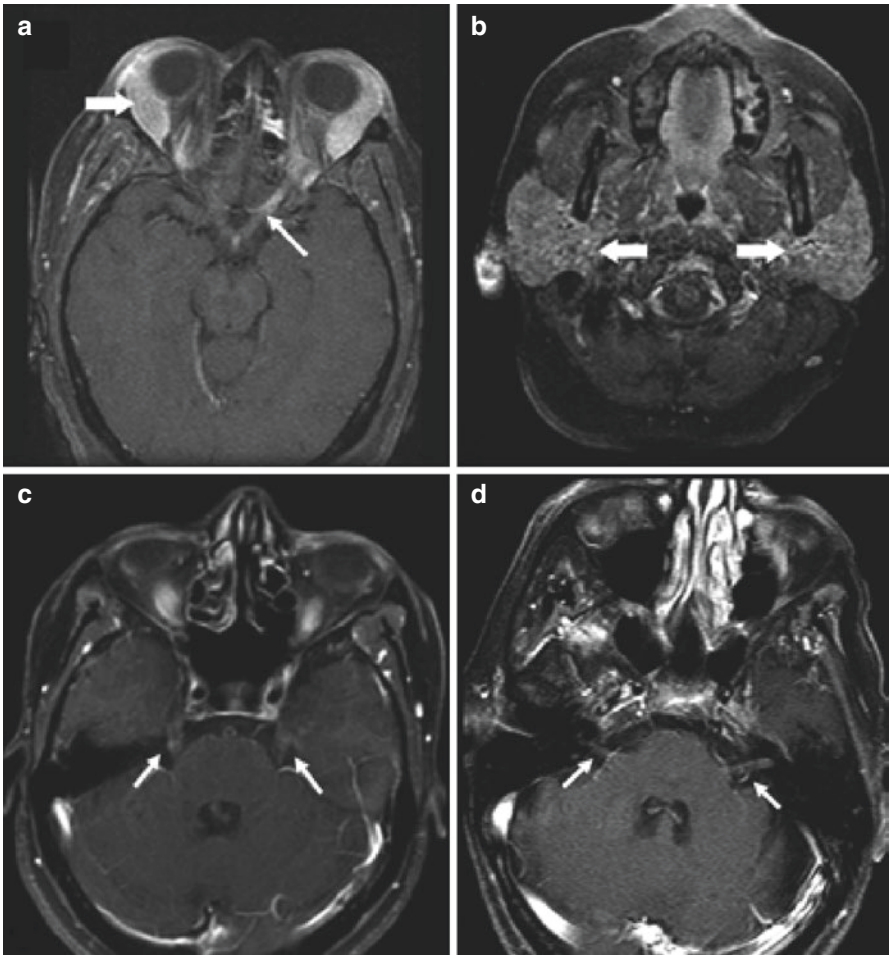

Fig. 5.6 Cranial nerve enhancement in sarcoidosis. (**a**, **b**) Axial fat-suppressed T1 images show enhancement of the left optic nerve (*thin arrow*). Lacrimal and parotid glands are enlarged (*thick arrows* in **a** and **b**, respectively). (**c**) Bilateral trigeminal nerve enhancement is seen in a different patient (*arrows*). (**d**) Enhancement of bilateral seventh to eighth nerve complexes is seen in another patient (*arrows*) (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

meningeal enhancement. In acute phase the affected spinal cord appears swollen and expanded, while chronic cases manifest with spinal cord atrophy. However, acute lesions may at times be nonenhancing as well.

Examination and analysis of cerebrospinal fluid (CSF) also assists clinicians to establish the correct diagnosis and exclude other differential diagnoses. The authors of this chapter routinely perform spinal tap on all patients suspected of having neurosarcoidosis. CSF examination of these patients reveals inflammatory features such as increased protein concentration (≥200 mg/dL) and elevated white blood

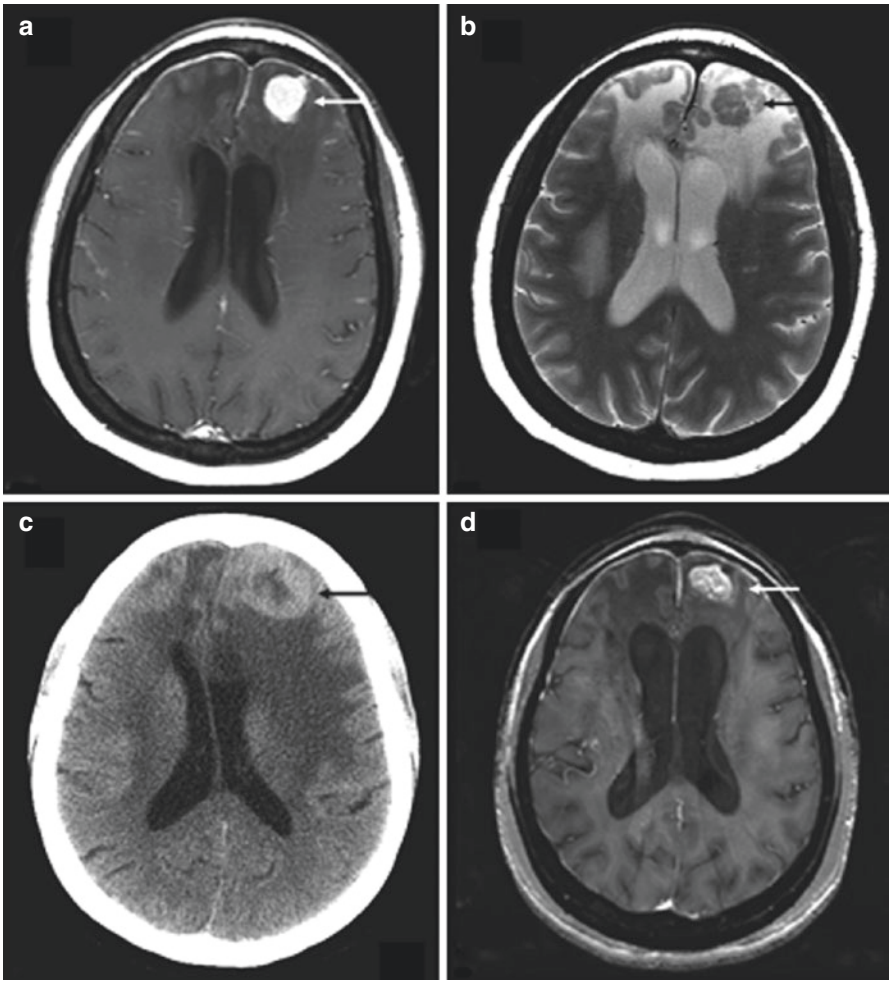

Fig. 5.7 Parenchymal lesion in sarcoidosis. (**a**, **b**) Enhanced axial T1- and T2-weighted images at presentation demonstrate an enhancing T2-hypointense left frontal mass (*arrow*). There is surrounding nonenhancing T2-hyperintensity due to vasogenic edema. Also note thin dural enhancement overlying both frontal lobes. (**c**) Noncontrast CT scan obtained 1 year later shows worsening lesion size and edema (*arrow*). The patient had been on low-dose prednisone and was symptomatically stable. (**d**) MR image obtained following high-dose prednisone therapy shows a decrease in edema but only partial resolution of the enhancing left frontal mass (*arrow*). There was no further decrease in size of the mass on serial scans during the next 2 years with the patient on immunosuppressive therapy (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

cell count (mononuclear pleocytosis) [>50 cells μL] and the presence of oligoclonal bands along with elevated IgG indices. In some cases CSF glucose level is low. A normal CSF panel (which may be present in one-third of patients even in the presence of contrast-enhancing MR lesions or biopsy-proven neurosarcoidosis or in

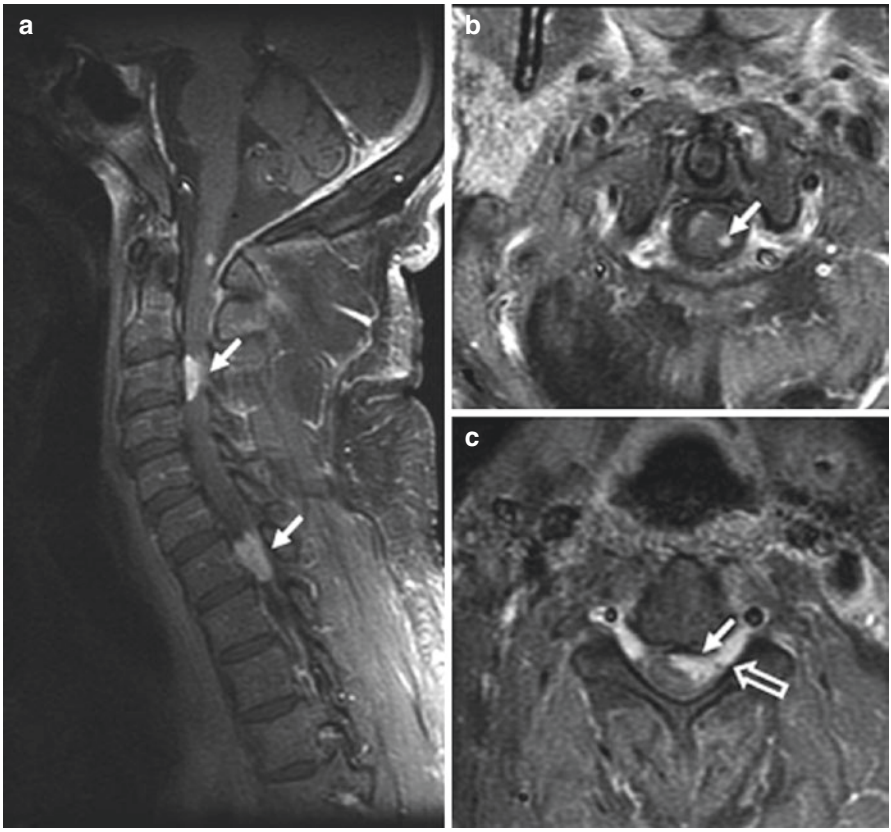

Fig. 5.8 Spinal cord involvement in sarcoidosis. (**a**–**c**) Enhanced parasagittal and axial T1-weighted images of the cervical cord show multiple enhancing parenchymal nodules (*arrows*). The peripheral distribution of these nodules, which are abutting the surface of the cord, suggests a leptomeningeal origin of these nodules. Note enhancement extending along the nerve roots (*open arrow*, **c**) (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

patients with isolated facial palsy) does not exclude such diagnosis. In all patients, the CSF examination should include search for malignant cells utilizing flow cytometry, serology for various infections, bacterial cultures, PCR assays for viral agents, and serologic studies for a number of infections. Angiotensin-converting enzyme (ACE), which is produced by granulomas, is increased in 24–55 % of patients, and while it is a nonsensitive marker of neurosarcoidosis, it is highly specific [19, 21].

Electromyography and nerve conduction studies enable clinicians to diagnose patients with neuromuscular diseases such as neuropathy, mononeuritis multiplex, and myopathy. This test also helps the neurophysiologist to determine whether the disease process is demyelinating versus axonal, how severe and widespread the neuropathic process is, and whether it is acute or chronic. Routine nerve conduction

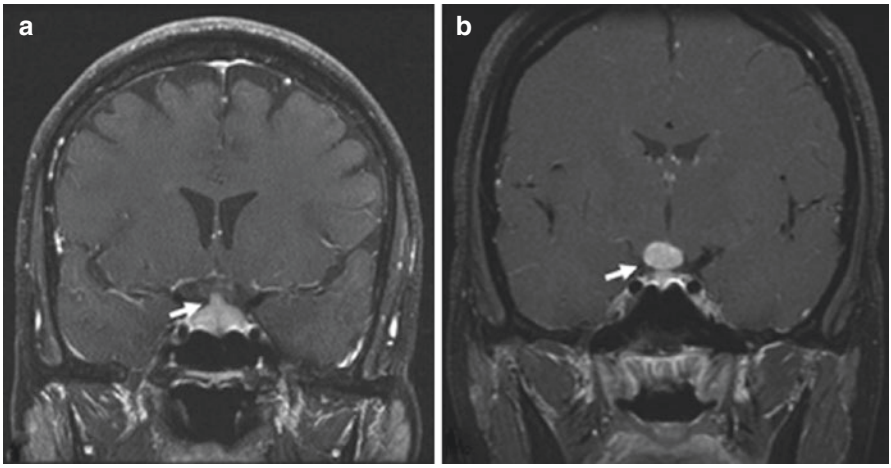

Fig. 5.9 Sellar-suprasellar involvement in sarcoidosis. (**a**) Enhanced coronal T1-weighted image shows an enlarged and enhancing pituitary infundibulum (*arrow*). This patient also had multiple enhancing parenchymal nodules in a perivascular distribution. (**b**) Enhanced coronal T1-weighted image from a different patient shows a homogeneously enhancing infundibular and hypothalamic mass (*arrow*) (From Shah et al. [19]. Copyright permission obtained from American Society of Neuroradiology)

Table 5.1 Proposed diagnostic criteria for neurosarcoidosis

Definite	Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology
Probable	Clinical syndrome suggestive histology of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CAF protein and/or cells, the presence of oligoclonal bands, and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence of systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from gallium scan, chest imaging and serum ACE)
Possible	Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met

From Zajicek et al. [20] Copyright permission obtained

study with main concentration on large nerve fiber may miss a diagnosis of small fiber neuropathy. In cases where a systematic diagnosis approach fails to establish a diagnosis, the neurologist should consider muscle and nerve biopsy. In such cases the presence of epineural and perineural granulomas and granulomatous vasculitis may indicate a diagnosis of neurosarcoidosis. Accurate diagnosis of small fiber neuropathy is necessary since it causes disabling problems such as cardiac sympathetic denervation, periodic limb movement disorder, and restless leg syndrome. Evaluation of intraepidermal nerve fiber density along with other examinations such as quantitative sudomotor axon reflex testing and tilt table test are currently being utilized to accurately diagnose small fiber neuropathy [22].

Conjunctival, as well as tongue, biopsy is an informative, technically simple, and relatively safe procedure, which can demonstrate the presence of non-caseating granulomas in support of sarcoidosis. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is utilized to examine the mediastinal and hilar lymphadenopathy in patients suspected of sarcoidosis.

In cases when the initial screening tests failed to provide adequate evidence in support of sarcoidosis, a pan-body fluorodeoxyglucose positron emission tomography (FDG-PET) scan should be considered. Studies have shown that FDG-PET is more sensitive than ^{67}gallium nuclear scan in detecting systemic sarcoidosis. In addition, FDG-PET helps visualize neurologic disease activity otherwise not evident on the MRI and when combined with CT (PET/CT) assists neurologist to assess disease activity and response to therapy [23]. ^{67}Gallium nuclear scan is used in clinical practice since it potentially can reveal elevated uptake at the sites of active inflammation (hot spots), which are appropriate for biopsy.

In patients with exclusive CNS sarcoidosis, a tissue biopsy of the region of interest is the most definitive diagnostic test. Biopsy also helps in ruling out alternative diagnoses in patients who do not respond well to immunosuppressive therapy or with worsening disease.

Treatment

There is no known cure for sarcoidosis and its treatment rests on immunosuppression as well as symptomatic treatment. Neurosarcoidosis is a devastating condition and carries a significant mortality and morbidity rate. In addition, there are not any randomized, controlled, and well-executed clinical trials to establish the superiority of one treatment over the other options. Therefore, most of the available treatment approaches are based on small case series and anecdotal case reports. In general, patients with neurosarcoidosis require aggressive treatment. Left untreated, neurosarcoidosis with brain and spinal cord involvement is potentially fatal, and rapid immunosuppression with corticosteroids is necessary to block such path. The most significant concept in treatment of neurosarcoidosis is profound immunosuppression. Presently, corticosteroids remain the foundation of its treatment. Patients with mild to moderate neurosarcoidosis can be treated with oral prednisone with doses in the range of 40–80 mg daily, and since this is a chronic ailment, patients need long-term treatment.

In many cases the dose of corticosteroid should be tapered slowly and systematically, over a course of 6–12 months. The authors treat neurosarcoidosis patients with pulse intravenous infusion of methylprednisolone (Solu-Medrol) 1000 mg daily for 5 days followed by oral maintenance dose of prednisone of 40–80 mg daily for at least 1 year. This pulse therapy should be followed by the use of oral prednisone. The treatment of neurosarcoidosis patients is also an individualized process and dosing and duration of therapy with corticosteroids vary across the patients. Corticosteroids work by suppressing lymphocyte and mononuclear phagocytic activity, suppression of transcription of pro-inflammatory cytokines, downregulation of cellular receptors, and repairing the disrupted blood-brain barrier.

In severe cases with severe myelitis or brain parenchymal involvement, or in unresponsive patients, combined therapy with a second immunosuppressant should be planned. Once clinical response and improvement are observed, the clinician should think about slow tapering of the corticosteroids. Treatment of neurosarcoidosis with corticosteroids is associated with a number of complications such as iatrogenic hyperglycemia, hypertension, hypokalemia, significant weight gain, myopathy, premature cataract and glaucoma, and uncommonly aseptic necrosis of femur head.

Certain immune-suppressant cytotoxic agents such as methotrexate (a folate analogue), azathioprine (a purine analogue), mycophenolate mofetil, cyclosporine, and cyclophosphamide have been utilized to treat patients with inadequate therapeutic response to corticosteroids or those with features of poor prognosis and elevated chance of disease recurrence. Each one of these agents does possess its own hematologic, hepatotoxic, gastrointestinal, or urologic complications and close monitoring of these patients is necessary. In addition, chronic treatment with these agents may cause uncommon malignancies. Some cases of neurosarcoidosis have been treated with anti-malarial drugs such as hydroxychloroquine. However, this medication does have toxic effects on the retina, liver, and skin.

Few case reports exist on CNS radiation for treatment of patients with neurosarcoidosis with widespread encephalopathy and vasculopathy. These patients have been treated with either total nodal or craniospinal irradiation. CNS radiation should be considered only for very severe cases since it does have its own adverse complications and is not curative.

In neurosarcoidosis patients with large parenchymal lesions, which cause hydrocephalus or increase the intracranial pressure, urgent neurosurgical debulking and cerebrospinal fluid diversion procedures such as ventriculo-peritoneal shunt implant should be considered.

Tumor necrosis factor-α (TNF-α) antagonists, such as monoclonal antibody known as infliximab, have been utilized for treating refractory cases of neurosarcoidosis. TNF-α, a potent pro-inflammatory cytokine, is released by macrophages and other immune cells during formation of granuloma. By binding to TNF-α, infliximab blocks its interaction with the TNF-α receptor. It is used as monotherapy or combined with corticosteroids and is effective for patients with severe leptomeningeal, brain, and spinal cord involvement. Other monoclonal antibodies such as adalimumab and rituximab have been utilized to treat neurosarcoidosis. Significant adverse effects of this group of new therapies include lymphoma, progressive multifocal leukoencephalopathy, and recrudescence of tuberculosis. Another interesting and more recent experimental monoclonal antibody, adalimumab, which also serves as an antagonist against TNF-α, has been utilized for treatment of patients with corticosteroid-resistant patients.

In patients with small fiber neuropathy and autonomic dysfunction that are refractory to corticosteroids, IV immunoglobulin and TNF-α antagonists have shown their potential in alleviating the symptoms to a significant extent.

Treatment of complications of neurosarcoidosis is also an interesting subject which requires more discussion. Patients with hydrocephalus and raised intracranial

pressure need ventriculostomy with drainage and possibly shunt placement. Patients with epilepsy due to neurosarcoidosis should be treated with antiepileptics. Treatment of those with involvement of hypothalamic-pituitary axis with neurosarcoidosis requires consultation from endocrinologist, correction of water and electrolyte deficits, and hormone replacement treatment. Patients with peripheral neuropathy due to neurosarcoidosis should be treated with various agents such as antidepressants, antiepileptics, opioid or opioid agonists, and intravenous immunoglobulin. Those with ischemic stroke due to neurosarcoidosis should be treated with antiplatelets or anticoagulants. Depression and cognitive decline require psychiatric consult, treatment with antidepressants, and cognitive rehabilitation. Similar to other neurological diseases, once a diagnosis of neurosarcoidosis is established, the rehabilitation process with heavy emphasis on physical and occupational therapy begins to ascertain that patients will become independent as much as possible.

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