Neurosarcoidosis

Surabhi Ranjan MBBS (Dr. Ranjan of the National Cancer Institute has no relevant financial relationships to disclose.)
Amber J Giles PhD (Dr. Giles of National Cancer Institute has no relevant financial relationships to disclose.)
Deric M Park MD (Dr. Park of the National Cancer Institute has no relevant financial relationships to disclose.)
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Introduction

This article includes discussion of neurosarcoidosis, Besnier-Boeck-Schaumann disease, Heerfordt syndrome, sarcoidosis, uveo-parotid fever, and Löfgren syndrome. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

In this article, the authors present the current understanding of the epidemiology, diagnostic findings, proposed pathogenesis, relevant genetics, and therapeutic options for neurosarcoidosis. Although corticosteroids are the most widely employed form of therapy, various anecdotal reports have described use of more specific immunosuppressive agents, such as methotrexate, azathioprine, cyclophosphamide, thalidomide, and more recently, tumor necrosis factor (TNF)-α inhibitor infliximab. The cytokine, TNF-α, is generated in granulomas, and reports and small case series have shown a treatment response with infliximab in refractory cases of neurosarcoidosis. However, lack of controlled studies demands careful clinical assessment prior to trial of such glucocorticoid-sparing immunosuppressive medications.

Key points

- The etiology of neurosarcoidosis remains unclear.

- Optic and facial nerve dysfunctions are common neurologic manifestations of neurosarcoidosis.

- Definite diagnosis of neurosarcoidosis requires a positive central nervous system biopsy. There is no definitive noninvasive test for establishing a diagnosis of neurosarcoidosis. The CSF angiotensin-converting enzyme (ACE) level is not highly sensitive, and its level can be elevated in other conditions.

- Selection of therapeutic agents ranging from corticosteroids to glucocorticoid-sparing immunosuppressants should be tailored to specific clinical needs.

- Infliximab, a TNF-α inhibitor, has clinical benefit in refractory cases of neurosarcoidosis in small series and case reports.

Historical note and terminology

Sarcoidosis was initially described as a dermatologic disorder. Jonathan Hutchinson, an English physician, examined a patient with purplish, symmetric, nontender skin plaques in 1869 and concluded the condition was a manifestation of gout (Hutchinson 1877). The Norwegian dermatologist, Caesar Peter Moeller Boeck, proposed the term "sarkoid," or sarcoma-like, after detailed histological studies (Boeck 1899). Recognition of the multisystem nature of the disease is generally credited to Jorgen Schaumann, a Swedish dermatologist who in 1936 described involvement of the liver, spleen, lungs, and bone (Schaumann 1936). Involvement of the nervous system was reported perhaps most notably by Christian Frederick Heerfordt (Heerfordt 1909). This Danish ophthalmologist described 3 patients with parotid enlargement, uveitis, and facial nerve palsies in the setting of a febrile illness but attributed the condition to mumps. A retrospective diagnosis of sarcoidosis was given to Maximillien de Robespierre, who died in 1794 (Charlier and Froesch 2013). The diagnosis was based on an examination of his death mask and a historical account of persistent symptoms.

Clinical manifestations

Presentation and course

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Neurologic manifestations may occur in 10%

of patients with sarcoidosis either in addition to systemic sarcoidosis or as an isolated presentation (Bagnato and Stern 2015). Clinically isolated neurosarcoidosis without systemic involvement is extremely rare. Here we discuss the clinical manifestations of neurosarcoidosis.

Cranial nerves. Over 50% of patients with neurosarcoidosis have cranial neuropathy at initial presentation (Carlson et al 2015). There is a poor correlation between cranial nerve involvement on imaging studies and clinical cranial neuropathy. Many patients have imaging findings without clinical manifestation. Zajicek and colleagues reported cranial neuropathies in 72% of 68 patients who were thought "very likely" to have neurosarcoidosis (Zajicek et al 1999). Optic and facial nerves are most commonly involved. Facial nerve dysfunction is 1 of the most common neurologic abnormalities and may occur either in isolation or in combination with other cranial neuropathies. Another series examining 118 cases found facial paresis or palsy in 49% (Colover 1948). Of these, 65% had unilateral involvement. Distinction from idiopathic Bell palsy may be difficult, resulting in diagnostic overlap in some cases. Although the pathophysiology of facial nerve dysfunction remains unclear, pressure injury caused by enlarged parotid glands has been blamed. However, frequent association with hyperacusis, abnormal lacrimation, and taste disturbance suggests more proximal involvement.

The optic nerve is involved in up to 38% of patients suspected of neurosarcoidosis (Zajicek et al 1999). Some studies report optic neuropathy as the most common manifestation, typically presenting with optic disc edema and severe vision loss (Koczman 2008; Carlson et al 2015). Symptoms and signs tend to evolve subacutely and include enlargement of the blind spot, field defect, blurred vision, and pupillary dysfunction. Examination may reveal anterior uveitis, papillitis, papilledema, and optic atrophy. Retrobulbar optic neuritis can mimic a common finding in multiple sclerosis and confuse the diagnostician. Variable mechanisms are responsible for optic nerve dysfunction. Papilledema, which results from increased intracranial pressure, can be caused by hydrocephalus and parenchymal mass lesions; both granulomatous infiltration and direct compression of the nerve can cause optic atrophy. Retinal abnormalities can be seen in up to 60% of patients (Eckstein et al 2012). Nerves controlling extraocular movements are affected less frequently than the optic nerve, with the trochlear least commonly involved. This may in part be due to its origin on the dorsal surface of the brainstem, an area less likely involved by sarcoidosis.

Dysphagia and dysarthria may result from involvement of lower cranial nerves. Compression of the recurrent laryngeal nerve can cause hoarseness and dysphagia. The latter may contribute to aspiration pneumonia, particularly in the setting of compromised bronchi caused by hilar adenopathy.

In a study of 305 patients with neurosarcoidosis, 17% reported subjective hearing loss (Carlson et al 2015). The majority of the patients had a pure sensorineural hearing loss. Vestibular and auditory dysfunction of the 8th nerve can occur independently. Bilateral vestibular dysfunction has also been reported (Smith et al 2011). Isolated involvement of the cranial nerves can at times mimic schwannoma (Bangiyev et al 2015; Lyra et al 2015).

The mechanisms of cranial nerve paresis include epi- and peri-neural inflammation, granulomatous vasculitis that causes ischemia, increased intracranial pressure, or granulomatous basal meningitis (Hoitsma et al 2004; Carlson et al 2015).

Central nervous system. Clinical signs of parenchymal involvement depend on the location and size of the lesions. Granulomas mimicking neoplasms and demyelinating plaques have been found in virtually all regions of the neuraxis. Large or strategically located lesions can cause increased intracranial pressure with headache and papilledema. Seizures of various types are seen in up to 20% of those with intraaxial lesions. A review of nearly 500 cases of neurosarcoidosis revealed that 54 patients developed seizures over the course of their illness. Most of these patients also had associated granulomatous meningitis, which has poorer prognosis. Excluding 3 long-term survivors, overall mean survival was 9 months (Delaney 1980). Another review on 30 patients with neurosarcoidosis and seizures noted that 47% died with a median time to death of 2 years (Sponsler et al 2005). Neurosarcoidosis patients with seizures have a high mortality and morbidity. Presence of hydrocephalus, meningitis, and multifocal disease in these patients is associated with poor outcome. Involvement of basal ganglia, brainstem, cerebellum, and the spinal cord may lead to movement disorder, cranial nerve dysfunction, ataxia, progressive myelopathy, and anterior horn syndrome (Souayah et al 2010; Reda et al 2011). Spinal lesions may be solitary or multiple and can cause back and leg pain, paraparesis, quadriparesis, and sphincter dysfunction. Progressive development of motor dysfunction can even mimic anterior horn syndrome (Souayah et al 2010; Reda et al 2011). Isolated medullary neurosarcoidosis may present with intractable hiccoughs (John et al 2012; Lee et al 2013).

A well-recognized target is the hypothalamic-pituitary axis, characteristically resulting in diabetes insipidus. However, the clinical presentation can range from panhypopituitarism to selective disturbances of anterior or posterior pituitary function. A review of 42 patients revealed central hypogonadism (89%), hypothyroidism (67%), growth hormone deficiency (50%), corticoadrenal insufficiency (49%), diabetes insipidus (65%), and elevated prolactin (49%). Systemic sarcoidosis was present in 80% of these patients (Anthony et al 2016). Sarcoid-related diabetes insipidus is believed to result from direct hypothalamic osmoreceptor destruction, resetting the osmostat. Patients with hypothalamic-pituitary axis neurosarcoidosis can develop optic atrophy due to mass effect or invasion of the optic chiasm. Fundus abnormalities and visual field deficits are seen on examination. Treatment is directed towards replacement of pituitary hormone deficits and control of ophthalmologic symptoms. When starting treatment, it is imperative to monitor both endocrine and neurologic function throughout therapy.

Meningeal involvement, a relatively common finding, may occur in isolation but in its more complicated form may extend along the Virchow-Robin space to enter the brain parenchyma. Infiltration of the meninges is most prominent along the base of the brain. Clinical manifestations include aseptic meningitis, hydrocephalus from obstruction of CSF flow, and cranial neuropathies.

Neuropsychiatric and cognitive dysfunction. Neuropsychiatric disorders are well chronicled and include psychosis, bipolar disorder, depression, amnesic syndrome, dementia, and encephalopathy. Although rare, psychiatric symptoms can be the only presenting symptom (Celebi et al 2013). Occasionally, neuropsychiatric diseases are seen in sarcoid patients without documented central nervous system (CNS) involvement. Patients with neurosarcoidosis can develop cognitive decline due to ongoing inflammation, uncontrolled seizures, polypharmacy, and scarring from granulomatous infiltration (Oh et al 2010). Involvement of frontal or temporal lobe may cause abulia, personality changes, executive dysfunction, aphasia, and seizures.

Vascular involvement. Infiltration may extend to the wall of blood vessels and lead to spontaneous subarachnoid hemorrhage, intraparenchymal hemorrhage, and stroke. However, these events are relatively rare considering the frequent involvement of cerebral arteries with sarcoid granulomas. Cerebral vasculitis due to sarcoidosis is an uncommon entity which can present as stroke, transient ischemic attack, or encephalopathy (Kraemer and Berlit 2010; Macedo et al 2016). Rarely, dural vein thrombosis can present with symptoms of intracranial hypertension (Akova et al 1993; Degardin et al 2010).

Peripheral nerves. Involvement of the peripheral spinal nerves is another well-recognized feature of neurosarcoidosis, but the reported incidence varies. Mononeuritis, which may progress to a multiplex picture, was reported with an incidence of 17% in 1 series (Chapelon et al 1990). The same study found symmetric and often chronic neuropathy in up to 26% of cases. Clinically, patients typically have a mixed sensorimotor deficit, although pure motor and sensory types have been described. The pure motor manifestation may be clinically and electrophysiologically identical to Guillain-Barré syndrome. Polyradiculopathy is another rare finding, which usually presents as proximal leg weakness. Thoracolumbar and lumbosacral nerve roots are more commonly involved as compared to cervical nerve roots. Electromyography shows findings of active denervation consistent with nerve root lesion. Patients may present with solely lower motor neuron findings or a combination of upper and lower motor neuron findings if the spinal cord is also involved (Koffman et al 1999).

Nerve biopsy shows epineurial granulomas, perineurial inflammatory infiltrates with asymmetric involvement of nerve fascicles and axon loss, and occasional endoneurial infiltrates and granulomas. Inflammatory infiltrates are predominantly composed of macrophages and T cells. Granulomas predominate around nerve blood vessels and may cause lymphocytic necrotizing vasculitis (Said et al 2002). The sequence of damage to myelin and axons, which may result from compression and ischemia, is not known. Nerve fiber lesions, which are mainly axonal, are probably related to mechanical compression by noncaseating granulomas or to an ischemic process due to vasculitis. Cytokines and immune factors may also play a role, especially in certain cases with a clinical presentation of chronic inflammatory demyelinating polyneuropathy (Vital et al 2008).

Muscle. Muscle may be affected alone or in combination with nerves. Reports of symptomatic muscle problems range from less than 1% up to 26% (Oksanen 1986; Chapelon et al 1990). In a series of 11 patients with biopsy-proven sarcoid neuropathy, characteristic noncaseating sarcoid granulomas were found in 9 patients. In 2 of these patients, muscle granulomas were associated with necrotizing vasculitis (Said et al 2002). Common presentations of sarcoid myopathy include symmetric proximal weakness of the limbs, muscle soreness and stiffness, and occasionally palpable nodules. However, asymptomatic granulomatous involvement of muscle may occur in as many as 50% of

sarcoid patients. Care is necessary to prevent further muscle dysfunction caused by relatively common medications such as HMG-CoA reductase inhibitors (statins) and corticosteroids.

Prognosis and complications

The prognosis for neurosarcoidosis is highly variable. The condition may take the form of a monophasic illness with or without recovery, a relapsing-remitting course, or a progressively deteriorating course. Although attempts to prognosticate on the basis of particular clinical features have been largely unsuccessful, involvement of the peripheral nervous system appears to predict a more favorable outcome compared to those with CNS disease, eg, symptoms referable to the spinal cord and seizures (Zajicek et al 1999; Ferriby et al 2001). Approximately one third of patients experience progressive disease with considerable morbidity and mortality (Pentland et al 1985). Patients with neurosarcoidosis may be more susceptible to infections, as a result of impaired swallowing and micturition, and relative immobility. Progressive multifocal leukoencephalopathy can appear in patients with sarcoidosis (Jamilloux et al 2014). A report of 10 cases, 8 of which were men, describes young patients with mild CD4 lymphopenia.

Clinical vignette

Case report. A 45-year-old woman with a history of major depressive disorder presented with word finding difficulty, gait imbalance, and burning pain in the lateral thighs. Her neurologic examination was notable for impaired concentration, inattention, right arm drift, right hip flexor weakness, decreased sensation to light touch on the right lateral thigh, diffuse symmetric hyperreflexia in upper and lower extremities, impaired finger-to-nose in left arm, and gait ataxia. Brain MRI with and without contrast showed numerous T2 and FLAIR lesions in white matter, some of which showed enhancement. Differential diagnosis based on imaging included multiple sclerosis, Sjögren syndrome, systemic lupus erythematosus, progressive multifocal leukoencephalopathy, acquired immune deficiency syndrome, encephalitis, lymphoma, and neurosarcoidosis. Human immunodeficiency virus, antinuclear antibodies, Anti-Ro, and Anti-La were negative. C-reactive protein (CRP) and sedimentation rate were elevated. Serum angiotensin converting enzyme (ACE) was elevated at 132 U/L. Chest radiograph revealed hilar lymphadenopathy. Computed tomography of chest showed extensive mediastinal and hilar lymphadenopathy. Fine needle aspiration tissue biopsy of a mediastinal lymph node revealed noncaseating granulomas without any pathogens. The patient was rendered a diagnosis of probable neurosarcoidosis. She was treated with prednisone and azathioprine. Three months later, she was admitted for vertigo, headache, and bilateral hand tremor. Brain and spine MRI showed multiple new small nonenhancing lesions and improvement of previous contrast-enhancing lesions. She was discharged on a higher dose of steroid and azathioprine. A month later, azathioprine was discontinued due to elevated liver enzymes and she was switched to mycophenolate mofetil. Six months after initial diagnosis, her symptoms improved and prednisone was tapered off. She was continued on mycophenolate mofetil monotherapy.

Biological basis

Etiology and pathogenesis

The cause of sarcoidosis has yet to be identified. One possibility is exposure of a genetically predisposed population to a specific environmental agent, as has been proposed for multiple sclerosis. Expansion of T cells with a restricted receptor usage may reflect a response to specific antigens. Proposed agents, ranging from infectious to noninfectious, include a variety of viruses (including human herpesvirus 8), *Borrelia, Mycobacteria, Mycoplasma, Propionibacterium* acnes, aluminum, zirconium, talc, and pine tree pollen (Ebe et al 2000; Müller-Quernheim et al 2012). In addition, certain proto-oncogenes are overexpressed in granuloma-derived cells (Fireman and Topilsky 1994). The World Trade Center Health Registry identified 43 cases of post-9/11 sarcoidosis. Working on debris pile, firefighting, and hand digging were associated with sarcoidosis (Jordan et al 2011).

These hypotheses on the pathogenesis of sarcoidosis derive mainly from the pulmonary literature. The brain's status as an immunologically privileged organ may render it less susceptible to the formation of sarcoid granulomas, which possibly accounts for the low incidence of neurosarcoidosis. Specific anatomic and functional barriers to immune responses in the CNS as well as differences in matrix properties could account for this.

Why the nervous system is only occasionally affected and why it is targeted at all remain speculative.

Immunopathogenesis. Although the inciting antigenic stimulus remains elusive, sarcoidosis is characterized by overt Th1/Th17 bias, and a compartmentalization of CD4+ lymphocytes and activated macrophages in involved organs

(Facco et al 2011). Granulomas are formed as a reaction to confine pathogens and restrict inflammation when an antigen cannot be degraded by macrophages. Sarcoid granulomas are compact structured collections of macrophages and macrophage-derived epithelioid cells encircled by lymphocytes. The central part of a granuloma is composed of macrophages, epithelioid cells, plasma cells, multinucleated giant cells, and a large number of CD4+ T lymphocytes. The periphery of granuloma is composed of CD8+ T lymphocytes, CD4+ T lymphocytes, fibroblasts, fibrocytes, some macrophages, and occasionally collagen. Although caseous necrosis is absent, central necrosis presenting as a granular acidophilic area without a nuclear debris and a positive periodic acid Schiff reaction may be seen (Kosjerina et a 2012). The formation of granuloma is initiated by CD4+ T cells when they interact with antigen-presenting cells. Th1 cytokines such as interleukin 2 (IL-2), interferon-γ (IFN-γ), and macrophage-derived molecules like IL-15, CXCL10, CXCL16, CCL10, and CCL20 are involved in the early phase of sarcoid pathogenesis. Th17 cells and their proinflammatory molecules (IL-6, TNF-α) play an effector role in granuloma formation in early phase and aid in disease progression to the fibrotic phase (Iannuzzi et al 2007; Facco et al 2011). Regulatory T cells in sarcoidosis are increased in number; nevertheless, they exhibit poor suppressive capacity (Oswald-Richter 2013). The granulomas are a source of angiotensin-converting enzyme.

Activation of humoral immunity is well known, likely reflecting nonspecific polyclonal activation by neighboring T lymphocytes; its contribution to the pathogenesis of the disease is less clear. B lymphocytes are very rare in a granuloma. Levels of antiendothelial cell antibodies in serum and bronchoalveolar lavage of sarcoid patients may become an important tool for evaluation of extent and progression of disease (Inui 2008).

Genetics. Sarcoidosis presents with protean manifestations and a highly variable disease course. This is explained by interplay between genetic variations and environmental triggers, which cause an aberrant immune response. Genetic epidemiologic research using familial linkage, familial aggregation, candidate gene, and genome-wide association studies reveals that sarcoidosis is not due to mutation in a single gene or immune pathway. Scores of genes each contribute a small effect and drive the disease phenotype.

The human leukocyte antigen (HLA) region, which is pivotal to immune response and regulation, is the most strongly associated genetic risk for sarcoidosis. The suspected role of major histocompatibility complex haplotype in sarcoid susceptibility remains without definitive proof. Studies have suggested a link with specific major histocompatibility complex haplotypes, eg, HLA-DRB1 is most common in Swedish, Dutch, United Kingdom, and Spanish cohorts. Also, HLA-DQB1 has been reported in white United Kingdom and Dutch populations (Fingerlin et al 2015). HLA-DRB1*1101 is significantly associated with sarcoidosis in both African American and European American cohorts. HLA-DRB1*0401 is protective for blacks and whites (Rossman et al 2003). In Sweden, genetic testing for HLA-DRB1*0301 is being used to determine risk of progression versus remission (Fingerlin et al 2015). Currently, there are no similar recommended genetic tests to investigate genetic risk and guide practice in the United States.

Epidemiology"

Epidemiologic studies of sarcoidosis, and in particular neurosarcoidosis, face many challenges. First, data are subject to errors due to lack of a definitive diagnostic test for the disorder. In addition, the disorder is often asymptomatic. Also, large studies are hampered by inconsistent regional definitions of the disorder. Because most available data for epidemiology of neurosarcoidosis are extrapolated from that of systemic sarcoidosis, the following discussion should be interpreted realizing these limitations.

Though found worldwide, sarcoidosis is far more common in northern Europe and North America than it is in southern Europe, South America, Africa, or southern Asia (Sharma 1990). In the United States the annual incidence of sarcoidosis is 10.5 per 100,000 population in women and 9.4 per 100,000 population in men (Ungprasert et al 2016). In the United states there is an increased annual age-adjusted incidence of sarcoidosis in African Americans with an incidence rate of 35.5 per 100,000 compared to Caucasians with an incidence rate of 10.9 per 100,000 (Rybicki et al 1997). Women were at greater risk, particularly African-American women. Disease features are also affected by race. African Americans tend to have a more extensive disease than Caucasians and manifest more extrapulmonary sarcoidosis, affecting skin, bone marrow, eyes, and multiorgan damage, plus have more hospitalizations (Rybicki et al 1997). In a study reviewing sarcoidosis-related mortality over a period of 12 years, the mortality rate for African Americans was 12 times higher than for Caucasians (Mirsaeidi et al 2015). The Japanese may have more cardiac and ocular manifestations than other ethnic groups (Iwai et al 1993).

The peak incidence of sarcoidosis occurs in the 2nd to 3rd decades. Japanese and African-American women over 40

years of age show a second peak in incidence. In a retrospective case series of biopsy proven neuroophthalmic sarcoidosis, patients were predominately white females with a wide age range (Koczman 2008).

Isolated involvement of the nervous system without systemic sarcoid is exceedingly rare. In most cases thought to be isolated neurosarcoidosis, careful search usually reveals some systemic involvement. However, there are occasional reports of isolated involvement of the central nervous systems without evidence for activity in the systemic organs, including those restricted only to the spinal cord (Terada et al 2010; Wegener et al 2015).

Prevention

No preventive measures have been identified. In rare cases, use of TNF-α inhibitors in treatment of other autoimmune diseases can paradoxically cause new-onset sarcoidosis (Tong et al 2012; Durel et al 2013). Scattered reports have cited clustering of systemic sarcoidosis and possible transmission by transplantation, but firm evidence is lacking (Heyll et al 1994). Gastroenterology literature has cited reports of sporadic cases of possibly reversible sarcoidosis induced by exposure to interferon-α in those treated for hepatitis C (Gitlin 2002; Nawras et al 2002). Although the role of interferon-α in genesis and exacerbation of certain autoimmune disorders is well known, these claims need to be carefully assessed, particularly in light of Bonnet and colleagues' description of spontaneous development of sarcoidosis in 2 untreated patients with hepatitis C (Bonnet et al 2002). Epidemiologic studies have revealed ethnic differences in incidence and severity of the disease as outlined above. Genetic studies on patients with sarcoidosis show several immune-mediated loci that are shared between rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, psoriasis, systemic lupus erythematosus, Sjögren syndrome, and Crohn disease (Fingerlin et al 2015).

Differential diagnosis

The differential diagnosis of neurosarcoidosis depends on the clinical presentation. Meningeal involvement demands consideration of infectious and neoplastic meningitides, meningioma, leukemic infiltration, meningeal lymphoma, and meningeal plasmacytoma. If the lesion involves brain parenchyma, the differential diagnosis must be broadened to include multiple sclerosis, progressive multifocal leukoencephalopathy, leukodystrophy, CNS vasculitis, primary CNS angitis, CNS lupus, Sjögren syndrome-related vasculitis, Behcet disease, CNS lymphoma, glioma, neurotuberculosis, fungal infections, CNS Whipple disease, neurosyphilis, and neuroborreliosis. If lesions present in the spinal cord, differential diagnoses to be considered are multiple sclerosis, neuromyelitis optica, lymphoma, glioma, and tuberculoma. If there is involvement of spinal nerve roots or cauda equina, diagnoses of cauda equine lymphoma, systemic metastasis, arachnoiditis, Guillain-Barré syndrome, tuberculosis, cryptococcal granulomata, and toxoplasmosis should be considered.

Diagnostic workup

Definitive diagnosis of neurosarcoidosis requires the fulfillment of 3 conditions: consistent clinical history, demonstration of noncaseating granulomas affecting the nervous system, and exclusion of other conditions capable of producing noncaseating granulomas. A probable diagnosis of neurosarcoidosis can be made when there is a clinical syndrome consistent with neurosarcoidosis with laboratory support for CNS inflammation (MRI findings, elevated proteins, cells, or oligoclonal bands in CSF), exclusion of alternative diagnoses, and evidence of systemic sarcoidosis. A possible diagnosis of neurosarcoidosis is made when there is clinical presentation suggestive of neurosarcoidosis, exclusion of alternative diagnoses, but other criteria as above are not met (Zajicek et al 1999).

To reiterate, isolated cases of neurosarcoidosis are extremely rare, therefore diagnostic effort should begin with noninvasive tests in a quest to identify systemic sarcoidosis. A careful history should be taken to exclude infections and other granulomatous diseases mimicking sarcoidosis. In particular, tuberculosis and occupational health-exposure granulomatous diseases should be excluded. When CNS or peripheral nerve lesions are suspected due to sarcoidosis, a basic work-up starts with MR imaging of neuroaxis to evaluate the extent of involvement. Brain parenchymal lesions often appear as ill-defined areas of increased or reduced densities on CT scan. The MRI characteristics of these lesions can also vary, but most usually are hyperintense on T2-weighted images. The classic presentation of linear enhancement of the thickened meninges and focal nodular enhancement of the parenchymal lesions is a helpful diagnostic clue (Osborn 1994). Contrasted cranial MRI frequently shows pathologic enhancement of the visual pathway (Koczman 2008). Diffuse parenchymal involvement can mimic gliomatosis cerebri (Ramanathan 2013).

Supporting evidence for systemic sarcoidosis should be gathered with posteroanterior chest radiograph, serum

angiotensin converting enzyme, liver function test, serum protein electrophoresis, serum calcium, and urine calcium. Patients may have elevated serum ACE levels and increased serum and urinary calcium due to overproduction of vitamin D by the granulomas. Elevated CRP and sedimentation rate may be found in some patients and provide nonspecific measures of inflammation. Tuberculosis should be ruled out using tuberculin skin testing or an interferon-γ release assay. If chest radiograph is normal, further evidence can be gathered using high resolution CT of the chest. If suspicion of neurosarcoidosis is high and no accessible regions for biopsy are identified, Gallium 67 scan or fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to identify occult disease and to assess inflammatory activity. Both techniques have low specificity and their use should be decided on a case-by-case basis. The Kveim-Siltzbach procedure, which is rarely performed in the United States, consists of intradermal injection of heat-treated homogenate derived from sarcoid tissue. Development of a noncaseating granuloma at the injection site constitutes a positive response, but the sensitivity is limited.

Along with systemic work-up, evidence should be gathered for laboratory support of CSF inflammation by a lumbar puncture in all suspected cases of neurosarcoidosis. The majority of patients, in particular those with meningeal involvement, have a mononuclear pleocytosis ranging from 10 to 100 cells/mm3. The protein concentration may be as high as 200 mg/dl, glucose as low as 30 mg/dl, and the opening pressure may be increased (Pentland et al 1985). An elevated CSF IgG index is observed in many patients and oligoclonal bands may be present. CSF angiotensin-converting enzyme may be elevated, and shows a 24% to 67% sensitivity and 67% to 95% specificity (Dale and O'Brien 1999; Bridel et al 2015). However, ACE levels should be interpreted with caution because CNS infection and tumor may also increase the enzyme level. The low sensitivity and the false positive rate of CSF ACE levels often make it an unhelpful test (Aksamit 2008). There is no parallel between serum and CSF ACE level and ACE, which suggests intrathecal synthesis of ACE rather than passive transfer from serum (Pawate et al 2009). A report by Petereit and colleagues suggests that elevated level of soluble CSF interleukin-2 receptor (sIL2-R), a marker of T-cell activation, may distinguish neurosarcoidosis from other inflammatory disorders of the CNS. Elevation of sIL2-R above 150 pg/mL in the CSF identified neurosarcoidosis with a sensitivity of 61% and a specificity of 93% (Petereit et al 2010). In another study, sIL2-R was elevated in 4 out of 7 patients (Wegener et al 2015). The availability of CSF sIL2-R testing in United States is very limited.

If systemic lesions are present at an accessible site a biopsy may be performed to demonstrate the noncaseating granulomas. Areas of abnormality on an imaging study such as the Gallium 67 scan or PET should be targeted (Meenakshi et al 2012). If inaccessible, the distribution of sarcoid involvement should dictate the area of interest. Commonly targeted tissues include transbronchial lung, muscle, skin, lip, or an easily accessible lymph node. The best bet for a blind biopsy is of the conjunctiva. It has a negligible complication rate, moderate yield, and may be positive despite absence of eye findings. Bilateral conjunctival biopsy increases the sensitivity (Leavitt and Campbell 1998). Brain lesions in a patient with systemic sarcoidosis should not be assumed to be secondary to neurosarcoidosis until proven. In ideal circumstances, biopsy of nervous tissue is recommended. If biopsy of nervous tissue is not feasible due to risk or inaccessibility, then diagnosis of neurosarcoidosis should be made using a combination of neuroimaging, laboratory evidence of CNS inflammation, and supporting evidence of systemic sarcoidosis.

Electrical studies such as electromyography, nerve conduction velocity testing, visual evoked potentials, and brainstem auditory evoked potentials may be of use in the appropriate setting. The diagnostic value of steroid responsiveness is dubious when other disorders such as lymphoma, multiple sclerosis, and vasculitis are in the differential.

Management

Treatment of neurosarcoidosis for the most part consists of immunosuppression and is largely adopted from the pulmonary experience. Various modalities are routinely employed, but a controlled trial has yet to be performed.

Corticosteroid administered in various schedules is the standard therapy. Oral prednisone from 40 to 80 mg/day is generally sufficient to gain control of the disease and reverse symptoms. If successful in controlling the disease, prednisone can later be tapered to a lower dose. In severe cases of neurosarcoidosis or with acute presentation, intravenous methylprednisolone may be administered. The recommended time of treatment ranges from months to years and should be decided on a case-by-case basis. Those with intractable cases or dependence on high doses of chronic steroids may benefit from other classes of drugs (Scott 2007).

Chloroquine demonstrated efficacy in a controlled trial of pulmonary sarcoid (Baltzan et al 1999). Serial

ophthalmologic examination is recommended due to its association with retinopathy. Hydroxychloroquine is preferred over chloroquine due to lesser retinal toxicity, its beneficial effect of suppression of gluconeogenesis, prevention of insulin degradation in liver, and increase in peripheral utilization of glucose. It is of value in treating patients with hyperglycemia due to corticosteroids and in insulin-dependent diabetes (Sharma 1998).

Cyclosporine inhibits CD4+ T cell immune response and IL-2 release and interferes with the phosphatase activity of calcineurin. Several authors have reported success with low doses (4 to 6 mg/kg per day) of cyclosporine; steroid-dependent patients with neurosarcoidosis were able to substantially reduce the dose of steroids (Chapelon et al 1990; Stern et al 1992). In an open-label study on 6 patients with refractory neurosarcoidosis who received cyclosporine, corticosteroid dose could be decreased to 30% to 58% of the initial stabilization dose in combination therapy with cyclosporine. Four patients deteriorated while on treatment with corticosteroid and cyclosporine (Stern 1992). Due to the small number of patients, lack of a control group, and the patient selection of refractory cases, it is difficult to ascertain the clinical benefit of cyclosporine.

Methotrexate, an antimetabolite, can also stabilize symptoms (Chapelon et al 1990). One patient with suprasellar disease responded to cladribine (2-chlorodeoxyadenosine), a purine analog used in the treatment of hairy cell leukemia (Tikoo et al 2004). Early use of cladribine may be indicated in steroid-refractory cases (Bhagwan et al 2015). Cyclophosphamide is a mustard-alkylating agent which may be used in patients with refractory neurosarcoidosis. A study reported symptomatic improvement in 4 of 7 patients with refractory neurosarcoidosis treated with intravenous cyclophosphamide. One patient experienced complete remission (Doty et al 2003). Because of significant toxicity it is usually reserved after other second-line options have failed. Therapeutic use for the remaining immunomodulators, such as azathioprine, intravenous immunoglobulin, chlorambucil, and mycophenolate mofetil may prove worthwhile in appropriate cases (Zajicek et al 1999; Chaussenot 2007; Moravan and Segal 2009; Androdias et al 2011; Shenoy et al 2015).

Targeted therapy to a more specific component of the immune response is illustrated by promising effects of infliximab, a chimeric IgG monoclonal antibody directed against TNF-α, and thalidomide, an agent reputed to attenuate release of TNF-α. TNF-α plays a pivotal role in triggering and maintaining inflammation in neurosarcoidosis and elevated levels of TNF-α are found in lymph nodes and bronchoalveolar lavage in patients (Bagnato and Stern 2015). Infliximab, adalimumab, and etanercept are 3 anti-TNF-α chimeric antibodies. Of these 3, infliximab is the most explored agent in neurosarcoidosis. Anecdotal reports of infliximab use in neurosarcoidosis exist with promising results (Yee and Pochapin 2001; Pettersen 2002; Katz 2003; Kumar 2007; Toth 2007; Pereira et al 2011; Lorentzen et al 2014). Relapses after discontinuation of treatment with anti-TNF-α antibodies are reported, which warrant a close follow-up of patients after treatment is stopped. A multicenter study of 138 patients with chronic pulmonary sarcoidosis treated with infliximab showed a statistically significant improvement in forced vital capacity after 24 weeks of therapy, the primary endpoint of the study (Baughman et al 2006). Thalidomide has successfully treated refractory neurosarcoidosis (Hammond 2007; Hoyle 2008), but placebo-controlled trials are lacking.

The National Heart, Lung, and Blood Institute investigated the use of pentoxifylline, a xanthine derivative known to inhibit TNF-α release by peripheral blood mononuclear cells, as an adjunct to steroid therapy in systemic sarcoidosis (Park et al 2009). Although pentoxifylline reduced flares, its use was limited by gastrointestinal side effects.

Nonpharmacologic strategies include brain radiotherapy for drug-resistant disease (Motta et al 2008) and surgical approaches. Neurosurgical intervention is directed at relieving hydrocephalus by insertion of shunt and excision of large, accessible parenchymal lesions. Remaining management issues relate to controlling seizures, correcting endocrine abnormalities when necessary, and neuropsychiatric therapy.

Outcomes

A retrospective review of 54 patients of neurosarcoidosis with a follow up period of 5 ± 4.4 years showed that maintenance immunosuppression was needed in 72% of patients. Comparable efficacy was found between long-term use of methotrexate, mycophenolate mofetil, and azathioprine. Patients who presented with bilateral optic neuropathy had a poor visual prognosis. Unilateral optic neuropathy recovered better; 5 of 6 patients achieved a visual acuity of 20 over 30 or better. Patients with myelopathy either had improvement in symptoms or stabilization. Patients with seizures due to intracranial lesions maintained seizure control on immunosuppressants and antiepileptic medications. Patients with extensive parenchymal or meningeal involvement had poor outcomes (Pawate et al 2009). In an earlier study on 68 patients with an average follow-up of 4.6 years, those presenting with spinal cord manifestation had a

poorer prognosis and deteriorated in over 70% cases. In patients who presented with impaired visual acuity, less than half recovered their visual function (Zajicek et al 1999). It is suggested that disease manifesting as myelopathy, extensive parenchymal or meningeal involvement, or bilateral optic neuropathy has a worse prognosis than facial nerve palsies.

Treatment of the disease may cause complications. Chronic steroid use is associated with Cushing syndrome, glaucoma, cataracts, osteoporosis, diabetes, myopathy, gastric irritation, hypertension, and immunosuppression. Symptoms tend to recur in many cases at doses of prednisolone less than 20 to 25 mg/day or its other corticosteroid equivalent. Other forms of treatment such as irradiation, methotrexate, and cyclosporine are well-characterized neurotoxic agents. Methotrexate may cause anemia, neutropenia, hepatic dysfunction, and pneumonitis. Cyclophosphamide may cause cystitis and neutropenia. Cyclosporine can lead to renal failure and hypertension. Azathioprine and mycophenolate mofetil can cause hepatotoxicity, anemia, and neutropenia (Hoitsma et al 2004). Hydroxychloroquine can lead to retinotoxicity, ototoxicity, myopathy, neuropathy, and cardiomyopathy. Routine eye examinations must be scheduled during treatment. TNF-α inhibitor infliximab can cause severe demyelinating disease in central or peripheral nervous system. Another TNF-α chimeric antibody, adalimumab, may rarely trigger severe peripheral neuropathy (Bagnato and Stern 2015).

Special considerations

Pregnancy

There are no known adverse effects on pregnancy. As with many other Th1 immune-mediated diseases, including multiple sclerosis and rheumatoid arthritis, pregnancy is associated with a decrease in disease-related symptoms. The effect is transient with occasional exacerbation reported after parturition (Sharma 1990).

Anesthesia

There are no specific anesthetic risks regarding sarcoidosis in general or neurosarcoidosis in particular. Sarcoid-related clinical manifestations, such as thermal dysregulation, pulmonary dysfunction, and seizures, need to be considered on a case-by-case basis.

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**References especially recommended by the author or editor for general reading.

Former authors

Kelley Nicholas MD PhD (original author), Anna Delios MD, and Chelsea Gloeckner MD

ICD and OMIM codes

ICD codes

ICD-9:

Sarcoidosis: 135

ICD-10:
Sarcoidosis, unspecified: D86.9

OMIM numbers

Sarcoidosis: #181000

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

female>male

Family history

family history may be obtained

Heredity

heredity may be a contributing factor

Population groups selectively affected

African Americans
Japanese
Northern Europeans

Occupation groups selectively affected

Post 9/11 firefighters and rescue workers

Differential diagnosis list

infectious meningitides
neoplastic meningitides
meningioma
leukemic infiltration
meningeal lymphoma
meningeal plasmacytoma
primary tumors
metastatic tumors
abscesses
multiple sclerosis
other demyelinating diseases
progressive multifocal leukoencephalopathy
leukodystrophies
CNS vasculitis

primary CNS angitis
CNS lupus
Sjögren syndrome-related vasculitis
Behcet disease
CNS lymphoma
glioma
neurotuberculosis
fungal infections
CNS Whipple disease
neurosyphilis
neuroborreliosis
neuromyelitis optica
lymphoma
tuberculoma
cauda equine lymphoma
systemic metastasis
arachnoiditis
Guillain-Barré syndrome
tuberculosis
cryptococcal granulomata
toxoplasmosis

Associated disorders

Bell palsy
Guillain-Barre syndrome

Other topics to consider

Acute inflammatory demyelinating polyradiculoneuropathy
Bell palsy
Cerebral vasculitis presenting with dementia
Sarcoid neuropathy