SMGroup

Neurosarcoidosis

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Published Date: March 10, 2016

INTRODUCTION AND EPIDEMIOLOGY

Sarcoidosis is an inflammatory granulomatous disease that can affect multiple organ systems, most commonly affecting the lungs, lymph nodes, eyes and skin. It can also affect other organs including the nervous system. Although the exact etiology of sarcoidosis is unknown, it involves the development of noncaseating granulomas in various organs. Noncaseating epithelioid granulomas are the pathological hallmarks of sarcoidosis and symbolize the inflammatory sign of the disease.

There exists some inherent difficulty in providing accurate estimates of sarcoidosis as there is variation in definition and absolute diagnosis without biopsy is problematic. Worldwide incidence of sarcoidosis in all races occurs with an average incidence of 16.5 per 100,000 in men and 19 per 100,000 in women. The disease is most common in Northern European countries (including people of Scandinavian and Icelandic descent). The highest annual incidence is in Sweden and Iceland where it occurs in 60 per 100,000 people. In the United States, sarcoidosis

is more common in African-Americans than Caucasians, with annual incidence of 35.5 and 10.9 per 100,000 respectively [1,2]. Sarcoidosis has a bimodal age distribution as it often affects young adults during the second and third decades, however there is a second peak for women over age 50 [2]. In the United States, the lifetime risk of developing sarcoidosis is 2.4% in African-Americans and 0.85% in Caucasians.

Sarcoidosis affects multiple organ systems, most commonly the lungs, in up to 90% of patients and the nervous system in 5-15% of patients [3,5]. The occurrence of neurosarcoidosis has been reported to be as high as 25% on autopsy in postmortem patients. Isolated neurosarcoidosis without systemic involvement only occurs in about 1% of patients [4].

The diagnosis of neurosarcoidosis is often challenging, and requires an array of compatible clinical findings supported by histologic findings of noncaseating granulomas and important laboratory results which have more specificity and sensitivity. Neurosarcoidosis is also a diagnosis of exclusion given its clinical presentation which may mimic other infectious diseases (like tuberculosis), demyelinating diseases (like multiple sclerosis), neoplasms and connective tissue diseases [6]. Although biopsy of neural tissue is the gold standard for the diagnosis of neurosarcoidosis, this is often not practical and the diagnosis must be inferred through other tests, often coupled with biopsy of extraneural organs.

Neurologic complications occur in approximately 5 to 13% of patients with sarcoidosis [7-10]. Neurosarcoidosis is a diagnostic consideration in patients with known sarcoidosis who also develop neurological complaints and in patients presenting de novo with a constellation of find ings consistent with the disease. Approximately 50% of patients with neurosarcoidosis present with neurologic difficulties at the time sarcoidosis is first diagnosed. One-third of those with neurosarcoidosis has or develops more than one neurologic manifestation of their disease. Neurosarcoidosis is caused by inflammation and abnormal cell deposits in the central and/or peripheral nervous system, including the brain, spinal cord, or peripheral nerves. The spectrum of clinical manifestations of neurosarcoidosis extends to various components of the nervous system including cranial nerves, meninges, spinal cord, brain parenchyma (especially the hypothalamic-pituitary axis), vascular system, peripheral nerves, muscles, and includes psychiatric symptoms.

In this review, we intend to give a brief overview of the epidemiology, pathogenesis, and common neurologic manifestations of sarcoidosis, and discuss the diagnosis including diagnostic tests and diagnostic criteria, therapeutic approaches and prognostic considerations.

ETIOLOGY AND PATHOGENESIS

The central nervous system is vulnerable to the disease as granulomatous inflammation, which typically occurs in lymph nodes and more commonly in the lungs, can extend to the nervous tissue through Virchow-Robin spaces. It has a tendency to involve the meninges, particularly the dura, nerve pathways, the brain and the spinal cord.

Neurosarcoidosis can present with cranial neuropathies, endocrinopathy and tract involvement. Imaging can reveal abnormalities that may be confused for multiple sclerosis. It is important to evaluate and rule out other disease processes through clinical evaluation, radiographic imaging, CSF analysis and biopsy if plausible. The neurological symptoms can include encephalopathy, seizures, meningitis, neuro-endocrinopathy and myelopathy. Careful evaluation for neurological complications of sarcoidosis is important, and in some cases the neurological presentation can precede systemic diagnosis.

CLINICAL MANIFESTATIONS OF NEUROSARCOIDOSIS

Onset of neurosarcoidosis is most common in the fourth or fifth decades, and typically occurs after patients have had systemic symptoms for some time.

Sarcoidosis of Cranial Nerves

Cranial mononeuropathies frequently occur in neurosarcoidosis. In 2009, Joseph and Scolding conducted a study of 30 new cases of sarcoidosis, and reported cranial neuropathies in 80% of the patients. Cranial nerve (CN) VII is the most common to be involved and was seen in 23% of patients [13]. Isolated Bell's palsy may be the first manifestation of sarcoidosis, resolving prior to the development of additional symptoms. The facial nerve palsy can be unilateral or bilateral (simultaneous or sequential) and recurrent [9]. Facial nerve palsy from sarcoidosis has been thought to result from inflammation in the parotid gland, but may also arise from basilar meningitis, and some cases can be attributed to granulomatous inflammation of the extracranial part of the nerve [14]. Symptoms are usually self-limited and tend to resolve within a few weeks without leaving residual deficits in the majority of cases [22]. Occasionally, patients may present with the rare Heerfordt syndrome, characterized by fever, uveitis, parotid gland swelling, and facial nerve palsy [20].

Another common cranial neuropathy is optic neuritis (CN II) which usually presents with unilateral involvement; bilateral disease is uncommon but predicts poor prognosis [13]. Patients present with blurry vision, retrobulbar ocular pain, papilledema and pupillary abnormalities. Involvement of the Vestibulocochlear nerve (CN VIII) causes vertigo and unilateral, more often than bilateral, acute sensorineural hearing loss. Bilateral involvement, when present, is highly suggestive of neurosarcoidosis [15]. Extraocular movements can become impaired due to involvement of CN III, CN IV, and/or CN VI. Olfactory involvement is rare, but has been reported in some cases, leading to anosmia and impaired taste. Hence, both isolated or multiple cranial nerve involvement may be seen with sarcoidosis [9]. In general, isolated cranial neuropathies present acutely and resolve, whereas multiple cranial neuropathies usually have a chronic course [16].

Sarcoidosis of Neuroendocrine System

Neuroendocrine dysfunction typically occurs with granulomatous infiltration into the hypothalamo-hypophysial region, resulting in polyuria, disturbances in thirst, morbid obesity

from sarcoid invasion into the satiety center, insomnia, complete loss of the counter-regulatory response to hypoglycemia, change in libido and marked personality changes [18,19]. Direct hypothalamic involvement can lead to central diabetes insipidus or primary polydipsia, while hypercalcemia (due to production of calcitriol by activated macrophages) can cause nephrogenic diabetes insipidus [20]. Thus, patients with sarcoidosis and polyuria may require a water restriction test to establish the correct diagnosis.

Sarcoidosis of Meninges

Neurosarcoidosis has a predilection to infiltrate the meninges and can cause aseptic meningitis. Meningeal involvement can take the form of either acute aseptic meningitis or chronic meningitis. Its clinical manifestations are similar to other causes of meningitis, including fever, headache and rigid neck [21]. Seizures, cognitive and behavioral problems, along with focal neurologic deficits can occur. Examination of the cerebrospinal fluid typically shows mononuclear leukocytosis and elevated proteins. Aseptic meningitis usually presents acutely [16], and usually has a good prognosis, even if it recurs [9]. However, chronic persistent meningitis may develop and usually requires long-term therapy [21]. One of the important differentials in the setting of chronic corticosteroid therapy is cryptococcal meningitis which may have a similar presentation [41]. Hydrocephalus can be seen in almost one third of neurosarcoidosis patients [9,39,40]. Whereas impaired CSF absorption from arachnoidal granulations and associated possible elevated secretion leads to communicating hydrocephalus, granulomas obstructing either the aqueduct of Sylvius or outlets of the fourth ventricle cause noncommunicating hydrocephalus [9,71]. Asymptomatic ventricular enlargement may be incidentally detected by imaging studies. Sudden death can rarely result from acute obstruction to CSF flow and neurological deterioration can follow a Lumbar Puncture. Meningeal mass lesions also can develop and may be mistaken for meningiomas [15].

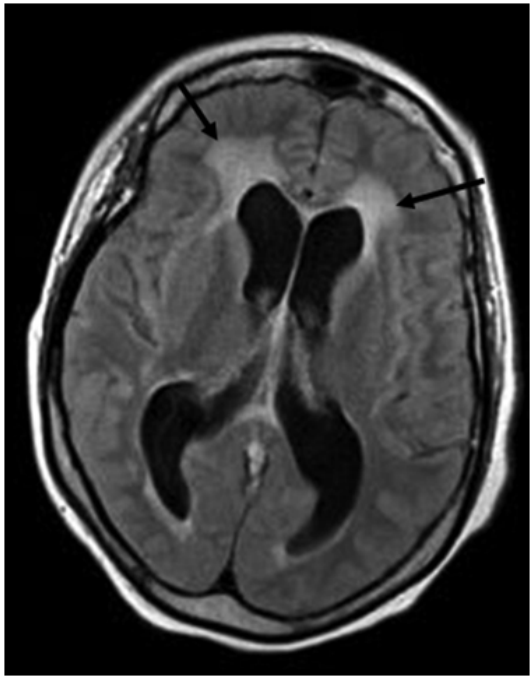

Figure 1: Hydrocephalus and abnormal T2/FLAIR signal in a patient with neurosarcoidosis. Axial FLAIR image demonstrates enlargement of the lateral ventricles and confluent areas of abnormal signal in the periventricular white matter reflecting transependymal CSF flow (arrows) [21].

Image produced from: Vitaly Terushkin, BS, New York University School of Medicine, 550 First Ave, New York, NY 10016. E-mail: vt382@nyumc.org. Copyright © 2010 by Lippincott Williams & Wilkins ISSN: 1074-7931/10/1601-0002 DOI: 10.1097/NRL.0b013e3181c92a72. [21].

Sarcoidosis of Peripheral Nerves and Muscles

Peripheral neuropathic presentations include mononeuropathy, mononeuritis multiplex, and generalized sensory, small fiber sensory, sensorimotor, motor and autonomic polyneuropathies. The symptoms can be acute, subacute, or chronic; electromyography usually reveals an axonal neuropathy. Sensory deficits are more common than motor abnormalities. The pathologic process is focal or multifocal and involves most classes of nerve fibers from nerve roots to peripheral nerves. An acute generalized demyelinating sensori-motor neuropathy similar to Guillain-Barré syndrome also has been described [25]. Chronic pain is one of the most common neuropathic symptoms in neurosarcoidosis patients. Small fiber neuropathy is thought to be a cause of this pain. It may also cause autonomic disturbances including cardiac sympathetic dysfunction [26,27]. Nerve biopsy typically shows noncaseating granulomas, but necrotizing vasculitis of the Vasa Nervorum may also be seen. Additionally, carpal tunnel syndrome appears to be more common among patients with sarcoidosis than the general population [26-28].

Muscle involvement is commonly seen, and is typically secondary to granulomas in the perimysium; however, only a very small number of patients are actually symptomatic. Onset of myopathy usually occurs later in the course of the disease, after involvement of other organ systems has already been noted. Muscle involvement includes asymptomatic microscopic nodules, isolated palpable nodules, an acute or chronic proximal myopathy, and muscle atrophy. Patients may present with acute myositis with diffuse muscle swelling and pain affecting proximal muscles symmetrically that progresses to muscle contracture, hardening and hypertrophy [29,30]. They may also present with chronic myopathy with a slowly progressing weakness and atrophy in proximal symmetric muscles [29].

Myasthenia Gravis is very rare in sarcoidosis as are the thymomas. Combination of all three conditions was reported in a 59 year old female patient who did well after thymectomy, post thymectomy irradiation, large doses of corticosteroids and Pyridostigmine [77].

Cognitive and Behavioral Symptoms

Spiegel et al. [31] noted psychiatric manifestations, such as delirium and psychosis, in about 20% of neurosarcoidosis patients, which is equivalent to approximately 1% of all patients with sarcoidosis. In rare occurrences, these patients can experience striking auditory and visual hallucinations as well as delusions. A high prevalence of depression has been reported associated with sarcoidosis in 60 to 66% of patients, in a number of studies [34,35]. Neuropsychiatric symptoms, such as memory loss, fatigue, mood disturbances, and other behavioral changes, without evidence of a CNS lesion can occur. These nonspecific symptoms, which are often referred to as ''sarcoidosis fog,'' tend to be multifactorial in nature as a result of underlying systemic disease, medication side effects, and/or depression. Sleep disturbances, such as sleep apnea and primary hypersomnia, may also contribute to the sarcoidosis fog. When psychosis occurs in patients who are receiving corticosteroids, corticosteroid-induced psychosis also needs to be considered.

Sarcoidosis of Spinal Cord and Other CNS Findings

Granulomatous infiltration and inflammation in a perivascular distribution is seen in spinal cord, cerebral cortex, cerebellum and other brain parenchymal regions. Granulomas in various parts of the brain parenchyma and meninges have even been known to mimic brain tumors such as gliomas, meningiomas, and schwannomas. Myelopathy and Radiculopathy often affect the cervical and thoracic regions presenting as paresthesias, weakness or sudden paraplegia [36]. Rarely cauda equina involvement with radiculopathic involvement of the lower extremity along with bowel and bladder dysfunction can occur [37,38]. Generalized seizures can be seen as an initial finding in 10% of patients, as a manifestation of a restricted or generalized encephalopathy/vasculopathy [13,23]. Patients can present with cognitive or behavioral problems and/or focal neurologic deficits referable to the anatomic area involved. In rare cases, this manifests as a focal cerebral infarction [26].

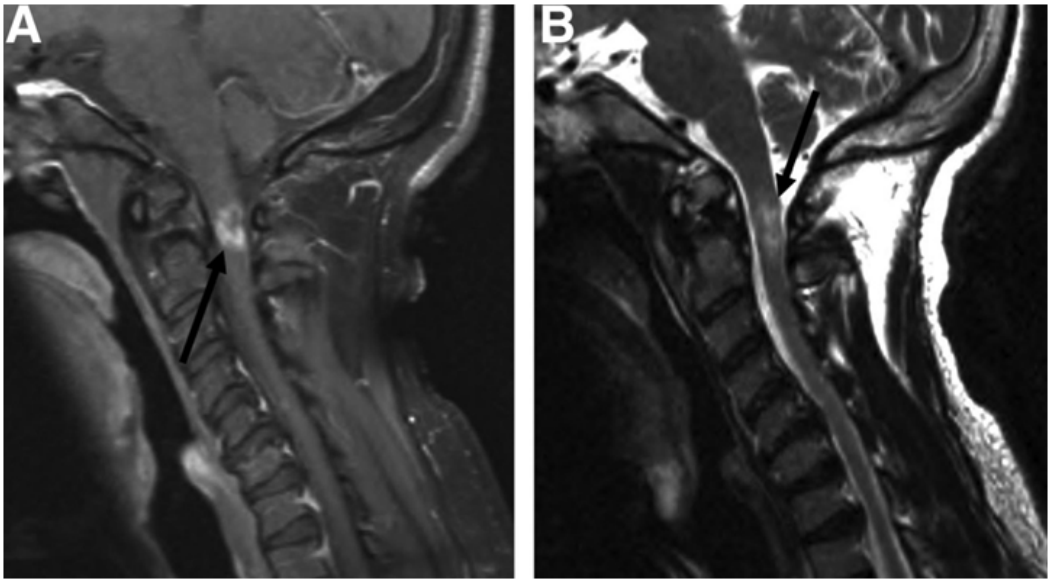

Figure 2: Spinal cord neurosarcoidosis. Sagittal contrast enhanced, fat-saturated T1-weighted image (A), and sagittal T2-weighted image (B) of the cervical spine demonstrate a small area of irregular enhancement and T2 hyper-intense signal within the spinal cord (arrows) [21].

Image produced from: Vitaly Terushkin, BS, New York University School of Medicine, 550 First Ave, New York, NY 10016. E-mail: vt382@nyumc.org. Copyright © 2010 by Lippincott Williams & Wilkins ISSN: 1074-7931/10/1601-0002 DOI: 10.1097/NRL.0b013e3181c92a72. [21].

Atypical presentations

Symptoms of Neurosarcoidosis are diverse and can mimic several other disease processes, such as Guillain-Barre Syndrome, Multiple Sclerosis, and psychiatric disorders. Patients have also reportedly presented with hypersomnolence and hyperphagia consistent with Kleine-Levine-Critchley syndrome [32]. In summary, neurosarcoidosis can present in many ways and clinicians should maintain a high index of suspicion for the disease, especially in those patients who are not known to have sarcoidosis prior to presenting with neurological manifestations.

PROGNOSIS OF NEUROSARCOIDOSIS

In general the outcome of patients with neurosarcoidosis depends on multiple factors including the severity of the disease and the type of neurological problem. Patients with neurosarcoidosis can have a monophasic illness (approximately two-thirds of patients), a relapsing-remitting course, or progressive disease punctuated by episodic deteriorations [13,40,42]. Current management strategies have substantially improved patient survival. The long-term course of neurosarcoidosis has not been clearly defined. Prognosis of each clinical manifestation of neurosarcoidosis is rated

from favorable to poor prognosis. Recent studies have shown patients with acute meningitis, peripheral or cranial neuropathy have a better prognosis and lower risk of progression over time [74]. Facial nerve palsy, which is the most common neurologic manifestation in most case series, tends to resolve within a few weeks (usually two to four weeks). For optic neuropathy, the outcome is mixed, with some series reporting improvement with treatment over several weeks, while some patients in other studies developed marked visual impairment or blindness [23,43]. Patients with vestibulocochlear nerve involvement and acute hearing loss typically recover at least partially with treatment, although significant chronic hearing loss could be the outcome of the patient with bilateral vestibulochoclear nerve involvement. Aseptic meningitis usually resolves over several weeks however chronic meningitis has an increased risk of progression [44]. Seizure control is usually not difficult as long as the underlying inflammatory process is controlled [45], otherwise neurosarcoidosis manifesting with seizure can also portend a poor prognosis and may have a high mortality [33,46]. Sarcoid involving the spinal cord carries the worst prognosis among the other neurological manifestations [47]. Overall a 10% mortality has been reported in patients with neurosarcoidosis. These patients are high risk patients with CNS parenchymal disease, hydrocephalus, mass effect, or other severe symptoms, who are likely to have profound immunosuppression secondary to aggressive treatments [74].

DIAGNOSTIC TESTING

Histology

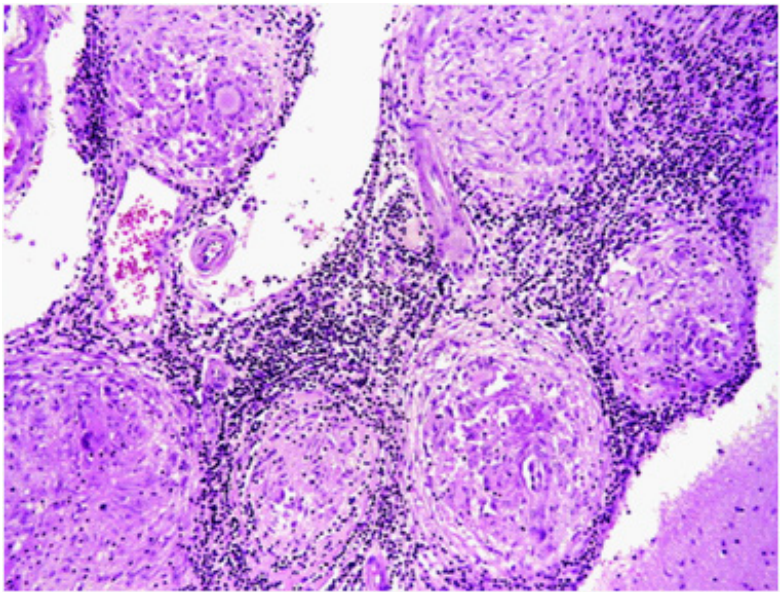

Figure 3: Noncaseating granuloma in parietal lobe showing the granuloma surrounded by epithelioid cells and nodular inflammatory infiltrates (hematoxylin and eosin, 10x) [75].

Granulomatous inflammation on neural tissue biopsy is the most specific diagnostic test for neurosarcoidosis, but is not 100 percent specific as alternative causes of granulomatous inflammation may occur. Biopsy from central or peripheral nervous tissue may be associated with significant morbidity, and therefore the diagnosis of neurosarcoidosis is often made indirectly by histologic confirmation from extraneural sites coupled with clinical evidence of neurosarcoidosis. The neural sites commonly biopsied are the meninges and mass lesions. The sensitivity of meningeal biopsy improves when the specimen is obtained from lesions that enhance on imaging studies [15]. The Kveim test is an old diagnostic test for sarcoidosis where a splenic suspension from a spleen involved with sarcoidosis is inoculated intradermally [48]. It is positive if in 4 to 6 weeks a skin nodule appears at the inoculation site, is biopsied, and reveals noncaseating granulomas. The Kveim test is highly specific for the diagnosis of sarcoidosis but is not a standard diagnostic test. However, it may be considered in cases of neurosarcoidosis as a Kveim test (skin) biopsy is much less invasive than biopsy of neural tissue.

Imaging of The Extraneural Organs

Chest radiographs, High resolution chest CT (HRCT), Whole-body Gallium (Ga-67) scan, and F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scan are major tools in the radiological diagnosis of neurosarcoidosis.

In patients with normal chest radiographs, HRCT is helpful in establishing multisystemic sarcoid involvement [46]. High resolution chest CT reveals nodules along the bronchovascular bundle and subpleural regions. Lymphadenopathy, ground glass attenuation are better evident and it often shows images of the superior portion of the abdomen, which may show evidence of extrathoracic disease such as hepatomegaly, splenomegaly, hepatic or splenic nodules, or upper abdominal lymphadenopathy [46].

Whole-body Gallium (Ga-67) scan and FDG-PET scanning may also detect multisystem disease [33]. Both these tests are found to frequently display positive activity in areas of active granulomatous inflammation from sarcoidosis and are useful for selection of a biopsy site [9]. But (Ga-67) scan and FDG-PET scan show positive results with other inflammatory and malignant disorders, including tuberculosis and lymphomas [33]. In a small number of patients the diagnosis of sarcoidosis is supported further if a Panda-pattern (bilateral salivary gland and parotid gland uptake) and/or Lambda-pattern (bilateral hilar and right para-tracheal lymph node uptake) appearance is seen in the Gallium (Ga-67) scan.

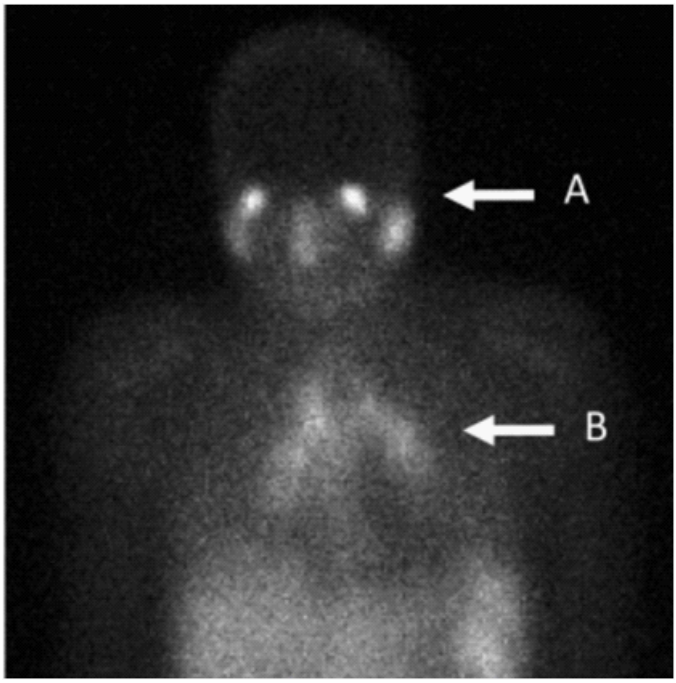

Figure 4: Panda (A) and Lambda (B) patterns.

Image produced from: Allard, A.B., Buscombe, J. and Kidd, D.P. (2014) The Role of Gallium (Ga-67) Scintigraphy in the Diagnosis of Sarcoidosis. Modern Research in Inflammation, 3, 99-107. http://dx.doi.org/10.4236/mri.2014.33012 [76].

In a large prospective trial of the application of PET scans in sarcoidosis patients, this modality also helped identify potential biopsy sites [13].

Brain and Spine MRIs

As discussed earlier, meningeal involvement is seen commonly with neurosarcoidosis causing hydrocephalus, headaches, seizures and cranial nerve neuropathies. Leptomeningeal involvement is found more often in meninges covering the fronto-basal, suprasellar, hypothalamic and pituitary areas.

Important differentials to consider while making a diagnosis of neurosarcoidosis are Wegener granulomatosis, lymphomas, leptomeningeal carcinomatosis, and fungal or tubercular meningitis among others [15,52]. Brain MRI is non invasive, very sensitive and preferred as a radiological test. It has also been shown to be more specific than brain CT in the diagnosis of neurosarcoidosis [33,55]. Leptomeningeal involvement is usually seen in the form of nodules or plaques spread over focal or diffuse thickening which is better seen with a brain MRI contrast enhancement. MRI has also been helpful in monitoring the response to therapy. Although normal brain MRI does not rule out disease, it does help in guiding therapy towards reversible vs irreversible lesions [54].

Non-enhancing brain parenchymal lesions have poor correlation with clinical symptoms and do not reliably respond to anti-sarcoidosis therapy. They are thought to have a different etiology than granulomatous inflammation [51].

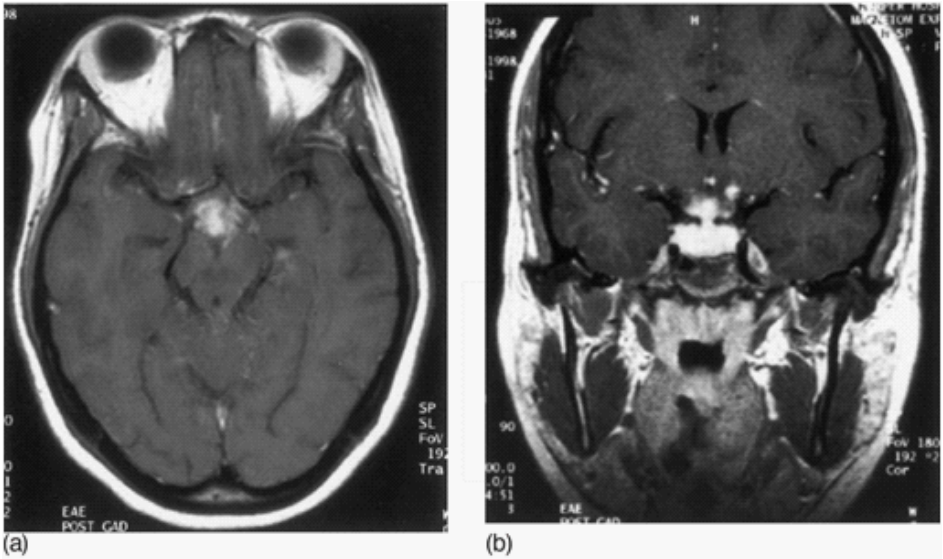

Figure 5: Neurosarcoidosis involving the pituitary-hypothalamic axis. T-1 gadolinium-enhanced Axial (a) and coronal (b) views shows an area of abnormal enhancement involving the sellar, suprasellar regions and the interpeduncular cistern. The diagnosis was confirmed by a biopsy [72].

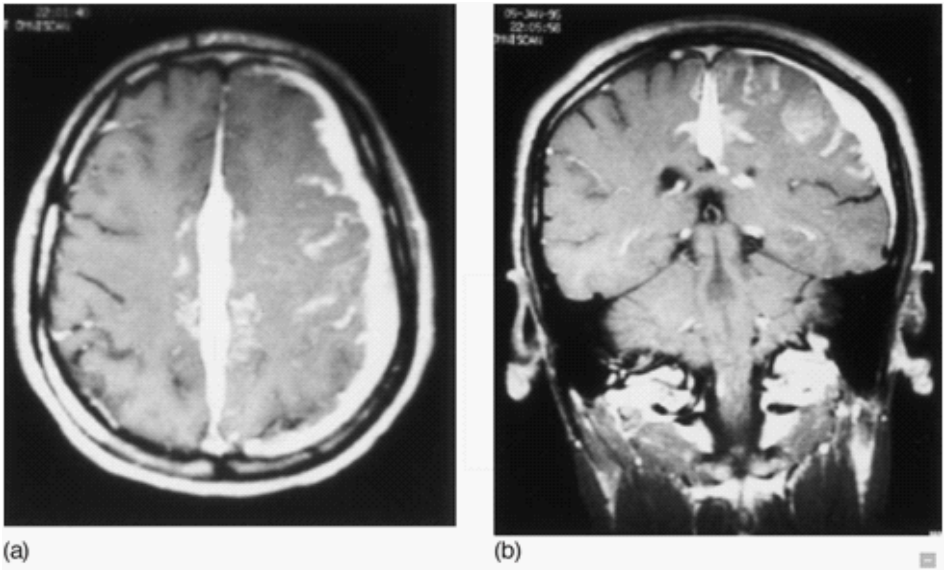

Figure 6: Meningeal neurosarcoidosis. Axial (a) and coronal (b) MRI T-1 weighted images post infusion of gadolinium DTPA in a patient with systemic sarcoidosis showing thickening and enhancement of the dura surrounding the left hemisphere [72].

Other important differentials for neurosarcoidosis are demyelinating disease and intraparenchymal mass. Both these conditions may present as a solitary or multiple enhancing lesions. Persistent enhancement despite corticosteroid and other immunosuppressive therapy suggests neurosarcoidosis rather than multiple sclerosis. Similarly linear enhancement of Virchow–Robin spaces also suggests neurosarcoidosis caused by granulomatous inflammation of blood vessels in the region of white matter predominantly [15,33].

Laboratory Studies

Cerebrospinal fluid (CSF) findings specific to neurosarcoidosis include elevated protein levels and lymphocytosis. Active inflammatory phase is accompanied by pleocytosis and hypoglycorrhachia; positive oligoclonal bands are seen in almost one third of neurosarcoidosis cases [9,13,23,33]. A normal CSF study does not exclude the disease and also these tests are relatively nonspecific for the diagnosis of neurosarcoidosis. Even though these CSF findings are not specific, a lumbar puncture with CSF analysis should be performed to exclude other disorders, including cryptococcal, tuberculous, and lymphomatous meningitis [9]. CSF angiotensin converting enzyme (ACE) levels for the diagnosis remains controversial and found to be elevated in many other non-neurosarcoidosis disease states. Hence the use of CSF should be sought more as a supporting evidence for the diagnosis of Neurosarcoidosis [46,56].

Other Studies

Ophthalmologic evaluation including slit lamp examination and fundoscopic examination is often useful as ocular sarcoidosis may occur concomitantly with neurosarcoidosis [57,58]. Peripheral nerve involvement most commonly axonal neuropathy needs nerve conduction studies and electromyography. Visual and brain stem auditory evoked responses could be abnormal and help in monitoring the course of the disease [15].

Diagnostic Criteria

In 1999 Zajicek et al. [33] proposed diagnostic criteria based on an extensive study consisting of over 300 patients who were identified as having clinical presentations similar to neurosarcoidosis. The gold standard for establishing the definitive diagnosis was set as having the typical positive histology of nervous system tissue illustrating non-caseating sarcoid granulomas filled with central epitheloid cells and macrophages surrounded by inflammatory cells in the periphery. Histological identification must be accompanied by clinical certainty to fulfill criteria for definite diagnosis. In the absence of positive histology of nervous system 'probable' and 'possible' criteria were proposed where other important lab tests were used to make the diagnosis as clear as possible for neurosarcoidosis. Other causes of granulomatous response were filtered out and after final scrutiny a diagnostic criteria was proposed which is outlined here.

Definite

Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology.

Probable

Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (either through positive histology , including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging or serum angiotensin converting enzyme-ACE).

Possible

Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met.

Judson et al also proposed diagnostic criteria which required histological granulomatous non-caseating inflammation to be present in neural or extraneural tissue for a definitive diagnosis of neurosarcoidosis. Other important auxiliary features like MRI images of nervous system, specific clinical findings, CSF studies and electrodiagnostic studies were included to make a definite diagnosis when the histologic evidence was granulomatous inflammation in extraneural tissue. This could eliminate the need for a neural tissue biopsy. Here is the outline of the proposed criteria [55,59].

A *Definite* diagnosis included any of the following besides positive histological extraneural granulomatous inflammation

- Positive magnetic resonance imaging (MRI) with uptake in meninges or brain stem
- Positive MRI of spinal cord showing intradural extramedullary or elongated intramedullary lesions, occupying more than 3 spine levels
- Cerebrospinal fluid with increased lymphocytes and/or protein
- Diabetes insipidus
- Bell's palsy
- Other Cranial nerve dysfunction

A *Probable* diagnosis included any of the following besides positive extraneural granulomatous inflammation

- Other abnormalities on MRI
- Unexplained neuropathy

- Positive electrodiagnostic studies

A *Possible* diagnosis included any of the following besides positive extraneural granulomatous inflammation

- Unexplained headaches
- Radiculopathy

(Assumes no other cause identified, such as infection, trauma, pre-existing condition, or co-existing disease for the neurologic manifestation).

MANAGEMENT OF NEUROSARCOIDOSIS

While sarcoidosis is a progressive autoimmune disease and there is currently no cure, symptomatic treatment is available. The goals of management are to stop the ongoing inflammation, prevent worsening of disease, and restore neurologic function. Corticosteroids have become the treatment of choice for neurosarcoidosis. The dosage and duration of therapy varies based upon the type and severity of the symptoms. For most patients, the initial starting dose of oral prednisone is 0.5 mg/kg/d to 1 mg/kg/d or about 60 mg/d for at least 3 months, depending on the severity of disease. Pulse dose IV methylprednisolone at 1000 mg/d for 5 days followed by maintenance oral corticosteroids should be considered for patients with potentially disabling neurologic disease, such as spinal cord lesions, severe meningitis with or without hydrocephalus, and intracranial disease with edema. Over the next several months, patients should be carefully monitored with close clinical follow-up and imaging studies, especially while tapering the dose [60].

The exact mechanism by which corticosteroids have benefited patients with neurosarcoidosis is unclear, but is generally believed to be secondary to its anti-inflammatory and immunomodulatory effects. Corticosteroids are known to prevent leukocytes from gaining access to sites of inflammation, interfere with their function along with that of endothelial cells and fibroblasts, and suppress production of various humoral factors [61]. It is always important to keep in mind, however, that as with all medications, corticosteroids are not without side effects. Common side effects of corticosteroids include cognitive and personality changes, weight gain with central obesity, development of striae, diabetes mellitus, cataracts and predisposition to various infections. Cardiovascular effects are also known to occur, such as hypertension, dyslipidemia, and increased risk of myocardial infarction and stroke. Patients receiving long term corticosteroid therapy are at risk for osteoporotic fractures, especially in the setting of other general risk factors such as being over age 60 or having osteoporosis prior to corticosteroid treatment. Additionally, avascular necrosis, especially of the hip, has been known to occur in a number of patients. Therefore, it is important to carefully monitor the dosage, and to always use the lowest possible effective dose. If treatment with corticosteroids is to be discontinued, it is essential to decrease the dose gradually. Abrupt discontinuation of corticosteroid therapy can cause adrenal insufficiency.

Alternative Therapies for Refractory Neurosarcoidosis

Several therapies have been proposed for those patients in whom corticosteroid treatment is unsuccessful, or in those who have contraindications to treatment. Many of these studies have shown methotrexate to be an effective treatment. Methotrexate has been successful in two-thirds of sarcoidosis patients regardless of the organ systems that are affected. Lower et al. [8] studied 554 sarcoidosis patients, 71 of whom, had neurosarcoidosis. They found that treatment with methotrexate and cyclophosphamide was associated with higher response rates than treatment with corticosteroids alone.

In 2007, Scott et al. [62] used aggressive therapy with corticosteroids and alternative immuno-suppressants in 48 patients. Over half of these cases had favorable outcomes. Later, in 2011, Androdias et al observed a small group of patients with neurosarcoidosis, and found evidence suggesting that Mycophenolate mofetil was effective in treating CNS symptoms. The agent was also found to have a steroid sparing effect and was better tolerated than several other immunosuppressive agents [63]. Additional studies have shown anti-TNF agents such as infliximab to be effective; cytokine modulators such as thalidomide and pentoxifylline have also been used in a limited number of cases [64]. It is important to be aware that various neurological deficits are reported during treatment with TNF-a blocker, including CNS or PNS demyelination [65].

Chloroquine and its derivative, hydroxychloroquine are anti-malarial drugs that also have anti-inflammatory effects. These drugs are used to treat rheumatoid arthritis and lupus erythematosus [66]. They are also effective in sarcoidosis, especially in those with sarcoidosis-induced hypercalcemia and sarcoidosis skin lesions. Hydroxychloroquine is preferred to chloroquine, since hydroxychloroquine has lower risk of ocular toxicity, but has similar efficacy. Since hydroxychloroquine reduces serum glucose levels, it may be useful for patients with steroid induced hyperglycemia. Sharma gave chloroquine sulfate 200 mg twice daily, or chloroquine phosphate 250 mg twice daily to 12 cases of neurosarcoidosis who could not tolerate or did not want to take prednisone, and obtained controlled or stabilized neurological status in ten (83%) [66]. In a case series of small fiber neuropathy in sarcoidosis, intravenous immuno-globulin ameliorated intractable neuropathic pain and/or autonomic dysfunction which were resistant to various immuno-suppressants and narcotic analgesics [67]. Infliximab has also been shown to be useful in a few patients with sarcoidosis associated small fiber neuropathy [68].

Other Treatments

Radiotherapy to CNS might be considered when medical therapy fails or causes intolerable side effects. Based on their own four cases and a literature review, Menninger et al. [70] recommended that radiotherapy was effective in preventing the progression of local symptoms of neurosarcoidosis; sarcoid meningitis was responsive to radiotherapy; and the radiation dose in the treatment of neurosarcoidosis was 20 to 25 Gy [69]. The mechanism of action for radiation effect

in sarcoidosis is not well understood. However, direct cytotoxicity to the cellular component of the granulomatous lesions, or cellular matrix alterations resulting in the inhibition of autocrine and paracrine signals, is considered. Surgical resection of CNS mass lesions is usually not recommended, unless the mass persists or continues to enlarge despite appropriate immunomodulatory therapy. If the patient presents with symptomatic hydrocephalus, a ventriculoperitoneal shunt can be placed. It is important to continue immunosuppressive treatment following placement of the shunt as inflammation can lead to obstruction. Additionally, symptom-specific treatment may be needed, such as hormone replacement therapy for hypopituitarism, and antipsychotics for patients with psychosis.

CONCLUDING REMARKS

Neurosarcoidosis can range from mild to severe and could be life threatening. It is a great mimicker of other clinical problems, can affect any component of the nervous system, and can present at any point during the course of the disease process, even before systemic symptoms are seen, as the initial manifestation of the disease. Although it affects only about 5 to 15% of those patients with sarcoidosis, it may prove difficult for clinicians to make a diagnosis, particularly if it is the initial presentation. While many studies have addressed long term outcomes, the course is so variable that no definite conclusions can be made as of yet. This review has attempted to highlight the clinical manifestations, diagnostic studies and prognostic implications of the various neurological presentations of the disorder.

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