J Neurology Neuromedicine
www.jneurology.com
Journal of Neurology & Neuromedicine

Mini Review Open Access

Neurosarcoidosis

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Article Info

Article Notes
Received: May 30, 2018
Accepted: August 07, 2018

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Keywords
Neurosarcoidosis
Sarcoidosis
Extrapulmonary Sarcoidosis

Abstract

Neurosarcoidosis is a multisystemic disease that involves the the brain, spinal cord, meninges, cranial, or the peripheral nerves. As sarcoidosis is a multiorgan granulomatosis, neurological features may represent the systemic effects of sarcoidosis in other organs or neurosarcoidosis. For the diagnosis of neurosarcoidosis, consistent histological changes in neurologic tissues should occur with systemic involvement in other organs, essentially in the lungs, lymph nodes, skin, or eyes. The prevalance of neurosarcoidosis is difficult to establish because most patients are either asymptomatic, have minor undiagnosed neurologic symptoms, incidence of neurosarcoidosis is variable, and different clinical criteria are used for the identification of neurologic involvement. Neurosarcoidosis occurs in approximately 5 percent of the sarcoidosis patients while postmortem studies reveal that 10 percent of the sarcoidosis cases have neurologic disease. Furthermore, less than 1 percent of sarcoidosis patients may present with isolated neurosarcoidosis. Because of diverse clinical appearence, lack of specific laboratory or radiogic findings, and difficulty to obtain neural tissue biopsy the diagnosis of neurosarcoidosis poses a challenge for the clinician. The prognosis of neurologic involvement is another difficult aspect to predict. Identification of neurosarcoidosis constitutes one of the most crucial aspects of sarcoidosis as the delayed diagnosis may lead to an unfavorable prognostic outcome for the patient.

Introduction

Sarcoidosis is a systemic granulomatous disease with unknown etiology that can involve any organ in the body. Sarcoidosis primarily affects the lymphoreticular system. There is also involvement of the smaller scattered lymphatic collections in solid organs like spleen, liver and lymphoid tissues surrounding glandular organs such as the parotid and lacrimal glands.

It is unknown whether sarcoidosis results from a dysfunctional immune system or is a secondary response to environmental antigens. Sarcoid granulomas may be seen in solid organs such as liver, kidney, and spleen. The lesion consists of lymphocytes and mononuclear phagocytes surrounding a noncaseating epithelioid cell granuloma. The lungs are the most frequently affected organ while extrapulmonary organ involvement can be encountered in approximately half of the sarcoidosis patients[1,2]. Involvement of the central nervous system occurs in 5-15% of patients with sarcoidosis. Neurosarcoidosis results from nervous system involvement by sarcoid granulomas. It is a diagnostic consideration in patients with known sarcoidosis that may be easily identified. In patients without a previous history of sarcoidosis neurosarcoidosis is a difficult diagnostic challenge for clinicians that warrants many diseases to be excluded in the differential diagnosis. Half of the neurosarcoidosis patients present with neurologic manifestations that pose a diagnostic dilemma. One-third of those with neurosarcoidosis may have more than one neurologic manifestation of their disease. Neurosarcoidosis may

have a severe prognostic outcome and sometimes may lead to life-threatining fatal complications[3-5].

Neurosarcoidosis generally occurs only in cases of sarcoidosis with substantial systemic involvement. Manifestations of neurologic disease are usually present in active disease. Definitive diagnosis of neurosarcoidosis requires the exclusion of other causes of neuropathy with the identification of non-caseating granulomas by pathologic analysis of nerve and muscle biopsy specimens.

Curently, there is no cure for neurosarcoidosis. Spontaneous remissions has been observed but long term treatment is often needed. Immunosuppression is the principal method for controlling the disease. Long term immunosuppressive treatment is often required with corticosteroids being the hallmark of management.

Epidemiology

Neurosarcoidosis is a rare manifestation of sarcoidosis with a varying prevalence of 5-13% among sarcoidosis patients. The frequency of neurologic disease is accepted to occur in 5% of all cases but the neurologic involvement may reach up to 45% in sarcoidosis patients[4,6]. Almost one fourth of sarcoidosis patients were found to have CNS disease on autopsy while 10% were identified by radiologic studies[7]. Approximately half of the patients with neurosarcoidosis present with neurologic difficulties when sarcoidosis is first diagnosed. Any portion of the central or peripheral nervous system can be affected by sarcoidosis. Peripheral neuropathy is present in 5-15% of neurosarcoidosis patients. In another study, one fourth of the patients had central nervous system involvement on autopsy while 10% of these had radiologic evidence of CNS disease[8].

Furthermore less than 1% of sarcoidosis patients may have isolated neurosarcoidosis without any evidence of extraneural sarcoidosis[4]. The silent asymptomatic clinical course, absence of accurate diagnostic criteria and the difficulty with the unavailability of tissue biopsy in every case appear to be the main factors for the underestimation of neurosarcoidosis prevalance among sarcoidosis patients.

Clinical Manifestations

Sarcoidosis can effect any portion of the nervous system as it is the case for extrapulmonary organ or ocular involvement. The clinical features of neurosarcoidosis depend on the site of neuraxis involved. While neurosarcoidosis most commonly affects the central nervous system, a subset of patients demonstrate predominantly peripheral nervous system involvement. Allen et al reported neurologic involvement in 26% of white patients with sarcoidosis. The following frequencies of neurologic abnormalities were observed: cranial neuropathy (59%), peripheral neuropathy (47%), mononeuropathy (25%), myopathy (25%), psychiatric disorders (19%), cerebellar ataxia (13%), papilledema (6%), and hydrocephalus (6%)[9]. Clinically symptomatic neurologic disease occurs in only 5%-13 of the sarcoidosis patients in whom the manifestations of neurosarcoidosis become appearent usually within the two years of initial diagnosis[6,10,11].

Cranial neuropathies are the most frequent site of involvement in sarcoidosis patients developing in up to 50-75 percent of the cases with neurologic disease. Peripheral facial nerve palsy occurs in one fourth to one half of the patients with neurosarcoidosis that can be unilateral or bilateral and recurrent. Facial nerve palsy is the most common site of involvement and may often precede the sarcoidosis diagnosis. Facial nerve involvement is usually unilateral[6]. Optic nerve is the second most frequent site of cranial neuropathy usually presenting with visual defects. Optic neuropathy and cranial nerve VIII dysfunction can lead to intermittent or progressive visual, auditory or vestibular dysfunction[12]. Cranial neuropathies may present with the following manifestations: impaired taste, blindness, blurry vision, double vision, visual field defects, pupillary abnormalities, dry or sore eyes, slurred speech, impaired swallowing, hoarseness, vertigo, sensorineural deafness, tinnitus, muscle weakness, and tongue deviation.

Acute or chronic meningitis occurs in 8 to 40% of the patients. It is due to the infiltration of basal leptomeninges. Acute sterile menengitis may develop leading to fever, stiff neck and headaches. Cerebrospinal fluid analysis is normal in approximately one third of the cases. These patients usually have cranial nerve or peripheral nerve involvement. The CSF analysis may reflect a nonspecific abnormal pattern and in some cases serial CSF analyses may be necessary. CSF reveals lymphocytosis, elevated protein and ACE levels while hypoglycorrhachia develops in one third of the patients. The sensitivity and the specifity of elevated cerobrospinal fluid is 55% and 94%, respectively[13,14]. Seizures may develop in up to 22% of patients with neurosarcoidosis due to leptomeningeal involvement, granulomas, encephalopathy, or hydrocephalus[6,12]. Peripheral neuropathy of sarcoidosis may present with a wide clinical spectrum of manifestations. There may be Gullain-Barre syndrome like presentations with muscle weakness, pain, paresthesias, dysesthesias, autonomic dysfunction and abnormal thermal dysfuction[15,16]. Peripheral nerve disease may lead to sensory or motor mononeuropathy, mononeuropathy multiplex, or polyneuropathy. Sensory neuropathy may cause loss of sensation and abnormal sensation like tingling, numbness, extremity pain and stocking or glove deficits. Muscle weakness due to motor neuropathy leads to immobility and joint stiffness. Patients may reveal focal findings associated with the nerve involved. Small-fiber neuropathy may be evaluated by thermal threshold

testing (TTT). Sympathetic skin responses and cardiac autonomic testing (by Ewing test and iodine-123 meta-iodobenzylguanidine [^{123}I-MIBG] myocardial scanning) may be used for small- fiber neuropathy with limited diagnostic value. Electromyography/nerve conduction studies (EMG/NCS) may confirm neuropathy. The most frequent electrodiagnostic finding is mononeuropathy multiplex, showing axonal degeneration and segmental demyelination. EMG may reveal myopathic potentials. Visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) are abnormal in one third of the neurosarcoidosis patients[4,6,13].

Neurosarcoidosis may involve the base of the skull and lead to neuroendocrine related pathologies. Neuroendocrine dysfunction typically occurs with hypothalamic inflammation, resulting in polyuria or disturbances in thirst, sleep, appetite, temperature or libido disturbances. Hypothalamic or pituitary lesions may also cause thyroid, gonadal, or adrenal abnormalities. Diabetes insipidus (17-90%) and hyperprolactinemia (3-32%) are the most common endocrine disorders in neurosarcoidosis. Endocrinopathies are caused by graulomatous infiltration of the hypothalamus[17,18]. Neuroendocrine dysfunction due to hypothalamic inflammation may lead to sleep, appetite, temperature, or libido. Hypothalamic or pituitary lesions may also cause thyroid, gonadal, or adrenal abnormalities Hypothyroidism, hypoadrenalism, growth hormone deficiency and morbid obesity may also develop in these patients. Polydipsia, polyuria, obesity, alveolar hypoventilation, galactorrhea, amenorrhea, impotence, change in menstrual period, loss of judgment, amnesia, confusion, and seizures may occur. Seizures may come out as the initial manifestation of sarcoidosis. Seizures indicate a severe prognostic outcome. Patients with simple partial or complex partial seizures due to isolated mass lesions usually have better a better prognosis than patients with generalized tonic-clonic seizures only[19,20]. The disease may involve the spinal cord. Presence of spinal lesions on neuroimaging extending more than three spine segments strongly suggests neurosarcoidosis in such patients[21]. Other features of neurosarcoidosis include seizures, psychiatric disorders, peripheral neuropathy, and hydrocephalus. These manifestations are possibly related to granulomatous central nervous system inflammation and scarring from meningeal involvement[13].

A neurologic disease compatible with neurosarcoidosis in patient without a previous history of sarcoidosis is a diagnostic challenge for the clinician. Although the gold standart for the identification of neurosarcoidosis requires histopathologic confirmation of neural tissue, this is an invasive procedure. Because histopathologic identification is needed for final diagnosis of sarcoidosis and more than 90% of the sarcoidosis patients have extrapulmonary organ involvement, the biopsy should be minimally invasive and done from the site with the the least morbidity or mortality. As a result, superficial biopsy sites like skin, lacrimal gland, lymph nodes, or lung are preferred[22]. Identification of peripheral neuropathy is determined by establishing the existence of a peripheral neuropathy while excluding the common causes of peripheral neuropathy in differential diagnosis such as vitamin deficiency, diabetes mellitus, or toxins.

The diagnosis is confirmed if presence of neurosarcoidosis occurs together with the histopathologic or clinical evidence such as Heerfordt syndrome. Histopathological evidence of noncasefied granulomatous inflammation from neural tissue is the hallmark of definite diagnosis. Tissue biopsy for neurosarcoidosis is cumbersome due to the complications associated with the procedure. Otherwise, neurosarcoidosis poses as a difficult clinical diagnosis due to its silent or diverse the clinical profile and nonspecific laboratory or imaging findings. For a definitive diagnosis of neurosarcoidosis biopsy of neural tissue is required. But in clinical practice this approach is not possible in the majority of the patients. Clinical profile, imaging and laboratory findings are used for possible, probable, and final diagnosis. Extraneural evidence of sarcoidosis plus existence of neurologic signs and laboratory findings may provide an algorithmic diagnostic pathway for neurosarcoidosis+. MRI with intravenous gadolinium is the imaging technique of choice that may reveal diffuse, focal, or multifocal central nervous system involvement with a predilection for the basal meninges. The most common findings are dural involvement, leptomeningeal, parenchymal, and cranial nerve enchancement[11,13]. Positron emission tomography, electroencephalography, electromyography, and nerve conduction studies are other tests that may be useful for diagnosis. PET/CT is not only useful to identify neural sarcoidosis but also determine the other sites of involvement thereby faciliating the diagnosis. Positron emission tomography can demonstrate disease activity and is also a potentially useful imaging modality to evaluate the treatment efficacy in neurosarcoidosis. Radiologic abnormalities of neurosarcoidosis are not specific enough. Biomarkers that can adequately identify neurosarcoidosis are not currently available while interleukin-2 receptor may be useful[25]. Neurosarcoidosis may imitate lymphoma, multiple sclerosis or other neurologic diseases. Although definitive diagnosis requires hispathological confirmation of the affected neural tissue, clinical manifestations, gadolinium-enhanced MRI patterns and cerebrospinal findings may support the diagnosis in the absence of neural biopsy[26]. Identification of neuro-inflammatory disease is best achieved by contrast enhanced MRI and cerebrospinal fluid analysis[27].

There is no known effective cure for neurosarcoidosis.

Spontaneous remission that usually emerges within six months while such an occurence is extremely rare and long-term therapy often is required. Immunosuppression is the hallmark mode of treatment and corticosteroids are the cornerstone of therapy. Neurosarcoidosis rarely shows spontaneous remission in contrast to pulmonary sarcoidosis. The disease does not have a benign or self-limiting course but usually carries a chronic progressive prognosis. Among the involved neural compartments only isolated cranial nerve disease and aseptic meningitis may come out with spontaneous resolution[28,29]. Steroids are the the mainstay of treatment. For mild to moderate neurosarcoidosis, an initial dose of 20-100 mg/day prednisone is recommended while the starting dose of prednisone is usually between 40 to 80mg/day. In severe cases a dose of 1mg/kg prednisone or equivalant is given. Intravenous 500-1000 mg methyprednisolone is commenced in severe disease for a few days. Patients with a peripheral facial nerve palsy or aseptic meningitis are started with prednisone 0.5 mg/kg per day. For neuropathy and myopathy prednisone 0.5 mg/kg per day is given. Encephalopathy, hydrocephalus, a cerebral or a meningeal mass lesion requires 1.0-1.5 mg/kg prednisone treatment[29]. An intravenous dose of methylprednisolone 20 mg/kg per day for three days followed by prednisone 1.0 to 1.5mg/kg per day is used severe conditions. A significant number of patients are refractory to steroid treatment and relapse when the steroid dose is lowered. Exacerbations may develop when the prednisone dose is about 10 mg/day. Consequently, the dose should be decreased by 1 mg decrements every one to two weeks when the dose approaches to 10 mg/kg day. Acute deterioration is unusual if corticosteroids are tapered in this fashion and patients are closely monitored. If the patient's symptoms recur, the prednisone dose should be doubled. The prednisone dose should be doubled if the deterioration or relapse occurred at a dose of prednisone above 10 mg/day. The dose should be increased to 10 to 20 mg/day if a relapse occurred at lower doses[11,13,28]. Moderate to high doses of steroids is the hallmark of neurosarcoidosis treatment while relapse is common after steroid dose is tapered that necessisates immunosuppresive agents[31].

Hydroxychloroquine, chloroquine, mycophelenate, methotrexate, cyclosporine, and cyslophosphamide may be useful for neurosarcoidosis as steroid sparing agents. Cyclosporine dose is 4mg/kg while methotrexate can be started at a dose 5-15mg/week[24,32-35]. TNF-α blockers like infliximab and adalimumab can be commenced to patients with refractory disease[36,37]. For mass lesions neurosurgery and radiotherapy may be applied. Radiotherapy can be used in patients with CNS disease refractory to medical treatment. Radiotherapy should be considered if corticosteroid therapy is not successful and at least two alternative agents have been tried[38]. The modality has also occasionally been required for patients with acute, life-threatening disease. Immunosuppression is generally continued during radiation therapy, albeit at less intense levels. In general, neurosarcoidosis shows a severe prognostic outcome. Facial nerve and meningeal involvement may have more a benign disease course. Many patients have a slowly progressive chronic prognosis with intermittent exacerbations. Neurosarcoidosis usually have a progressive disease with intermittant relapse and remissions[39,40]. Definitive treatment for neurosarcoidosis is still lacking due to the rarity of the disease. TNF-α blockers appear to be useful treatment alternatives for neurosarcoidosis but further studies with large samples sizes are still needed to reach a precise conclusion. Approximately 10 percent of patients die as a result of neurosarcoidosis. These patients frequently have CNS parenchymal disease and mostly cerebral or brainstem granulomas.

Conclusions

Neurosarcoidosis is a rare manifestations of sarcoidosis. The diagnosis is difficult and creates a challenge for the clinician. Even if neurologic involvement occurs in patients with a known previous history of sarcoidosis, a detailed clinical investigation and a through differential diagnosis should be performed as the symptoms of neurosarcoidosis coincide with many neurologic disease or may simulate them. Another difficulty in diagnosis lies in the fact that there are no specific laboratory or imaging findings of neurosarcoidosis. Corticosteroids are the mainstay of treatment with variable success. In patients who are unresponsive to steroids, who have a contrindication to steroids, or in whom steroids lead to major side effects, other alternative immunosuppressive agents may be commenced. Infliximab may be useful in patients refractory to corticosteroid therapy. Cranial or spinal irradiation may be used for refractory disease. Radiotherapy is considered if patients fail corticosteroid therapy and trials of at least two alternative agents and in patients with acute, life-threatening disease due to space occupying lesions.

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