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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