

Challenges in Diagnosis of Neurosarcoidosis

Adel Ekladios^{1,*}

¹Senior consultant in Acute medical unit Canberra Hospital , ACT health Australia. Associate Professor of Medicine University of Western Australia Australian national university

Abstract

Sarcoidosis is granulomatous autoinflammatory autoimmune remitting relapsing disease affecting every organ in the body, it is the most difficult disease to diagnose in the absence of serum or imaging biomarker. Differential diagnosis is broad which included inflammatory, infective, neurodegenerative and neoplastic, histological biopsy is the only confirmative marker, and even histological confirmation is not robust as infection, malignancy and some drugs can induce granuloma, the most common organs affected are lung, lymph nodes, skin, eyes, liver, and less commonly pituitary gland, bones, brain, peripheral nerves, and heart, causing bilateral hilar lymphadenopathy, granulomatous lymphadenitis.

Introduction

Neurosarcoidosis is the most difficult and challenging diagnosis in medicine, and even confirmation of granulomatous disease by biopsy is not sufficient to make the diagnosis, and because neurosarcoid has many mimics, all mimics needs to be ruled out before starting on immunosuppressive medication for neurosarcoid [1], Despite the advances and progress in neuroimaging and serum testing there is no one biomarker which can confirm the diagnosis [2],

The major challenge in diagnosing neurosarcoid, it is one of the very rare diseases which can affect any part of the brain and any organ of the body [3], although biopsy can help with ruling out mimics, still the diagnosis is mainly clinical [4]

We presenting a case of neurosarcoid and we will expand on the diagnosis of neurosarcoid and few mimics

Case history

49 year old women working as a teacher in a secondary school and highly regarded by her colleagues and students for her excellent skills in teaching , she is married and has three children, all are healthy and highly functioning, patient has no medical history of note , she is not taking any medication , her vaccination is UpToDate, she has no family history of autoimmune diseases , her dad died from stroke at the age of 80, her mother died from heart attack at the age of 76, there was no history of cancer in the family, patient was admitted to the hospital because of three months duration of cognitive deterioration, headache and recent

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Corresponding author:

Adel Ekladios, Senior consultant in Acute medical unit Canberra Hospital , ACT health Australia. Associate Professor of Medicine University of Western Australia Australian national university.

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memory loss and confusion, general examination by registrar was unremarkable, neurological examination by the senior registrar revealed that patient has difficulty to recall the history of her illness, she was oriented in time and person but in place and situation, she was unable to perform seven calculations or to spell the world sky backward, she was unable to do two step

Task, remainder of neurological examination was unremarkable, the complete blood count with differential count, and test results for liver, kidney function, electrolytes, glucose, thiamine, copper, cobalamin were normal, as well as syphilitic serology, HIV, thyroid and parathyroid functions,

ANA, DNA binding, C3, C4, CH50, anti-centromere antibodies, Anti RPN, ani La, Anti Ro, Anti Smith,

Anti synthetase, Anti myeloperoxidase, Anti Protenease, Anti GBM were all either normal or negative, ESR and CRP were within normal , Tumer markers were negative , Septic screen including blood culture and urine culture were sterile, CT head with and without contract did not show any Hemorrhage, ischemia or mass ,CSF study showed normal opening pressure, white cell count was 60 per microfilter(reference range 0-4)with lymphocyte count of 98%(reference range of 40-70) CSF culture and gram stain was negative , Xanthochromia and oligoclonal ban were not detected, serology for Herpes simplex viruses 1 and 2 DNA , Varicella Zoster by PCR were negative, VDRL and RPR for syphilis were negative , Listeria antibodies was not detected,Entrovirus RNA histoplasma antibodies was negative as well as Cryptococcal antigen, Arbovirus antibodies was not detected , DNA for Epstein -Barr virus and

Enterovirus RNA was negative, MRI of the head T2 -weighted fluid – attenuated inversion recovery image showed abnormal diffuse hyperintensity in the frontal sulci, T1 weighted image with intravenous gadolinium showed diffuse leptomenigeal enhancement, CT of the neck, chest, abdomen and pelvis

Showed bilateral hilar lymphadenopathy and parenchymal infiltrates-,CT- PT scan showed FDG uptake in the lung, brain and porta hepatis,

Bronchoscopy was performed, multiple biopsies for the hilar lymph nodes and bronchoalveolar lavage, Showed non- necrotizing tightly packed central tissue composed of macrophages, epithelioid cells, multinucleated giant cells, and lymphocytes which confirmed by flowcytometry to be CD4 and few CD8,

The ratio of CD4/CD8 was 5.8, ACE level was 90 micro/L (reference less than40 micrograms per liter), Patient was diagnosed with neurosarcoid and started on methylprednisolone 1000 mg daily for 5 days followed by oral prednisolone 60 mg daily in a tapering dose over 6 months and mycophenolate as steroid sparing agent , patient started to improve gradually after three weeks, and started to receive neurorehabilitation in neurorehab facility, six months later patient was independent and able to resume her job 16 hours a week , repeated imaging for the brain , chest , abdomen and pelvis were reported as normal,

Discussion

Sarcoidosis is a multisystem granulomatous disease that affect almost any organ in the body, it also affects people from all ages and races, lungs and lymph nodes, skin and eyes are the most commonly affected [5],

Neurosarcoidosis is a very rare manifestation of sarcoidosis, it has a protean presentation and can

masquerade as many other diseases, many of the current knowledge of neurosarcoid obtained from retrospective, autopsy studies and rare case reports, treatment of neurosarcoid are similar to those of systemic sarcoidosis and they have been not subjected to placebo-controlled, double-blinded studies,

Symptoms of neurosarcoid are very vague and nonspecific which includes and not limiting to headache, Fatigue, nausea, vomiting, seizure, sensory disturbance, cognitive dysfunction, depression, aphasia, tremors, weakness, ataxia, eye pain, blurring of vision, confusion, falls, polyuria, constipation

Common neurological manifestations

Unilateral and bilateral simultaneous or sequential fascial nerve palsy through various mechanisms which encompass meningitis, parotitis, stroke, vasculitis, compression from intraparenchymal lesions,

Other structures of the brain can be involved in the same time, Heerfordt – Waldenström syndrome causes parotitis, facial palsy, fever ocular inflammation and considered pathognomonic of neurosarcoid [6], ischemic optic neuritis is the second most frequent in sarcoid cranial palsy, usually painless which differentiates it from demyelinating optic neuritis, 30% of patients with optic neuritis develop bilateral disease and one third develop concurrent uveitis [7], other cranial nerves are not immune from being affected in sarcoidosis and confirmation of the diagnosis is difficult even with biopsy and needs all other possible differential diagnosis to be ruled out,

Meningeal involvement

Leptomeningitis commonly affects the base of the skull followed by the brain and the spinal cord,

Meningitis present with intractable headache and radiographic leptomeningeal inflammation, meningeal signs including fever and nuchal rigidity is rarely the presenting manifestation which makes the diagnosis difficult even after thorough spinal fluid examination and meningeal biopsy, excluding other common and uncommon differential diagnosis is of paramount importance in order to decide about the duration of management [8]

Neurosarcoid can present as a pseudotumor of the orbit which mimics IgG4-disease as well as malignancy and lymphoma [9],

Sarcoid myelitis can present with spastic weakness of the lower limbs and cause a diagnostic challenge with other causes of spastic paraplegia specially when associated optic neuritis, any segment of the spinal cord can be affected, Common MRI finding is leptomeningeal enhancement, Neuromyelitis Optica spectrum disorder (NMOSD)

is important differential diagnosis to be ruled out specially if the sarcoid myelitis involved three or more vertebral length, symptoms of intractable hiccup, nausea, and vomiting suggest postrema syndrome which is pathognomonic of NMOSD [10],

Myelin-oligodendrocyte glycoprotein-associated disease (MOGAD) is another differential diagnosis to be ruled out which usually does not affect the brainstem or the cerebellum, and can be confirmed by

Anti-myelin oligodendrocyte glycoprotein antibodies [11],

Autoimmune encephalitis which includes Anti NMDAR receptor encephalitis, Hashimoto encephalitis, G11/CASPR2 antibody encephalitis, limbic encephalitis and Rasmussen encephalitis are needed to be ruled out as they are all treatable diseases,

Pachymeningitis

Pachymeningitis cause dural inflammation which can affect any part of the cranial cavity, Basal ganglia

and convexity of the brain when affected are mainly presented by a mass lesions and focal neurological signs, around 40% of sarcoid pachymeningitis present with multifocal involvement, cranial neuropathy Can be a manifestation of sarcoid pachymeningitis when involving the cavernous sinus [11],

Peripheral neuropathy

Around 10% of neurosarcoid affects the peripheral nerves causing sensory, motor or sensory motor neuropathy, mononeuritis, and mononeuritis multiplex had been recognized in neurosarcoid, Hypercalcemia, polydipsia, gonadotrophin and thyrotropin deficiency, pituitary insufficiency and hypothalamic involvement are all recognized manifestation of neurosarcoid, [12],

Differential diagnosis is broad and Exclusion of mimics remains an important part of the management, especially when patients do not respond in a timely manner to medication,

The diversity of neurosarcoidosis is such that each patient present with a unique set of manifestations that dictate the relevant differential diagnosis for such patient,

Mimics that share systemic and neurological features should be ruled out first, followed by mimics which share only neurological findings,

There is no one serum marker which can definitely diagnose sarcoid and exclude mimics, even serum angiotensinogen converting enzyme which is a marker of granulomatous inflammation, it lacks sensitivity and specificity,

One recent study showed that serum soluble IL-2 receptor, which is a surrogate marker for T cell activation, could be a promising biomarker for neurosarcoidosis, in addition to the neuroimaging, CT-Pet and biopsy, the most useful serologic test for diagnosing neurosarcoid is testing to exclude mimics,

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