

Case Report

Isolated neurosarcoidosis presenting with multiple cranial nerve palsies

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Received: 12 August 15 Accepted: 19 February 16 Published: 19 April 16

Abstract

Background: As an extremely rare subtype of sarcoidosis that develops exclusively in the nervous system, isolated neurosarcoidosis is difficult to diagnose. In addition, its exact clinical features are not known.

Case Description: A 61-year-old man presented with right ear hearing loss, diplopia, and fever. Computed tomography (CT) and magnetic resonance imaging revealed mass lesions in the right cerebellum and left side body of the lateral ventricle. Neither systemic CT nor positron emission tomography revealed extracranial lesions. A neuroendoscopic biopsy was performed on the lateral ventricle lesion, and a histopathology analysis revealed epithelioid granulomatous inflammation. By systematic exclusion of other possible granulomatous diseases, isolated neurosarcoidosis was diagnosed. The lesions disappeared immediately upon corticosteroid (methylprednisolone) treatment and had not recurred as of a 12-month follow-up examination.

Conclusions: Isolated neurosarcoidosis is difficult to diagnose. Successful diagnosis requires compatible clinical findings, histological demonstration of noncaseating granulomas, and exclusion of other granulomatous diseases. Isolated neurosarcoidosis has a relatively good clinical prognosis, which could be characteristic of the disease.

Key Words: Cranial nerve palsy, granulomatous inflammation, isolated neurosarcoidosis

Access this article online

Website:www.surgicalneurologyint.com**DOI:**

10.4103/2152-7806.180765

Quick Response Code:

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Sarcoidosis can occur in the central or peripheral nervous system with other organ involvement (neurosarcoidosis), however, when sarcoidosis develops exclusively in the nervous system, it is called isolated neurosarcoidosis. Although its precise prevalence has not been determined, isolated neurosarcoidosis is estimated to account for <1% of sarcoidosis cases.^[18] Because of its rarity, it is difficult to diagnose and its exact clinical features are not known. In this case report, we describe a

patient with isolated neurosarcoidosis who presented with multiple cranial nerve palsies. This case followed a good clinical prognosis, which could be typical of this disease.

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How to cite this article: Shimizu K, Yuki K, Sadatomo T, Kurisu K. Isolated neurosarcoidosis presenting with multiple cranial nerve palsies. *Surg Neurol Int* 2016;7:44.
<http://surgicalneurologyint.com/Isolated-neurosarcoidosis-presenting-with-multiple-cranial-nerve-palsies/>

CASE REPORT

A 61-year-old man with a history of hypertensive cerebellar hemorrhage visited our hospital because of diplopia and fever. The diplopia was recognized when he gazed at the right side and disappeared with monocular vision. In addition, he became aware of right-ear hearing loss a few months before visiting the hospital. He was alert and had no paralysis. The deep tendon reflexes were normal, and any upper motor neuron pathological reflexes were not seen. His tandem walk was disturbed and leaned to the right side. An ocular examination showed faint right lateral gaze palsy. Fundus examination revealed papilledema. Laboratory results included the following: C-reactive protein 0.01 mg/dL (0–0.3 mg/dL), lactate dehydrogenase 142 U/L (119–229 U/L), erythrocyte sedimentation rate = 24 mm/h (0–10 mm/h), albumin = 3.8 g/dL (4.0–5.0 g/dL), calcium = 8.6 mg/dL (8.6–10.1 mg/dL), angiotensin conversion enzyme = 7.7 IU/L (8.3–21.4 IU/L), soluble interleukin 2 receptor = 291 U/ml (145–519 U/ml), and immunoglobulin G4 = 40.6 mg/dL (4.8–105 mg/dL). Antinuclear antibody test was negative. QuantiFERON® blood tests were negative, and tests for Epstein-Barr virus, cytomegalovirus, toxoplasma, syphilis, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus were all negative. Cerebrospinal fluid (CSF) study revealed a lymphocytosis and elevated protein levels: Cell count 349/mm³ (pleocyte 16/mm³, lymphocyte 333/mm³) and total protein 153 mg/dL. Oligoclonal band was negative.

The chest X-ray was normal and no bilateral hilar lymphadenopathy was seen. Magnetic resonance imaging

(MRI) revealed intracranial mass lesions in the right hemisphere of the cerebellum and the left body of the lateral ventricle [Figure 1]. Systemic enhanced computed tomography and positron emission tomography showed no extracranial lesions. Two weeks later, the right cerebellar lesion disappeared [Figure 2a]; however, after 2 more weeks, the lateral ventricular lesion was enlarged and new mass lesions developed in the choroid plexus of the fourth ventricle [Figure 2b and c]. A neuroendoscopic biopsy was performed on the lesion of the left body of the lateral ventricle [Figure 3]. The histopathology studies revealed epithelioid granulomatous inflammation and large numbers of lymphocytes and plasma cells infiltrating perivascular spaces [Figure 4]. The biochemical examinations and blood and CSF culture revealed no organisms, and the histopathology findings ruled out vasculitis. Based on the clinical course and the exclusion of these other granulomatous diseases, isolated neurosarcoidosis was diagnosed. Methylprednisolone (1000 mg/day) was administered for 3 days, and the intracranial lesions almost disappeared [Figure 5]. Corticosteroids were continued and gradually tapered off over a period of 12 months. No exacerbations or recurrences were found even up to a year later [Figure 6].

DISCUSSION

Isolated neurosarcoidosis is an extremely rare disease, and its accurate diagnosis is difficult. The accurate diagnosis of isolated neurosarcoidosis requires compatible clinical symptoms, a histological finding of noncaseous granulomatous inflammation, and exclusion of other granulomatous diseases.^[19] In addition, this disease is

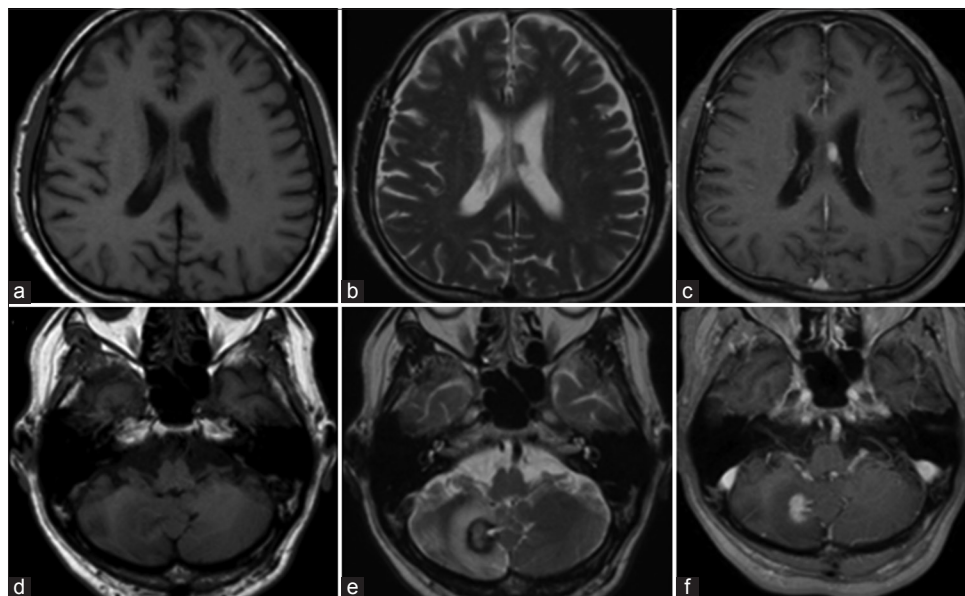


Figure 1: Magnetic resonance imaging on admission. The two mass lesions in the left body of the lateral ventricle and the right cerebellum hemisphere were isointense on T1-weighted images (a and d), and hypointense on T2-weighted images (b and e). The lesions were enhanced after gadolinium-diethylenetriamine pentaacetate injection (c and f)

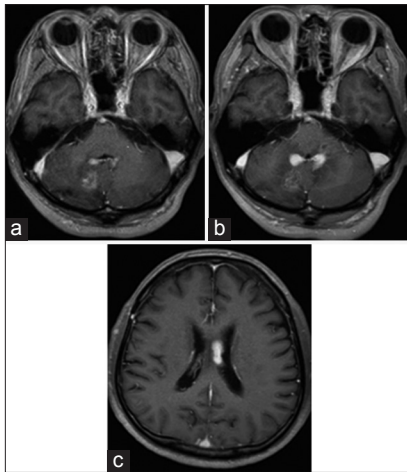


Figure 2: Two weeks following hospital admission, the right cerebellum lesion almost disappeared (a). Two weeks later, new enhanced lesions emerged in the choroid plexus of the fourth ventricle (b). Enlarged image of the left body of the lateral ventricle lesion (c)



Figure 3: Intraoperative neuroendoscopic image showed irregular surface in the lateral ventricle. Many small particles were floating in the cerebrospinal fluid, which was suggestive of leptomeningeal dissemination

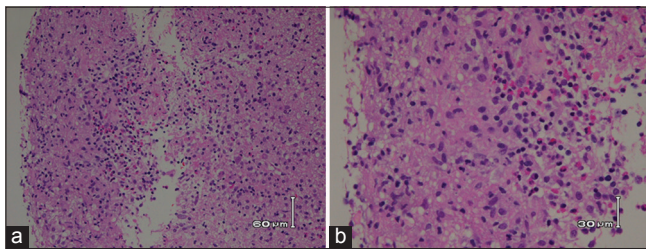


Figure 4: Pathological findings: Original magnification $\times 20$ (a), $\times 40$ (b). H and E staining revealed epithelioid granulomatous inflammation

reported to have a better clinical prognosis compared with systemic neurosarcoidosis.^[12] The disorder's good clinical course could be a typical feature of isolated neurosarcoidosis.

An accurate diagnosis of isolated neurosarcoidosis requires characteristic clinical presentations, the presence of granulomatous inflammation on tissue biopsy, and exclusion of other possible diagnoses. Neurosarcoidosis could occur in any part of the nervous systems; however, the basal leptomeninges, the hypothalamus, and the pituitary gland are most commonly involved.^[6] Isolated neurosarcoidosis may have more tendency to involve the basal leptomeninges than neurosarcoidosis.^[12] Various neurological symptoms could be exhibited and cranial nerve palsy, especially facial nerve palsy, is the most common clinical manifestation.^[11] Optic neuritis is the second most common presentation, and other cranial nerve palsies can occur but are less common.^[7] Eighth cranial nerve are rarely involved and typically presented as sensorineural hearing loss. It is commonly unilateral involvement; however, bilateral involvement is highly suggestive for neurosarcoidosis.^[5] The etiology of sensorineural hearing loss is various and unilateral

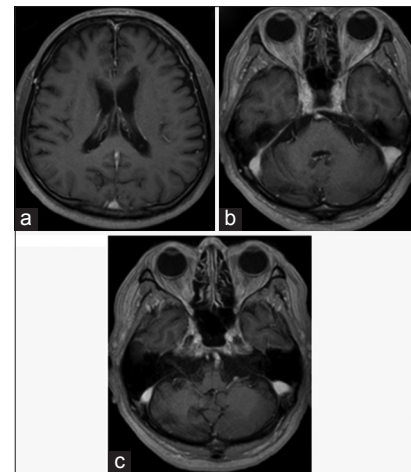


Figure 5: (a-c) After steroid pulse treatment, the lesions almost disappeared

involvement is common in most cases, with bilateral involvement reported in $< 5\%$.^[13] Lyme disease is one of the important differential diagnosis for sensorineural hearing loss in the endemic area. Unilateral involvement is a common feature and bilateral involvement is never reported in Lyme disease.^[15] Monocranial nerve palsy is a common symptom of neurosarcoidosis, whereas multiple cranial nerve palsies are a rare manifestation. If multiple cranial nerve dysfunction is confirmed; however, it is highly suggestive of neurosarcoidosis, especially when facial or optic nerve is involved.^[10] In this present case study, optic neuritis, abundant nerve palsy, and acoustic nerve palsy were noted and contributed to the diagnosis. There are no typical imaging patterns for neurosarcoidosis. It could present as solitary or multiple enhancing intracranial parenchymal masses and might be mistaken for a primary or secondary tumor or a demyelinating disease in the central nervous system.^[18]

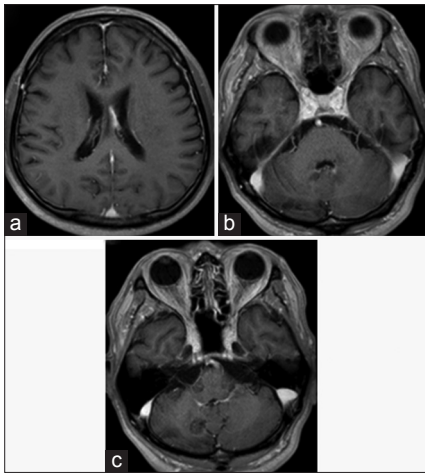


Figure 6: (a-c) After 12 months, all the lesions had resolved and had not recurred

In addition, relapsing and remitting courses are relatively common in neurosarcoidosis.^[17] In the present case study, there were enhanced lesions on the MRI in the right cerebellum at the time of hospital admission, and they almost disappeared after 2 weeks. Furthermore, the left lateral ventricle lesion followed a relapsing and remitting pattern. Although relapsing and remitting courses are also a common feature of multiple sclerosis (MS), the duration of the enhancement of lesions on the MRI in neurosarcoidosis patients is reported to be longer than that in MS patients.^[17] Neurosarcoidosis commonly exhibits enhancement of lesions for more than a few weeks. In contrast, MS does so for less than a week.^[17] In the present case study, the mass lesions exhibited enhancement for more than a month, which is a longer duration than that in MS. CSF studies are not specific for the diagnosis of neurosarcoidosis but very important for differential diagnosis. Typical CSF findings include elevated protein levels and a lymphocytosis, but it is not insensitive and about a third of patients with neurosarcoidosis have normal CSF. Moreover, positive oligoclonal bands are seen in 19–37% of neurosarcoidosis cases and elevated IgG is seen in a third of neurosarcoid patients, which makes it difficult to differentiate neurosarcoidosis from MS.^[9,18] Although CSF findings of neurosarcoidosis are not specific, CSF analysis should be performed to exclude other disorders including cryptococcal, tuberculous, and lymphomatous meningitis. Cytology and cultures of CSF may be useful. The noncaseating granulomatous inflammation exhibited in tissue biopsies is diagnostically suggestive of, but not a specific feature of, sarcoidosis, so alternative causes for granulomatous inflammation need to be excluded.^[8] In the present case study, atypical granulomatous inflammation was evident in the pathology analysis, so isolated neurosarcoidosis was diagnosed to the exclusion of other granulomatous diseases (e.g., tuberculosis, other parasitic infections,

or vasculitis). The rarity of isolated neurosarcoidosis and certain other granulomatous diseases can cause misdiagnosis, as Riku *et al.* described in a case in which germinoma was misdiagnosed as isolated neurosarcoidosis.^[16] Thus, it is necessary to consider other possible etiologies carefully when granulomatous inflammation is discovered through biopsy.

Isolated neurosarcoidosis tends to have a more favorable clinical prognosis than does neurosarcoidosis with extracranial organ involvement.^[12] A previous study noted that one-third of neurosarcoidosis patients had refractory illness associated with higher morbidity and mortality.^[1] Thus, the relatively good clinical course could be indicative of isolated neurosarcoidosis. It is noteworthy that neurological symptoms are the initial manifestation of sarcoidosis in approximately 50–70% of neurosarcoidosis cases.^[4] In these cases, some patients who are initially diagnosed with isolated neurosarcoidosis may eventually develop extra-neurological involvement, including the correspondingly poorer clinical outcome associated with systemic neurosarcoidosis. Neurosarcoidosis patients who truly have the isolated form respond well to therapy. However, when the treatment is delayed, responsiveness to treatment may also be reduced. Brinar and Habek reported on an isolated neurosarcoidosis case that had been initially diagnosed as tuberculosis.^[2] In that case, the diagnosis of isolated neurosarcoidosis was confirmed after 21 years of clinical follow-up, but corticosteroids or other immune-modulating/cytotoxic agents were not effective. This demonstrates that the prognosis could be poor unless treatment begins immediately. In addition, it is noteworthy that some other lesions such as primary nervous system lymphoma (PCNSL) can respond to steroids. Renal cell carcinomas, neuroblastomas, malignant melanomas, and germ cell tumors are reported to be able to respond to corticosteroid therapy.^[14] However, in these cases, the regression is transient and relapse can occur after some durations. The median duration of remission of PCNSL after steroid administration is reported to be 7 months.^[3] Therefore, careful observation after steroids administration could be helpful for differentiating other lesions which can respond to steroids from isolated neurosarcoidosis.

The diagnosis of isolated neurosarcoidosis requires compatible clinical findings, histological demonstration of noncaseating granulomas, and exclusion of other granulomatous diseases. In the present case study, multiple cranial nerve palsies, a relapsing and remitting clinical course, and granulomatous inflammation in the tissue biopsy contributed to the diagnosis. Isolated neurosarcoidosis tends to have more favorable clinical outcomes than neurosarcoidosis with extracranial organ involvement. Such a good prognosis was experienced by our patient, and this information could be useful to clinicians seeking to mitigate stress-related complications

in patients anxious over the symptoms they are experiencing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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