Brief Clinical Note

A case of neurosarcoïdosis with recurrent episodes of neurological dysfunction and diffuse cortical lesions on magnetic resonance imaging

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Abstract: We report a case of a 35-year-old man with histologically confirmed neurosarcoïdosis who developed recurrent episodes of right-hemispheric dysfunction with diffuse cortical lesions of the right hemisphere on magnetic resonance imaging (MRI). A brain biopsy revealed granulomatous inflammatory cells in both the subarachnoid space and Virchow-Robin space, which might relate to the recurrent neurological dysfunction and MRI findings.

Key words: Sarcoïdosis, Neurosarcoïdosis, Magnetic resonance imaging, Diffuse cortical lesion

Sarcoïdosis, a multisystem disorder of unknown cause, commonly affects young and middle-aged adults and frequently presents with pulmonary, ocular and skin lesions. It is diagnosed when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid-cell granulomas

About 10% of patients with sarcoïdosis develop neurological symptoms; neurosarcoïdosis can present in a variety of ways. Although magnetic resonance imaging (MRI) is a sensitive test for neurosarcoïdosis, diverse findings have been reported in neurosarcoïdosis

Therefore, neurosarcoïdosis is a diagnostic challenge, particularly when systemic sarcoïdosis has not been confirmed

Furthermore, brain biopsy—is necessary to make a definite diagnosis of neurosarcoïdosis— is difficult because of complications of accessing cerebral tissue.

We describe a case of a patient with histologically confirmed neurosarcoïdosis who developed recurrent episodes of neurological impairment of the right hemisphere with diffuse cortical lesions of the right hemisphere on MRI.

Case Report

A 35-year-old man developed fever and neurological dysfunction involving confusion and left-sided hemiplegia and was admitted to our hospital in early April, 2007 (1st admission). Cerebrospinal fluid (CSF) evaluation revealed leukocytosis with a predominance of mononuclear cells, low glucose levels and increased protein levels. He was treated as having a viral or bacterial meningitis with aciclovir and ceftriaxone. The neurological symptoms completely resolved in a week.

After one month, he developed fever and drowsiness after general malaise and was treated for recurrent meningitis (2nd admission) because of similar CSF findings to those of the 1st admission. His consciousness improved in several days. He had neither headaches nor nuchal rigidity throughout either clinical encounter.

In late September, five months after the 1st admission, he developed general malaise the night prior to admission. His family found him to be confused, and he was readmitted to our hospital (3rd admission). Physical examination revealed a temperature of 37.3°C and nuchal rigidity. Neurological examination revealed confusion, bilateral occasional conjugate deviation, rotation of the neck to the right, left unilateral spatial neglect, dysarthria, left-sided hemiplegia and mild lower facial palsy, and left-sided dysesthesia. His left-sided limbs were hypertonic and left plantar reflex was extensor.

At this 3rd admission, routine laboratory studies were notable for C reactive protein of 1.65 mg/dL (normal: < 0.24

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mg/dL) with normal calcium levels. Angiotensin-converting enzyme (ACE) level was 21.5 U/L (normal; 8.3-21.4 U/L). Soluble interleukin-2R (sIL-2R) level was 2,200 U/mL (normal; 220-530 U/mL). Examination of the CSF revealed leukocytosis of 7 mm$^3$ (normal; 0-5/mm$^3$) comprising 27% polymorphonuclear cells and 50% mononuclear cells, with protein levels of 185 mg/dL (normal; 15-50 mg/dL) and a glucose of 33 mg/dL (blood glucose level was 121 mg/dL). Tuberculin skin test was positive. Chest radiograph showed neither bilateral hilar lymphadenopathy nor lung lesions. The clinical course and laboratory data from the 1st admission are shown in Fig. 1.

The following were examined at either the 1st or 3rd or both admissions: anti-human immunodeficiency virus antibodies, anti-nuclear antibodies, anti-Sjögren syndrome-A antibodies, cytoplasmic and perinuclear staining for anti-neutrophil cytoplasmic antibodies, microbiology and culture of CSF for bacteria including tuberculosis and cryptococcus, PCR for tuberculosis and herpes simplex virus, and cytology. All of the above were negative.

Head MRI repeatedly taken from the 1st admission, demonstrated diffuse cortical lesions of the right hemisphere of hyperintensity on fluid-attenuated inversion recovery (FLAIR) (Fig. 2A, B) and T2-weighted images, especially remarkable at the 1st admission, with leptomeningeal enhancement at the right hemisphere on gadolinium-enhanced T1-weighted image (Fig. 2C). The signal intensities on diffusion-weighted image were not changed.

His left hemiplegia gradually became worse for a few days after the 3rd admission, but then improved after a week although he remained slightly confused. Neither nystagmus nor convulsions were noticed. Follow-up MRI revealed no change. Electroencephalogram taken four days after admission showed mild slow waves around frontal lobes, but neither laterality of background activities nor epileptiform discharge were found. Six days after admission, he developed vomiting and abdominal bulging, and abdominal computed tomography (CT) confirmed adynamic ileus and lymphadenopathy within the intraabdominal cavity. Chest CT revealed mediastinal lymphadenopathy, but no lung lesions.

**Fig. 1** The clinical course involving part of the laboratory data from the 1st admission. †: At the 1st and the 3rd admission, confusion and bilateral occasional conjugate deviation, rotation of the neck to the right, left unilateral spatial neglect, dysarthria, left-sided hemiplegia and mild lower facial palsy, left-sided hypertonic limbs, dysesthesia and left extensor plantar reflex were revealed. At the 2nd admission, only drowsiness after general malaise developed. mPSL; metylprednisolone. PSL; prednisolone. poly; polymorphonuclear cells. mono; mononuclear cells.
Fig. 2  Magnetic resonance imaging (MRI) of the patient before therapy (1.5T, MAGNETON VISION PLUS, SIEMENS) at the 1st admission (A) and the 3rd admission (B) shows right-hemispheric diffuse cortex lesions of hyperintensity (arrow) on fluid-attenuated inversion recovery (FLAIR) image (TR = 8,000, TE = 110). Bilateral, periventricular foci of hyperintensity are also noticed. Gadolinium-enhanced T1-weighted image (TR = 621, TE = 12) at the 3rd admission shows leptomeningeal enhancement at the right hemisphere (arrowhead) (C). Lymph node biopsy of the mediastinum reveals noncaseating epithelioid granulomas and multinucleated giant cells (D; hematoxylin-eosin, original magnification ×100). Right temporal lobe biopsy shows noncaseating epithelioid granulomas and related inflammation in the subarachnoid space (arrow) (E; hematoxylin-eosin, frozen section, original magnification ×100) and in the Virchow-Robin space (F; hematoxylin-eosin, and G; hematoxylin and anti-CD34 staining vascular endothelium, original magnification ×400).

Whole-body gallium scan was negative. Bronchoalveolar lavage was not performed.

After receiving informed consent from the patient and his family, we performed a biopsy of the lymph nodes of the mediastinum under mediastinoscopy (Fig. 2D) and a brain biopsy from the right temporal lobe (Fig. 2E, F, G). Both revealed noncaseating epithelioid-cell granulomas without findings of tuberculosis, fungus, or malignancy. In the brain, the granulomas and lymphocytic infiltration were seen both in the subarachnoid space and Virchow-Robin space. We did not see any degeneration or inflammation of vessel walls, or necrosis of neurons.

We diagnosed his disease as neurosarcoidosis and started prednisolone 1.0 mg/kg/day after pulsed intravenous methylprednisolone were given because of a recurrence of neurological symptoms and adynamic ileus. The symptoms sub-
sided in a week as in the past. Tapering the dosage of prednisolone to 0.3 mg/kg/day, his neurological symptoms have not recurred for a year. Follow-up laboratory data revealed improvement of his CSF findings including the CSF-ACE level, and a decrease in the serum-ACE and sIL-2R levels. Follow-up MRI after four months revealed improvement of cortical and leptomeningeal lesions.

Discussion

According to the criteria proposed by Zajicek et al, our patient had definite sarcoidosis: clinical presentation suggestive of neurosarcoidosis (meningitic illness) with exclusion of other possible diagnoses and positive nervous system histology\(^4\). These findings coupled with the positive mediastinal biopsy also fulfilled the criteria for sarcoidosis used in Japan\(^5\).

He only showed drowsiness at the 2nd admission, but we thought his recurrent neurological impairments were likely related to the right-sided diffuse lesions on MRI. What was the mechanism that caused the lesions and recurrent episodes of neurological impairments? Based on seven autopsied cases, Matsushita reported that the pathology of neurosarcoidosis was associated with perivascular—predominantly perivenous—noncaseating epithelioid-cell granulomatous inflammation in both the meninges and parenchyma. Narrowing of the vascular lumen was sometimes noted when inflammation involved the walls at later stages\(^6\). Generally in sarcoidosis, other than the fact that granulomatous inflammatory cells take up space and thus their bulk modifies the local architecture, for all except late-stage cases, there is no evidence that the cells injure the affected organ by releasing mediators that damage the normal structure\(^7\). Organ dysfunction in sarcoidosis results mostly from the accumulated inflammatory cells distorting the architecture of the affected tissue\(^8\). If the disease is suppressed, either spontaneously or with therapy, the mononuclear inflammation is reduced\(^7\). The absence of vasculitis in our patient suggests an early stage of neurosarcoidosis although biopsy results may be unreliable. The cortex was only mildly affected by the granulomatous inflammation, and corticosteroid therapy appeared to help the inflammatory cells disperse before fibrosis and irreversible parenchymatous damage developed.

Various MRI findings of neurosarcoidosis have been reported, including periventricular and white matter lesions, solitary/multiple brain and spinal lesions, solitary intra/extraxial mass, leptomeningeal enhancement, hydrocephalus, intracranial hemorrhage, cerebral infarction and enhancing nerve roots\(^9\)–\(^10\). The diffuse cortical lesions seen in our patient—which have not been discussed thoroughly in neurosarcoidosis—suggest that granulomatous inflammatory cells invaded the Virchow-Robin space.

References