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A Case of Miller Fisher Syndrome with Cerebellar Hypoperfusion

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We report a case of a 76-year-old man with Miller Fisher syndrome presenting with acute ophthalmoplegia and ataxia. Cerebrospinal fluid analysis showed normocytosis with an increased protein level. Serum anti-GQ1b IgG and anti-GT1a IgG antibodies were positive. Based on these results, the patient was diagnosed with Miller Fisher syndrome. He was treated with two courses of intravenous immunoglobulin, which improved his neurological symptoms. Brain perfusion single-photon emission computed tomography showed that cerebellar blood flow was decreased in the acute stage of the disease and improved after treatment. Although the prevailing view is that ataxia in Miller Fisher syndrome patients is of a peripheral origin, this case suggests that cerebellar hypoperfusion contributes to the development of ataxia in Miller Fisher syndrome.

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Introduction

Miller Fisher syndrome (MFS) is characterized by the classical triad of ophthalmoplegia, ataxia and areflexia, and is considered a variant of Guillain–Barré syndrome (GBS) (Fisher 1956). Anti-GQ1b IgG antibodies are associated with neurological symptoms in MFS (Chiba et al. 1992). Complete improvement of signs and symptoms occurs over an average of 10 weeks, and almost all patients have a good prognosis (Mori et al. 2001; Arányi et al. 2012). The GQ1b ganglioside is expressed in the oculomotor, dorsal ganglion neurons, and muscle spindles (Chiba et al. 1992; Liu et al. 2009; Yuki and Hartung 2012).

Whether ataxia in patients with MFS is of a central or peripheral origin remains unclear. Currently, the prevailing view is that ataxia is of a peripheral origin and is caused by selective involvement of Ia afferent fibers (Ropper and Shahani 1983; Kuwabara et al. 1999; Mori et al. 1999). However, there have been cases that showed abnormalities in the brainstem or cerebellum of patients with MFS (Al-Din et al. 1982; Barontini and Sitá 1983; Taphoorn et al. 1989; Petty et al. 1993; Urushitani et al. 1995; Kim et al. 2009; Sandler et al. 2015).

To our knowledge, few studies have examined the cerebellar blood flow on brain perfusion single-photon emission computed tomography (SPECT) in patients with MFS. Here, we report the first case of a patient with MFS presenting with decreased cerebellar blood flow on brain perfusion SPECT in the acute stage.

Case Presentation

A 76-year-old Japanese man was referred to our hospital for acute onset of double vision and gait disturbance. He had watery diarrhea 13 days before the onset of symptoms, and his neurological symptoms gradually worsened over the past 11 days. He was hypertensive. His previous medical history included an inguinal hernia, bilateral cataract, and an old lacunar infarct.

On admission, the general physical examination revealed no abnormalities. Neurological examination showed dilated pupils (6 mm/6 mm) and attenuated pupillary light reflex in both eyes. The oculocephalic reflex (OCR) and the convergence reflex were absent in both eyes. Eye movement was limited: the right eye was fixed at the midline, while the left eye had movement restriction when gazing to the left. He had binocular diplopia in all directions. No dysphagia or dysarthria was noted. He had dysdiadochokinesia, and the finger-to-nose and knee-heel tests

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revealed decomposition of movement and dysmetria. These symptoms did not change with closed or opened eyes. The deep tendon reflexes were normal. Vibration sensation and joint position sense were maintained in both the lower extremities. No superficial sensation loss or peripheral motor deficit was noted. When standing, the trunk was upset from the time of opening the eyes, but Romberg's sign was negative. Moreover, he was unable to stand on one foot. Walking was highly agitated and in an open-leg position; therefore, it was almost impossible to perform tandem gait.

Cerebrospinal fluid analysis showed normocytosis and an elevated protein level (105.3 mg/dl; reference range ≤ 40.0 mg/dl). The serology test was positive for anti-GQ1b IgG and anti-GT1a IgG antibodies. The nerve conduction study was mildly abnormal. In the lower extremity nerves, motor nerve conduction velocity and minimal F-latency were mildly decreased. All sensory parameters showed normal responses. Brain magnetic resonance imaging (MRI) showed no abnormalities. However, after suspecting cerebellar involvement, we performed technetium-99m ethyl cysteinate dimer (Tc-99m ECD) SPECT, which revealed reduced cerebellar blood flow. Informed consent was obtained for this from the patient (Fig. 1A).

Based on the diagnostic examination results, the patient was diagnosed with MFS (abortive type). He received two courses of a 5-day course of intravenous immunoglobulin (IVIg), and his symptoms gradually improved. Repeat SPECT after treatment showed improvement in cerebellar blood flow (Fig. 1B). He continued rehabilitation, and his neurological symptoms normalized approximately 5 months after the onset. The course of symptoms is shown in Fig. 2.

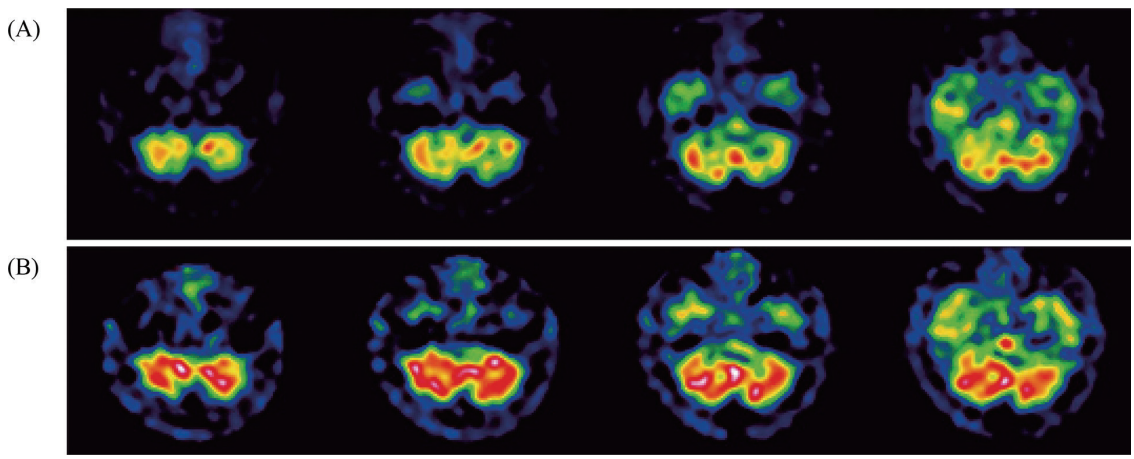

Fig. 1. Changes in cerebellar blood flow pre- and post-treatment.
Brain perfusion single photon emission computed tomography (SPECT; 99mTc-ECD) showed decreased cerebellar blood flow in the acute stage of the disease (A: onset 25 days). On follow-up SPECT study, cerebellar blood flow increased with subsequent improvement of ataxia (B: onset 46 days). Cerebellar blood flow was calculated using the three-dimensional stereotaxic Region of Interest template method. (A) Regional cerebral blood flow (rCBF) (mL/100 g/min): 40.19 (right), 36.53 (left). (B) Regional cerebral blood flow (rCBF) (mL/100 g/min): 51.63 (right), 48.80 (left). SPECT, Brain perfusion single photon emission computed tomography.

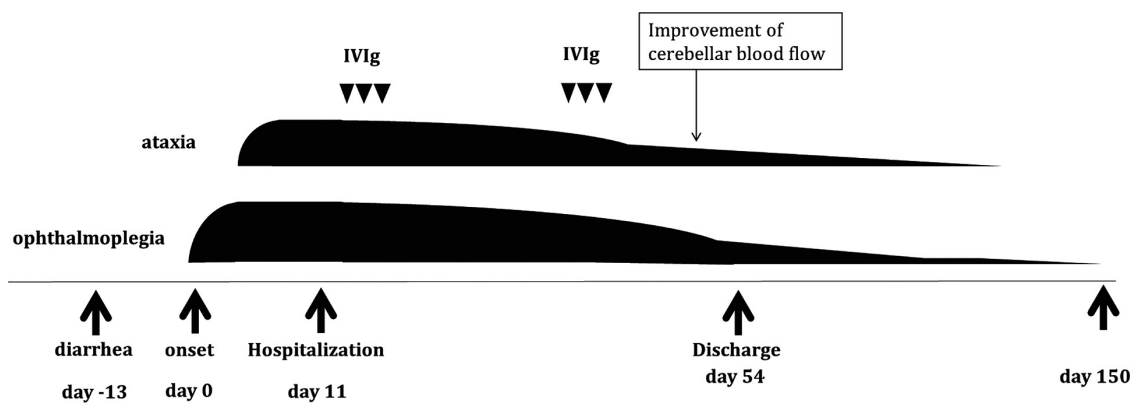

Fig. 2. Clinical course.
The time course of this patient is shown. Two courses of 5-day course of intravenous immunoglobulin (IVIg) were administered, and his symptoms gradually improved. He continued rehabilitation and approximately 5 months following onset, his neurologic symptoms normalized.

Discussion

We describe a case of MFS presenting with cerebellar hypoperfusion in the acute stage of the disease that manifested as acute ophthalmoplegia and ataxia. Cerebellar blood flow was restored as the symptoms improved. In this case, whether the ataxia was of central or peripheral origin was unclear. We considered the neurological, imaging findings and anti-GQ1b IgG antibody.

Fisher (1956) reported that it is difficult to determine from clinical observations whether ataxia is a cerebellar or deep sensory disturbance. However, he speculated that the responsible lesions for the loss of tendon reflexes were the areas comprising the reflex arc. He proposed that ataxia was of a peripheral origin and caused by a widespread and selective attack on sensory neurons (Fisher 1956). In this case, the patient's deep tendon reflexes in the extremities were preserved. Additionally, no disturbance of deep sensibility, such as loss of vibration or joint position sense, was observed. Furthermore, his limb and truncal ataxia did not worsen with closed eyes. His neurological findings clinically indicated cerebellar ataxia rather than sensory ataxia.

The most interesting finding is that cerebellar blood flow on brain perfusion SPECT decreased in the acute stage of MFS and increased once ataxia improved. Tc-99m ECD, a lipid-soluble tracer, undergoes ester hydrolysis, and the acid metabolite is trapped intracellularly for a prolonged period. Therefore, the Tc-99m ECD distribution might reflect not only cerebral blood flow but also neuronal dysfunction (Shelley and Trimble 2004; Kataoka et al. 2007). In this case, the temporal changes in cerebellar blood flow indicated that cerebellar hypoperfusion contributed to ataxia. This case supports the hypothesis that ataxia is of a central origin, at least in part, in patients with MFS. Central nervous system abnormalities have been detected in patients with MFS on MRI, magnetic resonance spectroscopy (MRS), or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (Al-Din et al. 1982; Barontini and Sitá 1983; Taphoorn et al. 1989; Petty et al. 1993; Urushitani et al. 1995; Kim et al. 2009; Sandler et al. 2015). On MRI, several cases with MFS showed abnormal intensities in the brainstem, including the midbrain, medulla oblongata, and posterolateral brainstem peduncular area around the fourth ventricle (Al-Din et al. 1982; Barontini and Sitá 1983; Taphoorn et al. 1989; Petty et al. 1993). Moreover, one case with MFS–GBS overlap showed enhanced lesions in the spinocerebellar tract at the level of the lower medulla on MRI (Urushitani et al. 1995). Meanwhile, in a case of MFS, MRS showed decreased N-acetylaspartate/creatine ratio in the cerebellum (Sandler et al. 2015). Furthermore, in 10 cases with MFS, FDG-PET studies showed decreased cerebellar glucose metabolism (Kim et al. 2009). In a case of Bickerstaff's encephalitis, which is known to be on the same disease spectrum as MFS (Yuki et al. 1993a; Odaka et al. 2001), SPECT of the brain using ^{123}I-N-Isopropyl-4-iodoamphetamine showed hypoperfusion of the brainstem and bilateral cerebellar cortex during the acute phase, with an improvement during the recovery phase (Yoshida et al. 2018). However, multiple enhancement in the cranial nerves in MFS has been reported (Pedotti et al. 1998; Tanaka et al. 1998; Kiphuth et al. 2009), providing direct evidence that MFS is a peripheral origin disease. In the present case, although SPECT was abnormal, no cranial nerve enhancement was observed.

The anti-GQ1b IgG antibody is detected in approximately 90% of patients with MFS (Chiba et al. 1992). Therefore, it is considered a useful diagnostic marker of MFS. Although the pathological role of anti-GQ1b IgG antibody remains unclear, its activity is associated with ophthalmoplegia and ataxia severity (Yuki et al. 1993b; Mizoguchi 1998; Kusunoki et al. 1999). The GQ1b ganglioside is expressed in the paranodal regions of the oculomotor, trochlear, and abducens nerves, dorsal ganglion neurons, and muscle spindles (Chiba et al. 1993; Siemieniuk et al. 2012). Immunocytochemical staining showed that serum from patients with MFS or GBS had increased levels of anti-GQ1b IgG antibodies that selectively stained the cerebellar molecular layer (Kornberg et al. 1996). In rat models of MFS, anti-GQ1b IgG antibodies inhibited voltage-dependent calcium channel currents in cerebellar granule cells (Nakatani et al. 2009). Moreover, autopsy cases of MFS or ataxic GBS showed loss of Purkinje neurons (Berlit and Rakicky 1992) or degeneration of posterior and Clarke columns (Richter 1962). These findings suggest that diseases associated with anti-GQ1b IgG antibodies involve the central nervous system and peripheral nerves.

We reported the first case of MFS with cerebellar hypoperfusion on brain perfusion SPECT. This case suggests that decreased cerebellar blood flow due to cerebellar damage directly or secondary to the involvement of the spinocerebellar tract contributes to ataxia. Generally, SPECT is not performed frequently due to medical radiation exposure; however, we performed SPECT pre- and post-treatment to differentiate whether there was any other disease involvement in his cerebellar ataxia other than MFS. No improvement in cerebellar blood flow would suggest that he had degenerative diseases. The limitations of this report are that there was only one case. Second, it is important to note that not all the cerebral blood flow hypoperfusion are of central origin, as mistimed peripheral nerve input could also cause changes in cerebellar blood flow (Bain et al. 1996; Suzuki et al. 2012). Whether ataxia in patients with MFS is of a central or peripheral origin remains controversial. However, temporal changes in cerebellar blood flow support the hypothesis that ataxia is of a central origin, at least in part, in patients with MFS.

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Conflict of Interest

The authors declare no conflict of interest.

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