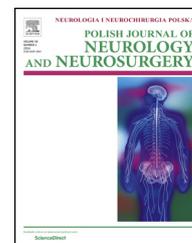


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Case Report and Review

Miller-Fisher syndrome associated with unilateral cerebral white matter lesions

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ABSTRACT

Miller-Fisher syndrome (MFS) is characterized by classical triad of ophthalmoplegia, ataxia and areflexia. The involvement of cerebral white matter in MFS is very rare. We report a typical MFS patient whose brain MRI showed unilateral and extensive involvement in cerebral white matter. We also found mild pleocytosis and raised protein concentration in cerebrospinal fluid. Deficits resolved completely after treatment with intravenous immunoglobulins. Subsequent brain MRI shows cavity formation in involved white matter.

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1. Introduction

Miller-Fisher syndrome (MFS), which is characterized by ataxia, ophthalmoplegia and areflexia, is considered to be a variant of Guillain-Barré syndrome (GBS) [1]. It is reported that central nervous system (CNS) could also be involved in MFS [1]. The involvement sites of CNS in MFS are mainly pons, medulla oblongata [1], cerebellar peduncles [2], and occasionally, optic nerves [3]. However, the involvement of cerebral white matter in MFS is very rare. Here, we report a typical MFS patient whose brain MRI showed unilateral and large lesions in cerebral white matter.

2. Case report

A 37-year-old man who had no history of toxic substance exposure or alcohol abuse, no past medical or family history was admitted with double vision and unsteadiness of gait. The patient also had dizziness, left eyelid ptosis and distal numbness on both of the upper limbs. He had antecedent infections 5 days before the onset of the disease. He had no fever on admission and was fully conscious without signs of meningeal irritation. He had asymmetrical partial ptosis and external ophthalmoplegia, and left eye was more severe than the right eye; the light reflex of the pupils was well maintained. Examination of other cranial nerves showed no positive findings. The patient showed no weakness of all the limbs, but all tendon reflexes were absent. No pathological reflexes were found. Finger-to-nose and heel-to-knee tests in both

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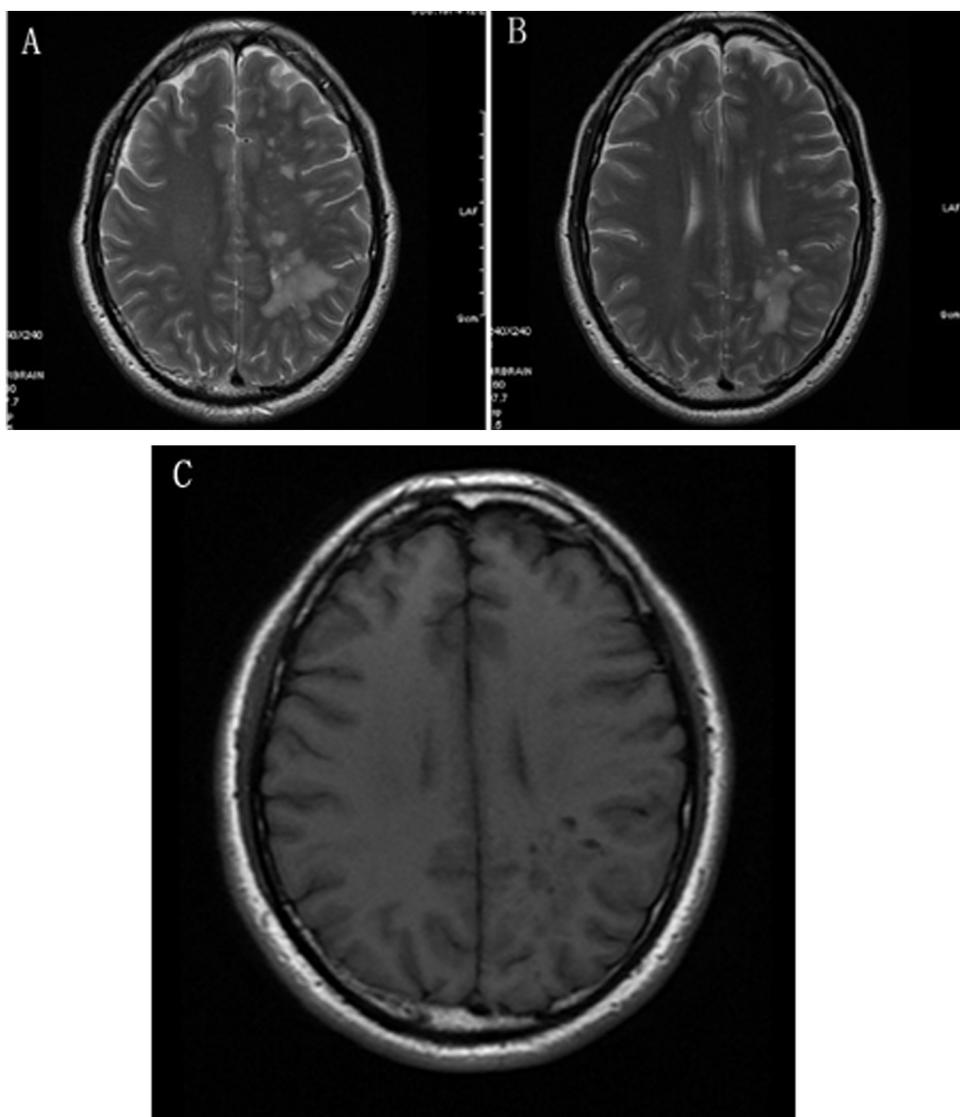


Fig. 1 – T2 weighted MRI on day 6 shows multiple lesions in the juxtacortex, subcortex and deep white matter in the left frontal and occipital lobe (A and B), and T1 weighted MRI shows cavity formation on day 360 (C).

sides were positive, and the patient had cerebellar gait. Pinprick sensation was impaired on the distal part of both of the upper limbs. Cardiovascular, respiratory, gastrointestinal, and ear, nose and throat findings were normal. There were no ticks found on the skin, and no rash.

Biochemical, hematological, liver and renal function investigations were normal. Serological tests for syphilis and HIV were negative. Concentrations of gammaglobulin and complement were normal, auto-antibody screen and rheumatoid factor were negative. Chest radiography and ECG showed no abnormality. Lumbar puncture showed that pressure was 200 mmH₂O, and CSF contained 10 lymphocytes/mm³ and 0.26 g/l protein (on day 7). On day 6, brain MRI showed multiple lesions in the juxtacortex, subcortex and deep white matter in the left frontal and occipital lobe (Fig. 1A and B). The signals were hypointensive in T1-weighted images and isointensive in DWI images (not shown). The lesions were not enhanced after contrast administration (not

shown). The cerebellum and brainstem were not involved. Brain CT angiography and Orbital CT scan were normal (not shown). Electromyography of limb muscles was normal. Neurophysiological examination showed tibial H reflexes were absent. However, the motor and sensory nerve conduction velocity in ulnar, median, tibial, peroneal and sural nerves was normal, and distal motor latencies were normal. Intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) was started on day 5. Tendon reflexes re-appeared and pinprick sensations of upper limbs were normal on day 18, and gradual improvement in ataxia and ocular movement ensued in the following 2 weeks until the time when recovery was complete (day 60). On day 18, lumbar puncture showed that the pressure was 195 mmH₂O, the CSF contained 0.58 g/l protein and 14 lymphocytes/mm³. Brain MRI of day 180 and day 360 were similar to that of day 6, but cavity formation in the involved matter could be found in brain MRI of day 360 (Fig. 1C). No recurrence was seen in one-year follow up.

3. Discussion

MFS which is characterized by the classical triad of ataxia, ophthalmoplegia and areflexia described by Fisher in 1956 is now considered as a clinical variant of GBS [1]. MFS is an acute postinfectious paralytic illness [1]. In our case, the antecedent infections, the classical triad of symptoms, symmetrical impaired superficial sensation on distal part of limbs, elevated CSF protein concentration, absent H reflexes and clinical course support the diagnosis of MFS.

Several reports consider that MFS can involve both peripheral nervous system (PNS) and CNS [2,4]. The brainstem and cerebellum are the most common CNS sites involved in the MFS [1]. Some reports described MFS could involve optic nerves [3], one MFS case reported the involvement of spinocerebellar tracts [5]. Ito et al. [6] reported a large series of Bickerstaff's brainstem encephalitis and MFS which contains 466 MFS patients. In this series, only 1% of 353 MFS patients have abnormal CNS findings in MRI, and the abnormal CNS lesions only include midbrain, cerebellum, or middle cerebellar peduncle. To the best of our knowledge, only one MFS case reported involvement of cerebral white matter [7]. In this report, only one small lesion on each side of the cerebral matter was found, and the brainstem was also involved. In our case, we found that the lesions in cerebral white matter were multiple, unilateral and extensive. The involved sites include juxtacortex, subcortex and deep white matter. The brainstem and cerebellum are not involved. These findings are not reported before in MFS case. The previously reported GBS patients with CNS involvement usually had CNS symptoms, such as reduced consciousness level or seizure [8,9]. However, the CNS clinical manifestations in our case were not obvious although CNS involvement in MRI is extensive, which indicates that an association of CNS involvement in MFS patients may be underestimated because some lesions can be clinically silent.

There are some possible explanations for the CNS lesions in our patient. White matter demyelination is possible. The CNS and PNS may share some common pathogenic epitopes [10,11]. Animal studies showed that peripheral nerve antigen could induce CNS lesions [12], and PNS lesions could be induced in experimental allergic encephalitis [13]. Okumura et al. also observed demyelinated lesions in subcortex and deep white matter in a GBS patient [14]. In MFS, serum anti-GQ1b antibody was positive in about 85% of patients [15]. Apart from anti-GQ1b, other antibodies associated with development of MFS include anti-GT1a, anti-LM1, anti-GD3, anti-GM1b, GD1b, GalNAc-GD1a, GD1b, etc. [1,16,17]. Maybe there are other uncommon antibodies associated with development of MFS to be discovered. Some of these uncommon antibodies may induce subcortex and deep white matter lesions in MFS. Echaniz-Laguna et al. [7] found bilateral cerebral white matter lesions in brain MRI in a MFS patient, but the search for anti-ganglioside antibodies (including GQ1b, GT1a/b, GM1/2/3, GD1a/b, etc.) was negative. Even in the absence of demyelination, CNS involvement in MFS is possible. Maier et al. [18] researched the CNS pathology in GBS patients, and found perivascular cuffing of lymphocytes and microglial activation in CNS. Patients with reversible posterior leukoencephalopathy often have visual disturbance, loss of

consciousness and seizures, and this syndrome is often with a condition in which blood pressure rises sharply. Our patient did not have hypertension and CNS symptoms, MRI lesions were unilateral. It seems like reversible posterior leukoencephalopathy is unlikely in our case.

MFS is one part of anti-GQ1b antibody syndrome which is in fact a spectrum of disease because of their common clinical and immunological profiles. Anti-GQ1b antibody syndrome includes MFS-Bickerstaff brainstem encephalitis (BBE) syndrome (including MFS and BBE), pharyngeal-cervical-brachial weakness (PCB), MFS-BBE syndrome overlapped by PCB, and MFS-BBE syndrome overlapped by GBS. MFS also includes some incomplete forms, such as acute ophthalmoparesis, acute ptosis, acute mydriasis, etc. The lipo-oligosaccharides of the bacteria (such as *Campylobacter jejuni*) isolated from MFS or BBE patient were proved to mimic GQ1b, so patients with certain immunogenetic backgrounds infected with *C. jejuni* strains will produce anti-GQ1b antibodies. GQ1b is highly expressed at oculomotor, trochlear, abducens nerves, glossopharyngeal and vagal nerves, group Ia afferents in muscle spindles. Binding of anti-GQ1b antibody at these sites could explain most of the symptoms of anti-GQ1b antibody syndrome [19].

The demyelinated lesions in central nervous system could persistently exist. For example, in multiple sclerosis (MS), the demyelinated lesions will present as a new white spot on proton density/T2-weighted MRI after the acute phase. Variable myelin and axon injury exists in inflammatory demyelinating disease of CNS (such as MS). However, the environment in CNS is unfavorable for the regrowth of axons and the axons cannot be remyelinated completely [20]. The subsequent axon degeneration and gliotic process results in scar formation and presents as a T1-black hole or a T2-bright spot [21]. Andoni Echaniz-Laguna et al. [7] also reported that the abnormal lesions in white matter in a MFS case had only partially regressed 160 days later after the onset. For the demyelinating diseases of PNS (such as GBS), the axons are relatively preserved, the environment of PNS is much more favorable than that of CNS for the regrowth of axons and remyelination of axons, and myelin cells of PNS (Schwann cells) can remyelinate the axons completely [22]. So it is not surprising that in our case, the peripheral symptoms resolved completely after treatment, but the lesions in the white matter still existed one year after the onset of the disease.

In the second lumbar puncture in our case, mild pleocytosis could be observed. This pleocytosis may be attributable to the use of immunoglobulin. Aseptic meningitis is one of the common complications of intravenous immunoglobulin injection. However, there is no headache and meningeal irritation sign for this patient. In MFS itself, the CSF pleocytosis is also possible. A clinico-pathological research in a fulminant GBS case shows that on day 1 CSF contained 100 leukocytes/mm³. A repeated CSF examination in the same case showed 10 leukocytes/mm³ 12 days later [23]. Another clinico-pathological investigation of 5 GBS cases also showed a CSF cell count of more than 50/ul in two cases and a significant proportion of polymorphonuclear granulocytes in the CSF sediment in three cases [24]. Ito et al. [6] reported a large series which contains 466 MFS patients. In this series, CSF pleocytosis could be observed in about 4% MFS patients, and the cell

count in CSF could be more than 100/ μ l. Pronounced inflammation of nerve roots may lead to an increased CSF cell count or a proportion of polymorphonuclear granulocytes, and the CSF pleocytosis may not exclude the diagnosis of GBS or MFS. CSF pleocytosis is also seen in demyelinating CNS disorders such as multiple sclerosis. In our case, the inflammation of nerve roots or the leakage of blood–brain barrier may cause the mild pleocytosis in CSF.

Our case shows the involvement of cerebral white matter in MFS, which further indicates that MFS can affect not only brainstem and cerebellum, but also cerebral white matter in CNS.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at [doi:10.1016/j.pjnns.2015.07.008](https://doi.org/10.1016/j.pjnns.2015.07.008).

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