Anti-GQ1b IgG and Anti GD1b IgG Positive Recurrent Miller Fisher Syndrome

Sir,

Miller Fisher syndrome (MFS) is a clinical condition first reported in 1956 by Miller Fisher at Harvard Medical School. It is characterized by total external ophthalmoplegia, ataxia, and reduced or absent deep tendon reflexes.[1] MFS is often associated with various other disorders such as infections caused by Hemophilus influenza, Campylobacter jejuni, Epstein-Barr virus, Salmonella enteritidis, Cytomegalovirus, Chlamydia pneumonia and Mycoplasma pneumonia, and Burkitt lymphoma.[2] Though the presentation of MFS is dramatic, it is a benign, self-limited disease with complete recovery within weeks.[3] Both central nervous system changes (abnormalities at pons, brainstem, cerebellar tract, or posterior column) and peripheral nervous system changes have been reported in MFS.[3,4] However, available evidence indicate MFS to be a variant of Guillain-Barre syndrome with peripheral nerve demyelination as the classic pathologic mechanism.[3] Anti GQ1b immunoglobulin G (lgG) antibodies have been found in 80-100% of patients with MFS, especially in cases with ophthalmic involvement.[3,5] However, anti GD1b IgG antibodies have not been reported with MFS. Rather, it is used to differentiate ataxic variant of GBS from MFS in clinical practice. Here, we report a rare case of recurrent MFS. To the best of our knowledge, this is the first case of recurrent MFS with ophthalmic involvement and ataxia associated with anti GQ1b lgG and anti GD1b IgG antibodies.

A 42-year-old male patient presented at the emergency department with double vision and difficulty to walk for 3 days. He reported headache and tendency to cough after taking fluid. There was no history of fever, seizure, loss of consciousness, trauma, slurred speech, chest pain, or palpitation. It was also learned that he had past history of two admissions with diplopia and ataxia in 2001 and 2009, respectively, and that he improved within one month. No document regarding previous treatments were available. Available information from wife of the patient revealed that he was treated with dexamethasone in 2009 episode. No antibody titres were done during last 2 episodes.

A neurological evaluation revealed ophthalmoplegia, ataxia, areflexia, dysarthria, hand grip weakness and positive Rhomberg sign. He was clinically diagnosed as Miller Fisher variant with hand grip weakness and bulbar involvement. In view of potential respiratory muscle involvement, he was started on IV IgG and given for 5 days. Initial nerve conduction study (NCS) and NCS repeated after one week was normal. Nerve conduction study was done 3rd day of illness and repeated on 9th day of illness. Studied nerves were CMAP and SNAP of median and ulnar in both upper limbs, CMAP of peroneal and tibial nerve both lower limb and SNAP of superficial peroneal and sural nerve both lower limb. Both nerve conduction studies were absolutely normal. H reflex was not done. No information regarding nerve conduction study of previous episodes were available. CSF study was not done as the patient not given the consent. Meanwhile antiganglioside antibody assay was done and it showed very high titre for anti GD1b and anti GQ1b antibody. He completed his IVIgG (400 mg/Kg body weight for 5 days), and his condition slowly improved.

Recurrent MFS is rarely reported in the published literature. However, a recent study that looked at patients admitted with GBS, MFS, and Bickerstaff brainstem encephalitis (BBE) in a tertiary hospital showed that recurrence of symptoms occurs at a higher rate in patients with MFS or BBE than GBS. The study also found that patients with recurrent MFS had a tendency to be younger at the first episode than patients with non-recurrent MFS (median, 22 versus 37 years old), and symptoms and signs were less severe during relapses than

during the initial episode in recurrent patients.[6] Our patient is a middle aged male who had recurrent MFS since 2001, and in all episodes he had ophthalmic involvement which is relatively uncommon presentation.[3] Ito *et al*., also reported the case of a 33-year-old male patient with GQ1b-seronegative BBE (Bickerstaff brainstem encephalitis)-GBS after two prior episodes of MFS-GBS. Like our case, the reported case also showed ophthalmoplegia in all episodes.[7]

MFS is thought to result from an aberrant acute autoimmune response to a preceding infection through molecular mimicry directed toward the myelin or the axon of the peripheral nerve.[8] Several studies have suggested that antibodies against gangliosides, the IgG anti-GQ1b antibody, are a specific feature of MFS.[5] The GQ1b antigen is highly expressed in the oculomotor, trochlear and abducens nerves as well as in muscle spindles in the limbs.[9] The presence of ophthalmoparesis in MFS is thought to result from a direct action of anti-GQ1b antibodies on the neuromuscular junction between the cranial nerves and ocular muscles.[5]

Anti-GD1b antibodies are usually used clinically to differentiate between ataxic variant of GBS from MFS.[10] A diagnosis of the ataxic variant of GBS is considered for cases with anti-GD1b and without anti-GQ1b, whereas the diagnosis of MFS can be made in cases where there is ophthalmic involvement with anti-GQ1b and without anti-GD1b.[10] Anti-GDIb antibodies binds to perinodal myelin, primary sensory neurons, and dorsal root ganglion cells, and can exist in the cerebellar granular layer, the dentate nucleus, and the olivary nucleus.[10] MFS with positive anti-GD1b and anti-GQ1b antibodies is extremely rare. A recent study exploring the clinical relevance of serum antibodies to GD1b in immune-mediated neuropathies found that 3 of the 29 patients with GBS and MF-GBS had IgG antibodies to both GD1b and GQ1b (10.3%). The study also highlighted that specificity of serum anti-GQ1b antibodies that they were solely found in MFS, MF-GBS and GBS patients. Moreover, approximately one third of the GBS and MF-GBS patients with anti-GD1b antibodies had additional antibody reactivity to GM1 and presence of anti-GD1b antibodies indicates a favourable outcome.[11] Our case also indicate the lack of specificity of anti-GD1b in differentiating ataxic variant of GBS from MFS, but highlights its association with the clinical symptom of ataxia.

However, it should be kept in mind that the presence of GD1b antibodies could also be due to their cross-reaction with GQ1b/GT1a complex antibodies.

The electrophysiological abnormalities reported in MFS show reduced or absent sensory responses without slowing of sensory conduction studies with little electrophysiologic evidence of demyelination which is distinct from GBS.[12] NCS in our patient was normal during initial evaluation and on repetition after one week.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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