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Editorial Open Access

The Miller Fisher Syndrome

Eduardo A. De Sousa[1] and Jin Jun Luo[2]*

[1]Department of Neurology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104 m, USA
[2]Department of Neurology and Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA 19140, USA

Editorial

The eponym Miller Fisher syndrome (MFS) was named after Dr. Charles Miller Fisher (December 5, 1913- April 14, 2012). Besides his significant contributions to our current understanding of cerebrovascular disease, such as carotid occlusion syndromes, lacunar infarcts and related syndromes, Dr. Fisher is also credited in the field of neuromuscular medicine for describing a syndrome now known to be a variant of Guillain-Barré syndrome (GBS). In his original manuscript published in 1956, Dr. Fisher described 3 patients with acute onset of ophthalmoplegia, ataxia and areflexia that followed acute upper respiratory infections. All 3 patients eventually improved in the following months. At the time the pathophysiology for MFS was uncertain but suspected to affect peripheral nerves. The findings of areflexia and elevated cerebrospinal fluid protein described his original article were reminiscent of GBS [1].

Currently MFS variant of GBS is thought to occur in up to 5% of all GBS cases in Western countries, with higher incidence in Asian countries [2-4]. Differently from other autoimmune diseases, MFS occurs more frequently in men than women by a ratio of approximately 2:1 [5]. The onset of MFS varies from 13 to 78 years of age with a mean of 43.6 years. The triad of ataxia, ophthalmoplegia, and areflexia constitutes the core symptoms of MFS. The diagnosis of MFS is usually made based on clinical grounds. The common initial symptom is diplopia due to bilateral extraocular muscles weakness with horizontal, followed by vertical, gaze inability. Eyelid ptosis may be present at the peak of disease course in more than half of cases but pupillary function is usually spared. Ataxic gait is a predominant symptom of MFS. Muscle strength is usually preserved but superimposed incoordination from sensory ataxia may emerge. Gradual and complete recovery over weeks to months is common in most of MFS patients.

Concern for brainstem disease, mainly stroke or CNS demyelination from multiple sclerosis, is often encountered due to the ominous signs of oculomotor cranial nerve dysfunction and diminished muscle stretch reflexes that can occur in the acute phase of a CNS disease. The key clue to MFS is the presentation of profound sensory ataxia. Wernicke encephalopathy also presents with ataxia and ophthalmoplegia but typically affects the lateral recti causing esotropia, and it is often seen in individuals with malnutrition, such as alcoholics with thiamine deficiency. Wernicke encephalopathy patients usually have apparent symptoms and signs of peripheral neuropathy.

Advances in research have shed light on the pathogenesis of MFS. Findings of antiganglioside antibodies have disclosed immune-mediated mechanisms in GBS and in MFS via molecular mimicry [6]. Exogenous pathogens, such as *Campylobacter jejuni*, may have specific capsular antigens that share epitopes with peripheral nerve myelin and can provoke immune responses that cross-react with myelin causing demyelination. Ganglioside GM1 appears to cross-react with *C jejuni* lipopolysaccharide antigens, resulting in the immunologic damage to the peripheral nervous system seen in GBS. IgG GQ1b antibodies, initially described by Chiba and colleagues, have a relatively high specificity and sensitivity for MFS [7]. Findings of dense concentrations of GQ1b ganglioside in the oculomotor, trochlear, and abducens nerves may explain the relationship between anti-GQ1b antibodies and the development of ophthalmoplegia [8]. Notably, anti-GQ1b antibodies were also found in Bickerstaff brainstem encephalitis, and at present both syndromes are considered as part of a spectrum of similar disorder [9-13].

In this issue, Tang and colleagues reported one case of MFS with the presence of elevated GQ1b antibody titers [14]. Interestingly, increased muscle stretch reflexes in the upper and lower extremities, instead of decreased or absent reflexes, were observed. However, cervical myelopathy, compressive, degenerative, or nutritional, could have been considered upon finding brisk stretch reflexes. The increased reflexes normalized in 3 months in their case, suggesting that a concomitant occult cervical myelopathy was less likely. To precisely assess cervical myelopathy, a cervical spine MRI is critical. Conversely, if a brisk jaw reflex was noted, it would suggest that the hyperreflexia were caused by CNS motor dysfunction above the cervicomedullary junction. In addition, malnutritional disorders, such as vitamin B12 or copper deficiency, may also cause myelopathy [15].

Nevertheless, the diagnosis of MFS should not be precluded by the concurrence of normal or hyperactive muscle stretch reflexes when other core signs and symptoms of MFS are present. In support of this view, similar findings of increased stretch reflexes have been observed in subtype GBS with acute motor conduction block [16] and in Bickerstaff brainstem encephalitis [12]. To substantiate our knowledge on MFS symptomatology, attentive observation in our routine practice is the key. An approach on a solid neuropathophysiologic background with scrutinized neurologic evaluations and necessary laboratory evidence would secure the task in disclosing more unusual findings.

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***Corresponding author:** Jin Jun Luo, Departments of Neurology and Pharmacology, Temple University School of Medicine, 3401 North Broad Street, Suite C525, Philadelphia, PA 19140, USA, Tel: 1-215-707-3040; Fax: 1-215-707-8235; E-mail: jluo@temple.edu

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