Case Report

Anti-GQ1b-negative Miller Fisher Syndrome Associated with Syndrome of Inappropriate Antidiuretic Hormone: A Case Report

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Miller Fisher syndrome [MFS] is an immune mediated polyradiculoneuropathy associated with antiganglioside antibody. The immunopathological mechanism of antiganglioside directly attack the nodal and paranodal regions of peripheral nerve. Though anti-GQ1b antibody was strongly associated with MFS, other antigangliosides and negative antibody cases were occasionally mentioned. This current study reports the clinical characteristic and non-neurological presentation of syndrome of inappropriate antidiuretic hormone [SIADH]. The possible pathophysiology of non-neurological symptoms was briefly reviewed.

Keywords: Miller Fisher syndrome, SIADH, Ataxia, Ophthalmoplegia, Anti-GQ1b antibody

J Med Assoc Thai 2018; 101 (2): 279-81
Website: http://www.jmatonline.com

Miller Fisher syndrome [MFS], a variant of Guillain-Barré syndrome [GBS], has the clinical triad of ataxia, areflexia, and ophthalmoplegia[1]. Anti-GQ1b IgG antibody, an antiganglioside antibody found in 85% of MFS cases, directly attacks the paranodal regions of peripheral nerves, cranial nerves, and possibly central nervous tissue resulting in the neurological syndrome[2]. The non-neurological manifestations of MFS were rarely reported. We reported a case of anti-GQ1b antibody negative MFS associated with the syndrome of inappropriate antidiuretic hormone [SIADH]. The present study was approved by the Ethical Committee of the Faculty of Medicine, Prince of Songkla University.

Case Report

A 64-year-old male presented with complaints of incoordination of the limbs and trunk. He had been healthy until 10 days prior to admission when he developed an upper respiratory tract infection [URI] with complete resolution after four days of oral clarithromycin. One week later, he developed imbalance gait and incoordination in doing daily tasks by hands. Three days later, bilateral incomplete ptosis and total ophthalmoparesis was encountered. On admission, he also complained of malaise and fatigue, nausea and vomiting. His vital signs were normal. The neurological examination revealed symmetrical bilateral incomplete ptosis and total ophthalmoparesis with both pupils equally reactive to light. He had a wide-based gait, truncal ataxia, scanning speech, and limbs dysmetria without motor weakness. Deep tendon reflexes were absent in all extremities. Pinprick, pain, and temperature sensation were intact, whereas the patient presented with loss of proprioceptive and vibratory sensation in all extremities with bilateral pseudoathetosis of fingers.

The basic laboratory evaluations included complete blood count, renal function test, liver function test, anti-HIV serology, chest radiography, and magnetic resonance imaging of the brain. They were all within normal limits. A cerebrospinal fluid [CSF] analysis revealed an elevated CSF protein of 48.7 mg/dl, but the CSF pressure and CSF/serum glucose ratio were normal and no blood or malignant cells were found. The CSF polymerase chain reaction panels for human herpesvirus types 1-6 were negative. Serum and CSF markers for paraneoplastic syndrome and antiganglioside antibodies (GM1, GM2, GM3, GD1a, GD1b, GT1b, and GQ1b antibodies) were all negative. A nerve conduction study revealed only prolonged F wave latency of both tibial nerves. Magnetic resonance spectroscopy of the cerebellum revealed a decreased N-acetylaspartate [NAA] to creatine [Cr] ratio of 0.98 at the cerebellar vermis (normal range >1).

On presentation, symptomatic euvolemic hyponatremia was evidenced by a serum sodium level of 122 mmol/L, urine sodium level of 204 mmol/L and

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How to cite this article: Korathanakhun P, Sathirapanya P, Setthawatcharawanich S. Anti-GQ1b-negative Miller Fisher syndrome associated with syndrome of inappropriate antidiuretic hormone: a case report. J Med Assoc Thai 2018;101:279-81.

urine osmolarity of 574 mOsm/kg. The morning cortisol and thyroid function assessments were unremarkable. The patient was diagnosed as SIADH. The other possible causes of SIADH were excluded as well.

A total dosage of 2 gm/kg of intravenous immunoglobulin [IVIg] was administrated for five consecutive days. The truncal and limbs ataxia showed a dramatic response at day 2 after the administration of IVIg, and the patient nearly fully recovered after six days. The bilateral incomplete ptosis followed by ophthalmoplegia gradually improved at 10 and 14 days after IVIg, respectively, and both symptoms resolved completely three months later. Treatment of SIADH was successful after 10 days with prompt fluid restriction and sodium chloride supplement. There was no clinical or laboratories evidence of relapse at the 10-month follow-up.

Discussion

MFS is an uncommon variant of GBS with an estimated incidence of 5% to 6% of GBS[3]. The major pathophysiology of MFS is the antiganglioside antibody that directly destroys the paranodal sites of peripheral nerves. Immunohistochemical studies revealed the relatively higher prevalence of GQ1b molecules at the oculomotor cranial nerve, trochlear nerve, abducens nerves, Ia-afferent neuron of the spinal dorsal horn cells, and muscle-spindle afferents causing classical triads of the disease including abnormal sensory nerve conduction and absence of H reflex studies[4-6]. In addition, anti-cerebellar antibodies may attribute to cerebellar ataxia that is associated with a decreased NAA to Cr ratio at the cerebellar vermis without structural change in magnetic resonance spectroscopy[7,8]. Thus, these evidences may support both central and peripheral nervous system involvement in MFS.

A negative anti-GQ1b antibody test was found in approximately 10% to 15% of MFS cases[2,9]. In contrast to classical GBS, the level of serum anti-GQ1b antibody is usually elevated during the first week of the disease and gradually declines in the second week when the patients commonly seek medical care. Compared to anti-GQ1b positive MFS, the distinctive features in anti-GQ1b negative MFS patients are predominately male, precedent gastrointestinal tract infection while antecedent URI and initial diplopia at the onset are found less frequently[9]. Some authors reported atypical findings of anti-GQ1b negative MFS such as horizontal gaze palsy[10]. Non-neurological symptoms included SIADH were also mentioned[11].

Hyponatremia associated with acute polyneuropathy patients was first described in 1967 by Posner et al[11]. SIADH associated with MFS was approximately 17% with variable severity from mild to fatal conditions[12,13]. The key pathogenesis of SIADH is hypothalamic dysfunction. Various hypotheses of immunologically mediated mechanism of SIADH in MFS have been postulated. Koga et al demonstrated that some patients with anti-GQ1b negative MFS had other antiganglioside antibodies[9]. Some case reports showed the association between anti-GD1b and SIADH[14]. Furthermore, a recent study revealed abundant expressions of gangliosides GM1, GD1a, GD1b, and GT1b in all of the hypothalamic nuclei, including paraventricular, medial preoptic nuclei, and anterior hypothalamic areas[15]. Therefore, SIADH in anti-GQ1b negative MFS may be an immune-mediated disorder involving hypothalamic nuclei by other antiganglioside antibodies.

Conclusion

A negative serologic test of anti-GQ1b antibody does not exclude MFS since this depends on the time of assessment. Furthermore, many other unidentified antiganglioside antibodies may play a role in both neurological and non-neurological symptoms in MFS. SIADH can be a non-neurological associated condition or even a presentation of MFS.

What is already known on this topic?

MFS is an acute inflammatory polyradiculoneuropathy that strongly associate with anti-GQ1b antibody. Negative antibody testing is scarcely found. In addition, non-neurological presentation is not well described.

What this study adds?

The present study reports a rare anti-GQ1b negative MFS. Other subtype of antiganglioside antibodies might play this important immunopathological role. Furthermore, non-neurological presentation of SIADH was also associated with MFS as a result of systemic effect of antiganglioside antibodies to hormonal neural tissue of the hypothalamus. Nowadays, the evidences of non-neurological presentation of MFS is quite limited. Hence, further study should be conducted.

Acknowledgement

The authors would like to thank you Mr. Glenn Shingeldecker for English editing the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

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