Scientific Research Publishing

International Journal of Clinical Medicine, 2017, 8, 123-127
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

A Patient with Post Infectious Immune Mediated Neuropathy (Miller Fisher Syndrome)

Sharlene Sanchez, Azad Esack

Eric Williams Medical Sciences Complex, Mount Hope, Trinidad
Email: sanchezsharlene32@yahoo.com

How to cite this paper: Sanchez, S. and Esack, A. (2017) A Patient with Post Infectious Immune Mediated Neuropathy (Miller Fisher Syndrome). *International Journal of Clinical Medicine*, **8**, 123-127.
https://doi.org/10.4236/ijcm.2017.83011

Received: January 29, 2017
Accepted: March 12, 2017
Published: March 15, 2017

Abstract

The Miller Fisher variant is an uncommon but well known syndrome being described as a triad of areflexia, ataxia and complex ophthalmoplegia. It is characterized by antibodies against myelin that affects peripheral nerves, extraocular muscles and Schwann cells. Anti-ganglioside antibodies have been recognized in disease pathogenesis and decreasing antibody production is the mainstay of treatment. The course is usually benign with improvement after immunomodulation. This case report describes the approach to a patient suspected of having a demyelinating disorder. It delineates the subsets of immune mediated neuropathies in evaluating the diagnosis and emphasizes the need for early therapeutic intervention in achieving a good clinical outcome.

Keywords

Miller Fisher, Anti-Ganglioside, Demyelinating, Immune Mediated

1. Introduction

Anti GQ1b antibodies target peripheral nerves, activate complement and cause conduction block. This leads to an immune mediated neuropathy affecting extraocular muscles. Miller Fisher syndrome (areflexia, ataxia and complex ophthalmoplegia) encompasses a spectrum of immune mediated motor and sensory neuropathies.

A 35-year-old female with a prior history of an upper respiratory tract infection presented with diplopia, bilateral orbital pain and headache. Clinical examination revealed an ataxic gait, areflexia and a complex ophthalmoplegia consistent with the clinical triad of Miller Fisher Syndrome.

The hallmark of this syndrome is the presence of anti GQ1b antibodies. This condition usually has an excellent prognosis with treatment as it usually follows an uncomplicated course without remissions. Treatment is based on reducing antibody levels.

2. Case Report

A 35-year-old woman presented with a two day history of diplopia, bi-frontal headache and bilateral orbital pain. Two weeks prior to these symptoms, she had a non-specific upper respiratory tract infection. There was no significant past medical history. Drug history included analgesics when necessary. The patient did not use alcohol, cigarettes or illicit drugs.

On examination she had a right sided ptosis and bilateral lateral rectus weakness. Other cranial nerves were normal. Diplopia was pronounced on bilateral horizontal gaze.

Tone and power were normal in the upper and lower limbs. Reflexes throughout were all absent and plantars were equivocal bilaterally. There was bilateral dysmetria but no dysdiadochokinesia. Gait was ataxic with inability to tandem walk. Position, vibration and pin prick sensation were all intact. Romberg's test was negative. Cardiovascular, respiratory and abdominal examinations were all unremarkable.

Investigations included the following: complete blood count, urea and electrolytes, liver enzymes and inflammatory markers were all within normal limits. The cerebrospinal fluid (CSF) protein was mildly elevated at 73 (12 - 60) mg/dl. The fluid was acellular with a normal glucose level. Electromyography (EMG)/nerve conduction study showed normal sensory action potentials. Small and splayed common peroneal compound muscle action potentials with normal nerve conduction velocities and normal F wave latencies were found. The findings were in keeping with bilateral common peroneal nerve dysfunction. Muscle sampling was normal. Computed Tomography (CT) brain (non contrast) was normal. Magnetic Resonance Imaging (MRI) brain non contrast was normal. Anti GQ1b Ig G was elevated, >1:100 (Negative-<1:100).

Treatment was initiated with intravenous Immunoglobulin (IVIG) 0.4 grams/kilogram/day for 5 days. There was significant clinical improvement during the hospital stay. However at six weeks the patient still exhibited an ataxic gait and a further course of IVIG was given at 0.4 g/kilogram/day for 5 days. The patient showed further improvement and at three months was normal. She remains well two years on. Informed consent was obtained from this patient for reporting her case.

3. Discussion

The clinical triad of ophthalmoplegia, ataxia and areflexia is in keeping with the Miller Fisher Syndrome discovered in 1956 [1]. As the years progressed, new cases were reported and anti-ganglioside antibodies were recognized as a possible pathophysiologic process underlying the disease mechanism. Therapeutic measures targeted at this pathway proved to be successful in management.

The patient had a history of a recent viral infection and subsequently developed ophthalmoplegia, ataxia and areflexia. The clinical symptoms developed within days and improved with treatment highlighting the pathogenesis of molecular mimicry known to this syndrome and antiganglioside antibodies attack-

ing extraocular nerves and Schwann cells. In Miller Fisher Syndrome, patients initially have diplopia and/or limb and gait ataxia [2]. The full clinical picture of ataxia, areflexia and ophthalmoplegia usually occurs within 5 to 10 days [2]. The Miller Fisher Syndrome is a diagnosis made on clinical grounds. The detection of anti-ganglioside antibodies in serum, CSF for elevated protein, EMG, and MRI-brain aided in reinforcing the diagnosis and excluding others. The patient presented developed similar symptoms over a period of 14 days consistent with the presentation and chronology of Miller Fisher syndrome. She also had a mild elevation of CSF protein with EMG findings supporting our diagnosis.

Antibodies to GQ1b bind to human peripheral nerves; predominantly oculomotor nerves and exhibits the a-latrotoxin-like effects [3]. This involves complement activation targeting nerve terminal architecture and Schwann cells [4] [5] [6] [7]. GQ1b gangliosides can be found in the oculomotor, trochlear, and abducens nerves [8]. The development of complex ophthalmoplegia can be explained by this as antibodies binding to myelin provoke an immune response causing demyelination. Antibodies to GQ1b are most likely induced during the infection preceding the onset of neurological symptoms by the mechanism of molecular mimicry [9].

Intravenous immunoglobulin preparations counteract these effects [10]. The immunomodulatory effects of intravenous immunoglobulin target several components of the immune system including B-cells, T-cells, macrophages, complement, cytokines and cellular adhesion molecules. Different stimuli activate B cells and they differentiate into plasma cells. Soluble immunoglobulins are produced by plasma cells against autoantigens [11]. These are responsible for the majority of clinical features in antibody mediated autoimmune diseases. The formation of immune complexes activate the classical complement cascade resulting in the production of membrane attack complexes (MAC) which induce the organ specific tissue damage seen in Miller Fisher Syndrome. The anti-inflammatory activity of intravenous immunoglobulin G is mediated by its ability to prevent the formation of MAC and subsequent tissue destruction. Inhibition of macrophage function reduces phagocytosis of antigen-presenting cells and antibody-mediated cellular cytotoxicity, thus inhibiting macrophage-mediated demyelination. Intravenous immunoglobulin also reduces the production of interleukin-2 and interferon-γ (gamma) by T-cells preventing the development of disease. These mechanisms of intravenous immunoglobulin G modulate the disease process seen in Miller Fisher Syndrome.

Miller Fisher Syndrome usually follows a benign course leading to complete remission without residual deficits [1] [2]. Relapses of Miller Fisher Syndrome are rare, but may occur with disease-free intervals [2]. Supportive treatment usually is sufficient in patients with mild disease. Intravenous immunoglobulin or plasma exchange is effective in treating patients with severe Miller Fisher Syndrome [10].

This patient presenting with ophthalmoplegia, ataxia and areflexia prompts the consideration of a demyelinating neuropathy. Although, Guillain Barre Syn-

drome has an areflexic component and a pathophysiologic emphasis on molecular mimicry as one of the underlying mechanisms responsible for disease manifestation, our patient did not fully fit this subset of immune mediated neuropathies. The added clinical findings of complex ophthalmoplegia and ataxia further reinforced the diagnosis of the Miller Fisher variant.

The learning points in this case include: the prompt recognition of clinical findings and consideration of differentials, establishing an early diagnosis in order to initiate treatment and pursuing the relevant investigations.

The other differentials that can be considered in this case are other autoimmune and non autoimmune causes. Autoimmune differentials include: sub-acute ophthalmoplegia, sub-acute ataxia, Guillain Barre Syndrome with ophthalmoplegia, pharyngeal cervical brachial variant and Bickerstaff brainstem encephalitis. Non autoimmune differentials include: brainstem lesions, neuromuscular transmission disorders, meningitis carcinomatosa and lymphomatosa, metabolic disorders, infections (Lyme's neurosyphillis, botulism), intoxications and nutritional deficiency (thiamine).

A complex eye movement disorder, ataxia and areflexia in a 35 year old female without known medical conditions should immediately lead to a detailed exploration of the prodrome and evolution of symptoms. The acquisition of the diagnosis of Miller Fisher Syndrome in this patient was based primarily on history and clinical findings. Cerebrospinal fluid analysis revealed a mildly elevated protein. Electrodiagnostic studies confirmed a demyelinating neuropathy and the presence of anti-GQ1b Ig G antibodies further reinforced a post infectious immune mediated syndrome. Treatment was immediately started with subsequent improvement of symptoms. Although after six weeks this patient had an ataxic gait, she responded to another course of intravenous immunoglobulin and remained symptom free. This highlights the underlying pathogenesis of Miller Fisher Syndrome and the course of disease with plasmapheresis or immunoglobulin administration.

Anti GQ1b antibodies is the hallmark of Miller Fisher syndrome. These antibodies are responsible for the extraocular manifestations, ataxia and areflexia seen in this patient. Management was successful with courses of intravenous immunoglobulin G.

References

[1] Fisher, M. (1956) An Unusual Variant of Acute Idiopathic Polyneuritis (Syndrome of Ophthalmoplegia, Ataxia and Areflexia). *The New England Journal of Medicine*, **255**, 57-65. https://doi.org/10.1056/NEJM195607122550201

[2] Berlit, P. and Rakicky, J. (1992) The Miller Fisher Syndrome. *Journal of Clinical Neuro-Ophthalmology* **12**, 57-63.

[3] Chiba, A., Kusunoki, S., Obata, H., *et al.* (1993) Serum Anti-GQ1b IgG Antibody Is Associated with Ophthalmoplegia in Miller Fisher Syndrome and Guillain-Barré Syndrome: Clinical and Immunohistochemical Studies. *Neurology*, **43**, 1911-1917. https://doi.org/10.1212/WNL.43.10.1911

[4] Plomp, J.J., Molenaar, P.C., O'Hanlon, G.M., *et al.* (1999) Miller Fisher Anti-GQ1b

Antibodies: Alpha-Latrotoxin-Like Effects on Motor End Plates. *Annals of Neurology*, **45**, 189-199. https://doi.org/10.1002/1531-8249(199902)45:2<189::AID-ANA9>3.0.CO;2-T

[5] Jacobs, B.C., Bullens, R.W., O'Hanlon, G.M., Ang, C.W., Willison, H.J. and Plomp, J.J. (2002) Detection and Prevalence of Alpha-Latrotoxin-Like Effects of Serum from Patients with Guillain-Barré Syndrome. *Muscle Nerve*, **25**, 549-558. https://doi.org/10.1002/mus.10060

[6] O'Hanlon, G.M., Plomp, J.J., Chakrabarti, M., *et al.* (2001) Anti-GQ1b Ganglioside Antibodies Mediate Complement-Dependent Destruction of the Motor Nerve Terminal. *Brain*, **124**, 893-906. https://doi.org/10.1093/brain/124.5.893

[7] Halstead, S.K., O'Hanlon, G.M., Humphreys, P.D., *et al.* (2004) Anti-Disialoside Antibodies Kill Perisynaptic Schwann Cells and Damage Motor Nerve Terminals via Membrane Attack Complex in a Murine Model of Neuropathy. *Brain*, **127**, 2109-2123. https://doi.org/10.1093/brain/awh231

[8] Chiba, A., Kusunoki, S., Obata, H., Machinami, R. and Kanazawa, I. (1997) Ganglioside Composition of the Human Cranial Nerves, with Special Reference to Pathophysiology of Miller Fisher Syndrome. *Brain Research*, **745**, 32-36. https://doi.org/10.1016/S0006-8993(96)01123-7

[9] Willison, H.J. and Yuki, N. (2002) Peripheral Neuropathies and Anti-Glycolipid Antibodies. *Brain*, **125**, 2591-2625. https://doi.org/10.1093/brain/awf272

[10] Jacobs, B.C., O'Hanlon, G.M., Bullens, R.W., Veitch, J., Plomp, J.J. and Willison, H.J. (2003) Immunoglobulins Inhibit Pathophysiological Effects of Anti-GQ1b-Positive Sera at Motor Nerve Terminals through Inhibition of Antibody Binding. *Brain*, **126**, 2220-2234. https://doi.org/10.1093/brain/awg235

[11] Jacob, S. and Rajabally, Y.A. (2009) Current Proposed Mechanisms of Action of Intravenous Immunoglobulins in Inflammatory Neuropathies. *Current Neuropharmacology*, **7**, 337-342. https://doi.org/10.2174/157015909790031166