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Case Report

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A CASE STUDY ON MILLER FISHER SYNDROME MANAGED SYMPTOMATICALLY

Dr. Maryam*[1], Mohammadi Fizza Khan[1], Ramsha Farheen[1], Heerat Fatima[1] and Masarrath Unnisa[1]

Department of Pharmacy Practice, Deccan School of Pharmacy, Darussalam, Aghapura, Hyderabad -500001, Telangana, India.

***Corresponding Author: Dr. Maryam**

Department of Pharmacy Practice, Deccan School of Pharmacy, Darussalam, Aghapura, Hyderabad -500001, Telangana, India.

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ABSTRACT

Miller Fisher Syndrome (MFS) is particularly a subtype of Gullian Barré syndrome (GBS) and is distinguished based on the cardinal signs i.e., ophthalmoplegia, ataxia and areflexia. It is also called Fisher's Syndrome and was first recognized by James Collier in the year 1932. The cardinal features were also given by James Collier. The name Miller Fisher Syndrome came after Charles Miller Fisher first reported it in 1956 as a particular variant of Gullian Barré syndrome (GBS). Here, we are writing a case of a patient who not only experienced the primary triad of symptoms but also, giddiness, diplopia and headache. The patient is also a known case of hypothyroidism and hypertension. The diagnosis of MFS was made by taking into account the triad of symptoms, CSF analysis which gave slightly elevated protein levels and MRI of brain which showed mild prominence of sulcal, cisternal and ventricular systems. The patient was treated with corticosteroids and certain symptomatic treatments were given to ease the giddiness and headache that the patient was experiencing. Also, the patient was given gait training, deep breathing exercises and ambulation and balance training to make him regain his muscle strength and ability to walk independently.

KEYWORDS: Miller Fisher Syndrome (MFS), Guillain-Barré Syndrome (GBS), Autoimmune, Ophthalmoplegia, Ataxia and Areflexia.

INTRODUCTION

Definition: Miller Fisher Syndrome (MFS) is an acute, autoimmune polyneuropathy, a subgroup of Guillain-Barré Syndrome (GBS) and clinically characterized by ataxia, ophthalmoplegia, and areflexia.[1]

Epidemiology: Miller Fisher Syndrome (MFS) variant of Guillain-Barré Syndrome (GBS) represent a small subset of the cases (1 to 2 in 1,000,000).[2] 1%-7% of GBS cases reported FS in countries in the Western hemisphere, it is much more common in Asia,18%-19% of cases of GBS comprised FS in a study in Taiwan and 25% of GBS in Japan. (3) FS is predominant in men than in women, and though it is less common in children than in adults, it has been described in people of all ages, including infants.[3]

Etiology: MFS can be related with infectious, autoimmune, and neoplastic disorders.[4] Most commonly involved pathogens are Campylobacter jejuni and Haemophilus influenza; however, various others such as Mycoplasma pneumonia, and cytomegalovirus are also associated, with Upper respiratory infection being the most commonly described premonitory disease, followed by gastrointestinal illness.[5] Demonstration of common autoantibodies, antecedent infections, and results of detailed clinical neuroimaging and neurophysiological investigations from recent large study suggest that Fisher Syndrome (FS), Guillain-Barré Syndrome (GBS), and Bickerstaff brainstem encephalitis (BBE)are not separate disorders, rather they form a continuous spectrum with variable involvement of Central and Peripheral Nervous System.[6] Very few cases of post inoculation with vaccines such as the influenza vaccine and Pneumovax has reported FS.[3,7]

Pathogenesis of Miller Fisher (Fisher) Syndrome Associated With IgGanti-GQ_{1Bb} Antibody Subsequent to Campylobacter Jejuni Enteritis[8]

Though documented cases of MFS have been reported for most of the cranial nerves, it is mainly associated with dysfunction of the third, fourth, and sixth cranial nerves.[2,9] Molecular mimicry exists between peripheral nerve antigens and microbial components through Humoral and Cell-mediated immunity.[2] Figure-1 represents Pathogenesis of Miller Fisher Syndrome associated with IgGanti-GQ_{1Bb} Antibody subsequent to Campylobacter Jejuni Enteritis. C.Jejuni bears GQ_{1b}-like LPS which is associated with Penner's serotype-2 (PEN-2) antigenic determinant.PEN-2 may end self-tolerance and induce GQ_{1b}-like LPS to increase the synthesis of IgG anti-GQ_{1b} antibody with the help of T-cells and B-

cells. These IgG anti-GQ_{1b} antibodies bind to third, fourth, sixth cranial nerves and to cerebellar nuclei resulting in development of clinical features of MFS(Ophthalmoplegia, Ataxia).MFS with negative IgG anti-GQ_{1b} antibodies is seen in less than 15% cases.[10]

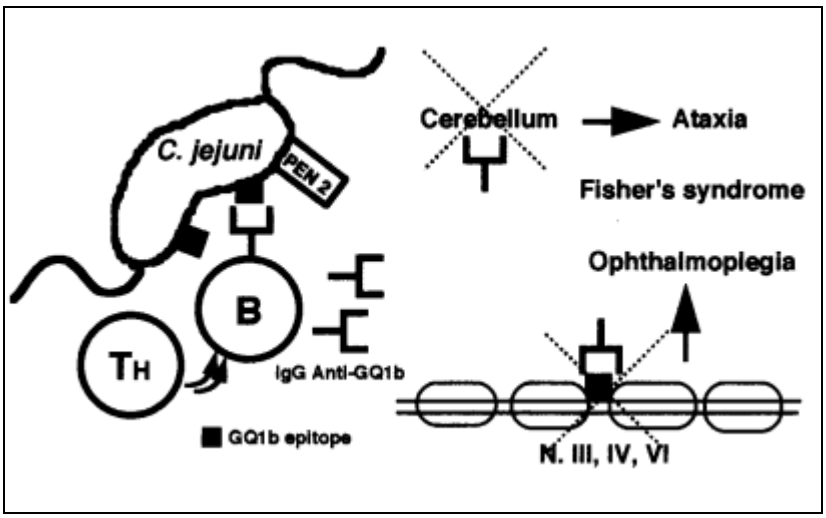

Figure-1: Pathogenesis of Miller Fisher Syndrome associated with IgGanti-GQ_{1Bb} Antibody subsequent to Campylobacter Jejuni Enteritis.

PEN-2 = Penner's serotype 2, Th = T cells, B = B cells, III = Oculomotor nerve IV = Trochlear nerve, VI= Abducens nerve.

Clinical Presentation

The clinical triad of Ophthalmoplegia, Ataxia, and Areflexia is characteristic feature of Miller Fisher Syndrome (MFS).[1,7] Other symptoms associated with MFS include distal paresthesia; diplopia; dysarthria; blepharoptosis; mild (grade 4) motor weakness; face, bulbar, and pupillary palsies; limb dysesthesia; and micturition disturbance, etc.[2,11]

Risk Factors

Analytical acute autoimmune response to a preceding infection (e.g., Campylobacter jejuni, Epstein-Barr virus, Cytomegalovirus, or Human Immunodeficiency Virus) is thought to be a risk factor for MFS.[2] Use of certain drugs (heroin, streptokinase, suramin, and isotretinoin), other concurrent autoimmune diseases (Hodgkin disease, systemic lupus, and sarcoidosis), use of TNF-alpha antagonist therapy, surgery ,bone marrow transplant, epidural anesthesia, immunizations, etc are some other risk factors of MFS.[12,13,14,15,16]

Diagnosis

Patient can be mistakenly diagnosed as Guillain-Barré Syndrome (GBS) and Bickerstaff brainstem encephalitis (BBE) as they have overlapping clinical features as that of MFS. GBS and MFS can though be diagnosed on clinical grounds(Clinical history, cardinal symptoms), it can be confirmed with the help of imaging (e.g. ultrasound and MRI), serologic testing (e.g.Anti-GQ_{1b} antibodies etc), cerebrospinal fluid (CSF) analysis and electrodiagnostic (EMG, nerve conduction, or evoked potential).[2,11,17]

Treatment[2]

Goal: Achieving optimal muscle use as tolerated by pain, and usage of supportive equipment to help patient resume functional activity as close to baseline as possible are the principal goals of therapy.

Non-Pharmacological Treatment: Strengthening highly weakened muscles as close to the previous function as possible with the help of physical and neurological rehabilitation which usually consists of 1 to 2 weeks of intense rehabilitation with an extensive team of health professionals.

Pharmacological Treatment: Adequate supportive care, pain control, respiratory support as needed, and immunotherapy is given. Initially, clinicians must eliminate other neurologic disorders or conditions that are similar to Fisher syndrome, such as vitamin B1 deficiency (Wernicke's encephalopathy), multiple sclerosis, vascular disease, Behçet disease, collagen disease, neoplasm of the brainstem, sarcoidosis and infectious diseases such as viral infections (e.g., herpes encephalitis), diphtheria and botulism etc.[18]

As oral or intravenous (IV) steroids are ineffective, they are now no longer suggested in the therapy of GBS or MFS. Corticosteroids are adviced only in the setting of radicular or neuropathic pain.

As MFS have a good prognosis and impetuous recovery, patients usually do not need immunotherapy. Immunotherapy with either IV immunoglobulin (IVIg) or plasma exchange is both effective treatments for GBS and severe cases of MFS.

IV immunoglobulin (IVIg): Despite lack of supporting evidence of benefit, IVIg should be considered in

patients with severe Miller Fisher syndrome who have dysphagia and respiratory difficulties. Due to convenience, availability, and minimal adverse effects, IV Ig is preferred over exchange, however; it is not economic for some low income or underinsured patients. Since patients with IgA deficiency are at higher risk of anaphylaxis, physicians should check serum IgA levels before initiating IV immunoglobulin therapy. Usual IVIg dose is 2 g/kg divided over 2 to 5 days. For few patients, a second treatment course may be necessary. In children and adolescents, a dose of 1 g/kg per dose IV daily for 2 days is recommended. In patients with renal impairment, approximately 50% of the usual dose should be used by physicians.

Plasma exchange: When given within 2 weeks of illness onset in patients who are unable to walk, plasma exchange is effective and is highly effective within seven days of weakness onset. Standard course of plasma exchange sessions for patients who are unable to walk without assistance is 2 to 3 L of plasma/body weight over 2 weeks. 2 plasma exchanges of 1.5 plasma volumes will still benefit mildly affected patients with low disability score. Recent prior use of IV immunoglobulin infusion therapy, sepsis, hemodynamic instability, hypocalcemia and pregnancy are few contraindications for plasma exchange.

Pain Management: Optimal pain regimen is essential in early course of the disease as it boosts the recovery. Because of the mixed nature of the pain, a combination of medications is usually required. Indicated medications include gabapentin, pregabalin, carbamazepine, and amitriptyline.

Administration of prophylactic doses of subcutaneous heparin or enoxaparin is appropiateto reduce the risk of pulmonary embolism in Deep Vein Thrombosis (DVT). Patients with at least 1 major criterion or 2 minor criteria are recommended for ICU admission and mechanical ventilation. Table-1 represents major and minor criteria required for ICU admission and mechanical ventilation.

Table-1: Major and minor criteria required for ICU admission and mechanical ventilation.

Major criteria	Hypercapnia(PaCO2greater than 48 mm Hg)	Hypoxemia (PaO2 less than 56 mm Hg at room air)	Vital capacity (less than 15 mL/kg of body weight)	Negative inspiratory force (less than -30 cm H_2O)
Minor criteria	Inefficient/weak cough	Dysphagia	Atelectasis as evidenced in a chest x-ray.	

CASE STUDY

A 41 years old female patient was brought to a multispecialty hospital and was admitted to neurology department with chief complaints of giddiness, ophthalmoplegia (weakness of eye muscles), ataxia (impaired coordination) since 2 days. At the presentation, patient reports showed Hemoglobin and Red Blood Cells levels were reduced. The patient had a past medical history of Hypothyroidism and was on medication Tab. Thyronorm 100 mcg (thyroxine) and hypertension Tab. Amlodipine 5 mg since 5 years. He had a family history of hypertension. The patient was non-alcoholic, non-smoker, had a mixed appetite and disturbed sleep. Patient did not have any allergies or any other comorbidities. The provisional diagnosis was Miller Fisher Syndrome.

Physical examination showed that patient was conscious, obeying verbal command, memory intact, pupils bilateral reacting to light, 3 mm. Patient complaint of generalized weakness.

On cardiac auscultation regular heartbeat with no murmur was heard and a heart rate of 80 beats/min was recorded. Respiratory auscultation revealed symmetrical breath sounds, normal bronchial airway entry with a respiratory rate of 20 breaths/min. Her abdomen was soft, regular, non-tender.

On day 1 the patient had complaints of Giddiness, ophthalmoplegia and ataxia which had a sudden onset. For his giddiness, ataxia and headache tab. Vertin (betahistine) 16mg Oral TID and tab. Spinfree (cinnarizine (20mg) + dimenhydrinate (40mg)) Oral BD was given. Erythrocyte Sedimentation rate was high which indicated inflammation in the body and was managed by Inj. Decadron (dexamethasone) 4mg in 100ml NS was prescribed. The patient's condition of MFS was treated with methylprednisolone and IVIG therapy was not considered as the patient did not have severe swallowing and respiratory difficulties.

After 6 days of hospital stay the patient had a significant improvement. He was then planned to discharge from the hospital with discharge medications, tab. Wysolene (prednisolone) 40mg (to taper the given corticosteroids), tab. Vertin (betahistine), tab. Spinfree (cinnarizine (20mg) + dimenhydrinate (40mg)), tab. Amlodipine 5mg and tab. Pantop (pntoprazole) 40mg. He was asked to review in the OPD after 5 days.

Laboratory Investigations

Investigations such as MRI of Brain plain with contrast, CBP, ADA, ESR, ECG, RFT, Serum Electrolytes, GRBS, Gram staining of CSF, ANA and thyroid profile were ordered. MRI of Brain plain with contrast revealed mild prominent sulcal, cisternal and ventricular system were. Complete Blood Picture (CBP) showed reduced

levels of Haemoglobin (HGB) - 11.4 gm% (Normal Range- 12.0 - 15.5 gm%), Red Blood Cells (RBCs)- 3.8 million/cumm (Normal Range- 4.2 - 5.4 million/cumm). All the other Hematology parameters were normal. Adenosine deaminase (ADA) was reduced i.e., 0.3U/L (Normal Range- 14U/L). Erythrocyte Sedimentation Rate (ESR) for the 1st hr 35mm/hr (Normal Range- 0-10mm/hr) and 2nd hr 72mm/hr (Normal Range- 10-20mm/hr) were elevated. Electrocardiography revealed Normal sinus rhythm, normal ECG. Other Lab investigations such as Renal Function Test, Serum Electrolytes, GRBS, Gram stain of CSF, Anti-Nuclear Antibody and Thyroid profile were normal. The patient's final diagnosis was Miller Fisher Syndrome.

DISCUSSION

This is the typical case of a patient showing clinical triad of Fisher's Syndrome along with Giddiness, diplopia and headache. This is a condition of acute inflammatory polyneuropathy, which is preceded in most cases by an infectious illness, and Campylobacter jejuni, is the most common antecedent to GBS and its ocular variant, Miller Fisher syndrome (MFS). O (Penner) serotyping is useful to distinguish between C. jejuni strains based on the differences in lipopolysaccharide (LPS) structure.[19]

Guillain–Barré syndrome (GBS), Miller Fisher syndrome (MFS), and Bickerstaff brainstem encephalitis (BBE) are usually monophasic, so first we need to rule out all the other neuropathies before starting MFS management.[20] MFS is associated with acute-phase IgG antibodies to GQ1b and GT1a gangliosides in most of the cases which are disease specific.[21] This Anti-GQ1b antibody testing has made the clinicians easy to detect MFS and differentiate among other neuropathies.

MFS is usually mistaken with acute stroke. Cerebellar ischemia has clinical symptoms of unsteady gait, dizziness, headache, eye movement dysfunction.[22] Ataxia and ophthalmoplegia usually takes one to three months to resolve, and complete recovery is seen in six months.[23] Miller Fisher Syndrome is a self-limiting autoimmune disease, but still immunomodulatory therapies including intravenous immune globulin and plasma exchange is used to manage MFS that will ease in disease recovery and thus decreased the chance of progression to more severe diseases like GBS.[24]

In our case the patient did not require Intravenous Immunoglobulin therapy and was treated symptomatically only.

At the time of discharge the patient and attenders were counselled regarding medications given. They were counselled to never stop the corticosteroids abruptly and to follow up in the OPD after 5 days without fail.

CONCLUSION

A typical case of MFS (Miller Fisher Syndrome) is being studied with a known history of Hypertension and Hypothyroidism. The patient was conscious, obeying verbal commands and had weakness due to low Blood Pressure. MRI Scan showed mild prominent sulcal, cisternal and ventricular systems. Antihistamines, Vitamin B and Corticosteroids were given in the course of treatment. After the due course, the symptoms were managed successfully and the patient was discharged. This case study basically emphasizes on the diagnosis of MFS, ruling out the other possibilities and its successful management.

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