



3-2017

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Recommended Citation

Waqar, Kiran; Nasir, Sadaf; Sher, Khalid; Fatima, Meraj; and Malik, Abdul (2017) "Frequency of miller fisher variant of guillain barré syndrome at a tertiary care hospital, Karachi," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 12 : Iss. 1 , Article 4.

Available at: <http://ecommons.aku.edu/pjns/vol12/iss1/4>

FREQUENCY OF MILLER FISHER VARIANT OF GUILLAIN BARRÉ SYNDROME AT A TERTIARY CARE HOSPITAL, KARACHI

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Date of submission: June 13, 2016 **Date of revision:** October 5, 2016 **Date of acceptance:** November 9, 2016

ABSTRACT

Background: Miller fisher syndrome is generally considered a rare but important variant of Guillain Barré Syndrome (GBS) having geographically variable incidence. Patients with this clinical syndrome are often misdiagnosed and mismanaged due to lack of awareness on the part of physician. **Objective:** To determine frequency of Miller fisher syndrome (MFS), variant of GBS in patients presenting to a tertiary care hospital in Karachi. **Methods:** This descriptive cross sectional study was conducted in the Department of Neurology, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The duration was from April, 2014 to April, 2016 (two years). A total of 100 patients were included in this study. Patients were classified into GBS, MFS and GBS/MFS overlap according to their clinical presentation, CSF analysis and electrophysiological findings. Data was collected on a predesigned proforma. **Results:** Out of 100 cases, 62 (62%) were males and 38 (38%) were females. Frequency of Miller fisher syndrome (MFS) in patients of GBS was 14% predominantly involving male, with male to female ratio is 6:1. Majority of patients had duration of symptoms for 11 ± 6 days before presentation. The mean age of patients with MFS was 46.03 years (SD ± 12.6). **Conclusion:** We report a high frequency of MFS in our population with predominant involvement of male gender.

Keywords:

Frequency, GBS, Miller fisher syndrome, Tertiary Care

INTRODUCTION:

GBS is an acute immune-mediated polyneuropathy characterized by rapidly evolving, symmetrical, often ascending limb weakness and loss of deep tendon reflexes. It is a heterogeneous condition with several variants forms including regional, functional and electrophysiological.^[1,2] In typical cases, the first symptoms of GBS are pain, numbness, paresthesia, and weakness in the limbs, however it can also present without weakness. MFS is one of the examples of such variants.

In 1956, Dr. Charles Miller Fisher described three patients with the clinical triad of ophthalmoplegia, ataxia and areflexia without prominent signs of peripheral neuropathy.^[3] These patients usually

complain of difficulty in walking, maintaining balance, coordination and blurring of vision. MFS has a higher incidence in Asia, where the incidence is estimated to be 18%–26% of GBS compared with 3%–5% in the Western countries like Europe.^[3,4] MFS occurs more frequently in men than women by a ratio of approximately 2:1^[3]. The onset of MFS varies from 13 to 78 years of age with a mean of 43.6 years^[3]. The typical patients usually do not have motor weakness, but they can present with motor weakness like GBS called Overlap syndrome^[5]. Some time patients may present without ataxia or ophthalmoplegia called incomplete form of MFS^[5].

The pathogenesis of MFS is characterized by the presence of serum monoclonal antibodies anti-GQ1b that can bind to human peripheral nerves,

predominantly oculomotor nerves.^[6] Antibodies to GQ1b are most likely induced during the infection preceding the onset of neurological symptoms^[3]. *Campylobacter jejuni* isolates from MFS patients have been identified which contain lipo-oligosaccharides showing molecular mimicry with GQ1b antibodies and other gangliosides, which can cross-react to GQ1b and other gangliosides in peripheral nerves.^[3,6]

Anti-GQ1b IgG antibodies may also be found in patients with acute ataxia (without ophthalmoplegia), acute ophthalmoplegia (without ataxia), GBS with ophthalmoplegia, lower bulbar variant of GBS and Bickerstaff encephalitis ^[6].

On Electrophysiological studies the most consistent findings in MFS are reduced sensory nerve action potentials and absent H reflexes.^[7] Other findings on further investigation are albuminocytological dissociation on CSF studies and contrast enhancement of nerve roots in few cases.^[8]

Most patients with MFS show a monophasic and benign course of disease leading to complete remission without residual deficits ^[9]. Most patients spontaneously start to improve within 2 to 4 weeks after onset of neurological symptoms. The recovery usually is completed after weeks to months with a mean recovery time of 10 weeks ^[9]. These clinical presentations can occur in other neurological disorder so careful clinical assessment and focused investigations such as brain imaging and electrophysiological examinations can rule out other conditions. The differential diagnosis of MFS includes Wernicke's encephalopathy, myasthenia gravis, botulism, and brainstem stroke.

MFS is considered to be a variant of GBS because they share the presence of

- Areflexia essential for the diagnosis of GBS
- Increased protein levels in absence of increased cells in cerebrospinal fluid
- Usual monophasic course of disease,
- Antecedent infection,
- Anti-ganglioside antibodies in serum and
- Presence of cross-over cases in which MFS patients may progress to GBS.

The Miller Fisher syndrome appears to be more common in eastern Asia than among those who live in other parts of the world ^[4, 5]. There is limited data on the frequency of MFS in Pakistan. The aim of our study was to find out the frequency of MFS in our setup.

SUBJECTS AND METHODS:

This study was conducted at the Department of Neurology, JPMC, Karachi over a period of two years (April 2014-16). We enrolled 100 patients in our study. Patients aged 14 years and above, regardless of their gender with history of < 4 weeks duration of difficulty in walking and evidence of hyporeflexia/areflexia on clinical assessment were included in this study. Patients were classified into MFS according to their clinical presentation (areflexia, ataxia and ophthalmoplegia), lab parameters like CSF with albuminocytological dissociation and electrophysiology showing decreased or absent sensory nerve action potentials (SNAP). Exclusion criteria included history of exposure to toxins, presence of upper motor neuron signs, Brain-stem stroke, Wernicke's encephalopathy and myasthenia gravis. These patients were excluded on the basis of clinical history, neurological examination and relevant investigations including neuroimaging where indicated. Vitamin B12 deficiency and Diabetes mellitus were also ruled out in suspicious cases of ataxia with absent reflexes. A questionnaire was designed to collect data. Verbal informed consent was taken prior to enrollment in study. All patients were reviewed by consultant neurologist. Bias was controlled by having the CSF detailed reports and nerve conduction studies by same lab and same investigator. We offered Plasmapheresis to all patients diagnosed with MFS/ GBS as a treatment option. Data analysis was done with the help of statistical package for social sciences (SPSS) version 17. Descriptive statistic was applied on demographic variables like age and gender.

RESULTS

A total of 100 patients were included in this study. The average age of the patients was 36.03 ± 12.62 years with 62% were males and 38% were females. Majority of patients had symptoms before hospitalization for 11 ± 6 days.

Frequency of Miller fisher syndrome (MFS) was found to be 14%, 12 patients (86%) were male and 2 patients (14%) were female. The mean age of the patients with MFS was 46.03 years ($SD \pm 12.6$). It was significantly high in patients above 50 years of age. Effect of duration of disease was not significant. It was also observed that out of 14 patients, 2 patients (14%) had incomplete MFS i.e. only ophthalmoplegia and areflexia while 4 patients (28%) had overlap syndrome i.e. gradually developed generalized weakness.

Out of 14 patients 11 underwent Plasmapheresis, 3

refused for that and left against medical advice. All patients were improved during course of Plasmapheresis and advised for follow up after 3 months. Seven patients lost follow-up after discharge and remaining 4 patients completely improved after 3 months. Improvement on treatment strengthens our diagnosis.

Frequency of Miller Fisher Variant of Gbs with Respect to Age Group

Age Groups (Years)	MILLER FISHER SYNDROME		Total
	Yes n=14	No n=86	
≤20 Years	2(13.3%)	13(86.7%)	15
21 to 30 Years	0(0%)	25(100%)	25
31 to 40Years	0(0%)	22(100%)	22
41 to 50 Years	4(16.7%)	20(83.3%)	24
>50	8(57.1%)	6(42.9%)	14

Chi-Square=29.4 p=0.0005

Frequency of Miller Fisher Variant of Gbs with Respect to Gender

Gender	MILLER FISHER SYNDROME		Total
	Yes n=14	No n=86	
Male	12 (86%)	50 (58%)	62
Female	2 (14%)	36(42%)	38

Chi-Square=3.88;p=0.049

syndrome. New Engl J Med. 2012;366(24):2294–304.

DISCUSSION:

GBS is a common cause of acute flaccid paralysis worldwide. The overall incidence of GBS is found to be 1.1 to 1.8/100,000 population.^[4,5] Our study showed that GBS is more common in males as compared to females. The relative risk for men is 1.78 compared to women in different studies ^[4, 5]. Male preponderance is especially seen in older patients. In our study, the average age of the patients with GBS was 36.03±12.62 years. Different studies showed increase incidence of GBS with every 10 year rise in

age after first decade of life.^[5]

Review of literature showed, MFS a variant of GBS accounts for 5% of cases in Western Europe though prevalence might be higher in other areas, such as reported from Eastern Asia countries like Taiwan and Japan.^[4,9] keeping in view we also suspected high frequency of MFS in our country.

To our knowledge this is the first study conducted on a relatively large number of patients in Pakistan showing that MFS in our population is 14%, which is higher as compared to western countries where it is 5%. ^[4,5,9] Our results are comparable with a study conducted in Taiwan which showed frequency of MFS as 20%. ^[10] while similar study in Japan also showed same results. ^[9] According to one study it is about 5% to 7% in western countries and 20 to 25% in Asian ^[5]. In Taiwan, another study showed 11 of 60 patients with GBS had MFS (18%).^[11]

A recent analysis of 32 years in Hong Kong reported 9% and 7.7% in Thailand [12]. In a Spanish case series, 8 of 69 patients with GBS had MFS (11.5%) ^[13].

Stratification analysis with respect to age was observed and rate of MFS was significantly higher in above 50 years of age. The mean age of patients in our study was 46 years (SD±12.6). One study showed that the mean age of onset of MFS is 43.6 years^[4] though onset has been documented in individuals between the ages of 13 and 78 years.^[9] Another study also showed mean age of 44 years^[8]. In our study, MFS was more common in males as than females with 6:1 ratio respectively. Other studies also showed that MFS occurs more in men than women with ratio of 2:1^[4, 14] but this ratio is less as compared to our study. Considering the supposed autoimmune etiology of GBS and MFS, the male preponderance is somewhat unexplained.

It was also observed that out of 14 patients, 2 patients (14%) presented with incomplete MFS having only ophthalmoplegia and areflexia while 4 patients (28%) presented with overlap syndrome having generalized weakness. In comparison to other study which showed that half of the patients with MFS eventually experienced profound weakness (overlap syndrome) ^[15].

CONCLUSION:

In conclusion, our study demonstrated incidence and sex distribution of GBS similar to many other previous studies. The frequency of MFS in patients of GBS in our

study was found to be 14%, with predominantly involving male gender. High clinical suspicion is needed to diagnose MFS because all symptoms may not appear at the same time. Clinicians must remember this important variant while evaluating atypical combination of areflexia, ophthalmoplegia and ataxia, so that patients with these clinical presentations are not misdiagnosed and mismanaged and they can offer better care to their patients. Due to lack of data further studies are recommended in Pakistan to strengthen results of our study on this topic.

LIMITATION:

We diagnosed MFS on clinical basis and investigations like CSF analysis and NCS. More relevant investigation like anti-GQ1b antibodies level was not done because of financial constraints. All patients were treated with Plasmapheresis and IVIg was not given as a treatment option because of same reasons.

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Author's contribution:

Kiran Waqar: Study concept, design, data acquisition, analysis and manuscript writing.

Sadaf Nasir: Study concept, design, data analysis, manuscript writing and review.

Khalid Sher: Manuscript writing and review.

Shahnaz: Manuscript writing and review.

Meraj Fatima: Manuscript writing and review.

Abdul Malik: Manuscript writing and review.