

## Case Report

# Is headache a common symptom in Miller Fisher Syndrome? – Two Case Reports

Tiziana Pirota\*, Charmaine Chircop, and Norbert Vella

Department of Neuroscience, Mater Dei Hospital, Malta

## \*Corresponding author

Tiziana Pirota, Department of Neuroscience, Mater Dei Hospital, Tal-Qroqq, Msida, MSD 2090, Malta, Tel: 00356 99223854; Email: tizipir@gmail.com

Submitted: 22 June 2016

Accepted: 25 July 2016

Published: 18 August 2016

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## Keywords

- Miller fisher Syndrome
- Headache
- Anti-ganglioside antibodies
- Ophthalmoplegia

## Abstract

Miller Fisher syndrome (MFS) is an acute demyelinating disorder that is considered a cranial nerve variant of Guillain-Barré syndrome (GBS). The pathophysiological process behind MFS is immune-mediated nerve damage but there is some debate with regards to whether this is primarily due to central nervous system (CNS) or peripheral nerve involvement. Headache has been described more frequently in MFS than in GBS however it still remains a rare occurrence with few published case reports. In this review we describe two patients diagnosed with MFS in which headache was a prominent and persistent feature. Our patients were both male aged 37 and 38 years respectively with no relevant medical co-morbidities. Both cases of MFS were accompanied by severe headaches requiring regular analgesia for a prolonged period of time. The pathophysiology of headache in MFS is still uncertain but there are a number of postulated mechanisms described in the literature which we have explored in relation to our cases.

## ABBREVIATIONS

MFS: Miller Fisher Syndrome; IVIG: Intravenous Immunoglobulin; GBS: Guillain-Barré Syndrome, CT: Computed Tomography; MRI: Magnetic Resonance Imaging; CNS: Central Nervous System

## INTRODUCTION

There have been few published case reports of headache in association with confirmed cases of the Miller Fisher Syndrome. In this report we describe two patients who experienced severe headache as part of this syndrome who presented to our local neurology department.

## CASE PRESENTATION

## Case 1

A 37-year-old man presented to the ophthalmic emergency department with double vision on looking to the left side, decreased visual acuity and headache. A CT scan of the brain was normal apart from features of chronic sinusitis. He was discharged with a follow up ophthalmic review. However, the following day, he returned to the emergency department with unsteadiness and worsening diplopia in all directions of gaze. He denied any further symptoms but gave a history of gastroenteritis a week prior to presentation. The patient reported a persistent headache accompanying his symptoms which had not responded to oral paracetamol.

His neurological examination revealed impaired abduction

of both eyes. The other cranial nerves were intact. There was no papilloedema, and both pupils were equal and reactive to light. He was completely areflexic but both plantar responses were flexor. He had gait ataxia and was unable to tandem walk. Serial examination in the following days showed a complete left ophthalmoplegia and stable sixth nerve palsy in the right eye. A provisional clinical diagnosis of Miller Fisher syndrome was made and patient was treated with intravenous immunoglobulin (IVIg) (0.4g/kg for 5 days).

CSF examination yielded a protein of 342mg/l (150-450mg/l) and  $2 \times 10^7$  lymphocytes/L. Serum anti- GQ1b and GD1b antibodies titres were significantly raised (Table 1). The rest of the blood tests were unremarkable. A brain MRI revealed no abnormality or areas of enhancement.

**Table 1:** Anti-ganglioside antibody results from both patients.

	Patient 1	Patient 2	Normal values
Asialog GM1	118	<30	<30
GM1	38	265	<30
GM2	<30	<30	<30
GD1a	42	<30	<30
GD1b	463	<30	<30
GQ1B	395	373	<30

**Abbreviations:** Asialog GM1: Asialog ganglioside; GM1: Ganglioside M1; GM2: Ganglioside M2; GQ1b Ganglioside Q1b; GD3: Ganglioside GD3; GD1a: Ganglioside GD1a; GD1b: Ganglioside GD1b

The patient continued to suffer from severe holocranial headache which confined him to bed for most of the day and even woke him up at night. The pain was not typical of a low pressure headache, and had started prior to the lumbar puncture being performed. Phonophobia and photophobia were present but there was no associated nausea or vomiting. Initially there was only a partial response to opiates and non-steroidals but after a week the pain became responsive to simple analgesia. After two weeks he was completely pain free. There was no history of headache prior to this presentation. All his symptoms resolved completely eight weeks after onset.

## Case 2

A 38 year-old man presented to the emergency department with symptoms of acute diplopia and unsteady gait. On examination he was found to have right sided ptosis and diplopia in all directions of gaze. He was also hyporeflexia and his gait was ataxic. Brain MRI and blood investigations, including a vasculitic screen, were normal. He was discharged with a provisional diagnosis of a third cranial nerve palsy. However, he was re-admitted within 48 hours with worsening diplopia and gait disturbance. He also complained of intense headache, vertigo and recurrent vomiting as well as a mild sensory disturbance affecting the upper extremities. His examination now revealed complete right-sided ophthalmoplegia, absent reflexes and an ataxic gait. Brain CT was normal, and a lumbar puncture yielded a normal opening pressure (130 mm/CSF) but significantly elevated CSF protein at 1135 mg/L. Serum antiganglioside antibodies were positive (Table 1). The patient was diagnosed with Miller Fisher Syndrome and treated with a 5 day course of IVIg (0.4mg/kg/day).

The patient described a continuous frontal headache which occasionally became more intense. It was accompanied by nausea and vomiting but no photo- or phonophobia. It responded very well to regular paracetamol and non-steroidals. There was a past history of anxiety and he was on regular flupentixol, paroxetine and amitriptyline. However, he denied having similar headaches in the past. He claimed to be headache-free upon completing the IVI g treatment.

## DISCUSSION

Miller Fisher syndrome (MFS) is an acute demyelinating disorder that is considered a cranial nerve variant of Guillain-Barré syndrome (GBS). In 1956, Miller Fisher described three patients with ataxia, ophthalmoplegia and areflexia without signs of peripheral neuropathy as a separate entity [1]. Although there was only minor limb involvement in his cases, Miller Fisher recognized that the syndrome he delineated had a significant overlap with other inflammatory neuropathies such as GBS. He proposed that the high CSF protein and the fact that ophthalmoplegia can occur in classic GBS suggested that the pathology could be similar. Nowadays MFS is widely regarded a part of the GBS spectrum [2,3] along with Bickerstaff's encephalitis. In addition to the classical clinical triad, MFS patients frequently have other cranial nerve involvement. The facial nerve is affected in about 50% of cases followed by cranial nerves IX to XII. Many patients may also have mild sensory complaints, usually paresthesias and dyesthesia in the extremities, but severe sensory deficits are rare.

## Pathophysiology of MFS

The pathophysiological process behind MFS is immune-mediated nerve damage. Serum from the majority of MFS patients was found to have an antibody which reacts to peripheral nerve ganglioside GQ1b [4]. Gangliosides are sialic acid containing glycosphingolipids which are diverse and highly complex molecules located primarily on plasma membranes and are particularly abundant in the nervous system. Gangliosides are known to play important roles in biological functions, such as cellular growth and differentiation, modulation of signal transduction, and immune reactions [5].

Further evidence of an important role for anti-GQ1b antibodies in MFS is the finding that the third, fourth, and sixth cranial nerves contain appreciable amounts of GQ1b ganglioside, which may explain the prominent ophthalmoplegia in this syndrome in comparison to GBS. An initial study by Roberts et al. [6], and a further study by Buchwald et al. [7], demonstrated that anti-GQ1b IgG was capable of causing significant neuromuscular blockade suggesting that this could be the underlying pathogenesis.

MFS is commonly preceded by an infectious illness such as *Campylobacter jejuni* enteritis. Anti-GQ1b antibodies also cross-react with lipopolysaccharide in the bacterial coat of *Campylobacter jejuni* providing a possible mechanism by which these antibodies might be formed in patients with MFS and indeed other forms of GBS. Cross-reactivity with other organisms could explain cases unrelated to *C jejuni* [8].

The pathogenesis of MFS is debatable with regards to whether this is primarily due to central nervous system (CNS) or peripheral nerve involvement. Nerve conduction studies in MFS demonstrate predominately reduced amplitude as well as neurophysiological features of mild demyelination or axonal degeneration. On the other hand, in his original description of the disease, Miller Fisher noted that degree and symmetry of the ophthalmoplegia, comparatively mild ptosis, relative sparing of downward gaze and cerebellar-type ataxia, suggested a central lesion. However, he then concluded that the clinical signs of MFS were attributable to a GBS-like process affecting the peripheral nerves [1] and this was further supported by nerve conduction and electromyographic studies. Despite this, doubt about the existence of CNS pathology has continued and recently, increasing use of MR imaging in cases of MFS (and GBS), have shown abnormalities in the brainstem (usually hypo-intense on T1 and hyper-intense on T2-weighted images with minimal enhancement after contrast administration) [9].

## Headache and MFS

Headache has been described more frequently in MFS than in GBS, with the reverse being true for neuropathic pain. Most cases of headache associated with the GBS spectrum have been documented in cases of MFS and posterior reversible encephalopathic syndrome (PRES) [9]. It still however remains a rare manifestation of disease with very few published case reports.

In the largest reported case series of 50 MFS patients with strict entry criteria of the classical triad and without significant limb weakness or signs of CNS involvement [11], headache

was not included as a reported symptom although it is unclear whether this was specifically enquired about.

The pathophysiology of headache in MFS is uncertain but there are a number of postulated mechanisms.

The possible CNS involvement in MFS could be a cause for headache but whether this is due to direct inflammation or some other process is still debatable. In a similar case report by Freidmann & Potts [12] the effect of increased CSF protein was discussed as a possible cause for headache. Increased protein could theoretically lead to CSF outflow obstruction and increased intracranial pressure. Our case 1 however did not have increased CSF protein at the time of lumbar puncture and CSF opening pressure was normal in both cases. Similarly to the cited case report [12], our patient did not report decreased visual acuity, positional variation in the headache or nausea but did complain of photophobia.

Another possible cause for headache in MFS could be direct inflammation of the trigeminal pain pathway. In studies carried out by Chiba et al. [13], it was demonstrated that unlike the cranial nerves, the dorsal roots of spinal nerves did not contain significant amounts of GQ1b ganglioside. Freidman & Potts [12] therefore postulate that headache was unlikely to be the result of direct injury to these nerves by GQ1b antibodies. They conclude that headache in MFS is more likely to be due to the action of GD3 and GD1b antibodies which are found in a small proportion of patients with MFS [14]. In their case report they highlight that these antibodies may be the cause for headache as GD3 and GD1b gangliosides are found in all 12 cranial nerves as well as both dorsal and ventral nerve roots making them the more likely culprits for headache symptoms in MFS. Our case 1 had a high positive titre for GD1b whilst unfortunately GD3 was not part of the test panel used. Our case 2 on the other hand did not test positive for GD1b, but again levels of GD3 were not screened for.

## CONCLUSION

Headache in MFS is a rare symptom as documented in the medical literature thus far. However, this could be the result of under-reporting rather than it being a rare occurrence. The exact mechanism is still uncertain and needs further evaluation. Our case reports may highlight the importance of other gangliosides such as GD1b in the pathophysiology of MFS especially with regards to additional symptoms over and above the classical triad.

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### Cite this article

Pirotta T, Chircop C, Vella N (2016) Is headache a common symptom in Miller Fisher Syndrome? – Two Case Reports. *J Autoimmun Res* 3(1): 1011.