

# An Overlapping Case of Miller Fisher Syndrome and Acute Motor Axonal Neuropathy in Children

Kristopher May Pamudji<sup>1</sup>, Dewi Sutriani Mahalini<sup>2</sup>, IGN Made Suwarba<sup>3</sup>

<sup>1,2,3</sup> Department of Child Health Medical School, Udayana University/ Sanglah Hospital, Denpasar, Indonesia

**Abstract:** **Background:** Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barre syndrome (GBS), classically characterized by a triad consist of ophthalmoplegia, ataxia, and areflexia. It is an immune-mediated polyneuropathy which may be preceded by mild respiratory or gastrointestinal infection. The diagnosis is based on clinical patterns, cerebrospinal fluid (CSF) analysis, and nerve conduction studies. Some severe variant forms like limb weakness (overlapping GBS), lower cranial nerves involvement (bulbar palsy), or central nervous system involvement (Bickerstaff encephalitis) have been reported, which might need proper diagnosis and treatment. **Case Presentation:** A 6 years old boy presented with drooping of the upper eyelid, imbalance and tendency to fall on either side while walking. The past medical history showed upper respiratory tract infection 1 week earlier. Physical examination showed complete ophthalmoplegia, ataxia, and lost of deep tendon reflex. The patient later developed mild lower limb weakness, difficulty in swallowing and bilateral facial nerve palsy. Cerebrospinal fluid analysis showed albuminocytologic dissociation and nerve conduction studies showed mix type lesion (axonal and demyelination), predominantly motor axonal lesion which support AMAN variant of GBS. Intravenous immunoglobulin (IVIG) was given and the symptoms gradually improved. The patient was discharged from hospital after 3 weeks with mild ophthalmoplegia and completely recovered after 6 weeks. **Conclusion:** We have reported an overlapping case of Miller Fisher syndrome and AMAN in 6 years old boy. Intravenous immunoglobulin therapy gave a good outcome in this case.

**Keywords:** miller fisher syndrome, guillain barre syndrome, acute motor axonal neuropathy, ophthalmoplegia, ataxia.

## 1. Introduction

Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barre syndrome (GBS) which is characterized by a triad of ophthalmoplegia, ataxia and areflexia. It is observed in about 1%-5% of all GBS cases in Western countries and higher in Asia (19% in Taiwan and 25% in Japan) [1]-[4]. The annual incidence is about one patient per one million population [5]. This syndrome can be found in all ages, including infants, although it is less common in children than in adults. Male are more often affected than female in about 60%-68% [6].

The clinical triad of MFS mostly can be found together, but a purely ophthalmoplegic form and ophthalmoplegic with weakness or ataxia also exists. Ophthalmoplegia, whether occurring alone or with other parts, is almost associated with a specific antineural antibody, anti-GQ<sub>1b</sub> [6]-[8]. Glycans on lipooligosaccharides of preceding infectious organisms can induce anti-GQ<sub>1b</sub> antibodies that can bind to structurally identical glycan present on nerve gangliosides. This process can cause acute motor axonal neuropathy by antibody-mediated attack on the nerve axolemma driven by molecular mimicry between microbial and axolemmal surface molecules [9]. The titres of this anti-ganglioside antibody reach their peak at clinical presentation and decay rapidly in most cases concomitant with clinical recovery [10].

Diagnosis of MFS based on clinical features, but additional investigations can be helpful or even needed for confirmation [9], [11]. The presentation of clinical triad (ophthalmoplegia, ataxia and areflexia) in combination with absent or reduced sensory responses on clinical electrophysiology testing and elevated protein with a normal white blood cell in cerebrospinal fluid analysis could lead to the diagnosis of MFS [3].

We present an overlapping case of MFS and acute motor axonal neuropathy (AMAN) variant of GBS in children, which treated with intravenous immunoglobulin (IVIG).

## 2. Case

A 6 years old boys whom previously healthy child, admitted to Sanglah Hospital Emergency Department with drooping of the upper eyelid since 2 days. The drooping did not deteriorate after being awake longer. The patient cannot move his eyes to every direction, but there is no blurred or double vision. The patient also had imbalance and tendency to fall on either side while walking. There is no headache nor decrease of consciousness. Bladder and bowel function were normal. The past medical history showed upper respiratory tract infection 1 week earlier. There was no recent history of trauma, drug abuse, alcohol addiction and vaccination.

General physical examination was normal with stable vital signs. Cranial nerve examination revealed bilateral complete external ophthalmoplegia with ptosis that not improved with rest or ice pack test. The pupillary light reflex was sluggish in both eyes. Nystagmus was absent. Other cranial nerve examination showed normal result. Motor system examination showed normal muscle tone and power in both upper and lower limbs. There was no muscular wasting and involuntary movements. Deep tendon reflexes were absent in all four limbs with negative Babinski reflex. Sensations like thermal, pain and touch were normal. Romberg's test was positive. He had ataxic gait with grossly impaired Tandem walking and tendency to fall on either side. Finger nose test and other cerebellar signs were normal.

Laboratory examination revealed normal complete blood count. Initial cerebrospinal fluid (CSF) analysis at the fourth day of admission showed normal limit with white cell count

8 cell/uL, predominantly mononuclear 100%, and protein 99 mg/dL. Cerebrospinal fluid analysis at the second week revealed albuminocytologic dissociation with white cell count 39 cell/uL, predominantly mononuclear 90%, and protein 295 mg/dL. He was clinically diagnosed with MFS after having the MFS triad, and was managed conservatively.

After seven days of admission, he developed mild lower limb weakness with difficulty in swallowing and bilateral facial nerve palsy. Motor system examination showed mild decreased in muscle tone and power (4/5) on both lower limbs. Nerve conduction studies showed mix type lesion (axonal and demyelination), predominantly motor axonal lesion which support AMAN variant of GBS. He was later diagnosed with MFS overlap AMAN and admitted to pediatric intensive care unit (PICU) for monitoring of the risk of respiratory failure that may occurred. Enteral feeding with nasogastric tube was started since the patient cannot swallow. The patient began to be given intravenous immunoglobulin (IVIG) with dose 0.4 gram/kg/day for five days.

This patient showed slow response to IVIG therapy. Difficulty in swallowing was improved after 4 days of IVIG administration and limb weakness was gradually improved after 7 days. Ophthalmoplegia and ptosis did not showed significant improvement with IVIG therapy. Patient was consulted to rehabilitation specialist to get physiotherapy. The patient was discharged from hospital after 3 weeks of hospitalization with mild ophthalmoplegia. Outpatient follow-up three weeks after hospitalization revealed that he was well recovered without any residual deficit. His ocular symptoms, which were the first symptoms to come on, had been the slowest to resolve.

### 3. Discussion

Miller Fisher syndrome is characterized clinically as a triad of ophthalmoplegia, ataxia, and areflexia. The initial symptom in MFS is typically diplopia (65%), followed by gait disturbance (32%). Most patient with MFS exhibit bilateral, relatively symmetrical ophthalmoplegia and up to one third of patients have complete external ophthalmoplegia. Internal ophthalmoplegia is quite common in MFS with slow to absent pupillary constriction to light. Ataxia in MFS occurred because mismatch between proprioceptive input from muscle spindles and kinesthetic information for joint receptors [2], [3]. Areflexia is not always found in MFS. Ito et al found that 12% patient with MFS and Bickerstaff brainstem encephalitis (BBE) had normal deep tendon reflexes [6].

Microorganisms that have been identified became preceding infections are *campylobacter jejuni*, *haemophilus influenza*, Epstein-Barr virus, influenza A virus, cytomegalovirus (CMV), and *mycoplasma pneumonia* [1], [9]. *Campylobacter jejuni* and *haemophilus influenza* have been identified as the most commonly implicated pathogens and upper respiratory infection is the most commonly described prodromic entity, followed by gastrointestinal illness [1], [6]. Miller Fisher syndrome has an acute onset and neurologic symptoms usually appear in 8-10 days after antecedent

illness. This disease will continue to progress until reaching a clinical nadir in 6 days (range 2-21 days) after the initial neurologic symptoms [1]. In this case, patient had upper respiratory infection 1 week before ophthalmoplegia, which was the first symptom that appear.

Facial nerve involvement has been found in about 30-46% of patients, which can result in orbicularis oculi weakness and lead to dry eye syndrome [8]. Bulbar palsy also can be found in 26% patient in a large study [6]. Although limb weakness is not part of the clinical spectrum of this syndrome, it may be present in 20-25% of the patients [5]. Some patients have combined features of MFS and GBS, in which the oculomotor disturbance and limb weakness occur within a few days of one another and is called as MFS with GBS overlap variant (ophthalmoplegia, ataxia, areflexia, and weakness) [12], [13]. In this case, patient had MFS triad (ophthalmoplegia, ataxia, and areflexia) with facial and bulbar nerve involvement and limb weakness. Patient was diagnosed as MFS overlap GBS. The first symptom that appeared was ophthalmoplegia with ataxia, while lower limb weakness, difficulty in swallowing, and bilateral facial nerve palsy appeared 9 nine days after the onset of ophthalmoplegia.

The high protein content and low cell counts in the CSF named albuminocytologic dissociation. Miller Fischer syndrome has been considered as a GBS variant because albuminocytologic dissociation was found in the CSF of MFS patients. This is a typical feature in several neuroimmunological disorders such as acute demyelinating encephalomyelitis and BBE. Although albuminocytologic dissociation is common in these disorders, further CSF analysis did not distinguish between these entities [5]. Albuminocytologic dissociation may be absent at the time of initial symptoms, and becoming prominent over the next weeks. It seems to occur more frequently in the overlap syndrome of BBE/GBS than in MFS [6]. In this case, CSF analysis at the first week did not show albuminocytologic dissociation, but CSF analysis at the second week revealed albuminocytologic dissociation.

The diagnosis of MFS is still descriptive depending on the presentation of the triad ophthalmoplegia, ataxia, and areflexia. The combination of absent or reduced sensory responses on clinical electrophysiology testing and elevated protein with a normal white blood cell in CSF could lead to the diagnosis of MFS [3]. Electrophysiological study indicate that MFS is an axonal form of neuropathy which is associated with anti-ganglioside antibodies. Patients might show promptly reversible nerve conduction failure or axonal degeneration. This feature suggests a common pathogenetic mechanism of autoantibody-mediated dysfunction or disruption at the nodes of Ranvier, resulting in a continuum of nerve pathologies from transitory conduction failure to axonal degeneration [11]. Serial motor conduction velocities showed a marked reduction in the amplitudes of distal compound muscle action potential (CMAP), reaching low at 2nd to 3rd week, followed by a dramatic improvement in 5th week [14]. In this case, nerve conduction studies showed mix type lesion (axonal and demyelination), predominantly motor axonal lesion which support AMAN variant of GBS.

The diagnosis of MFS could be confirmed by positive anti-GQ1b antibody testing with a high level of sensitivity and specificity [3]. The GQ1b ganglioside is a cell surface component that is concentrated in the paranodal regions of the human third, fourth and sixth cranial nerves. It contains polysaccharides that identical to the lipopolysaccharides (LPS) contained in the outer membranes of certain bacteria and may thus be the target of an immune response initiated against epitopes shared by these nerve fibers and various agents. Yuki et al found that monoclonal antibodies to the GQ1b ganglioside reacted to LPS fractions from *Campylobacter jejuni* isolated from patients with MFS. These results proposed that through the mechanism of molecular mimicry, they were not only a marker for the disease, but actually played a role in its pathophysiology. Anti GQ1b antibodies also bind to LPS from MFS-related *Haemophilus influenzae* strains, suggesting a common pathogenesis. Anti GQ1b antibodies affect the neuromuscular junction, including axon and Schwann cell degeneration through complement mediated pathways [6], [16]. The process will activate complement, culminating in the formation of lytic membrane attack complex, causing structural rearrangement of the muscle spindles in the neuromuscular junction and therefore blocking nerve conduction. This causes paralysis that sequentially induces the characteristic triad seen in MFS [8].

Several disease processes can cause ophthalmoplegia, ataxia and areflexia that can be MFS differential diagnosis. Ophthalmoplegia caused by MFS is often rapid in onset compared to a more gradual course in chronic diseases such as myotonic dystrophy, thyroid eye disease, and myasthenia gravis. More than 50% of patients with myasthenia gravis present with ptosis and/or diplopia. The weakness of the ocular muscles may switch from one eye to another and improve or worsen over the course of a day, unlike MFS which progressively worsens until the nadir of symptoms has been reached before any recovery is seen. Ataxia presentation in MFS can be confused with an ischemic event. Ataxic patients with MFS typically lack lateralization which helps to differentiate MFS from majority of cerebellar lesions. Alcohol consumption can cause ataxia, but mostly affects the lower extremities and is also associated with poor fine motor control of the hands, slurred speech, and impaired vision. Areflexia is indicative of a lower motor neuron deficit. Spinal shock is an acute condition like MFS, while amyotrophic lateral sclerosis (ALS) typically has a gradual onset. Temporary paralysis and areflexia similar to MFS and GBS can also be caused by polio virus infection, with functional recovery occurring 4-6 weeks after paralysis [1]. Miller Fisher syndrome may be mistaken for a brainstem stroke at initial presentation. However, the gradual onset of MFS in particular distinguishes this syndrome clinically from an acute stroke. The differential diagnosis of MFS includes Wernicke's encephalopathy and brainstem encephalitis, but these diseases are associated with altered mental status. Patients with Wernicke's encephalopathy usually have nystagmus that cannot be found in MFS [3].

Miller Fisher syndrome is a self-limiting disease and there is no randomized controlled studies to find any benefits of the

standard treatments used as therapy. Despite that finding, MFS patients with overlapping diseases like GBS and BBE will most likely benefit from IVIG [8]. Overell et al found that although MFS follows a self-limiting course, immunomodulatory therapies including IVIG and plasmapheresis have been used to hasten time to disease recovery and perhaps decreased a likelihood of progression to more severe condition [15]. In this case, patient was diagnosed as MFS overlap GBS and given IVIG for 5 days. This patient showed slow response to IVIG therapy. Difficulty in swallowing was improved after 4 days of IVIG administration and limb weakness was gradually improved after 7 days. Ophthalmoplegia and ptosis did not show significant improvement with IVIG therapy.

Recovery in MFS patients usually occurs in 10-20 weeks, residual symptoms were reported in 33.2% cases and recurrence in 7% cases [2]. Most patients with MFS recover spontaneously and completely within 2-3 months of the onset. The median time from onset of neurologic symptoms to beginning of recovery in 28 untreated patients was 12 days for ataxia and 15 days for ophthalmoplegia in one study. The median time to achieve full recovery was 1 month for ataxia and 3 months for ophthalmoplegia. The recovery rate was not related to age, sex, evidence of prior infection, disability at illness peak, or latency to peak [6]. However, cases progressing to respiratory failure and requiring mechanical ventilation have also been described, particularly in children [2]-[4]. In this case, patient was discharged from hospital after 3 weeks of hospitalization with mild ophthalmoplegia. Outpatient follow-up three weeks after hospitalization revealed that he was well recovered without any residual deficit. His ocular symptoms, which were the first symptoms to come on, had been the slowest to resolve. This patient did not progress to respiratory failure.

#### 4. Summary

We have reported an overlapping case of Miller Fisher syndrome and AMAN in a 6-year-old boy. The diagnosis of MFS is based on clinical triad that consists of ophthalmoplegia, ataxia, and areflexia. Although uncommon, MFS is an important diagnosis to make since the presenting symptoms of ophthalmoplegia and ataxia may confuse the clinician and suggest an upper motor neuron sign or central cause. Miller Fisher syndrome is a benign condition which is self-limiting, however MFS patients with overlapping diseases like GBS and BBE will most likely benefit from IVIG. In this case, IVIG therapy was given to the patient and showed a good outcome.

#### References

- [1] Yepishin IV, Allison RZ, Kaminskas DA, Zagorski NM, Liow KK. Miller Fisher syndrome: a case report highlighting heterogeneity of clinical features and focused differential diagnosis. *Hawaii J Med Public Health*; 2016. 75(7):196-9.

- [2] Kodali VU, Borra S, Bolla SR. Miller Fisher syndrome- an atypical clinical presentation. *Intern Med*; 2013. 3:1-2.
- [3] Das PP, Biswash S, Karim E, Ahmed NS, Islam B, Mandal SK, et al. Miller Fisher variant of Guillain-Barre syndrome: a case report & clinical review. *BSMMU J*; 2012. 5(1):69-71.
- [4] Sever M, Aksay E, Gulec F. The diagnosis is made only with suspicion: Miller Fisher syndrome. *Hong Kong J Emerg Med*; 2011. 18(6):428-31.
- [5] Aranyi Z, Kovacs T, Sipos I, Bereczki D. Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings. *Eur J Neurol*; 2011. 19:15-23.
- [6] Snyder LA, Rismondo V, Miller NR. The Fisher variant of Guillain-Barre syndrome (Fisher syndrome). *J Neuro-Ophthalmol*; 2009. 29(4):312-24.
- [7] Ropper AH, Samuels MA, Klein JP. Diseases of the peripheral nerves. In: Adams and Victor's principles of neurology. 10<sup>th</sup> ed. New York: McGraw-Hill education; 2014. p.1322-30.
- [8] Rittenbach TL. A case presentation of a third-nerve palsy as a characteristic of Miller Fisher syndrome. *Optometry & Visual Performance*; 2014. 2(4):166-9.
- [9] Willison HJ, Jacobs BC, Doorn PA. Guillain-Barre syndrome. *Lancet*; 2016. 388:717-27.
- [10] Hanlon GM, Bullens RW, Plomp JJ, Willison HJ. Complex gangliosides as autoantibody targets at the neuromuscular junction in Miller Fisher syndrome: a current perspective. *Neurochemical Research*; 2002. 27:697-709.
- [11] Wakerley BR, Uncini A, Yuki N. Guillain-Barre and Miller Fisher syndromes-new diagnostic classification. *Nat Rev Neurol*; 2014. 10:537-44.
- [12] Sekiguchi Y, Mori M, Misawa S, Sawai S, Yuki N, Beppu M, et al. How often and when Fisher syndrome is overlapped by Guillain-Barre syndrome or Bickerstaff brainstem encephalitis?. *Eur J Neurol*; 2016. 23:1058-63.
- [13] Sahoo MR, Rout MR. Miller Fisher syndrome with GBS overlap- a rare case report. *Indian J Appl Res*; 2013. 3(8):1-2.
- [14] Santra G, Datta AK. Miller Fisher syndrome – an uncommon clinical presentation. *J Assoc Physicians India*; 2008.56: 898-900.
- [15] Bukhari S, Taboada J. A case of Miller Fisher syndrome and literature review. *Cureus*; 2017. 9(2):e1048.
- [16] Mahalini DS. Tatalaksana Guillain-Barre Syndrome (GBS). Dalam: Suparyatha IB, Sidiartha IGL, Kumarawati D, Sarangnga C, Indradjaja A, Kurniawati NW, Yuliana, Suradji RD, penyunting. Penanganan kegawatdaruratan neonatus dan anak pada fasilitas terbatas. Denpasar: Percetakan Bali; 2012. hal. 179-92.