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Case Report

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Overlapping Miller Fisher Syndrome Following Primary Varicella Zoster Infection: A Case Report

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ABSTRACT

Miller-Fisher syndrome (MFS) is a variant of Guillain-Barre syndrome (GBS). The typical presentation of MFS includes a combination of ataxia, areflexia, and ophthalmoplegia, usually without limb weakness. However, some patients with MFS may exhibit an incomplete set of symptoms or display features that overlap with those of typical GBS. We describe the case of a 9-year-old boy who presented with unsteady gait and bilateral lower limb weakness, along with a recent history of resolved Varicella-Zoster Virus (VZV) infection. Despite lacking fever, speech or swallowing difficulties, or abnormalities in sphincter control, he showed signs of ataxia, areflexia, and lower limb weakness on examination, without ophthalmoplegia. Further investigations revealed elevated protein levels and no cells in the cerebrospinal fluid (CSF), as well as evidence of acute focal and segmental inflammatory demyelinating polyneuropathy on nerve conduction studies. The child was diagnosed with an overlapped variant of MFS/GBS following primary VZV infection and achieved complete recovery with intravenous immunoglobulin (IVIg) treatment and other supportive measures. This case illustrates a subtype of MFS known as MFS/GBS overlapped syndrome, wherein the patient displayed MFS features alongside limb weakness. The presence of incomplete MFS symptoms and overlapping features with GBS posed a diagnostic challenge, underscoring the importance of considering rare variants when patients exhibit atypical presentations.

Keywords: Guillain-Barre Syndrome, Miller-Fisher Syndrome, Varicella Zoster, Acute Flaccid Paralysis.

INTRODUCTION

Guillain-Barre syndrome (GBS) is an immune-mediated polyneuropathy that typically presents with ascending limb weakness [1]. Miller-Fisher syndrome (MFS) is a major variant of GBS. Classic MFS presents with a triad of ataxia, areflexia, and ophthalmoplegia without limb weakness [1,2]. GBS and MFS have many subtypes, forming a continuous spectrum of distinct and overlapping syndromes. The similarity in pathophysiology, clinical manifestations, history of preceding infection, and investigation results suggests that these conditions belong to one clinical entity. Although MFS is a triad, patients with MFS can have an incomplete phenotype and present with only two of the three features. Occasionally

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patients with MFS can also have some features of typical GBS and are known as overlapping MFS [3].

The acute autoimmune response triggered by infections or vaccines is known to cause MFS. Although many viral infections are associated with MFS, the Varicella Zoster virus (VZV) is only rarely reported in children with MFS [2].

We report a 9-year-old boy who presented with a 2-day history of unsteady gait and bilateral lower limb weakness with a recent history of spontaneously resolved VZV infection. On examination, he had ataxia, areflexia, and weakness of lower limbs but no signs of ophthalmoplegia. The nerve conduction studies showed evidence of acute focal and segmental inflammatory demyelinating neuropathy. The child was managed as MFS/GBS overlapped variant following primary VZV infection with supporting evidence from the nerve conduction studies. The child had a complete recovery with intravenous immunoglobulin (IVIg) and other supportive measures.

The incomplete presentation of MFS, overlapping features with GBS, and a history of antecedent primary varicella zoster infection led to a diagnostic dilemma in this patient. Hence, we report this case to enlighten the readers on the importance of considering rare differentials and incomplete phenotypes when patients present beyond the typical clinical picture.

CASE REPORT

Nine years old previously well boy, presented with a 2-day history of lower limbs weakness and numbness with difficulty in walking. There was no associated fever, headache, seizure, speech difficulties, swallowing difficulties, or abnormalities in bowel and bladder control. There was no history of snake bites or exposure to any medications. On further inquiry, it was evident that the boy had developed VZV infection 2 weeks before admission and had resolved spontaneously.

His past medical history and surgical history were uneventful. The immunization was up to date and the development was age-appropriate. There was no significant family history. On general examination, his weight and height were 22 Kg and 123 cm respectively, with a BMI of 15 which were within the normal limits. The child was alert and oriented. An extensive generalized healed skin rash with scabs was noted.

On examination of the central nervous system (CNS), the tone of all 4 limbs was normal, power was grade 3 in both lower limbs and was normal in the upper limbs. The tendon reflexes of the upper limbs were present, but bilateral knee reflexes, ankle reflexes, and plantar reflexes were absent. There was no ascending paralysis and the single breath count was normal. The patient demonstrated an ataxic gait. Examination of the cerebellar system revealed positive past pointing and lateral nystagmus, but the other cerebellar signs were negative. Cranial nerves and the sensory nervous system were preserved. Examination of the respiratory system, cardiovascular system, and abdomen revealed no abnormality and the child's vital parameters were stable.

Based on the history and the examination, post-viral cerebellitis with or without neuritis or an atypical GBS following primary VZV were considered the main differential diagnoses. Basic blood investigations and a CT brain were performed and revealed normal results. Due to the ambiguity in this presentation, a paediatric neurological opinion was taken and relevant investigations were performed.

Lab investigations were as follows:

Investigation	Value
Full blood count (FBC)	Leucocytes - 17.47 (4-11×10^9)- Neutrophils-13.14 Hemoglobin - 14 (12-17) Platelet - 420 (150-450×10^9)
Serum electrolytes (SE)	Sodium - 138 mEq/L (135-145 mEq/L) Pottasium - 3.9 mEq/L (3.5-5.5 mEq/L)
Creatine phosphokinase (CPK)	72 U/L (24-190).
C- reactive protein (CRP)	93 mg/dL
CSF analysis	clear, colorless and acellular with protein of 150.7 mg/dL CSF glucose - 3.89 mmol/L
Random Blood Sugar (RBS)	4.9 mmol/dL
CT Brain	Normal

As per the paediatric neurologist's suggestion, the child was immediately started on IVIg infusion. Then the following day the boy underwent lumbar puncture and nerve conduction studies. The CSF studies showed an elevated protein with the absence of cells. The nerve conduction studies showed evidence of acute focal and segmental inflammatory demyelinating neuropathy. Due to limited resources, we could not perform VZV antibody or PCR in CSF and IgG anti-GQ1b antibody.

Intravenous Immunoglobulin treatment was continued. Limb physiotherapy was started with other supportive measures. Improvement of the limbs was noted 3 days after commencing IVIg. He was discharged on the 7th day of hospital admission with near total neurological recovery.

DISCUSSION

Guillain-Barré syndrome is a broad clinical entity that includes various types of immune-mediated polyneuropathies. GBS typically presents with ascending limb weakness. MFS is a variant of GBS that generally involves lower cranial nerves and it is characterized by a classic triad of ataxia, areflexia, and ophthalmoplegia [2]. Limb weakness is not a usual feature of MFS. Only 5% of MFS patients will have limb weakness.

GBS and MFS have many subtypes, forming a continuous spectrum of distinct and overlapping syndromes. The MFS is sub-classified into incomplete MFS, overlapping MFS/GBS, and Bickerstaff brainstem encephalitis. The analogy in the pathophysiology, similarity in the clinical manifestations, history of preceding infection, symmetrical limb or cranial weakness, CFS protein-cellular dissociation, evidence of demyelination in the nerve conduction studies, and positive antiganglioside antibodies suggest that these conditions belong to one clinical entity. Although MFS is a triad, patients with MFS can have an incomplete phenotype and present with only two of the three features. Occasionally patients with MFS can also have some features of typical GBS and are known as overlapping MFS [3,4].

The global incidence of MFS is 1-2 in 1,000,000. The triad was first recognized by James Coiller in 1932 and later the unique entity was described by Miller Fisher in 1956 [5]. The acute autoimmune response triggered by an infection or a vaccine can lead to MFS or GBS [6]. Campylobacter jejuni is identified as the most common pathogen. Epstein–Barr virus, Hemophilus influenza, Cytomegalovirus, Mycoplasma pneumonia, and Zika virus also can contribute to the pathogenesis [7]. However, Varicella zoster-associated GBS and MFS have been reported rarely [2]. Neurological complications following a Varicella zoster infection are generally rare, and the development of GBS or MFS is extremely rare [2].

The precise pathogenesis of GBS is still unknown, but the available evidence suggests that GBS is a broad clinical entity that encompasses several types of acute immune-mediated polyneuropathies. Polyneuropathies are divided into 2 major categories: demyelinating or axonal. Demyelinating neuropathies cause symptoms as the Schwann cells fail to interact appropriately with axons. Axonal neuropathies produce abnormalities due to axon damage and loss. In GBS, demyelinating polyneuropathy plays a major role in the pathophysiology. In patients with GBS, an immune response is mounted against the myelin sheath due to molecular mimicry and produces the clinical features typical of GBS [4]. Axonal and sensory neuropathy is the mainstay of the pathophysiology in MFS. GQ1b ganglioside is a component of the neuronal cell membrane and it is identical to the cell membranes of certain bacterial strains like Campylobacter. In MFS patients the newly formed GQ1b antibodies against the bacterial antigens cross-react with the neuronal sheaths due to molecular mimicry. This leads to the destruction of the neurons giving rise to the clinical picture of MFS [8].

In more than 85% of MFS patients, positive anti-ganglioside antibodies (GQ1b) are observed. Levels of GQ1b correlate with the severity of the disease [8]. Even though the GQ1b antibodies are closely related to ophthalmoplegia, GQ1b has been found in certain patients without ocular abnormalities. Although we couldn't perform anti-GQ1 b antibodies, the clinical picture was very much fitting into the MFS variant. Electrophysiologic abnormalities in MFS typically suggest a predominantly axonal, sensory polyneuropathy, but demyelinating forms do occur and may be underdiagnosed [9].

Although MFS is called a triad, as mentioned earlier there are reported cases with an incomplete presentation where only 2 of the three clinical features are observed. Similarly, limb weakness which is not a characteristic feature of MFS is observed in some of the diagnosed MFS patients. Among the patients with the incomplete presentation of MFS, the commonest manifestation is ophthalmoplegia followed by ataxia [10]. Our patient had only 2 features of the MFS triad making it an incomplete presentation. Despite ophthalmoplegia being a common feature of MFS, our patient didn't have any features suggestive of ophthalmoplegia.

In addition to the characteristic clinical features, MFS patients also can have symptoms like blurred vision, tingling sensation of the extremities with or without weakness, dysarthria, cranial nerve involvement, bulbar weakness, facial paralysis, and autonomic dysfunction [2,5]. There is no clear explanation some patients have only ataxia and areflexia but no ophthalmoplegia. However, it is thought to

be due to the sparing of the particular brain tissue based on the degree of extension and intensity of the damage [11]. An extensive literature survey revealed that atypical MFS is a common entity in adults whereas it is rarely described in children. We hereby present a list of a few selected cases of atypical MFS in children with details of their atypical manifestations (Table 1).

Table 1. Reported cases of paediatric MFS with atypical presentations

	Case report	Published year	Age/ Gender	Atypical features
1	Eyes wide open—an atypical presentation of Miller Fisher syndrome (MFS): case report [12]	2022	13 years Girl	Blurred vision and diplopia
2	Pediatric Miller Fisher syndrome; characteristic presentation and comparison with adult Miller Fisher syndrome [13]	2020	2 years Girl	Facial palsy, limb weakness, dysphagia, dysarthria
			7 years Girl	Voice change, tongue deviation, limb weakness
			1 year Girl	Limb weakness, dysphagia, hoarseness, hypertension
			15 years Girl	Tinnitus, uvula deviation, absent gag reflex
			17 years Boy	Lower limb pain
3	Miller Fisher Syndrome Presenting as Pseudotumor [14]	2002	9 years Girl	Nausea, diplopia, and convergent strabismus increased CSF pressure
			2 years Girl	

It would be challenging to diagnose the MFS at the outset if the patient doesn't have the classic triad. In our case the main complaint was unsteady gait, hence the initial suspicion was whether this was cerebellitis based on the recent history of VZ infection. However, with the examination findings of areflexia and ataxia, we had to consider the GBS variant as the likely diagnosis. The literature survey shows only one reported case of MFS triggered by VZV. Panagiota et al from Greece reported a case in 2021 where a 6-year-old child presented with Miller-Fisher syndrome following a varicella-zoster virus infection [15].

Nerve conduction studies (NCS) and electromyography (EMG) are very helpful tools in diagnosing GBS and its variants but can be normal at early stages [1]. In the first 2 weeks of the illness, it is abnormal in only 50% of patients and after the 2nd week, it is abnormal in 85% [15]. The NCS indicates demyelination of the nerve fibers which is specific and sensitive for classic GBS [1]. The NCS of our patient was suggestive of GBS and it helped to establish the diagnosis.

In the CSF analysis, the presence of albuminocytological dissociation is the hallmark of GBS [1,2,15]. It's defined as the elevation of CSF protein > 0.55g/L in an otherwise acellular CSF. It is a vital clue for differentiating other infectious and inflammatory causes of flaccid paralysis from GBS [1]. Our patient showed albunimocytological dissociation which was 1.5g/L. We were unable to perform VZV antibodies or PCR due to financial constraints.

IVIg is the primary treatment option for patients with GBS and MFS. There is class-I evidence for the usage of IVIg in GBS and its variants emphasizing its efficacy in these conditions (van doorn) [1]. Plasma exchange (PE) is another treatment option available. Both IVIg and PE have the same efficacy, but interestingly combined therapy doesn't improve the outcome [16,17].

Overall, the pathogenesis of the overlapping features or incomplete phenotype observed in some patients with MFS and GBS is multifactorial and likely involves a combination of immune-mediated mechanisms, individual variations, and external triggers. Although there is a temporal plausible link between the occurrences, no association can be confirmed. Further research is needed to fully elucidate the underlying mechanisms and improve diagnostic and therapeutic approaches for these conditions.

CONCLUSION

The case report depicts a variant of MFS known as MFS/GBS overlapped syndrome. Our patient had features of MFS with limb weakness. This is very rare and only 5% of MFS patients will have limb weakness. The incomplete phenotype of MFS and overlapping features with GBS led to a diagnostic dilemma. Hence, we report this case to enlighten the readers on the importance of considering rare variants when patients have atypical features. The patient had a complete recovery with intravenous immunoglobulin (IVIg) and other supportive measures and was discharged home on the 7th day of his illness. Subsequently, when the patient was followed up in the clinic there were no neurological deficits noted. This case illustrates the value of making allowance for the rare differentials when there are atypical clinical features.

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