CASE REPORT

Miller Fisher syndrome

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SUMMARY

A man aged 30 years presented to the emergency department (ED) with ataxia, areflexia, facial weakness, ophthalmoplegia, extremity weakness and back pain for 4 days. 4 days prior to attending the ED, the patient had suffered from diarrhoea for 2 weeks. The diagnosis of Miller Fisher syndrome was performed on the dual basis of clinical features in addition to an investigations report. Nerve conduction studies and anti-GQ1b IgG antibody analysis were requested. Once IgA deficiency was ruled out, the patient was started on intravenous immunoglobulin (400 mg/kg/day).

BACKGROUND

Guillain-Barre syndrome (GBS) is an acute, immune-mediated, monophasic illness usually triggered by a preceding infection. Miller Fisher syndrome (MFS), a clinical variant of GBS, occurs in ~5% of cases in the USA, 25% of cases in Japan and is characterised by areflexia, ophthalmoplegia and ataxia.¹ Extremity weakness, a major symptom of GBS, will develop in approximately one-quarter of MFS patients, further affirming the link between these two disorders. Incomplete forms of MFS exist, including acute ataxic neuropathy without ophthalmoplegia and acute ophthalmoplegia without ataxia.^{2,3} Anti-GQ1b is an antiganglioside antibody that is self-reactive to the GQ1b ganglioside component of a nerve and is present in about 85–90% of all patients with MFS.^{4,5} In addition, the GQ1b antibody is strongly associated with oculomotor nerves lesion and hence can also be found in patients with prominent oculomotor weakness and GBS.

The initial diagnosis of GBS is based on the clinical presentation. Lumbar puncture and cerebral spinal fluid (CSF) analysis of patients with GBS often reveals albuminocytologic dissociation. This describes an increase in CSF protein while cell count remains normal, that is, <5 cells/mm³, and is initially present in about 50–66% of GBS patients following their first week of symptoms, and in ≥75% of patients in their third week.^{2,6,7} Here, we present a case of MFS made evident by the presence of lower back pain, extremity weakness in addition to the characteristic triad of ataxia, ophthalmoplegia and areflexia.

CASE PRESENTATION

A man aged 30 years presented to the emergency department (ED) after suffering 4 days of multiple symptoms, including double vision, slurred speech and difficulty with his coordination, walking and hand movements, as well as finger numbness. The patient's symptoms began 2 days after he returned

from a trip to Montreal, about 2 weeks prior to his admittance to the ED. The patient's symptoms began with fatigue and developed into a fever of 103°F (at its peak), accompanied by severe diarrhoea that lasted for over a week. The diarrhoea had stopped 6 days previously; however, he then developed neurological symptoms such as double vision, light headedness, stumbling while walking, numb finger tips and odd chewing sensations. In addition, the patient also reported of lower back pain, was easily fatigued, had clumsier handwriting/typing, dropping of right eye as well as a slightly asymmetrical face due to weakness of right side of face. The patient denied worsening of double vision with any particular eye movement, trouble breathing and weakness of hand bilaterally. No neck pain, urinary retention, ileus or arrhythmia was noted. On review of history, there was no significant past, family, medical, surgical or allergy history.

The patient was examined and the following measurements recorded; temperature 98.3°F, heart rate: 78 bpm, respiration rate: 17 bpm, blood pressure: 128/68 mm Hg and partial pressure of oxygen (pO₂): 99%. A head, eyes, ears, nose and throat examination was nomocephalic/atraumatic and the cardiac, pulmonary and gastrointestinal examination were also found to be normal.

With regard to the mental status of the patient, he was alert and fully oriented. He had no aphasia or dysarthria and comprehension of language was normal. The patient's pupils were equal, round and reactive to light and accommodation; however, there was weakness with medial gaze and up gaze on the right eye. Extraocular movement on the left eye was intact. Weakness on the right side on the face was present. V1–V3 was intact to light touch (LT). Furthermore, hearing was intact and tongue was midline. Strength was 5/5 throughout, except the left triceps. LT and pinprick (PP) sensation were intact in the bilateral (B/L) upper extremity and stocking gradient was present to PP in the LE B/L. Reflexes were 0+ throughout while co-ordination testing revealed significant dysmetria/ataxia for finger to nose as well as heel to shin bilaterally. Gait examination was deferred.

INVESTIGATIONS

Investigations such as complete blood count, complete metabolic panel, blood culture, CSF examination and culture, CT scan without contrast to rule out stroke and MRI of the brain and cervical spine with and without contrast were ordered. The patient's NIH stroke scale score was 3/42 and his brain CT scan and MRI were normal. Serum thiamine and cyanocobalamin level were normal and his

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Table 1 Investigation report

Investigations	21 June 2016	22 June 2016	Investigations	21 June 2016	22 June 2016
Na ⁺ (136–145 meq/L)	137 meq/L	138 meq/L	RBC (4.7–6.1 million cells/ μ L)	4.79 million cells/ μ L	4.5 million cells/ μ L
K ⁺ (3.5–5.0 meq/L)	4.6 meq/L	4.7 meq/L	Hb (13–17 g/dL)	14.9 g/dL	13.6 g/dL
Cl (98–106 meq/L)	100 meq/L	102	Hct (41–51%)	43.7%	40.2%
CO ₂ (23–28 meq/L)	27 meq/L	26 meq/L	WCC (4.5–11 K/mcL)	9.5 K/mcL	5.8 K/mcL
Glucose (70–100 mg/dL)	82 mg/dL	100 mg/dL	Platelet (150–450 K/mcL)	417 K/mcL	388 K/mcL
BUN (8–20 mg/dL)	15 mg/dL	14 mg/dL	MCV (80–96 fL/red cell)	91.2 fL/red cell	89.3 fL/red cell
Cr (0.7–1.3 mg/dL)	1	0.9	MCH (27–33 pg/cell)	31.1 pg/cell	30.2 pg/cell
Total Ca (9–10.5 mg/dL)	9.5 mg/dL	9.2 mg/dL	CSF values		
Mg (1.5–2.4 mg/dL)	2.4 mg/dL	2.4 mg/dL	Colour	Colourless	
Bilirubin total (0.3–1.2 mg/dL)	0.8 mg/dL		Appearance	Clear	
AKP (36–92 U/L)	65 U/L		CSF WBC (0–5 cells/ μ L)	2 cells/ μ L	
ALT (0–35 U/L)	70 U/L		CSF lymphocytes	80%	
AST (0–35 U/L)	30 U/L		CSF neutrophils	20%	
Albumin	3.7 g/dL		CSF glucose (40–80 mg/dL)	55 mg/dL	
TSH (0.5–5 mIU/L)	1.62 mIU/L		CSF protein (15–60 mg/dL)	31 mg/dL	
Gq1b antibody	+ve		Cryptococcus Ag CSF	–ve	
ESR (0–15 mm/hour)	10 mm/hour		CSF Borrelia Ab IgG/IgM (N <0.9)	<0.90	
IgA gammaglobulin (70–300 mg/dL)	247 mg/dL	300 mg/dL	CSF culture	–ve	
AFB culture and direct smear	–ve		CSF West Nile virus and other virus detection	–ve	

oligoclonal IgG band was negative. Serum mycoplasma IgG titre was negative and culture of his stool was negative for enteric pathogens, including *Campylobacter jejuni*. GQ1b antibody was positive, suggestive of MFS. Electromyography was not performed. Nerve conduction study and cranial MRI including T1, T2 and diffusion-weighted images demonstrated no abnormality. The investigation report is attached here (table 1).

TREATMENT

Based on the history and the investigational findings, it was believed that he was suffering from a rare variant of GBS, that is, MFS. Before initiating intravenous immunoglobulin (IVIG) treatment, we measured the patient's IgA level and tested for the presence of albuminocytologic dissociation in his CSF. Both the investigations were normal and we proceeded to treat with acetaminophen 650 mg Q4 PRN and IVIG 25 000 mg (0.4 g/kg/day) for 5 days. The patient's negative inspiratory force (NIF) and vital capacity (VC) were checked every 4 hours. Fortunately, his NIF did not drop below 20, and so intubation was not required. The patient's symptoms improved with IVIG treatment. Even so, we referred him to a better equipped facility on third day of admission for fear that his symptoms may further deteriorate. Currently, he is in good health and his neurological symptoms are improving.

On review of his treatment history, 5 days after initiation of the treatment, his symptoms including ophthalmoplegia, ataxia and weakness of his lower extremities started to improve. After gradual improvement in his symptoms, he was discharged on the 14th day after admission. On his next follow-up on the 45th day in our office, he reported complete resolution of ataxia, dysarthria and ophthalmoplegia. His deep tendon reflexes were normal on examination.

DISCUSSION

GBS is an autoimmune disorder encompassing a heterogeneous group of acute, immune-mediated polyneuropathies and occurs with an overall incidence of 1–2 per 100 000 per annum, worldwide.^{2 8} Although all age groups can be affected, after the first

decade of life, there is an apparent 20% increase in incidence with every 10-year lived. Progressive, relatively symmetric muscle weakness is the characteristic clinical feature of GBS and is often accompanied by depressed or absent deep tendon reflexes. On average, patients present within a week of their symptoms manifesting and although weakness in the legs is a common initial symptom, ~10% of patients present with weakness beginning in either the arms or facial muscles. In addition, severe respiratory weakness is reported to occur in 10–30% of patients. Facial weakness occurs in >50% of cases, oculomotor weakness in up to 15%, oropharyngeal weakness in up to 50%, paresthesia in as many as 80% of cases, back or extremity pain, in particular in the acute phase of illness, in up to 66% of patients and dysautonomia occurs in around 70% of GBS patients.^{9–12}

MFS, a rare variant of GBS, typically presents as ophthalmoplegia with areflexia and ataxia.^{1 13} In contrast to GBS, respiratory symptoms have been to precede neurological symptoms in about 76% of MFS cases, and GI involvement is reported in only 4% of MFS patients.¹⁴ The presence of anti-GQ1b antibodies is believed to be associated with the pathogenesis of MFS. The ganglioside, GQ1b, can be found in abundance in the paranodal region of the extramedullary portion of the oculomotor, abducens and trochlear nerves, and it is these areas that are most affected by the self-reactive anti-GQ1b antibody.¹⁴ Similar to GBS, MFS can occur postinfection with 'molecular mimicry' believed to be the main pathogenic mechanism underlying this.⁴ Interestingly, the Gram-negative bacterium, *C. jejuni*, has been reported in as many as 30% of GBS cases, making it the most frequent pathogen to trigger this disease.¹⁵ MFS, in addition to *C. jejuni*, has also been associated with infection due to bacteria such as *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Helicobacter pylori*, as well as viral infection from Epstein-Barr virus, varicella-zoster virus, cytomegalovirus and HIV.^{4 15–18} A large prospective case-controlled serological study, however, revealed that the associated infective agents for the majority of cases remain unknown.¹⁹

In general, GBS patients have normal CSF cell counts, that is, <5 cells/mm³; however, mildly elevated CSF cell counts have

been documented in a minority of GBS patients. In the Massachusetts General Hospital (MGH) study, 110 GBS patients had their CSF cell count measured and 87% had <5 cells/mm³, 9% had 5–10 cells/mm³, 2% of patients had 11–30 cells/mm³, while 2% had a CSF cell count of >30 cells/mm³.⁶ In clinical practice, tests for anti-GQ1b IgG antibodies are available commercially and are extremely useful for the diagnosis of MFS. It is important to note however that anti-GQ1b antibodies may also be present in ophthalmoparesis-associated GBS, the pharyngeal-cervical-brachial GBS variant and Bickerstaff encephalitis.^{4,5} Of note, the normal CSF findings in our patient may have been due to obtaining the sample during the early period of the symptoms.

Other diseases that are known to cause ataxia, areflexia and ophthalmoplegia include: GBS, Bickerstaff's brainstem encephalitis, brainstem stroke, botulism, myasthenia gravis and Wernicke's encephalopathy. MFS is associated with rapid-onset ophthalmoplegia compared with gradual onset in chronic diseases such as myasthenia gravis, and myotonic dystrophy. On the other hand, MFS and cerebellar lesions are similar in presentation; however, lack of lateralisation of ataxia in MFS helps to differentiate these diseases. Similarly, medications and toxins are also known to induce acute onset ataxia. For example, phenytoin, fluorouracil and most notably alcohol can mimic such symptoms. Ataxia associated with chronic alcoholism presents with poor fine motor control of hands, impaired vision and slurring of speech.

Although recurrent MFS is rare disease, it may occur in genetically susceptible individuals.²⁰ After comparing the characteristics of patients with recurrent and non-recurrent MFS, they found no obvious electrophysiological or clinical differences except the age of the onset of symptoms. Patients with younger age of presentation experienced recurrent symptoms.²¹

Plasmapheresis and intravenous immune globulin are the main treatments recommended for GBS. Common issues such as when to admit the patient to the intensive care unit and when to consider mechanical ventilation can arise even before a specific treatment is initiated. Unfortunately, randomised, double-blind, placebo-controlled trials for MFS treatments

cannot be carried out due to the self-limiting clinical course of this disorder. A retrospective analysis, however, performed on 92 consecutive MFS cases reported that IVIG therapy lessened ophthalmoplegia and ataxia to some extent but had no significant effect on the overall outcome, likely due to the frequency of natural recoveries.²² Based on the observational data available, complete resolution of ataxia by 1 month and resolution of ophthalmoplegia within 3 months would be acceptable outcome measures. In conclusion, MFS presents with a wide range of clinical features, depending on the triggering agent and the specific immune response.

Contributors SKG and KKJ assembled the case history and investigations from hospital records, critically reviewed, analysed the data and wrote the paper. MDC and LTA assessed the patient data, and critically reviewed the paper.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Progressive, relatively symmetric muscle weakness is the characteristic clinical feature of Guillain-Barré syndrome (GBS) and is often accompanied by depressed or absent deep tendon reflexes. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory and bulbar muscles.
- ▶ GBS is an autoimmune disorder encompassing a heterogeneous group of acute, immune-mediated polyneuropathies. Miller Fisher syndrome (MFS) is a variant of GBS, characterised by ophthalmoplegia with ataxia and areflexia.
- ▶ The initial diagnosis of GBS is based on the clinical presentation. The diagnosis is confirmed by cerebral spinal fluid analysis and clinical neurophysiology studies. Therefore, these studies should be performed in all patients with suspected GBS.
- ▶ Testing for serum IgG antibodies to GQ1b is useful for the diagnosis of MFS and helps to facilitate the use of treatment already established for GBS.

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