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Case Report

Miller Fisher Syndrome and Acute Motor and Sensory Axonal Neuropathy (AMSAN) Variant Guillain-Barré Overlap Syndrome (MFS/AMSAN-GBS) After Upper Respiratory Tract Infection (URTI)

Tan Chun Chau* and Nik Azlan Nik Muhamad

Department of Emergency Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Kuala Lumpur, Malaysia

***Corresponding Author:** Tan Chun Chau, Department of Emergency Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Kuala Lumpur, Malaysia.

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Abstract

A 50-year-old woman was admitted to the emergency room (ED) with progressive weakness and ascending numbness of the body, back pain, dysphagia, and diplopia for two days. The neurological findings were preceded by an upper respiratory tract infection. Subsequently, severe weakness of the bulbar and limb muscles, areflexia, and ophthalmoplegia developed. Based on clinical features, Miller-Fisher syndrome (MFS) was diagnosed, while a nerve conduction study revealed an overlap with acute motor-sensory axonal neuropathy (AMSAN) variant Guillain-Barré syndrome (MFS/AMSAN-GBS). The panel of anti-ganglioside antibodies was positive. Early treatment with intravenous immunoglobulin favored the outcome.

Keywords: Demyelinating Disease; Polyneuropathies; Guillain-Barré Syndrome; Miller Fisher Syndrome

Introduction

Guillain-Barré syndrome (GBS) is an acute polyneuropathy resulting from immune-mediated destruction of peripheral nerve myelin sheath or axons. GBS is usually preceded by a viral or febrile illness, Campylobacter jejuni infection, or vaccination, followed by ascending symmetric weakness or paralysis and areflexia or hyporeflexia, and involvement of the autonomic, bulbar, and respiratory systems. GBS may have at least four major subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), axonal subtypes, i.e., acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS) [1].

The worldwide incidence of GBS ranges from 1.1/100,000/year to 1.8/100,000/year [1]. GBS remains a fatal disease with systematic morbidities, with a 3-7% mortality rate, primarily due to ventilatory failure or pulmonary complications, or autonomic dysfunction such as arrhythmia [2]. Diagnosis of acute GBS is challenging because it is a disease that often presents with weakness and for which there is no simple diagnostic laboratory test. Early diagnosis or suspicion is critical to ensure better treatment [3].

MFS usually develops over days with the rapid development of a clinical triad: ophthalmoplegia, ataxia, and areflexia [4]. It is distinct from the typical variants of GBS that begin with leg paralysis. The AMSAN variant is the most lethal but rare axonal variant of GBS. It has a rapid onset of severe symptoms leading to quadriparesis within a week [5].

In this case report, the patient presents with a clinical presentation of GBS with overlapping symptoms between subtypes. Typical weakness and numbness of the limbs are associated with an atypi-

cal MFS presentation that began with double vision and unilateral eye involvement and then progressed to bilateral ophthalmoplegia. Here, we discuss a case of overlapping MFS and AMSAN variant Guillain-Barré syndrome.

Case Report

A 50-year-old Indonesian woman with a herniated disk visited the emergency room (ED). She had been experiencing non-radiating back pain for two days, accompanied by rapidly progressive numbness rising from the leg toward the hand and mouth and generalized weakness. The patient had gotten up with an assistant the previous day but could not walk the following day. She also developed dysphagia and diplopia and could not urinate. A week earlier, the patient had a mild upper respiratory tract infection. Otherwise, she had no fever, diarrhea, vomiting, headache, urinary/bladder incontinence, dyspnea, history of trauma or tick bite, history of surgery, or occupational exposure to the neurotoxin.

On physical examination, vital signs were stable, and she was fully awake, conscious, and oriented. Her left eye had ptosis with lateral gaze nystagmus, and both pupils were round, equal in size, and responsive to light. There was no ophthalmoplegia, facial asymmetry, or bulbar palsy. Global areflexia was present, and the muscle strength test showed the mild symmetrical weakness of all four limbs with a strength of 4 out of 5. Her sensory examination was also globally impaired, and her gait could not be demonstrated. Respiratory and cardiovascular examination was unremarkable. However, abdominal examination revealed a palpable bladder, so a continuous urinary catheter was inserted, through which 1.1 liters of clear urine was drained. The next day, the condition worsened as the patient developed bilateral ptosis, partial ophthalmoplegia, and nasal speech. A clinical diagnosis of Miller Fisher syndrome (MFS) of GBS was considered.

Laboratory testing revealed a normal complete blood count, biochemical profile, thyroid function test, metabolic markers, cardiac markers, and inflammatory markers. Arterial blood gasses revealed no evidence of respiratory failure. The viral screening was nonreactive for human immunodeficiency virus (HIV), hepatitis, and rapid plasma reagin for syphilis, while screening for atypical pneumonia was unremarkable. The serum anti-cholinesterase antibody test was negative, ruling out myasthenia gravis. Electrocardiogram was normal. Chest radiography showed no evidence of pulmonary infection. Computed tomography (CT) of the brain, magnetic resonance imaging (MRI) of the brain or spine and cerebrospinal fluid (CSF) analysis by lumbar puncture was not performed because the clinical presentation was classic for the diagnosis of GBS and financial restrain. In the ward, a nerve conduction study (NCS) showed generalized sensorimotor axonal polyneuropathy suggestive of the AMSAN variant of GBS. The panel of anti-ganglioside antibodies sent private laboratory later came back positive for anti-GM1 and anti-GQ1b antibodies.

The patient was admitted to the High Dependency Ward (HDW) for close monitoring and treated with intravenous immunoglobulin (IVIG) for five days, even before NCS and anti-ganglioside antibodies. The GBS disability score on admission was 4, and the Medical Research Council sum score was 48. Muscle strength was symmetrical: the abduction of both shoulders 4, elbow flexion 4, wrist extension 4, hip flexion 4, and ankle dorsiflexion 4. The patient was fed with a Ryle tube to prevent aspiration, received anticoagulants to prevent deep vein thrombosis, and measured his vital capacity regularly to monitor diaphragmatic insufficiency. Clinical improvement occurred after IVIG therapy. The patient could move independently in a wheelchair or walk short distances with assistance (GBS disability score 3). She can self-feeding, and her vision improved. She was discharged after nine days of hospitalization with an appointment for physical therapy.

Discussion

GBS is an acute monophasic immune-mediated polyradiculoneuropathy that begins on average at the age of 40 years and slightly favors men of all ages, races, and nationalities [6]. The incidence of GBS increases with age after 50 years from 1.7/100,000/year to 3.3/100,000/year [1]. Pre-infection was found in two-thirds of cases. Mortality in Europe and North America varies from 3% to 7%, while a population study in an Asian country showed in-hospital mortality of 1.61%, associated with endotracheal intubation, mechanical ventilation, cardiac complications, systemic infections, and catastrophic illness [7]. A quarter of patients required mechanical ventilation, and many developed autonomic dysfunction requiring treatment in the intensive care unit [2].

The typical early symptom of GBS is acroparesthesia and severe radicular back pain, followed by symmetric weakness in an "ascending pattern" and hypo- or areflexia. The facial nerve is affected

in 70% of cases, dysphagia in 40%, and rarely (5%) ophthalmoplegia, ptosis, or both. Muscle weakness can range from mild to severe flaccid quadriplegia and can even lead to respiratory failure in 30% of cases within a few days. Dysautonomia may be manifested by sinus tachycardia or bradycardia, cardiac arrhythmias, labile blood pressure, orthostatic hypotension, neurogenic pulmonary oedema, changes in sweating, and even rarely (5%) bladder and gastrointestinal disturbances [6]. This patient had urinary retention, a rare form of dysautonomia.

GBS is diagnosed based on clinical history and examination. A CSF examination and electrodiagnostic studies are supportive investigations [8]. The published revised diagnostic criteria (Table 1) are well established [6]. GBS and its variants can present with a variety of neurologic symptoms. When GBS is suspected, comprehensive differential diagnoses must be considered (Table 2) [9]. There are very few conditions that cause rapidly progressive quadriplegia and cranial neuropathy. Acute cervical spinal cord injury and spinal stenosis need to consider when symptoms and signs are restricted to the limbs but excluded as there is no history of trauma. Transverse myelitis is possible but more common in younger patients and will not involve cranial nerves. Poliomyelitis occurs in epidemics, while tick paralysis can cause ascending paralysis but spares sensation. Miller Fisher syndrome is frequently mistaken as myasthenia gravis or brainstem stroke, but these can be excluded if fatigability or very acute onset.

Required	Supportive	Exclusionary
Progressive symmetric weakness of > 1 limb	Sensory symptoms or signs	Other causes excluded (toxins, botulism, porphyria, diphteria)
Hyporeflexia or areflexia	Cranial nerve involvement especially bilateral VII	
Progression < 4 weeks	Autonomic dysfunction	
Symmetric weakness	CSF protein elevation	
	CSF cell count < 10/ mm^3	
	Electrophysiologic features of demyelination	
	Recovery	

Table 1: Diagnosis criteria of Guillain-Barré Syndrome [6].

Location in nervous system	Differential diagnosis
CNS	Inflammation or infection of the brainstem (for example, sarcoidosis, Sjögren syndrome, neuromyelitis optica or myelin oligodendrocyte glycoprotein antibody-associated disorder) * Inflammation or infection of the spinal cord (for example, sarcoidosis, Sjögren syndrome or acute transverse myelitis) Malignancy (for example, leptomeningeal metastases or neurolymphomatosis) Compression of brainstem or spinal cord Brainstem stroke Vitamin deficiency (for example, Wernicke encephalopathy*, caused by deficiency of vitamin B1, or subacute combined degeneration of the spinal cord, caused by deficiency of vitamin B12)
Anterior horn cells	Acute flaccid myelitis (for example, as a result of polio, enterovirus D68 or A71, West Nile virus, Japanese encephalitis virus or rabies virus)
Nerve roots	Infection (for example, Lyme disease, cytomegalovirus, HIV, Epstein– Barr virus or varicella zoster virus) Compression Leptomeningeal malignancy
Peripheral nerves	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) Metabolic or electrolyte disorders (for example, hypoglycaemia, hypothyroidism, porphyria or copper deficiency) Vitamin deficiency (for example, deficiency of vitamins B1 (also known as beriberi), B12 or E) Toxins (for example, drugs, alcohol, vitamin B6, lead, thallium, arsenic, organophosphate, ethylene glycol, diethylene glycol, methanol or N-hexane) Critical illness polyneuropathy Neuralgic amyotrophy Vasculitis Infection (for example, diphtheria or HIV)
Neuromuscular junction	Myasthenia gravis Lambert–Eaton myasthenic syndrome Neurotoxins (for example, botulism, tetanus, tick paralysis or snakebite envenomation) Organophosphate intoxication
Muscle	Metabolic or electrolyte disorders (for example, hypokalaemia, thyrotoxic hypokalaemic periodic paralysis, hypomagnesaemia or hypophosphataemia) Inflammatory myositis Acute rhabdomyolysis Drug-induced toxic myopathy (for example, induced by colchicine, chloroquine, emetine or statins) Mitochondrial disease
Other	Conversion or functional disorder

Table 2: Differential diagnosis of Guillain-Barré Syndrome [9].

* Differential diagnosis for Bickerstaff brainstem encephalitis.

Clinical variants of GBS depend on the type of nerve fibers involved (motor, sensory, sensory-motor, cranial, or autonomic), the type of fiber damage (demyelinating or axonal), and the level of consciousness [6]. Variants may be purely motor or refer to cranial nerves (e.g., bilateral facial paralysis with paresthesias), upper limbs (pharyngeal, cervical, and brachial weakness), lower limbs (paraparetic variant), or the classic triad: ophthalmoplegia, areflexia, and ataxia in Miller-Fisher syndrome (MFS) (Table 3) [9]. Electrophysiologic studies can identify the subtypes of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), or acute motor-sensory axonal neuropathy (AMSAN) [6,9]. GBS variants often overlap with the classic syndrome or show mixed features [10].

Variant	Frequency (% of GBS cases)*	Clinical features
Classical sensorimotor GBS	30-85%	Rapidly progressive symmetrical weakness and sensory signs with absent or reduced tendon reflexes, usually reaching nadir within 2 weeks
Pure motor	5-70	Motor weakness without sensory signs
Paraparetic	5-10	Paresis restricted to the legs
Pharyngeal-cervical-brachial	<5	Weakness of pharyngeal, cervical and brachial muscles without lower limb weakness
Bilateral facial palsy with paresthesias	<5	Bilateral facial weakness, paraesthesias and reduced reflexes
Pure sensory	<1	Acute or subacute sensory neuropathy without other deficits
Miller Fisher syndrome	5-25	Ophthalmoplegia, ataxia and areflexia. Incomplete forms with isolated ataxia (acute ataxic neuropathy) or ophthalmoplegia (acute ophthalmoplegia) can occur 31. Overlaps with classical sensorimotor GBS in an estimated 15% of patients
Bickerstaff brainstem encephalitis	<5	Ophthalmoplegia, ataxia, areflexia, pyramidal tract signs and impaired consciousness, often overlapping with sensorimotor GBS

Table 3: Variants of Guillain-Barré Syndrome [9].

* Frequencies differ by region and study, contributing to the variability. Most studies are biased owing to exclusion of some of the variants.

In Western countries, MFS accounts for 1-5% of cases. In contrast, the proportion is 19% and 25% in Taiwan and Japan, respectively. The typical symptoms are diplopia (78%), ataxia (48%), or both (34%). Symptoms are less common, such as limb dysesthesia, blepharoptosis, facial, bulbar, and pupillary paralysis, mild motor weakness, and micturition disorders [4]. Classic MFS is the absence of limb weakness and is usually more benign and completely resolves in less than six months without treatment in most cases [9]. Limb weakness is considered a MFS-GBS overlap syndrome [8]. Reported cases vary from 3% to 15% [10,11].

AMSAN is a rare (3-5%) and severe subtype of GBS. It can be identified and differentiated by electrophysiologic studies. AMSAN usually presents rapidly progressive severe symptoms and a protracted and incomplete recovery [5]. The clinical manifestations in this reported case suggested the diagnosis of MFS/AMSAN-GBS overlap syndrome with the atypical presentation of MFS. Although CSF analysis was not performed, the diagnosis is supported by the positive anti-ganglioside antibodies and the demonstrated axonal polyneuropathy in nerve conduction study, which is characteristic of classic demyelinating polyneuropathy GBS. The neurological disorder usually took one to four days to complete the overlap syndrome [10]. There are few cases of sensorimotor axonopathy in MFS [12-14].

Immunologic treatments such as IVIG (0.4 g/kg body weight daily for five days) and plasma exchange (200-250 ml plasma/kg body weight in five sessions) is effective [14,15]. IVIG or plasma exchange must be started promptly before irreversible damage to the nerve occurs. IVIG is effective, especially in patients who can walk with assistive devices (Guillain-Barré syndrome disability score ≥3) within two weeks of disease onset [2]. IVIG is preferred because it is easy to administer and more accessible than plasma exchange [9]. Alternatives such as oral steroids and intravenous methylprednisolone are not beneficial [15].

Admission to the ICU should be considered in developing respiratory distress or impending respiratory failure, severe autonomic cardiovascular dysfunction, risk of aspiration (dysphagia and decreased cough reflex), and rapid progression of weakness [9]. This reported case required HDW admission as the rapid disease deterioration and exacerbation of bulbar palsy required close monitoring. Appropriate supportive care can control or reduce complications (Table 4). These include monitoring of respiration (measurement of vital capacity), heart, and hemodynamics (autonomic dysfunction), prophylaxis of deep vein thrombosis, manage-

ment of possible bladder and bowel dysfunction, early initiation of physical therapy and rehabilitation, and psychosocial support [2,9].

Complication	When to be alert
Choking	Bulbar palsy
Cardiac arrhythmias	All patients
Hospital-acquired infections (e.g., pneumonia, sepsis or urinary tract infection)	Bulbar and facial palsy, immobility, bladder dysfunction, mechanical ventilation
Pain and tactile allodynia	Limited communication
Delirium	Limited communication
Depression	Limited communication
Urinary retention	All patients
Constipation	Immobility
Corneal ulceration	Facial palsy
Dietary deficiency	Bulbar and facial palsy
Hyponatraemia	All patients
Pressure ulcers	Immobility
Compression neuropathy	Immobility
Limb contractures and ossifications	Severe weakness for prolonged period of time

Table 4: Important complications of Guillain-Barré Syndrome [9]. Most of these complications can occur in any patient with GBS, at any time, but the second column shows when they are most likely to occur and/or when to be especially alert.

Indicators of a poor prognosis in GBS include advanced age (over 40 years), a history of diarrhea in the past four weeks (or C. jejuni infection), and high disability at the nadir of the disease. Disease progression, the severity of limb weakness, peroneal nerve conduction blockade, and low vital capacity predicted respiratory failure [2]. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) (Table 5) is used at admission to stratify the risk of artificial ventilation [2,6,9,16]. The GBS disability scale (Table 6) and MRC muscle testing scale may be used during monitoring in addition to the standard neurologic examination [8]. This patient has moderate EGRIS, with a 24% risk of mechanical intubation. Fortunately, her symptoms were under control after IVIG administration, and the GBS disability score improved at discharge.

Measure	Categories	Score
Days between onset of weakness and hospital admission	> 7 days	0
	4-7 days	1
	≤ 3 days	2
Facial and/or bulbar weakness at hospital admission	Absent	0
	Present	1
MRC sum score* at hospital admission	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤ 20	4
EGRIS	NA	0-7

Medical Research Council (MRC) sum score is the sum of the score on the MRC scale for: muscle weakness of bilateral shoulder abduction; elbow flexion; wrist extension; hip flexion; knee extension; and ankle dorsiflexion. A higher MRC sun score denotes increased disability, up to a maximum score of 60.

EGRIS score	Risk required mechanical ventilation < 1 week of assessment
0 - 2	Low risk of mechanical intervention (4%)
3 - 4	Intermediate risk of mechanical intervention (24%)
≥ 5	High risk of mechanical intervention (65%)

This model is based on a Dutch population of patients with GBS (ages >6 years) and has not yet been validated internationally.

Table 5: Erasmus GBS Respiratory Insufficiency Score (EGRIS) [9].

Score	Description
0	Healthy
1	Minor symptoms or signs of neuropathy but capable of manual work/ capable running
2	Able to walk without support of a stick (5m across an open space) but incapable of manual work. running
3	Able to walk with a stick, appliance or support (5m across an open space)
4	Confined to bed or chair bound
5	Required assisted ventilation (for any part of the day or night)
6	Death

Table 6: Guillain-Barré Syndrome disability scale [8].

Conclusion

The overlap of the MFS and AMSAN variants of GBS is a rare occurrence and can be fatal because of the rapid deterioration of the disease. Once identified, early administration of IVIG, close monitoring, and supportive treatment result in a favorable outcome.

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