



밀러-피셔증후군과 중첩된 비전형 비대칭 길랭-바레증후군: 증례 보고

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Atypical Asymmetric Guillain-Barré Syndrome Overlapping with Miller-Fisher Syndrome: A Case Report

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Guillain-Barré syndrome (GBS) is an acute immune-mediated polyneuropathy that constitutes a heterogeneous syndrome with several variant forms. We experienced a patient who rapidly developed atypical variant GBS without a preceding history of infection. A 13-year-old female patient was admitted, presenting with left facial palsy and ophthalmoplegia. After a few days, right hand and ankle muscle weakness and paresthesia of both hands newly occurred. Electrophysiological findings revealed multifocal asymmetric motor and sensory axonal neuropathies compatible with multiple mononeuropathy. In blood testing, autoimmune-related antibodies were negative and anti-GQ1b antibodies were positive. We diagnosed the patient with overlapping Miller-Fisher syndrome and the acute motor sensory axonal neuropathy variant of GBS. After intravenous immunoglobulin therapy, the weakness of the limbs partially improved. Since the initial symptoms were similar to those of mononeuritis multiplex, it was difficult to recognize GBS. Electrodiagnostic studies and anti-ganglioside antibody screening tests are necessary for the early differential diagnosis of variant GBS.

Keywords: Guillain-Barré syndrome; Miller Fisher syndrome; Mononeuropathy multiplex

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Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyneuropathy, characterized by progressive symmetrical weakness and areflexia [1]. Several variant forms of GBS have been revealed which present with extremity, facial or bulbar muscle involvement [2]. According to electrophysiological findings, GBS is classified by acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute

motor sensory axonal neuropathy (AMSAN) [3]. AMSAN is a rare axonal variant of GBS, characterized by involvement of motor and sensory fibers [3]. Miller-Fisher syndrome (MFS) is clinical variant, which is characterized by ophthalmoplegia, ataxia, and areflexia [1]. We experienced overlapping case of AMSAN variant of GBS and MFS with positivity for anti-GQ1b antibodies, whose initial presentation resembled mononeuritis multiplex.

Case Report

This study was conducted with informed consents of the patient and guardian. A 13-year-old female patient with no medical illness history presented at the emergency department with left facial palsy, diplopia, and paresthesia of right hand that had evolved over 24 hours. She didn't reported vomiting, diarrhea, or upper respiratory symptoms previously. Vital signs were within normal limits. Cranial nerves' examination was notable for limitation of abduction of the right eye and diminished left facial muscles' strength. Strength of all limbs was preserved and paresthesia of right hand disappeared at the time of examination. Deep tendon reflexes (DTRs) were preserved at all four limbs. The patient was negative for Hoffmann reflex and Babinski signs. Ataxia and symptoms of autonomic dysfunction were absent. Blood sample showed hemoglobin 12.9 g/dL (normal range, 11.5-15.5 g/dL); white blood cell 7,310/mm³ (3,700-9,500/mm³); C-reactive protein (CRP) 0.12 mg/dL (0-0.5 mg/dL); potassium 3.8 mEq/L (3.5-5.5 mEq/L), lactate dehydrogenase (LDH) 421 U/L (200-485 U/L); creatine phosphokinase (CPK) 125 U/L (33-211 U/L); urine analysis was normal. Serum IgM antibodies to Epstein-Barr virus, cytomegalovirus, varicella zoster virus, measles virus, mumps virus, and rubella virus were negative. Magnetic resonance image (MRI) of the brain was normal. There were no lesion with T1 high signal intensity on gadolinium-enhancement images. These presentations led to suspicion of left facial nerve palsy and right abducens nerve palsy. The patient was admitted to the pediatric neurology department and was empirically treated with valacyclovir 3,000 mg and prednisolone 50 mg for 14 days (Table 1).

An electrodiagnostic study was performed on 16 days from the onset (day 16). On the day of study, left facial palsy and ophthalmoplegia of right eye persisted. Right hand intrinsic muscle weakness developed with showing claw hand deformity, and left hand grip and release strength slightly weakened and right ankle and toe plantarflexion weakness and paresthesia of right 4-5th and left 1-2nd finger newly occurred; right hand intrinsic muscles were medical research council (MRC) 2/5; left hand grip and release strength was 4/5; right ankle and toe plantarflexion were 3/5. Muscle power of left lower extremity was normal. Sensory nerve conduction studies showed decreased amplitude of both median, right ulnar and right sural sensory nerve action potentials (SNAP) with normal peak latencies (Table 2). Motor nerve conduction studies showed markedly reduced amplitude of both median, right peroneal and right tibial compound muscle action potentials (CMAP) with normal latencies and conduction velocities. The right ulnar CMAP was not obtained from the abductor digiti minimi muscle. F-waves in right median and ulnar

nerves were not formed. Electroneurographic study (ENoG) showed that the paralyzed/healthy side ratio of facial nerve was 26.1%. Bilateral blink reflex test was in normal range. Needle electromyography (EMG) study showed increased insertional activities and abnormal spontaneous activities, and decreased motor unit potentials recruitment pattern in right abductor pollicis brevis (APB), right first dorsal interosseous (FDI), right flexor carpi radialis, right flexor carpi ulnaris, and left APB (Table 3). Somatosensory evoked potentials after bilateral median and tibial nerves stimulation showed normal latencies. These electrodiagnostic findings were multifocal asymmetric motor and sensory axonal neuropathies compatible with multiple mononeuropathy.

For differential diagnosis, cerebrospinal fluid (CSF) studies, MRI of the whole spine and auto-immune related antibodies screening were performed on day 17. CSF studies showed normal range without albuminocytologic dissociation. The CSF oligoclonal band screening test was negative. MRI of the whole spine was normal. There was no enhancement of the nerve roots after gadolinium administration on fat-saturated T1-weighted image and was no spinal cord lesion with T2 high signal intensity on MRI of the whole spine (Fig. 1). Antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), rheumatoid factor (RF), anti-dsDNA, anti-RNP, anti-Sm, anti-SSA, anti-SSB antibodies were in normal range. In anti-ganglioside antibodies screening, anti-GQ1b IgM antibodies were positive, and anti-GM1, anti-GD1b were negative. Based on these findings, this patient was diagnosed with MFS with multiple mononeuropathy, and received methylprednisolone 1,000 mg for 3 days and intravenous immunoglobulin (IVIG) injection at a dose of 1 g/kg for 2 days.

On day 29, left facial palsy, right eye ophthalmoplegia and

Table 1. Laboratory Test Results

Parameter	Result (normal value)
Hemoglobin (g/dL)	12.9 (11.5-15.5)
White blood cell (/mm ³)	7,310 (3,700-9,500)
C-reactive protein (mg/dL)	0.12 (0-0.5)
Potassium (mEq/L)	3.8 (3.5-5.5)
Lactate dehydrogenase (U/L)	421 (200-485)
Creatine phosphokinase (U/L)	125 (33-211)
Oligoclonal bands	Negative
Antineutrophil cytoplasmic antibody	Negative
Antinuclear antibody	Negative
Anti-GQ1b	Positive*
Anti-GM1	Negative
Anti-GD1b	Negative

*Abnormal value.

Table 2. Results of the Nerve Conduction Studies

Nerve	Day 16						Day 67					
	Latency (ms)		Amplitude		CV (m/s)		Latency (ms)		Amplitude		CV (m/s)	
	R	L	R	L	R	L	R	L	R	L	R	L
Sensory												
Median	2.76	2.86	10.8*	11.8*	-	-	3.49	2.71	4.4*	12.0*	-	-
Ulnar	2.34	2.19	3.0*	27.6	-	-	3.07	3.02	2.9*	12.5*	-	-
Radial	1.61	1.88	17.6	23.1	-	-	1.88	1.88	5.7*	25.9	-	-
Sural	2.97	2.97	4.5*	11.3	-	-	2.97	2.81	4.0*	7.6*	-	-
SPN	2.97	3.07	12.6	20.5	-	-	3.18	2.86	8.5*	15.3	-	-
Motor												
Median wrist	3.18	2.66	0.4*	4.4*	-	-	4.01	3.07	1.2*	6.4	-	-
Median elbow	7.24	6.77	0.4*	4.2*	56.6	58.3	8.96	7.60	1.0*	5.7	46.5	59.6
Ulnar wrist	NR*	1.93	NR*	14.7	-	-	3.07	2.19	0.4*	11.5	-	-
Ulnar below elbow	NR*	5.78	NR*	14.6	NR	62.3	7.71	6.46	0.2*	11.1	51.8	67.9
Radial forearm	1.93	2.03	4.1	4.7	-	-	1.51	1.56	3.9	4.8	-	-
Radial elbow	4.69	4.79	3.8	4.4	58.0	58.0	3.70	3.96	3.7	4.7	59.4	58.4
Peroneal ankle	3.59	2.76	2.2*	9.6	-	-	3.96	3.49	2.6*	5.5*	-	-
Peroneal fibular head	10.68	9.32	1.4*	8.3	48.0	51.8	12.29	11.15	1.6*	4.3*	42.0	43.1
Tibial ankle	3.28	3.75	6.9*	14.8	-	-	3.23	3.65	7.3*	7.7*	-	-
Tibial knee	11.04	10.94	5.0*	11.6	49.0	52.8	12.66	12.71	4.8*	6.6*	44.6	46.3
Facial nasalis	3.75	4.11	2.6	0.6*	-	-	3.65	3.54	2.6	1.3*	-	-

Amplitudes are measured in microvolt (µV, sensory) and millivolt (mV, motor).
 CV, conduction velocity; R, right; L, left; SPN, superficial peroneal nerve; NR, no response.
 *Abnormal value.

Table 3. Results of Needle Electromyography

Muscle	Day 16								Day 67							
	Fibrillation		PSW		MUAP		Recruitment		Fibrillation		PSW		MUAP		Recruitment	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
APB	1+	1+	1+	1+	N	N	Dis	Red	3+	3+	3+	3+	N	N	Red	Red
FDI	1+	NT	1+	NT	N	NT	Dis	NT	3+	1+	3+	1+	N	N	Dis	Red
FCR	1+	N	1+	N	N	N	Dis	Red								
FCU	1+	NT	1+	NT	N	NT	Red	NT								
Biceps	N	NT	N	NT	N	NT	Full	NT								
Triceps	N	NT	N	NT	N	NT	Full	NT								
TA	N	N	N	N	N	N	Full	Full	1+	3+	1+	3+	N	N	Red	Red
GCM	N	N	N	N	N	N	Full	Full	1+	1+	1+	1+	N	N	Red	Red
CPS	N	N	N	N	N	N	NC	NC	N	N	N	N	N	N	NC	NC
LPS	N	N	N	N	N	N	NC	NC	N	N	N	N	N	N	NC	NC

PSW, positive sharp wave; MUAP, motor unit action potential; R, right; L, left; APB, abductor pollicis brevis; N, normal; Dis, discrete; Red, reduced; FDI, first dorsal interosseous; NT, not tested; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; TA, tibialis anterior; GCM, gastrocnemius; CPS, cervical paraspinals; NC, not checkable; LPS, lumbar paraspinals.

right ankle plantarflexion weakness improved slightly, and bilateral hand weakness was similar. Bilateral ankle dorsiflexion weakness and paresthesia of all distal limbs newly occurred; right hand was MRC 2/5 and left hand was 4/5; bilateral ankle dorsiflexion was 4/5. There were differences in the severity of left and right, but eventually, symmetric paralysis and paresthesia ap-

peared in all limbs as in the general course of GBS. The patient began to receive physical therapy to strengthen distal upper and lower extremities.

Follow-up electrodiagnostic study was performed on day 67. Left facial palsy and right eye ophthalmoplegia fully improved, and bilateral ankle dorsiflexion strength was 4/5, and right hand

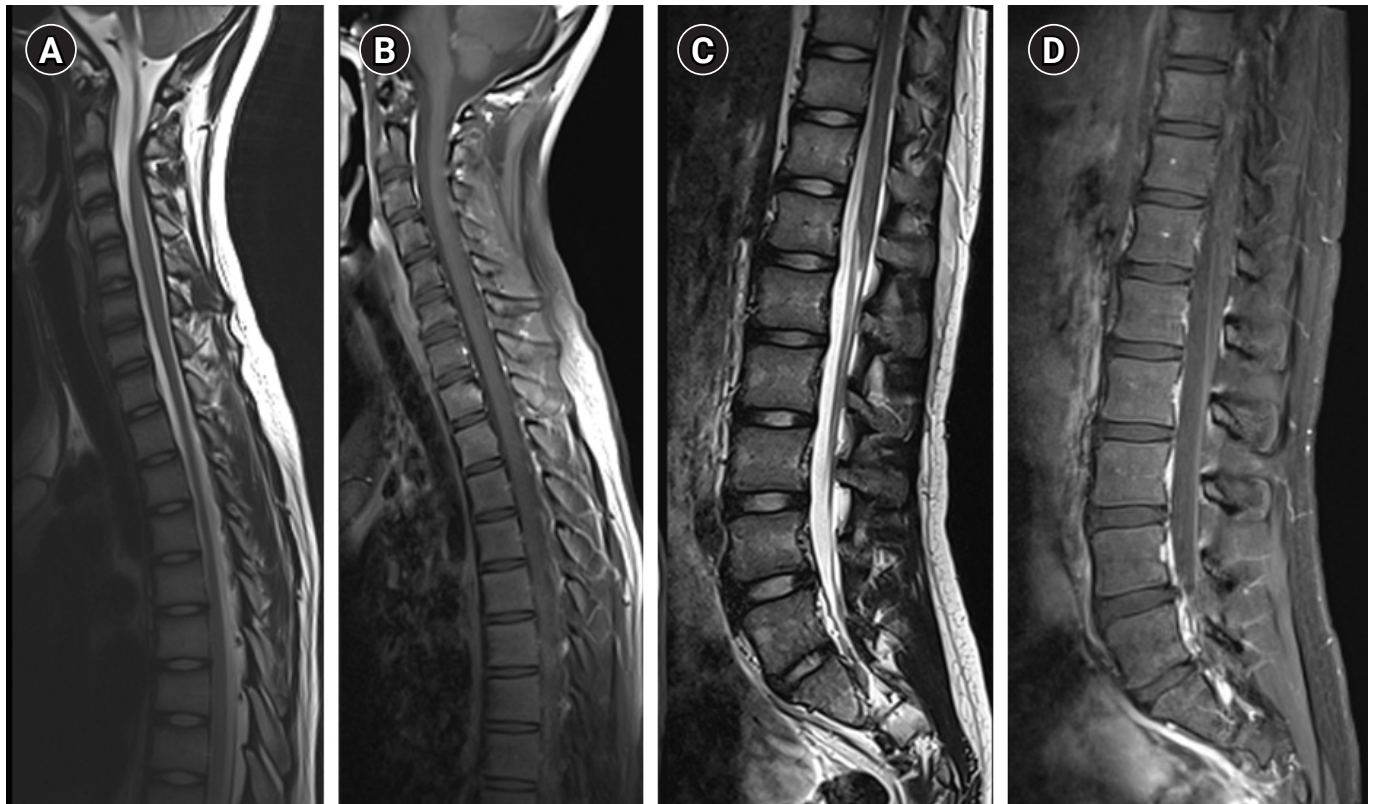


Fig. 1. Magnetic resonance imaging of the spine. (A) A T2-weighted image and (B) a T1-weighted image with gadolinium enhancement in the upper spine. (C) A T2-weighted image and (D) a T1-weighted image with gadolinium enhancement in the lower spine.

was able to use chopsticks. DTRs were preserved at all four limbs. Compared to previous examination, the amplitude of SNAPs of right median, right radial, right superficial peroneal, left ulnar, and left sural nerve more decreased with normal peak latencies. The amplitude of CMAPs of both median and right ulnar nerve increased showing reversible conduction block. The decreased amplitude of CMAPs of left peroneal and left tibial nerve newly appeared. The paralyzed / healthy side ratio of facial nerve ENoG increased from 23.1% to 50.0%. Needle EMG showed increased insertional activities and abnormal spontaneous activities, and decreased motor unit potentials recruitment pattern in bilateral APB, FDI, tibialis anterior and gastrocnemius muscles. In conclusion, these electrodiagnostic findings were consistent with symmetric motor and sensory axonal polyneuropathy compatible with GBS, and we diagnosed the patient with GBS overlapping AMSAN and MFS. At 14 weeks of symptom onset, muscle strength of all limbs improved for 4/5 and mild paresthesia of all limbs still remained.

Discussion

GBS is an acute immune-mediated polyneuropathy that oc-

curs after infection. GBS is characterized by symmetric ascending paralysis, areflexic paralysis, and albumin-cell dissociation [1]. This patient initially presented with unilateral facial palsy, ophthalmoplegia, asymmetric paralysis, and DTRs of all limbs were preserved. She had no history of infection/vaccination. CSF test was normal. Although GBS is a common cause of acute paralytic peripheral weakness, this patient had an atypical course, which made it difficult to suspect GBS. Therefore, we performed an EMG to determine the patient's electrophysiological condition, and revealed findings consistent with multiple mononeuropathy.

Multiple mononeuropathy is a form of peripheral neuropathy in which one or more non-adjacent peripheral nerves are asymmetrically invaded over the upper and lower extremities. It is the most common clinical presentation of vasculitic neuropathy, which is one feature of a systemic vasculitis and is associated with connective tissue diseases such as polyarteritis nodosa, Churg-Strauss syndrome, and rheumatoid arthritis [4]. Vasculitic neuropathy is caused by multifocal peripheral nerve infarction due to obstruction of blood vessels distributed in the nerve [4]. Ischemic injury initially occurs in the distal part of the nerve and induces pain, weakness or sensory abnormality in the distal ex-

tremities [5]. Although other organ systems are often involved, initial clinical manifestation of systemic vasculitis may only appear in the peripheral nervous system and in that case, diagnosis is difficult [6].

The finding of multiple mononeuropathy is suggestive of but not specific for vasculitis. Various non-vascular etiologies should be considered, such as infection, hereditary neuropathies, and neoplasm [4]. For differential diagnosis, medical history, physical examination, laboratory tests, and electrophysiologic study with nerve conduction studies and EMG were required. The patient had no medical illness, vaccination, and previous infection history. Complete blood count and differential, serum creatinine and estimation of glomerular filtration rate, liver function tests, urinalysis, erythrocyte sedimentation rate, CRP, CPK, LDH and autoimmune-related serologic assays, such as ANA, ANCA, RF, anti-dsDNA, anti-RNP, anti-Sm, anti-SSA, anti-SSB to evaluate for underlying systemic rheumatic or infectious diseases are helpful and all were within normal range in this patient.

GBS typically exhibits symmetric paralysis, but asymmetric paralysis has been reported in some variants [7]. Since the proportion of axonal variant GBS is high in East Asia [3], if asymmetric paralysis is shown as in this patient, the electrophysiological findings may be similar to multiple mononeuropathy, making it difficult to diagnose. Preserved tendon reflexes are mostly associated with the AMAN subtypes, but all GBS subtypes and MFS may present with hyper-reflexia [8]. Some variants of GBS invade the cranial nerves and may exhibit facial palsy, dysphagia symptoms, and MRI of the brain and electrophysiological examinations should be performed to discriminate brain-stem stroke, Wernicke's encephalopathy, myasthenia gravis [1]. In general, the axonal type of GBS showed history of infection with *Campylobacter jejuni* [3], but there were no signs of infection in the patient's report and we didn't perform stool examination for *C. jejuni* infection. CSF studies can be normal for the initial one week, and albumin dissociation is observed in 75% of patients after 3 weeks [1]. Our patient underwent CSF test 2 weeks after symptom onset, but it was normal.

In the past, GBS was used as a synonym for AIDP, and Brighton's diagnostic criteria using electrophysiological findings were widely used [2]. Since the 1990s, with the report of axonal variant GBS, immune-mediated pathology involving anti-ganglioside antibodies was revealed [1]. In recent years, anti-ganglioside antibodies have been used to diagnose and classify various subtypes of GBS, such as axonal, MFS, and pharyngeal-cervical-brachial variant [2]. Anti-ganglioside antibodies screening revealed that anti-GQ1b IgM antibodies were positive and anti-GM1, anti-GD1b were negative. Anti-GQ1b antibodies are found in 83%

of MFS [2]. Based on the clinical features, electrodiagnostic evaluation and antibody test, it could be diagnosed by overlapping of MFS and AMSAN variant of GBS. A study in Korea reported that anti-ganglioside antibody tests in children with GBS showed a lower positive rate (20%) than adults [9]. However, since the number of cases reviewed (10 cases) was small and information on clinical features and whether the MFS cases were included was limited, further studies are needed to determine the diagnostic value of anti-ganglioside antibodies in children with GBS.

IVIg injection and plasma exchange are well-established treatments, and equivalent effects have been reported [1]. This patient was administered IVIg 1 g/kg for a total of 2 days and showed a response. The weakness and numbness of the limbs gradually recovered from 4 weeks after the onset of symptoms. After receiving the rehabilitation treatment of the limb strength training, the strength of all limbs recovered to 4/5 at 14 weeks.

Previously, one case of overlapping of MFS and AMSAN variant of GBS was reported in Korea but did not show an asymmetric feature [10]. In another case, asymmetric GBS, which was mistaken for cauda equina syndrome, was reported [11], but there was no detailed description of electrodiagnostic findings. We performed nerve conduction test and needle EMG repeatedly, and it was confirmed that the pattern of asymmetric multifocal axonal neuropathy initially progressed symmetrically after time.

In summary, the most important point we want to emphasize is that variants of GBS are so diverse that GBS should be suspected despite atypical symptoms. When physicians face a patient with atypical symptoms of asymmetric weakness in the cranial nerves or limbs, early electrophysiologic study should be performed to discriminate for type of peripheral neuropathy. Considering that axonal variant of GBS is frequent in East Asia, anti-ganglioside antibodies screening test should be considered to discriminate GBS, and IVIg or plasmapheresis treatment must be performed without delay to prevent serious complications such as respiratory system invasion. This diagnostic approach is thought to be helpful in the early diagnosis and treatment of GBS.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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