DOI:10.4274/tnd.2021.86094
Turk J Neurol 2022;28:51-54

Case Report / Olgu Sunumu

Different Guillain-Barré Syndrome Variants Associated with COVID-19: Report of 4 Clinical Cases

COVID-19 ile İlişkili Farklı Guillain-Barré Sendromu Varyantları: 4 Olgu Sunumu

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Abstract

Since the first case has emerged, different neurological complications associated with Coronavirus disease-2019 (COVID-19) have been reported all over the world. The association between coronavirus and Guillain-Barré syndrome (GBS) has also been reported before. Unfortunately, there is no certain mechanism about this association yet. Molecular mimicry is one of the first hypotheses to express the undesirable autoimmunity in GBS. According to this; the antibodies produced against virus may target peripheral nerves or spinal nerve roots. The entity of direct viral neurotoxicity has also been discussed. Here, we presented four variants of GBS associated with coronavirus that we followed up in our clinic between September-December 2020. While the first patient had demyelinating sensorimotor neuropathy concurrent with COVID-19, the other ones were postinfectious. The second patient had motor axonal neuropathy and the third one had sensorimotor axonal neuropathy. There was Miller-Fisher syndrome and GBS overlap in the fourth patient.

Keywords: COVID-19, Guillain-Barré syndrome, MFS-GBS overlap

Öz

İlk koronavirüs olgusu ortaya çıktığından beri dünyanın çeşitli bölgelerinden Koronavirüs hastalığı-2019 (COVID-19) ile ilişkili nörolojik komplikasyonlar bildirilmektedir. Koronavirüs ile ilişkili Guillain-Barré sendromu (GBS) olguları bildirilse de ilişki halen net değildir ve kesin bir yargıya varmak için vaka sayısı yeterli değildir. Moleküler benzerlik GBS'deki istenmeyen immüniteyi ifade eden ilk hipotezlerdendir. Bu hipoteze göre immün sistemin patojenle veya başka şekilde aktiflenmesi ile oluşan antikorlar periferik sinirler ve spinal kökleri hedef alır. Patojenin doğrudan immün sistemi hedef aldığı direkt viral nörotoksisite kavramı üzerinde de durulmuştur. Burada Eylül-Aralık 2020 tarihleri arasında merkezimizde takip ettiğimiz 4 olguyu sunuyoruz. Olguların ilki COVID-19 ile eşzamanlı demiyelinizan sensorimotor polinöropati iken diğer olgularda GBS, COVID-19 enfeksiyonu sonrası saptanmıştır. İkinci olgu motor aksonal nöropati, üçüncü olgu sensorimotor aksonal nöropatidir. Dördüncü olguda Miller-Fisher sendromu-GBS birlikteliği söz konusudur.

Anahtar Kelimeler: COVID-19, Guillain-Barré sendromu, MFS-GBS birlikteliği

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy presenting with ascending paralysis, loss of deep tendon reflexes (DTR) and autonomic symptoms (1). GBS could be both parainfectious and postinfectious. It is a rare disease with an incidence 0.8-1.9/100,000, and its association with Campylobacter jejuni, Citomegalovirus, Epstein-Barr virus and recently Zika virus has been reported (2).

Molecular mimicry is one of the first hypotheses to state aberrant autoimmune response targeting peripheral nerves and their spinal roots in GBS. However, direct viral neurotoxicity, in which the pathogen directly targets the immune system, has also been emphasized (3,4).

Since November 2019, neurological complications associated with Coronavirus disease-2019 (COVID-19) have been reported all around the world. GBS is one of these complications (5). There is also a regional study pointing out the incidence of GBS is increasing with COVID-19 (6). However, the relationship is still unclear and the number of patients is not enough to make a certain judgment.

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Received/Geliş Tarihi: 22.06.2021 **Accepted/Kabul Tarihi:** 22.12.2021

Here, we reported 4 patients that could be related to different GBS subtypes that we followed up in our center between September-December 2020. Thus, we aimed to underline that different GBS variants associated with COVID-19 could be seen and to contribute to the limited number of literature.

Case Reports

Patient 1

A 61-year-old male was admitted to the neurology outpatient clinic with weakness on both legs, flu-like symptoms, diarrhea and low-back pain for 3 days. The muscle strength of both lower extremities was 3/5 and both upper extremities was 4/5 according to the medical research council (MRC) muscle strength scale. DTR were absent. There was no lesion in cranial magnetic resonance imaging (MRI). Acute phase reactants (C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-dimer.) were at the upper limit and mild leukocytosis was detected. Nerve conduction studies showed long distal latencies and slow velocities, and patient's tibial and ulnar F-responses both prolonged. The patient was diagnosed as having acute inflammatory demyelinating polyneuropathy. Intravenous immunoglobulin (IVIG) was started at a dose of 0.4 g/kg/day and 5-day treatment was planned. A thorax computed tomography (CT) was performed in the patient, whose oxygen saturation was low in the pulse oximeter. Multifocal ground glass-consolidation areas were detected in the CT and the appearances were found to be compatible with COVID-19 pneumonia (typical findings for CORADS-5 COVID) (Figure 1). The patient's nasopharyngeal swab polymerase chain reaction (PCR) test was also positive. He was transferred to the intensive care unit and intubated and antiviral treatment was started. Despite all the interventions, the patient died on the 25th day of his hospitalization due to respiratory failure.

Patient 2

A 47-year-old male patient was admitted to the neurology clinic with weakness in both his arms and legs. The patient had suffered from COVID-19 pneumonia 1.5 months ago. He had back pain at that time, and weakness started 2 weeks later. Neurological examination showed 4/5 muscle strength in 4 extremities according to MRC. Sensory examination was within normal limits. DTR were hypoactive. Routine blood tests were within normal limits. Nasopharyngeal swab sample taken for coronavirus was found negative 2 times in a row. The amplitudes of the tibial, fibular and ulnar motor nerves were low in the electroneuromyography (ENMG). The patient's GBS disability score (ERASMUS GBS outcome score) was calculated as 1.5. One month had passed since the onset of the disease which was evaluated as acute motor axonal polyneuropathy (AMAN). Physical therapy was initiated and the patient was followed-up. During his controls, a partial improvement in the motor nerves' amplitudes was observed.

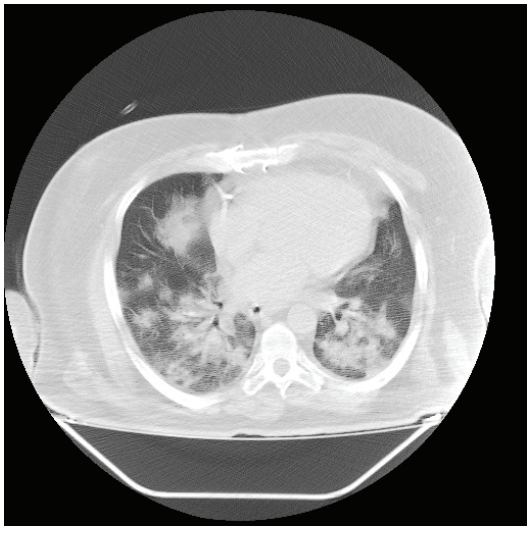

Figure 1. Multiple ground glass opacities-consolidation areas in the thorax CT of patient 1
CT: Computed tomography

Patient 3

A seventy-one-year-old male presented with the numbness and weakness both his hands and feet. He had learned that he was positive for COVID-19 1 month before his complaints started and he recovered with home isolation and antiviral treatment. Numbness had started two weeks ago, and weakness had been added. Bilateral stocking-like hypoesthesia was detected in his neurological examination. DTR were absent. Muscle strength of both upper extremities was 4/5, and of both lower extremities was 3/5. Right ulnar sensory and bilateral sural sensory nerves were not stimulated. The compound muscle action potential (CMAP) amplitudes of the tibial, fibular and ulnar motor nerves were low. The patient was hospitalized with the diagnosis of motor-sensory axonal neuropathy. The patient's ENMG findings are summarized in the table (Table 1). No cells were seen in the CSF in lumbar puncture and CSF protein was 180 mg/dl. IVIG was given at a dose of 0.4 g/kg/day for 5 days. Routine blood tests and acute phase reactants were within normal limits, no pathology was found in cranial and spinal MRI. The patient was discharged from the clinic as his complaints regressed after treatment.

Patient 4

A 46-year-old female was admitted to the emergency service with loss of balance and diplopia. Neurological examination revealed ataxia and loss of DTR. Her muscle strength was 5/5 in all extremities and external ocular movements were limited bilaterally. The patient had suffered from COVID-19 pneumonia 3 weeks ago. When the first ENMG was performed, all nerve conduction studies, and tibial and ulnar F-latencies were within normal limits. The patient was hospitalized anyway, but lumbar puncture could not be performed because she refused. In her follow up period, the patient developed facial paralysis, weakness and the muscle strength decreased to 4/5. ENMG was performed again, low CMAP amplitude and long distal latency were detected in ulnar motor nerves and right median motor nerve. Ulnar sensory nerves could not be stimulated bilaterally. Other nerve conduction studies were within normal limits. The result was evaluated as upper extremity dominant sensorimotor polyneuropathy (Table 1).

Cranial MRI was within normal limits. Spinal MRI revealed contrast-enhanced areas at the lower thoracic-lumbar levels, conus medullaris and cauda equina fibers (Figure 2). Blood tests were within normal limits. The patient was accepted as having Miller Fisher syndrome-GBS overlap and was given 0.4 g/kg/day IVIG treatment for 5 days. The patient whose complaints decreased after

Table 1. ENMG findings of all patients

	Nerve	Patient 1	Patient 2	Patient 3	Patient 4
SNAP (mV)	Sural	Absent	8.8	Absent	6.6
	Ulnar	6.3	5.0	Absent	Absent
SNCV (m/s)	Sural	Absent	47.3	Absent	40.0
	Ulnar	33.0	44.9	Absent	Absent
SNdL (ms)	Sural	Absent	3.3	Absent	3.0
	Ulnar	3.3	2.0	Absent	Absent
MNAP (mV)	Tibial	4.9	2.3	1.1	3.4
	Fibular	3.0	0.7	0.7	5.7
	Ulnar	6.2	0.9	1.7	2.6
	Median	55	0.3	0.9	1.8
MNCV (m/s)	Tibial	43.0	41.0	44.0	48.0
	Fibular	550	43.0	41.0	42.0
	Ulnar	57.0	47.0	44.0	55.0
MNdL (ms)	Tibial	6.9	4.5	9.7	4.2
	Fibular	3.8	3.4	15.2	3.4
	Ulnar	4.1	2.3	6.56	3.7
Result		Demyelinating sensorimotor neuropathy	Motor axonal neuropathy	Motor-sensory axonal neuropathy	Upper extremity dominant sensorimotor neuropathy

SNAP: Sensory nerve action potential, SNCV: Sensory nerve conduction velocity, SNdL: Sensory nerve distal latency, MNAP: Motor nerve action potential, MNCV: Motor nerve conduction velocity, MNdL: Motor nerve distal latency, ms: Millisecond, mV: Millivolt, m/s: Meter/second, ENMG: Electroneuromyography

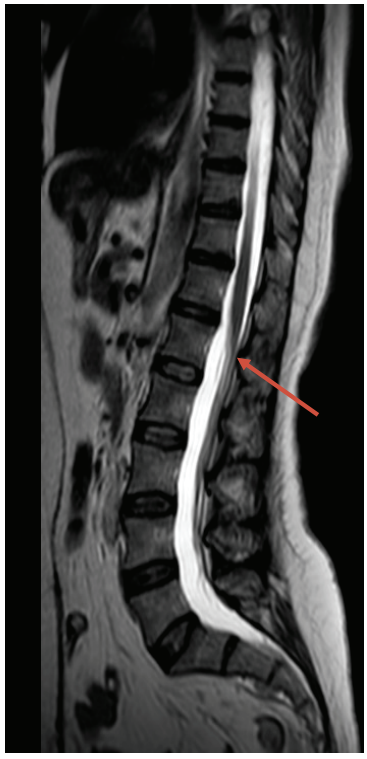

Figure 2. Soft linear enhancement in thoracic and lumbar spinal cord of patient 4 in the sagittal T2-weighted contrast-enhanced MRI
MRI: Magnetic resonance imaging

the treatment was transferred from the clinic to physical therapy department.

The demographic data of all patients are summarized in the table (Table 2).

Discussion

The COVID-19 mainly affects the respiratory system and digestive system. However, its nervous system involvement has also been reported as headache, myalgia, dizziness, loss of taste and smell (5). In addition, COVID-19 has been associated with encephalopathy, cerebrovascular diseases, neuromuscular junction diseases, and peripheral nerve damage (7). Although COVID-19 related GBS has been reported, the number of patients is still not much and the association is still unclear.

Although it has been stated in a case series from China that severe COVID-19 requiring hospitalization may cause more neurological complications, it seems a bit early to come to a conclusion (5). The 2nd, 3rd and 4th patients we followed up had COVID-19 before GBS, and only the 4th patient was hospitalized. All three patients improved in their follow-up and even IVIG treatment was not required in the second patient. The first patient was presented with GBS, and the swab sample for COVID-19 during hospitalization was found positive. The most severe and mortal one was the first patient, in whom GBS was detected simultaneously with COVID-19. Starting from here, one can be think that parainfectious GBS-COVID-19 may be more severe than others. The reason may be the simultaneous observation of respiratory muscle paralysis due to GBS and severe respiratory failure associated with COVID-19. As far as we know, there are only two patients in the literature similar to our first patient who

Table 2. Features of all patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age	61	47	71	46
Gender	Male	Male	Male	Female
Complaints	Weakness on both legs	Weakness on both legs and arms	Numbness and Weakness on both legs and arms	Ataxia, diplopia
GBS variant	AIDP	AMAN	AMSAN	MFS
Association with COVID-19	Parainfectious	Postinfectious	Postinfectious	Postinfectious
MRI findings	No	No	No	Yes

AIDP: Acute inflammatory demyelinating neuropathy, AMAN: Acute motor axonal neuropathy, AMSAN: Acute motor sensory axonal neuropathy, MFS: Miller-Fisher syndrome, GBS: Guillain-Barré syndrome, COVID-19: Coronavirus disease-2019, MRI: Magnetic resonance imaging

had pulmonary ground glass opacities and typical findings for COVID-19 on CT after he presented with neurological symptoms (8,9).

In a case series from Italy, it was reported that GBS symptoms appeared within 5-10 days after COVID-19, and typical MRI findings for GBS were not seen in patients (10). In our first patient, while COVID-19 and GBS were detected at the same time, GBS symptoms started 2-3 weeks after COVID-19 in other 3 patients. Only the fourth patient's spinal MRI showed thickening and enhancement of the spinal cord. Spinal MRIs of the others were within normal limits.

There were 45 patients with GBS associated with COVID-19, and diagnosis of COVID-19 was not clear in 8 of them (11). Only 1 of the other 37 patients was reported from Turkey (12). AMAN was reported in only one patient (11). Three of our 4 patients were male as accordant with the literature, two of them were over 50 years old. The second patient was 47 years old and the fourth patient was 46 years old. Since one of our patients was in the plateau stage, no treatment was required in this patient. The others were treated with IVIG. Thromboembolic side effects were not observed in any of them.

Unfortunately, lumbar puncture and CSF analysis could not be performed in some of our patients, due to the lack of patients' consent. However, coronavirus PCR was found negative in the CSF of other patients with COVID-19-related GBS reported in the literature (11). From this point of view, direct neural infection mechanism in GBS associated with COVID-19 can be evaluated with low possibility. Considering the time of onset of the disease, the most likely mechanism seems to be the molecular similarity or mimicry (13).

There was also a regional study pointed out that the incidence of GBS increased with COVID-19 (8). In this study, it was declared that the incidence of GBS associated with COVID-19 was higher than the normal incidence of GBS and it was more severe. Again, the same study suggested that the most common form of GBS associated with COVID-19 was the demyelinating form. Among the patients we presented, GBS developing after COVID-19 had a relatively good prognosis, but it was mortal when the two diseases were seen at the same time. The patients were presented in 4 different variants.

Consequently, GBS can be either parainfectious or postinfectious. Again, different variants of GBS associated with COVID-19 can be seen. Although more studies are needed to clearly determine the strength of this relationship and which variants are seen more frequently, it is thought that our publication may contribute to the limited number of literature on the subject.

Ethics

Informed Consent: Written consent was obtained.
Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.H.Ö., B.H., Ç.E., Concept: Ç.E., Design: Ç.E., Data Collection or Processing: Z.Ü., Ç.H.Ö., B.H., Ç.E., Analysis or Interpretation: Z.Ü., Ç.E., Literature Search: Z.Ü., Ç.E., Writing: Z.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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