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Case Report

Increased Cases of Acute Polyneuropathy in COVID-19 Pandemic: What Awaits Neurologists?

Sinan Eliaçik*, Funda Uysal Tan

Department of Nephrology, Hitit University Corum Erol Olcok Training and Research Hospital, Corum, Turkey

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), originating from Wuhan, is spreading around the world and the outbreak continues to escalate. Patients with Coronavirus Disease 2019 (COVID-19) typically present with fever and respiratory illness. Finally, it is recognized that research on the relationship between COVID-19 and the nervous system surely would not be limited to the current period but would also serve basis for providing knowledge and treatment for future pandemics.

Keywords: COVID-19; SARS-CoV-2; Neuropathy; Electroneuromyography; Ferritin

INTRODUCTION

COVID-19 primary affects the respiratory system but central and peripheral neurological manifestations associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection have been increasingly reported [1-3]. Guillain-Barre Syndrome (GBS) represents the most common cause of acute flaccid paralysis. The classic form is an immune-mediated acute-onset demyelinating polyradiculoneuropathy (Acute Inflammatory Demyelinating Polyneuropathy-AIDP) typically presenting with ascending weakness, loss of deep tendon reflexes, and sensory deficits. Diagnosis of GBS relies on the results of clinical, electrophysiological, and Cerebrospinal Fluid (CSF) examinations (classically albuminocytological dissociation) [4,5]. There are three main subtypes of Guillain-Barre syndrome electrophysiologically: Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Acute Motor Axonal Neuropathy (AMAN) and Acute Motor Sensory Axonal Neuropathy (AMSAN) [4,6,7].

In this report, a retrospective analysis of COVID-19-related GBS patients was carried out determining age, sex, onset and clinical features of polyneuropathy symptoms including laboratory tests and electrophysiological findings to discuss the possible underlying pathophysiology.

CASE REPRESENTATION

TThe study consisted of patients with acute polyneuropathy that developed after COVID-19 infection. From January 2021 through March 2021, in our hospital in Çorum, we examined 10 patients who had acute polyneuropathy after the onset of Coronavirus Disease (COVID-19), the disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). All patients were confirmed serologically for COVID-19 PCR positivity and typical ground glass appearance in thorax tomography in case of respiratory involvement. In 10 patients, polyneuropathy was diagnosed with electrophysiological and neurological examination findings. Etiological research was conducted for all patients to exclude any other causes of acute polyneuropathy. None of the patients had features of myopathy. Clinically, there were no symptoms of autonomic dysfunction in the patients. There was no pathological evidence to explain acute paresis on the brain and spinal cord imaging of the patients as well as serologic tests related to any infective disorders other than COVID, which can cause acute polyneuropathy.

RESULTS

Characteristics of the patients, symptoms of acute polyneuropathy, cerebrospinal fluid and electroneuromyography findings, and abnormal findings detected in routine blood tests are given on Table 1. There was female preponderance as 1 of the 10 patients was male and the others were female. The average age of the patients was 74.8 (57-83) years. The interval between the onset of symptoms of COVID-19 and the first symptoms of acute polyneuropathy ranged from 11 to 18 days. One of the most common neurological symptoms of polyneuropathy was acute muscle weakness. The first symptoms of acute polyneuropathy were lower-limb weakness and paraesthesia in 9 patients whereas generalized, flaccid tetraparesis was detected in 1 patient. On Electroneuromyography (ENMG), there was demyelinating and predominantly motor and sensory

Correspondence to: Sinan Eliaçik, Department of Nephrology, Hitit University Corum Erol Olcok Training and Research Hospital, Corum, Turkey, Tel: 05426657563; E-mail: sinaneliacik@gmail.com

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axonal neuropathy (AMSAN) in two patients; three patients had motor axonal neuropathy (AMAN) and four patients had AMSAN findings. One patient had demiyelinating and predominantly axonal neuropathy (AMAN). Four patients accepted lumbar puncture; on analysis of the Cerebrospinal Fluid (CSF), one patient had normal protein level and the others showed albuminocytological dissociation, increased protein in the cerebrospinal fluid without increase in cell count, characteristic of the GBS. In all patients there was anaemia; serum iron-iron binding capacity and transferrin values were found to be low and ferritin was elevated. Blood tests also revealed lymphopenia and thrombocytopenia while 2 patients had normal lymphocyte and thrombocyte counts (Table 1).

Table 1: Tests for neurological examination and electrophysiology.

Age/sex	Days between COVID-19 symptoms and GBS onset	Neurological examaination	Respiratoy-comlints	GBS symptoms	Electrophysiol-ogy: Neuropathy type and GBS elec-trophysiologic subtype	CSF findings	Previous comorbidities	Blood findings
1.75 /M	15 days after	proximal and distal lower limb weakness, hypoactive deep tendon refexes in upper limb and absent in lower limb	Yes (concurrent pneumonia)	Progression of limb weakness and inability to walk Loss of ambulation,	Mixed demyelinating and axonal Predominantly AMAN	Increased total protein (56.61 mg/ dl).	HT	Ferritin 1079 ng/ ml Lymphopenia 0.6 × 9 × 10^9/ L Thrombocytopenia (140 × 10^9/ L, hgb 8.2 gr/dl, I 67gr/dl, TIBC 273 gr/dl,Tr % 24
2.74 /FM	17 days after	Hypoaesthesia, Paraparesis paraesthesia in the lower limb		Hypoaesthesia, weakness paraesthesia in the lower limb	Motor sensory, axonal, AMSAN	Increased total protein (78.39 mg/ dl)	HT	Ferritin247 ng/ ml Lymphopenia 0.22 × 9 ×10^9/ L Thrombocytopenia (102 × 10^9/ L,hgb 8.3 g/dl, I 14gr/dl, TIBC 137 gr/dl,Tr % 10
3.80 /FM	19 days after	Paraparesis, pain in the lower limb and hyporefexia at the lower limb	no	Lower limb weakness, and difficulty walking	Axonal AMAN		HT	Ferritin 466ng/ ml Lymphopenia 0.77 × 9 × 10^9/ L Thrombocyt (349 × 109/ L, hgb 9.7 g/dl, I 50gr/dl, TIBC 269 gr/dl,Tr % 19
4.80 /FM	12 days after	Paraparesis,paresthesia pain and arerefexia at the lower limb/ hyporeflexia inthe upper limb	yes	progressive ascending paraesthesia of distal lower limb,loss of ambulation	Motor sensory, axonal, AMSAN		HT CAD	Ferritin 597ng/ ml Lymphopenia 0.44 × 9 × 10^9/ L Thrombocytopenia (143 × 10^9/ L, hgb 10.8 g/dl, I 40gr/dl, TIBC 140 gr/dl,Tr % 10
5.70 /FM	16 days after	Paraparesis, and arerefexia at the lower limb	no	Flaccid paraparesis, arefexia a tlower limb and loss of ambulation	Axonal AMAN		HT	Ferritin 487.2ng/ml Lymphocyte 1.88 × 9 × 10^9/ L Thrombocyt (225 × 10^9/ L, hgb 9.9 g/dl, I 30 gr/ dl, TIBC 160 gr/dl, Tr % 9
6.83 /FM	16 days after	Lower limb weakness, hypoactive deep tendon refexes in Uupper limb and absent in lower limb	no	lower limb paraesthesia and paraparesis,difficulty walking	Motor sensory, axonal, AMSAN		HT	Ferritin 910ng/ ml Lymphopenia 0.56 × 9 × 10^9/ L Thrombocytopenia (124 × 10^9/ L, hgb 9.5 g/dl, I 32gr/dl, TIBC 152 gr/dl,Tr % 20

7.82 /FM	12 days after	Lower limb weakness, hypoactive and absent in lower limb	no	lower limb paraparesis difficulty walking	Axonal AMAN	Increased total protein (91.05 mg/ dl)	HT CAD	Ferritin 986ng/ml Lymphopcyt 1.85 × 9 × 10^9/ L Thrombocyt (279 × 10^9/ L, hgb 8.5 g/dl, I 35gr/dl, TIBC 165 gr/dl,Tr % 18
8.57 /FM	18 days after	Tetraparesis, generalized arefexia, hypoesthesia in the 4 limbs	no	Ascendant weakness Tetraparesis, generalized, sensory loss. weakness in four limbs	Motor sensory, axonal, AMSAN	normal total protein (47.12 mg/ dl)	no comorbid diseases	Ferritin 906.2ng/ml Lymphopcyt 1.89 × 9 × 10^9/ L Thrombocyt (310 × 10^9/ L, hgb 8.9 g/dl, I 15gr/dl, TIBC 175 gr/dl,Tr % 15
9.75 /FM	11 days after	Flaccid paraparesis,paresthesia generalized arefexia	no	paraparesis, generalized, sensory loss	Mixed demyelinating and axonal Predominantly AMAN		HT	Ferritin 1015 ng/ ml Lymphopenia 0.96 × 9 × 10^9/ L Thrombocytopenia (117 × 10^9/ L, hgb 8.7 g/dl, I 10 gr/dl, TIBC 130 gr/dl,Tr % 10
10.72 /FM	17 days after	Ascending weakness,paraparesis and paresthesia hypoactive deep tendon refexes in upper limb and absent in lower limb	no	Lower limb paraesthesia and weakness	Mixed demyelinating and axonal Predominantly AMAN		no comorbid diseases	Ferritin 1402 ng/ ml Lymphopenia 1.02 × 9 × 10^9/ L Thrombocyt (350 × 10^9/ L, hgb 7.7 g/dl, I 25 gr/dl, TIBC 145 gr/dl,Tr % 16

DISCUSSION

Peripheral and central nervous system damage in COVID-19 has been postulated to be the consequence of two different mechanisms: 1) haematogenous (infection of endothelial cells or leucocytes) or trans-neuronal (via olfactory tract or other cranial nerves) dissemination to central nervous system in relation with viral neurotropism, and 2) abnormal immune-mediated response causing secondary neurological involvement [8-10]. The first mechanism is supposed to be responsible for the most common neurological symptoms developed by patients with COVID-19 (e.g., hypogeusia, hyposmia, headache, vertigo, and dizziness). In contrast, the second can lead to severe complications during or after the course of the illness, either dysimmune (e.g., myelitis, encephalitis, GBS) or induced by cytokine overproduction (hypercoagulable state and cerebrovascular events) [9,10]. Since the onset of the COVID-19 pandemic, there have been reports of the possible link between GBS and the COVID-19 infection [11]. Weakness in the limbs and acute flaccid quadriparesis were observed in most GBS case reports after the diagnosis of COVID-19. Furthermore, demyelinating polyneuropathy was commonly observed in most of these reports. Some of the COVID-19- related GBS patients had the axonal variants of GBS [12]. Coronaviruses are thought to cause GBS in certain patients either directly through neuroinvasive capacity (ACE2 receptors on neuronal tissues) or indirectly through the response of the immune system (inflammatory mechanism) [13,14]. The data indicate that SARS-CoV-2 is able to cause an immune reaction with an increased Level of Interleukin-6 (IL-6) which stimulates the inflammatory cascade and damages tissues. Therefore, inflammatory factors may play an important role in the organ dysfunctions of patients with COVID-19 infection [15,16]. The actual data indicate that SARS-CoV-2 is capable of causing an excessive immune reaction with an increased level of cytokines as Interleukin-6 (IL-6), which are produced by activated leukocytes and stimulate the inflammatory cascade leading to extensive tissue damage. IL-6 plays an important role in multiple organ dysfunctions, which is often fatal for patients with COVID-19 [17,18].

In the literature, although polyneuropathy was found to be more common in men (50 vs. 23 cases: 68.5% vs. 31.5%), we had only one male patient in our series of ten cases [19]. On the basis of this observational series involving ten patients, it is not possible to determine whether severe deficits and axonal involvement are typical features of COVID-19–associated acute polyneuropathy. However, since March 2020, when the first COVID-19 cases were recorded in our country, we have found that the total numbers of acute polyneuropathy cases we have followed up in our clinic are increased, approximately three times more than the previous year. Thus, it is possible that acute polyneuropathy is linked to the COVID-19 infection. Common patient characteristics in this series beside COVID-19 were increased ferritin and anaemia. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm and it is known that they face a higher probability to experience serious complications from COVID-19 [20,21]. Laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life-threatening illness [22]. The height of ferritin detected during the COVID period also requires more caution in terms of polyneuropathy that may develop, however, concomitant iron deficiency might play a role in the etiology of polyneuropathy. When the literature is examined, we know that acute polyneuropathy is not observed in every case of COVID-19 with iron deficiency anemia. Thus, the association between COVID-19, iron deficiency anemia and acute polyneuropathy is obscure.

CONCLUSION

We add to the literature 10 cases of GBS related to COVID-19 infection supporting SARS-Cov-2 virus could be a triggering factor of GBS. Studies assisted by histopathological evidence could show us the fate of patients with axonal neuropathy, which occurs acutely but can be reflected in the chronic period. However, more cases with epidemiological data should be studied and future investigations should be carried out in this regard. Awareness of possible causal association between acute polyneuropathy and COVID-19, recommend long term follow up of COVID-19 patients for neurologic complications.

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