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

Sinan ELİAÇIK[1*] (ID) **and Özlem AKDOĞAN**[2] (ID)

[1]Department of Neurology, Hitit University School of Medicine, Turkey
[2]Department of Infection Disease, Hitit University School of Medicine, Turkey

*Corresponding author: Sinan ELİAÇIK, Department of Neurology, Hitit University School of Medicine, Turkey, Tel: 05426657563

Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 infection 2019 (Covid-19) primarily affects the respiratory system but central and peripheral neurological manifestations have been increasingly recognized and reported.

Materials and methods: The study consisted of patients with acute polyneuropathy that developed after the Covid-19 infection. All patients were confirmed serologically for PCR positivity and typical ground glass appearance in thorax tomography in case of respiratory involvement. In 16 patients, polyneuropathy was diagnosed with an electrophysiological and neurological examination. Etiological research was conducted for all patients to exclude any other causes of acute polyneuropathy.

Results: The average age of the patients was 64.3 (29-83) years; most cases were female (13 vs. 3). The interval between the onset of symptoms of Covid-19 and the first symptoms of acute polyneuropathy ranged from 11 to 63 (Mean: 21.5) days. The initial symptoms of acute polyneuropathy were lower-limb weakness and paraesthesia in 11 patients whereas generalized, flaccid tetraparesis was detected in 3 patients. Except for pure sensory symptoms, no motor findings were detected in the two patients. On electroneuromyography (ENMG), there was AMSAN in 7 patients; 7 patients had AMAN and 2 patients had AIDP findings. Five patients accepted lumbar puncture; on analysis of the CSF, one patient had normal protein level and the others showed an albumino-cytological dissociation, increased protein in the cerebrospinal fluid without increase in cell count, characteristic of the GBS.

Conclusion: Awareness of the possible causal association between acute polyneuropathy and Covid-19, recommends long-term follow-up of Covid-19 patients for neurologic complications.

Introduction

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 [1]. Covid-19 primarily affects the respiratory system but central and peripheral neurological manifestations associated with SARS-CoV-2 infection have been increasingly reported [2,3].

Guillain Barre Syndrome (GBS) is an inflammatory disease of the peripheral nervous system, characterized by rapidly progressive, symmetrical, and typically ascending weakness of the limbs with reduced or absent deep tendon reflexes, and upper and lower extremities non-length dependent paresthesia and sensory symptoms at onset. 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 albumino-cytological dissociation) [4,5]. There are three main subtypes of Guillain-Barre syndrome electrophysiologically: AIDP, acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN) [4,6,7].

GBS occurs with an approximate incidence of 0.16-3 cases per 100,000 annually in the general population; however, an accurate estimation of the incidence of GBS in Covid-19 patients is unknown, as a potential association remains uncertain. After a thorough literature review, found a substantial number of reported cases and case series of Covid-19 infection presented with GBS [8,9]. When compared to the same period of the previous year, we noticed that the cases of acute polyneuropathy have increased three times. We examined in detail those who had a Covid-19 infection from these cases. We excluded patients with additional risk factors for polyneuropathy.

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

Materials and Methods

The study was a retrospective study approved by Hitit University School of Medicine Ethics Committee (500/13.10.2021) and conducted by following STROBE guidelines for reporting observational studies (www.strobestatement.org) and the Declaration of Helsinki. All participants gave their informed consent for this study.

The study consisted of patients with acute polyneuropathy that developed after the Covid-19 infection. From January 2021 through March 2021, in our hospital in Çorum, we examined 16 patients who had acute polyneuropathy after the onset of Covid-19, the disease caused by 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 16 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-19, 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 in Table 1. There was female preponderance as 3 of the 16 patients were male and the others were female. The average age of the patients was 64.3 (29-83) years. The patients were evaluated for factors that play a role in the etiology of polyneuropathy. Concomitant risk factors excluded. Pneumonic findings on thorax tomography were detected in 10 patients in the acute period. The interval between the onset of symptoms of Covid-19 and the first symptoms of acute polyneuropathy ranged from 11 to 63 (Mean: 21.5) days. One of the most common neurological symptoms of polyneuropathy was acute weakness. Although the neurological examination findings of the patients were summarized in the Table 1, distal limb weakness was dominant in all patients with pathological findings in the motor system examination. The first symptoms of acute polyneuropathy were lower-limb weakness and paraesthesia in 11 patients where as generalized, flaccid tetraparesis was detected in 3 patients. Except for pure sensory symptoms, no motor findings were detected in the two patients. On electroneuromyography (ENMG), there was MSAN in 7 patients; 7 patients had MAN and 2 patients had IDP findings. Five patients accepted lumbar puncture; on analysis of the CSF, one patient had normal protein level and the others showed an albumino-cytological dissociation, increased protein in the cerebrospinal fluid without increase in cell count, characteristic of the GBS. Detected during the acute covid period blood tests also revealed lymphopenia and thrombocytopenia while blood analysis values were normal in 2 patients. Lymphopenia was found in 11 patients, and thrombocytopenia was found in 6 patients. As treatment for patients; intravenous immunoglobulin 0.4 grams/kg was administered for five days. Follow-up and symptomatic treatments continue.

We shared our experience with 16 Covid-19 patients who presented with GBS which were not preceded with any other systemic infection.

Discussion

Peripheral and central nervous system damage in Covid-19 has been postulated to be the consequence of two different mechanisms: 1) Hematogenous (infection of endothelial cells or leucocytes) or trans-neuronal (via olfactory tract or other cranial nerves) dissemination to the central nervous system in relation with viral neurotropism, and 2) Abnormal immune-mediated response causing secondary neurological involvement [10-12]. 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) [11,12]. Since the onset of the Covid-19 pandemic, there have been reports of the possible link between GBS and the

Table 1: Clinical electrophysiological and laboratory findings of patients.

Age/sex	Days between COVID-19 symptoms and GBS onset	Neurological examination	Chest radiographic features	GBS symptoms (GBS/Clinical)	GBS electrophysiologic subtype	CSF findings	Previous comorbidities	Blood findings
1.75/M	15 days after	Proximal and distal lower limb weakness, hypoactive deep tendon refexes in upperlimb and absent in lowerlimb	Yes	Progression of limb weakness and inability o walk Loss of ambulation, AMAN	MAN	Increased total protein (56.61 mg/dl).	HT	Ferritin 1079 ng/ml Lymphopenia 0.6 × 9 × 10⁹/L Thrombocytopenia (140 × 10⁹/L,
2.74/FM	17 days after	Hypoaesthesia, paraparesis paraesthesia in the lowerlimb	Yes	Hypoaesthesia, weakness paraesthesia in the lowerlimb AMSAN	MSAN	Increased total protein (78.39 mg/dl).	HT	Ferritin 247 ng/ml Lymphopenia 0.22 × 9 × 10⁹/L Thrombocytopenia (102 × 10⁹/L,
3.80/FM	19 days after	Paraparesis, pain in the lowerlimband hyporeflexia at the lowerlimb	No	Lowerlimb weakness, and difficulty walking AMAN	MAN		HT	Ferritin 466 ng/ml Lymphopenia 0.77 × 9 × 10⁹/L
4.80/FM	12 days after	Paraparesis, paresthesia pain and arerefexia at the lowerlimb/hyporeflexia in the upperlimb	Yes	Progressive ascending paraesthesia of distal lowerlimb, loss of ambulation AMSAN	MSAN		HT	Ferritin 597 ng/ml Lymphopenia 0.44 × 9 × 10⁹/L Thrombocytopenia (143 × 10⁹/L,
5.70/FM	16 days after	Paraparesis, and arereflexia at the lowerlimb	Yes	Flaccidparaparesis, arefexia at lowerlimb and loss of ambulation AMAN	MAN		HT	Ferritin 487.2 ng/ml
6.83/FM	16 days after	Lower limb weakness, hypoactive deeptendon reflexes in Uupperlimb and absent in lowerlimb	Yes	lowerlimb paraesthesia and paraparesis, difficulty walking AMSAN	MSAN		HT	Ferritin 910 ng/ml Lymphopenia 0.56 × 9 × 10⁹/L Thrombocytopenia (124 × 10⁹/L
7.82/FM	12 days after	Lowerlimb weakness, hypoactive and absent in lowerlimb	Yes	lowerlimb paraparesis difficulty walking AMAN	MAN	Increased total protein (91.05 mg/dl).	HT	Ferritin 986 ng/ml

No./Age/Sex	Onset	Clinical findings		Clinical description	EMG	CSF protein	Comorbidity	Laboratory
8.57/FM	18 days after	Tetraparesis, generalized areflexia, hypoesthesia in the 4 limbs	No	Ascendant weakness Tetraparesis, generalized, sensoryloss. weakness in four limbs AMSAN	MSAN	normal total protein (47.12 mg/dl).	No comorbid diseases	Ferritin 906.2 ng/ml
9.75/FM	11 days after	Flaccid paraparesis, paresthesia generalized arefexia	Yes	paraparesis, generalized, sensoryloss AMSAN	MSAN		HT	Ferritin 1015 ng/ml Lymphopenia $0.96 \times 9 \times 10^9$/L Thrombocytopenia (117 × 10^9/L,
10.72/FM	17 days after	Ascending weakness, paraparesis and paresthesia hypoactive deep tendonreflexes in upperlimb and absent in lowerlimb	Yes	Lowerlimb paraesthesia and weakness AMSAN	MSAN		No comorbid diseases	Ferritin 1402 ng/ml Lymphopenia $1.02 \times 9 \times 10^9$/L
11. 67/M	63 day	Ascending weakness, paraparesis hypoactive deeptendon refexes in lowerlimb	Yes	Lowerlimb weakness, and difficulty walking AMAN	MAN		No comorbid diseases	Lymphopenia $0.29 \times 9 \times 10^9$/L Thrombocytopenia (248 × 10^9/L
12. 68/M	30	Tetraparesis, generalized hypoactive deeptendon reflexes, hypoesthesia in the 4 limbs	Yes	Ascendant weakness Tetraparesis, generalized, sensoryloss. weakness in four limbs AIDP	Sensoriel predominant IDP		No comorbid disease	Ferritin 1219 ng/ml Lymphopenia $0.94 \times 9 \times 10^9$/L Thrombocytopenia (141 × 10^9/L
13. 49/FM	35	Tetraparesis, generalized areflexia, hypoesthesia in the 4 limbs	No	Ascendant weakness Tetraparesis, generalized, sensory loss. weakness in four limbs AMAN	MAN	Increased total protein (82.08 mg/dl).	No comorbid disease	Lymphopenia $1 \times 9 \times 10^9$/L
14. 33/FM	15	Lowerlimb weakness, hypoactive reflexes in lowerlimbs	No	paraparesis, generalized, sensoryloss AMSAN	MSAN		No comorbid disease	N
15. 36/FM	18	Generalized hyporeflexia, hypoesthesia in the 4 limbs	No	sensoryloss. in four limbs AMAN	MAN		No comorbid disease	Ferritin 2491 ng/ml Lymphopenia $0.94 \times 9 \times 10^9$/L
16. 29/FM	60	Generalized areflexia, hypoesthesia in the 4 limbs	No	sensoryloss. in four limbs AIDP	Sensoriel predominant IDP		No comorbid disease	N

HT: Hypertension; Ferritin: 13-150 ng/ml; Platelet: 150-450 × 10^9/L; Lenfosit: 1.26-3.35 9 × 10^9/L; AMAN: Acute Motor Axonal Neuropathy; AMSAN: Acute Motor Sensory Axonal Neuropathy; AIDP: Acute Inflamatory demiyelinating polyneuropathy; MAN: Motor Axonal Neuropathy; MSAN: Motor Sensory Axonal Neuropathy; IDP: Inflammatory demiyelinating polyneuropathy

Covid-19 infection [13]. 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 axonal variants of GBS like our cases [14].

In the review published in 2021; the most commonly reported GBS variants were classical sensorimotor GBS, followed by paraparetic GBS, Miller Fischer Syndrome, facial diplegia with paresthesia, pharyngeal-cervical-brachial GBS, and pure sensory GBS. CSF analysis was performed in 86 cases. Seventy-four cases have shown albumino-cytologic dissociation in the CSF analysis.

The predominant EMG variant of GBS was AIDP, followed by AMSAN, and AMAN and in the review report that 6 cases were complicated by death. However, the review suggests that men might be more prone to Covid-19-related GBS [15]. In our case series, MAN and MSAN EMG variants were observed more frequently. Female dominance was detected. Consistent with the literature, paraparesis was present in eleven patients, tetraparesis in three, and pure sensory symptoms in two patients. However, mortality from Covid-19 and GBS was not observed in our case series. The excess of the female gender, the high incidence of AMAN and AMSAN cases lead to the opinion that classically observed polyneuropathy cases may change the spectrum in the future.

Before the recent pandemic, few cases of coronavirus associated with GBS were reported, but a systematic review pointed to a significantly increased number of patients with GBS after the COVID-19 pandemic, with higher prevalence among older patients (mean age of 60 years) than with younger ones (mean age of 40 years) [16]. In our case series, eleven cases were over 60-years-old, four cases were between 30-60 years-old, and one of our cases was under 30-years-old.

While the mean time between GBS and Covid-19 was 21.5 days in our case series, a case report of GBS developing approximately 100 days later was reported [17]. None of the patients had a laboratory and electrophysiological findings suggestive of myopathy. None of our patients had an intensive care process. Disease activity was mild to moderate.

The exact pathogenesis of Covid-19-related neurological damage is still largely unknown. Considering that previous viral out breaks, molecular mimicry between SARS-CoV-2 and various human organs and tissues have been hypothesized as a potential trigger of multi-organ autoimmunity in Covid-19 [18-20]. For example, In a recent study by Lucchese and Flöel, sequence analysis of the 41 human proteins associated with acute and chronic immune-mediated neuropathies revealed that SARS-CoV-2 contained two immunologically-related hexapeptides (KDKKKK in nucleocapsid and EIPKEE in Orf1ab) with the human heat shock proteins 90 (HSP90B and HSP90B2) and 60 (HSP60), respectively [21]. These authors hypothesized that SARS-CoV-2 infection may trigger an adaptive immune response in which T cell-B cell interactions result in the production-specific antibodies similar to ganglioside-peptide sequences or structure, resulting in loss of self-tolerance [21]. The gangliosides located on them embranes of neurons and the Schwann-cells, which form the myelin sheath, act as receptors for antiganglioside antibodies, promoting neutralization of neurons complement inhibitory activity, which turns them into targets for autoimmune-mediated destruction of myelin sheaths or axons [21]. About 50 to 85% of previously reported cases with GBS or its variants have anti-ganglioside antibodies in their serum. However, there are limited data on the presence of antiganglioside antibodies in the patients with Covid-19 related GBS. Studies have not reported an increase in the serum titers of anti-ganglioside antibodies in GBS patients with Covid-19. Recently, Dufour, et al. reported the first case with Covid-19 related GBS with positive GM1 antibody [22,23]. Therefore, further studies are necessary to confirm the presence of antiganglioside antibodies in Covid-19 related GBS. We could not detect antiganglioside antibody and Interleukin-6 (IL-6) levels in our case series.

The role of neuroinflammation and the effect of cytokine storms caused by SARS-CoV-2 infection on the nervous system have been discussed. In Covid-19 patients, an increase has been observed in cytokines such as IL-1b, IL-6, IL-17, TNF-a, and interferon-g (IFN-g), along with other chemokines. Because many of the same cytokines have been implicated in the pathogenesis of typical GBS, the cytokine storm in Covid-19 may play a pivotal role in the simultaneous development and progression of GBS [23]. However, the role of cytokines in Covid-19 related GBS needs further investigation [24-26].

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 [27,28]. The data indicate that SARS-CoV-2 can 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 [29,30]. The actual data indicate that SARS-CoV-2 is capable of causing an excessive immune reaction with an increased level of cytokines as 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 are often fatal for patients with Covid-19 [29-32].

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 three male patients in our series of 16 cases [33]. Based on this observational series involving 16 patients, it is not possible to determine whether severe deficits and axonal involvement are typical features of Covid-19-associated acute polyneuropathy. In the cases we reviewed retrospectively, the IL6 level was not studied. Therefore, we could not decide whether IL6 levels would be a precursor biomarker in the development of acute polyneuropathy. Studies that are more comprehensive and include inflammatory markers will add new dimensions to the acute polyneuropathy Covid-19 relationship, which we shed light on with our case series. Covid-19 causes an exaggerated immune response with persistent fevers, elevated inflammatory markers, and elevated proinflammatory cytokines. Covid-19-associated immune dysregulation increases the risk of immune-mediated conditions such as GBS [34]. In our case series, interleukin levels were not studied in the acute period of covid. Therefore, we think that high ferritin levels only in the acute period can be associated with complications in the post covid period. It should also be considered that prospective studies will be needed to examine long-term complications in patients who have had a cytokine storm.

Common patient characteristics in this series besides Covid-19 were increased ferritin levels. 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 [35-36]. 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 [34]. The height of ferritin detected during the Covid-19 period also requires more caution in terms of polyneuropathy that may develop. An important question regarding the pathophysiology of GBS following Covid-19 is whether it reflects a para-infectious response related to the acute inflammation or a true post infectious immune-mediated response [28,37]. The case had presented would give credence to the hypothesis that it is the immune response to Covid-19 and not the virus itself or the acute vascular changes that underly the pathophysiology of long Covid-19 syndrome [38]. Although the interval between Covid-19 and GBS was 21.5 days on average, we found an interval between 30 and 63 days in four of our cases. The high number of women in our case series and the presence of motor axonal and motor-sensory axonal electrophysiological findings in the EMG examination were not compatible with the literature. With this case series, we can suggest that acute polyneuropathy occurring after Covid-19

should be addressed from this perspective. In addition to classical GBS cases, whether there will be an increase in AMAN and AMSAN cases should be examined with detailed studies. Therefore, with more comprehensive studies, new targets should be determined for both etiology and treatment in post-covid period GBS.

Conclusion

We add to the literature 16 cases of GBS related to Covid-19 infection supporting the 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 the possible causal association between acute polyneuropathy and Covid-19, recommends long-term follow-up of Covid-19 patients for neurologic complications. 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.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323: 1061-1069.

2. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77: 683-690.

3. Koralnik IJ, Tyler KL (2020) COVID-19: A global threat to the nervous system. Ann Neurol 88: 1-11.

4. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, et al. (2019) Diagnosis and management of Guillain-Barre syndrome in ten steps. Nat Rev Neurol 15: 671-683.

5. Kieseier BC, Mathey EK, Sommer C, Hartung HP (2018) Immune-mediated neuropathies. Nat Rev Dis Primers 4: 31.

6. Willison HJ, Jacobs BC, van Doorn PA (2016) Guillain-Barre syndrome. Lancet 388: 717-727.

7. Wakerley BR, Yuki N (2015) Polyneuritis cranialis-subtype of Guillain-Barre syndrome? Nat Rev Neurol 11: 664.

8. Shahrizaila N, Lehmann HC, Kuwabara S (2021) Guillain-Barre syndrome. Lancet 397: 1214-1228.

9. Elzouki AN, Osman MAM, Ahmed MAE, Al-Abdulmalek A, Altermanini M, et al. (2021) COVID-19 infection presented as Guillain-Barre Syndrome: Report of two new cases and review of 116 reported cases and case series. Travel Med Infect Dis 44: 102169.

10. Costello F, Dalakas MC (2020) Cranial Neuropathies and COVID19: Neurotropism and Autoimmunity. Neurology 95: 195-196.

11. Dalakas MC (2020) Guillain-Barre syndrome: The first documented COVID-19-triggered autoimmune neurologic

disease: More to come with myositis in the offing. Neurol Neuroimmunol Neuroinflamm 7: e78169.

12. Wang L, Shen Y, Li M, Chuang H, Ye Y, et al. (2020) Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Neurol 267: 2777-2789.

13. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K (2020) Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg 194: 105921.

14. Rahimi K (2020) Guillain-Barre syndrome during COVID-19 pandemic: An overview of the reports. Neurol Sci 41: 3149-3156.

15. Aladawi M, Elfil M, Abu-Esheh B, Abu Jazar D, Armouti A, et al. (2021) GuillainBarre syndrome as a complication of covid-19: A systematic review. Can J Neurol Sci 49: 38-48.

16. Gittermann LMT, Feris SNV, Giacoman AvO (2020) Relation between COVID-19 and Guillain-Barré syndrome in adults: A systematic review. Neurologıá (English Edition) 35: 646-654.

17. Fletman EW, Stumpf N, Kalimullah J, Levinson N, Deboo A (2021) Guillain-Barré syndrome associated with COVID-19: An atypical, late-onset presentation. Neurological Sciences 42: 4393-4395.

18. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, et al. (2016) Guillain-Barré syndrome outbreak associated with zika virus infection in french polynesia: A case-control study. Lancet 387: 1531-1539.

19. Cappello F, Marino Gammazza A, Dieli F, Conway de Macario E, Macario AJ (2020) Does SARS-CoV-2 trigger stress-induced autoimmunity by molecular mimicry? A hypothesis. J Clin Med 9: 2038.

20. Needham EJ, Chou SHY, Coles AJ, Menon DK (2020) Neurological implications of covid-19 infections. Neurocrit Care 32: 667-671.

21. Lucchese G, Flöel A (2020) SARS-CoV-2 and Guillain-Barré syndrome: Molecular mimicry with human heat shock proteins as potential pathogenic mechanism. Cell Stress Chaperones 25: 731-735.

22. Dufour C, Co T-K, Liu A (2021) Gm1 ganglioside antibody and covid-19 related guillain barre syndrome-a case report, systemic review and implication for vaccine development. Brain Behavior Immunity Health 12: 100203.

23. Hussain FS, Eldeeb MA, Blackmore D, Siddiqi ZA (2020) Guillian Barré syndrome and covID-19: Possible role of the cytokine storm. Autoimmun Rev 19: 102681.

24. Thepmankorn P, Bach J, Lasfar A, Zhao X, Souayah S, et al. (2020) Cytokine storm induced by SARS-CoV-2 infection: The spectrum of its neurological manifestations. Cytokine 138: 155404.

25. Garcia MA, Barreras PV, Lewis A, Pinilla G, Sokoll LJ, et al. (2021) Cerebrospinal fluid in covid-19 neurological complications: No cytokine storm or neuroinflammation. medRxiv 16: 636-734.

26. Shoraka S, Ferreira MLB, Mohebbi SR, Ghaemi A (2021) SARS-CoV-2 infection and guillain-barré syndrome: A review on potential pathogenic mechanisms. Front Immunol 12: 674922.

27. Zhou Z, Kang H, Li S, Zhao X (2020) Understanding the neurotropic characteristics of SARS-CoV-2: From neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 267: 2179-2184.

28. Zhao H, Shen D, Zhou H, Liu J, Chen S (2020) Guillain-Barre syndrome associated with SARS-CoV-2 infection: Causality or coincidence? The Lancet Neurology 19: 383-384.

29. Carod-Artal FJ (2020) Neurological complications of coronavirus and COVID-19. Rev Neurol 70: 311-322.

30. Sedaghat Z, Karimi N (2020) Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 76: 233-235.

31. Helm J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, et al. (2020) Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 382: 2268-2270.

32. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, et al. (2020) Guillain-Barre syndrome associated with SARS-CoV-2. N Engl J Med 382: 2574-2576.

33. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M (2020) Guillain-Barré syndrome spectrum associated with COVID-19: An up-to-date systematic review of 73 cases. J Neurol: 1-38.

34. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, et al. (2020) COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 395: 1033-1034.

35. Abbaspour N, Hurrell R, Kelishadi R (2014) Review on iron and its importance for human health. Research J Med Sci 19: 164-174.

36. American Diabetes Association (2020) How COVID-19 Impacts People with Diabetes.

37. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, et al. (2020) The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. Brain 143: 3104-3120.

38. Raahimi MM, Kane A, Moore C, Alareed AW (2021) Lateonset of GuillainBarré syndrome following SARS-CoV-2 infection: Part of 'long COVID-19 syndrome'? BMJ Case Rep 14: e240178.