Cerebrospinal fluid and serum interleukins 6 and 8 during the acute and recovery phase in COVID-19 neuropathy patients

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Abstract
This case series describes three patients affected by severe acute respiratory syndrome coronavirus 2, who developed polyradiculoneuritis as a probable neurological complication of coronavirus disease 2019 (COVID-19). A diagnosis of Guillain Barré syndrome was made on the basis of clinical symptoms, cerebrospinal fluid analysis, and electroneurography. In all of them, the therapeutic approach included the administration of intravenous immunoglobulin (0.4 gr/kg for 5 days), which resulted in the improvement of neurological symptoms. Clinical neurophysiology revealed the presence of conduction block, absence of F waves, and in two cases, a significant decrease in amplitude of compound motor action potential cMAP. Due to the potential role of inflammation on symptoms development and prognosis, interleukin-6 (IL-6) and IL-8 levels were measured in serum and cerebrospinal fluid during the acute phase, while only serum was tested after recovery. Both IL-6 and IL-8 were found increased during the acute phase, both in the serum and cerebrospinal fluid, whereas 4 months after admission (at complete recovery), only IL-8 remained elevated in the serum. These results confirm the inflammatory response that might be linked to peripheral nervous system complications and encourage the use of IL-6 and IL-8 as prognostic biomarkers in COVID-19.

KEYWORDS
COVID-19, IL-6, IL-8, interleukins, polyradiculonevritis

1 | INTRODUCTION

Since December 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has rapidly spread worldwide, causing an increased number of hospitalizations and intensive care admissions, due to severe respiratory distress. Even though respiratory symptoms play a critical role in the clinical picture, in the last year, systemic and multiorgan manifestations have been increasingly described, including neurological symptoms. Several neurological complications have been described, including cerebrovascular accidents, polyradiculoneuritis (Guillain Barré syndrome), and other inflammatory diseases.1–7 Among peripheral
nervous system manifestations, the most frequently observed are hyposmia, hypogeusia, and Guillain–Barré syndrome (GBS). GBS is a heterogeneous condition with several variant forms: the most common presentation is the progressively ascending tetraparesis (acute inflammatory demyelinating polyneuropathy), but other localized clinical variants are also recognized. About 60% of the above-mentioned autoimmune syndromes can be infection-related by humoral and cellular cross-reactivity. 

Symptoms on admission were fever and cough, in all three patients, significant impairment of taste and smell was also reported (Table 1). Due to respiratory failure, patients were admitted to the COVID-19 protected areas of the University Hospital of Trieste. COVID-19 diagnosis was confirmed in the emergency department after nasopharyngeal swab testing. COVID-19 management included a variety of treatments, including antiviral drugs (Lopinavir/Ritonavir, Darunavir), hydroxychloroquine, antibiotic therapy, and oxygen support (Table 1). Two patients received Tocilizumab, a monoclonal antibody targeting the interleukin-6 receptor. Patients developed progressive weakness of the upper and lower limbs, in a disto-proximal fashion; the latency between the onset of the respiratory symptoms and neurological involvement ranged from 14 up to 20 days. All the patients received neurological examination at symptom appearance; routine blood chemistry analyses, and a panel of anti-ganglioside antibodies, including anti-GM1, -GM2, -GM3, -GD1a, -GD1b, -GT1b, and -GQ1b, were performed according to standard procedures. CSF was collected and processed for standard analyses including pressure, cell count, proteins, and glucose. CSF culture and polymerase chain reaction (PCR) for possible organisms, such as bacteria, Mycobacterium tuberculosis, fungi, Herpes viruses, Enteroviruses, Japanese B virus, and Dengue viruses, were also performed, including analysis for SARS-CoV-2. Additionally, both CSF and serum samples were used in the acute and, only serum, in the post-acute phase, to assess IL-6 and IL-8 levels.

2.1 | Clinical neurophysiology

Motor and sensory nerve conduction studies were performed in the upper and lower limbs following standard international guidelines. The neurophysiological evaluation included electroneurography and electromyography (EMG) in all the patients in the COVID area. F waves were recorded from lower and upper limbs. Needle EMG was performed in all patients. The physician and the technician wore personal protective equipment including appropriate masks, face shields, gowns, and gloves following the guidelines of the American Association of Clinical Neurophysiology website (https://www.acnsp.org/practice/covid-19-resources). Neurophysiological evaluation was performed in the acute phase and during the recovery, approximately 4 months after the first admission to the hospital.

3 | RESULTS

Neurological examination revealed a flaccid paresis in all three patients, with variable lower or upper limb predominance. Two patients also reported paresthesia located at the lower extremities. Deep tendon reflexes were diffusely absent. All patients reported taste and smell impairment since the beginning of the respiratory symptoms. In all three patients, the results of routine blood chemistry tests, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, as well as a panel of serological tests for autoimmune disorders were unremarkable. A panel of anti-ganglioside antibodies, including anti-GM1, -GM2, -GM3, -GD1a, -GD1b, -GT1b, and -GQ1b, was negative. CSF analysis revealed clear CSF, normal pressure, and absence of blood cells (Table 1). The CSF/serum glucose ratio was normal in all patients, with a mild albumin-cytological dissociation (ranging from 52 to 72 mg/dl of proteins; normal protein level less than 45 mg/dl). CSF culture and PCR for possible organisms, such as bacteria, Mycobacterium tuberculosis, fungi, Herpes viruses, Enteroviruses, Japanese B virus, and Dengue viruses, yielded...
| Patient | 1 | 2 | 3 |
|---------|---|---|---|
| Age     | 72 years | 72 years | 76 years |
| Sex     | Male | Male | Male |
| Early symptoms of COVID-19 | Fever, dyspnea, hyposmia, and ageusia | Fever, cough, dyspnea, hyposmia, and ageusia | Fever, cough, dysuria, hyposmia, and ageusia |
| Need for mechanical ventilation | Yes | Yes | Yes |
| Latency of neurological symptoms | 18 Days | 36 Days | 22 Days |
| Neurological signs and symptoms | Flaccid tetraparesis, with proximal upper limb predominance | Flaccid tetraparesis with lower limbs predominance | Proximal weakness of lower and upper limb, with upper limb predominance |
| Deep tendon reflexes | Diffusely absent | Diffusely absent | Unassessable |
| Sensory disturbances | Tingling of distal lower extremities | Sense of having a tight bandage on legs and feet | None |
| Cranial nerve involvement | Mild right-sided lower face facial weakness, with sparing of the forehead muscles | Mild right-sided lower face facial weakness, with sparing of the forehead muscles | Mild left-sided lower facial deficit; reported mild transient diplopia fully recovered at the time of evaluation |
| CSF findings | Protein level 52 mg/dl; 1 cell/mm³ | Normal protein level (40 mg/dl); 1 cell/mm³ | Protein level 53 mg/dl; 2 cell/mm³ |
| PCR for SARS-CoV-2 | Negative | PCR for SARS-CoV-2: negative | PCR for SARS-CoV-2: negative |
| Antiganglioside antibodies | Negative | Negative | Negative |
| Serum interleukin level | IL-1β: 0.2 pg/ml ↑ | IL-1β: 0.5 pg/ml ↑ | IL-1β: 0.2 pg/ml ↑ |
| Interleukin | IL-6: 113.0 pg/ml ↑↑↑ | IL-6: 9.8 pg/ml ↑ | IL-6: 32.7 pg/ml ↑↑ |
| Level | IL-8: 20.0 pg/ml ↑ | IL-8: 55.0 pg/ml ↑↑ | IL-8: 17.8 pg/ml ↑ |
| TNF-α | 16.0 pg/ml ↑ | TNF-α: 16.0 pg/ml ↑ | TNF-α: 11.1 pg/ml |
| Follow up | IL-1β: 0.2 pg/ml | IL-1β: 0.7 pg/ml | IL-1β: 0.2 pg/ml |
| Serum | IL-6: 1.8 pg/ml ↑ | IL-6: 7 pg/ml↑ | IL-6: 6.1 pg/ml↑ |
| Interleukin | IL-8: 39.4 pg/ml ↑ | IL-8: 50 pg/ml ↔ | IL-8: 22.8 pg/ml ↑ |
| Level | TNF-α: 11.1 pg/ml | TNF-α: 17 pg/ml | TNF-α: 14.4 pg/ml |
| IP-10 | 170.8 pg/ml | IP-10: 57 pg/ml | IP-10: 230.6 pg/ml |
| INF-γ | 1.1 pg/ml | INF-γ: 1.13 pg/ml | INF-γ: 1.1 pg/ml |
| IL-10 | 7.2 pg/ml | IL-10: 6.5 pg/ml | IL-10: 6.6 pg/ml |
| IL-2R 8945 | IL-2R 2255 | IL-2R 1549 ↑ | |
| CSF interleukin level | IL-1β: 0.12 pg/ml | IL-1β: 0.1 pg/ml | IL-1β: 0.52 pg/ml |
| Level | IL-6: 9.6 pg/ml | IL-6: 1.4 pg/ml | IL-6: 5.9 pg/ml |
| IL-8 | 22.7 pg/ml | IL-8: 96.0 pg/ml | IL-8: 42.6 pg/ml |
| TNF-α | 0.3 pg/ml | TNF-α: 0.7 pg/ml | TNF-α: 0.25 pg/ml |
negative results, including PCR analysis for SARS-CoV-2. In all three patients, IL-6 and IL-8 were found to increase during the acute phase in both serum and CSF, suggesting an active inflammatory process (Table 1). Based on the clinical presentation, neurophysiological and CSF findings, intravenous immunoglobulins (IVIG) therapy was initiated in the three patients at a dose of 0.4 g/kg for 5 days. The neurological symptoms improved and partially resolved after the initiation of IVIG treatment in all of them, with no side effects reported after the use of IVIG therapy. After 4 months from admission, the patients showed a remarkable clinical improvement with motor recovery in lower and upper limbs, with only one patient presenting a minimal improvement of weakness. Concomitant serum analysis showed IL-6 values decreased compared to the acute phase, although without returning to normal values, while IL-8 remained stable in one patient or even increased in two patients.

3.1 | Clinical neurophysiology

All three patients showed the presence of conduction block mainly in lower limbs, two of them mainly in the upper limbs. All the patients showed either an increase in latency of F wave or the dispersion and the decrease in amplitude of F wave. In two of them, we noted the presence of denervation signs related to the marked decrease amplitude of peroneal and tibial nerve suggesting axonal damage. After 4 months, all patients showed a recovery of the amplitude of compound action potential and a recovery of latency and amplitude of F wave. The EMG showed a normal pattern with mild signs of reinnervation in one patient.

4 | DISCUSSION

This report confirms elevated interleukins levels (IL-6 and IL-8) in both serum and CSF during the acute phase of COVID-19 neuropathies patients, while in the recovery phase, only IL-8 remained elevated. Although in two of the three patients, the onset of the neurological signs fulfilled the time criteria for a postinfectious GBS, in one patient it is not possible to precisely determine this onset due to the prolonged intubation. This finding is consistent with the current evidence that the overproduction of inflammatory cytokines may lead to severe forms of COVID-19, increased risk of multorgan failure, and eventually, death, and the decrease of cytokines response is associated with clinical recovery. As such, the polyneuropathies observed in our patients may be considered as part of a
possible systemic overactive parainfectious inflammatory response, often reported as the "cytokine storm." Indeed, IL-6 and IL-8 resulted markedly increased in serum and CSF, with a CSF/serum ratio greater than 1 during the acute phase, suggesting the presence of an acute inflammatory process specifically targeting the nervous system. Interleukins IL-6 and IL-8 are inflammatory cytokines with wide-ranging biological effects via several types of cells (lymphocytes, monocytes, macrophages, vascular endothelial cells, smooth muscle cells, and fibroblasts), and might have a prognostic role in COVID-19 disease.25,72 IL-8 is a potent neutrophil chemokine known to have a role in inflammation and host defense. Previous studies showed that the CSF/serum IL-8 ratio was increased in GBS as compared to chronic neuropathies, such as the chronic inflammatory demyelinating polyneuropathy, thus it has been proposed as a possible biomarker of acute immune reaction against the nervous system.21,22 Serum levels of IL-8 have been consistently found increased in patients with mild and severe COVID-19, although there was not a clear correlation with the disease severity.25 In contrast, a possible association between serum IL-8 levels and disease duration has been suggested.23 Interleukin-6 levels suggest that neuroinflammation might play a critical role in the development of pathological pain.24

Indeed, nerve injury induced the elevation of IL-6 in close Dorsal Root Ganglia (DRG), but also in remote DRG, suggesting a general neuro-inflammatory reaction of the nervous system to local nerve injury.25 One limitation of the present report is the impossibility to compare CSF cytokines levels between COVID-19 neuropathies patients and non-COVID-19 neuropathies patients; indeed, due to the small sample, the authors feel that it might be incautious to propose differences between the different clinical conditions. Nevertheless, future studies are encouraged to assess these potential differences in larger samples of neuropathies with or without COVID-19, and whether IL-8 represents a prognostic marker of the disease.

Despite the exact mechanisms linking SARS-CoV-2 infection to neurological symptoms needing further investigation, it may be imprudent to exclude a direct penetration of the virus in the peripheral and central nervous system.26,27 Nevertheless, the pathogenic link between GBS and COVID-19 is still a matter of debate,28,29 with a possible influence of critical illness on neurological signs development.30 The neurophysiological examination was useful to detect subclinical findings and define the diagnosis of polyradiculoneuropathy, to start therapy with IVIG in the appropriate time useful to detect subclinical findings, better defining the diagnosis, and encouraging the start of the appropriate therapy with IVIG.17,31 Indeed, the clinical improvement after IVIG was successful in all the patients, although one of them showed only a partial rapid recovery of weakness which might be explained by the prolonged bed rest and intubation.32–34 In addition to the already recognized use of anti-IL-6 drugs (e.g., tocilizumab), new therapeutic approaches are considering the development and use of anti-IL-8 drugs (BMS-986253) to improve the health condition of individuals infected with COVID-19.35

In conclusion, this study reports the elevation and progressive changes of IL-6 and IL-8 in serum and CSF of patients with COVID-19 and peripheral nervous system complications, showing a specific pattern in relation to the clinical recovery, and encouraging the use of these biomarkers for a better prognosis of these patients.

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CONFLICT OF INTERESTS
The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS
Paolo Manganotti designed the study, collected and analyzed the data, and revised the manuscript. Giulia Bellavita collected and analyzed the data, and drafted the manuscript. Valentina Tommasini, Laura D’Acunto, and Martina Fabris collected and analyzed the data, and drafted the manuscript. Laura Cecotti, Giovanni Furlanis, and Lucia Bonzi collected the data and revised the manuscript. Arianna Sartori analyzed the data and revised the manuscript. Alex Buoiite Stella analyzed the data and drafted the manuscript. Valentina Pesavento designed the study, collected the data, and revised the manuscript.

DATA AVAILABILITY STATEMENT
Data associated with this manuscript are stored at the Clinical Unit of Neurology of ASUGI Trieste and available upon reasonable request to the corresponding author and following institutional and ethical board regulations.

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REFERENCES
1. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. J Clin Neurosci. 2020;77:8-12. https://doi.org/10.1016/j.jocn.2020.05.017
2. Uncini A, Vallat J-M, Jacobs BC. Guillain–Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry. 2020;91(10):1105–1110. https://doi.org/10.1136/jnnp-2020-324491
3. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain–Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol. 2020;1-38. https://doi.org/10.1007/s00415-020-10124-x
4. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurol Neurosurg. 2020;194:105921. https://doi.org/10.1016/j.clineuro.2020.105921
5. Manganotti P, Bellavita G, D’acunto L, et al. Clinical neurophysiology and cerebrospinal liquor analysis to detect Guillain–Barré syndrome and polyneuritis cranialis in COVID-19 patients: a case series. J Med Virol. 2021;93(2):766-774. https://doi.org/10.1002/jmv.26289
6. Manganotti P, Pesavento V, Buoiite Stella A, et al. Miller Fisher syndrome diagnosis and treatment in a patient with SARS-CoV-2. J Neurovirol. 2020;26:605-606.
7. Consonni M, Telesca A, Grazzi L, Cazzato D, Lauraia G. Life with chronic pain during COVID-19 lockdown: the case of patients with small fibre neuropathy and chronic migraine. NeuroL Sci. 2021;42(2):389-397. https://doi.org/10.1007/s10072-020-04890-9

8. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268-2270. https://doi.org/10.1056/NEJMoa2008597

9. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillian–Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence. Lancet Neurol. 2020;19:383-384. https://doi.org/10.1016/S1474-4422(20)30109-5

10. Hasan I, Saif L, Sharma K, Tengsupakul S, Sanchez O, Phaltas R, Maertens P, Guillian–Barre syndrome with COVID-19: a case report. J Med Virol. 2021;93:5437. https://doi.org/10.1002/jmv.25813

11. Lehmann HC, Hartung H-P, Kieseier BC, Hughes RAC, Miller Fisher syndrome with COVID-19: an observational multicentre study from two Italian hotspot regions. J Neurol Neurosurg Psychiatry. 2020. https://doi.org/10.1136/jnnp-2020-324837

12. Pusch E, Renz H, Skevaki C. Respiratory virus infection with COVID-19: an update review. J Clin Neurol. 2020;16(3):227-233. https://doi.org/10.2183/jcn.2020.16.3.227

13. Sellers SA, Hagan RS, Hayden FG, Fischer WA. The hidden burden of COVID-19: a systematic review and individual participant data meta-analysis. J Peripher Nerv Syst. 2020;25(4):335-343. https://doi.org/10.1111/jpns.12419

14. Kim JE, Heo JH, Kim HO, et al. Neurologiacal complications during treatment of Middle East respiratory syndrome. J Clin Neurol. 2017;13(3):227-233. https://doi.org/10.3988/jcn.2017.13.3.227

15. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm: what we know so far. Front Immunol. 2020;11:1446. https://doi.org/10.3389/fimmu.2020.01446

16. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-2629. https://doi.org/10.1172/JCI137244

17. Aziz M, Fatima R, Assay R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol. 2020;92(11):2283-2285. https://doi.org/10.1002/jmv.25948

18. Li L, Li J, Gao M, et al. Interleukin-8 as a biomarker for disease prognosis of coronavirus disease-2019 patients. Front Immunol. 2020;11:602395. https://doi.org/10.3389/fimmu.2020.602395

19. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020;8:46. https://doi.org/10.1016/S2213-2600(20)30216-2

20. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370. https://doi.org/10.1016/j.jcv.2020.104370

21. Sharma K, Tengsupakul S, Sanchez O, Phaltas R, Maertens P, Guillian–Barre syndrome with unilateral peripheral facial and bulbar palsy in a child: a case report. SAGE open Med case reports. 2019;7. https://doi.org/10.1177/2050313X19838750

22. Breville G, Lascano AM, Roux-Lombard P, Lalivé PH. IL-8 as a potential biomarker in Guillian–Barre Syndrome. Eur Cytokine Netw. 2019;30(4):130-134. https://doi.org/10.1684/ecn.2019.0436

23. Ma A, Zhang L, Ye X, et al. High levels of circulating IL-8 and soluble IL-2R are associated with prolonged illness in patients with severe COVID-19. Front Immunol. 2021;12:626235. https://doi.org/10.3389/fimmu.2021.626235

24. Zhou Y-Q, Liu Z, Liu Z-H, et al. Interleukin-6: an emerging regulator of pathological pain. J Neuroinflammation. 2016;13(1):141. https://doi.org/10.1186/s12974-016-0607-6

25. Brázda V, Klusáková I, Hradilová Šviženková I, Dubový P. Dynamic response to peripheral nerve injury detected by in situ hybridization of IL-6 and its receptor mRNAs in the dorsal root ganglia is not strictly correlated with signs of neuropathic pain. Mol Pain. 2013;9:42. https://doi.org/10.1186/1744-8069-9-42

26. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020. https://doi.org/10.1016/j.bbi.2020.104370

27. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11(7):995-998. https://doi.org/10.1021/acschemneuro.0c00122

28. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillian-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. J Neurol Neurosurg Psychiatry. 2020. https://doi.org/10.1136/ijnnp-2020-324837

29. Singh R, Shiza ST, Saadat R, Dawe M, Rehman U. Association of Guillian–Barre syndrome with COVID-19: a case report and literature review. Cureus. 2021;13(3):e13828. https://doi.org/10.7759/cureus.13828

30. Frithiof R, Rostami E, Kumlien E, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: a prospective study. Clin Neurophysiol. 2021. https://doi.org/10.1016/j.clinph.2021.03.016

31. Wakerley BR, Uncini A, Yuki N. Guillian-Barré and Miller Fisher syndromes—new diagnostic classification. Nat Rev Neurol. 2014;10(9):537-544. https://doi.org/10.1038/nrneurol.2014.138

32. Buoiête Stella A, Ajičevič M, Furlanis G, Manganotti P. Neurophysiological adaptations to spaceflight and simulated microgravity. Clin Neurophysiol. 2021;132(2):498-504. https://doi.org/10.1016/j.clinph.2020.11.033

33. Monti E, Reggiani C, Franchi MV, et al. Neuromuscular junction instability and altered intracellular calcium handling as early determinants of force loss during unloading in humans. J Physiol. 2021. https://doi.org/10.1113/JP281365

34. Arentson-Lantz EJ, English KL, Padlon-Jones D, Fry CS. Fourteen days of bed rest induces a decline in satellite cell content and robust atrophy of skeletal muscle fibers in middle-aged adults. J Appl Physiol. 2016;120(8):965-975. https://doi.org/10.1152/japplphysiol.00799.2015

35. Dallas M. Anti-interleukin-8 (anti-IL-8) for patients with COVID-19. NIH; 2020.