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RESEARCH ARTICLE

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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).[5,8–10] 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,[11,12] most frequently gastrointestinal (Campylobacter jejuni) or respiratory tract infections, including flu syndrome and pneumonia.[13,14] In coronavirus disease 2019 (COVID-19), a trigger for autoimmune reactions could be the release of a large amount of proinflammatory cytokines in an event known as "cytokine storm." Indeed, COVID-19 infection is accompanied by an aggressive inflammatory response the host immune response to the SARS-CoV-2 virus is hyperactive resulting in an excessive inflammatory reaction.[15]

Reports describing the immunological profile of critically ill patients with COVID-19 have suggested hyperactivation of the humoral immune pathway—including interleukin (IL)−6 and 8. IL-6, a chemokine, is an important biomarker of inflammation and has been shown in studies as an important predictor of severe COVID-19.[16] IL-6 is responsible for elevation of acute-phase reactants, such as C-reactive protein, serum amyloid A, fibrinogen, and hepcidin, and inhibition of albumin synthesis. The dysregulated production of IL-6 has been attributed to autoimmunity and chronic inflammation.[17] IL-8, a proinflammatory cytokine produced by blood cells and many types of tissue, might be increased in COVID-19, although its diagnostic and predictive role is still debated.[18]

This report describes a case series of three patients affected by COVID-19 who developed a spectrum of autoimmune polyneuropathies during hospitalization. The patients were monitored throughout the hospitalization, and the follow-up lasted 4 months after the first admission, until full recovery from neurological symptoms. Intriguingly, serum and cerebrospinal fluid (CSF) analyses, including interleukins measurements, revealed a characteristic pattern well aligned with the transition from the acute to the recovery phase.

2 | MATERIALS AND METHODS

This case series describes three patients admitted to the hospital affected by bilateral pneumonia due to SARS-CoV-2 infection from March to April 2020. Symptoms on admission were fever and cough, and in these 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.acns.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

TABLE 1 Demographic, clinical, and laboratory features of the patients

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[b]	18 Days	36 Days[a]	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/mm^3	Normal protein level (40 mg/dl); 1 cell/mm^3	Protein level 53 mg/dl; 2 cell/mm^3
	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	IL-1β: 0.2 pg/ml ↑	IL-1β: 0.5 pg/ml ↑	IL-1β: 0.2 pg/ml ↑
level[c]	IL-6: 113.0 pg/ml ↑↑↑	IL-6: 9.8 pg/ml ↑	IL-6: 32.7 pg/ml ↑↑
	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
			IL-2R: 1203.0 pg/ml
			IL-10: 4.6 pg/ml
			IP-10: 94.8 pg/ml
			INF-γ: 0.8 pg/ml
Follow up	IL-β: 0.2 pg/ml	IL-β: 0.7 pg/ml	IL-β: 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[d]	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
INFγ: 1.1 pg/ml	INFγ− 1.13 pg/ml	INFγ: 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[e]	IL-1β: 0.12 pg/ml	IL-1β: 0.1 pg/ml	IL-1β: 0.52 pg/ml
	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	

TABLE 1 (Continued)

Patient	1	2	3
		IL-2R: 24.6 pg/ml IL-10: 0.55 pg/ml IP-10: 60.8 pg/ml INF-γ: 0.63 pg/ml	
IL-8 CSF/serum ratio	1.1	1.74	2.39
Treatment of the neurological syndrome	IVIG cycle (0.4 g/kg for 5 days)	IVIG cycle (0.4 g/kg for 5 days)	IVIG cycle (0.4 g/kg for 5 days)
Other therapies	COVID-19 management included administration of hydroxychloroquine, oseltamivir, darunavir, methylprednisolone and tocilizumab	COVID-19 management included administration of hydroxychloroquine, lopinavir-ritonavir, methylprednisolone	COVID-19 management included administration of hydroxychloroquine, oseltamivir, darunavir, methylprednisolone,Tocilizumab, meropenem, linezolid, clarithromycin, doxycycline andfluconazole
Outcome	Improvement of tetraparesis	Minimal improvement of weakness	Progressive improvement

Abbreviations: COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; IL, interleukin; INF, interferon; IP-10, interferon-γ–inducible protein; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor nuclear factor.

[a]It is possible that symptoms appeared earlier in the course of the disease but were not evident as the patient was intubated and sedated.

[b]Days between early respiratory symptoms and neurological syndrome onset.

[c]Laboratory reference values for serum interleukins: IL-β: <0.001 pg/ml, IL-6: 0.8–6.4 pg/ml, IL-8: 6.7–16-2 pg/ml; TNF-α: 7.8–12.2 pg/ml, IL-2R: 440.0–1435.0 pg/ml, IL-10: 1.8–3.8 pg/ml, IP-10: 37.2–222.0 pg/ml, INF-γ: <0.99 pg/ml.

[d]Follow-up serum interleukin level: samples taken after 45 days (patient 1), 62 days (patient 2), 20 days (patient 3).

[e]Reference values for CSF interleukins were assumed equal to serum values, as standardized cut-off values are not yet recognized.

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 gr/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 multiorgan failure, and eventually, death,[19] 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 as 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.[17,20] 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.[18] 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 polyradiculonevritis, 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 Buoite 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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