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COVID-19

Post-COVID-19 longitudinally extensive transverse myelitis: is it a new entity?

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Abstract

Introduction To the best of our knowledge, here we present two post-COVID19 longitudinally extensive transverse myelitis (LETM) with atypical presentations

Case presentations A 44-year-old male who did not have any previous medical condition and a 73-year-old male foreigner who did not have any disease other than type 2 diabetes mellitus were admitted to our neurology clinic in the same period with similar clinical presentations of transverse myelitis. Upon admission, paraplegia and urinary-fecal incontinence were observed in their neurological examination. Neurological complaints had started within approximately 3–4 weeks following the resolution of the COVID-19 infection. Thoracic lower segment LETM was observed on spinal magnetic resonance imaging (MRI) in one of the patients, and long segment myelitis extending from the lower thoracic segment to the conus medullaris was observed in the other one. No significant diagnostic positivity was present in their diagnostic evaluation. In both cases, we assume a post-infectious etiology in terms of secondary immunogenic overreaction following COVID-19.

Conclusion Our patients improved with multiple treatments such as methylprednisolone, intravenous immunoglobulin, and plasmapheresis. Whether post-infectious myelitis behaves differently from other viral infections after COVID-19 is currently unclear. Long lag times appear to be a post-infectious neurological complication resulting from the host response to the virus.

Keywords COVID-19 · Transverse myelitis · Autoimmunity · Post-infectious

Introduction

COVID-19, a novel coronavirus, is an RNA virus that has been spreading rapidly since the first case reported in Wuhan, China, in December 2019. In March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic affecting more than 200 countries. Originally little was known about the mechanisms and pathophysiology of the disease. After a while, data on different aspects of the disease, such as symptoms, pathology, transmission, prevention, and management strategies, began to emerge. Pulmonary and cardiovascular complications had been the mainstay of SARS-CoV-2 studies until an alarming number of neurological complications began to be reported [1]. Neurological complications of COVID-19 have been reported in one-third of hospitalized patients [2]. Lots of COVID-19 cases with central nervous system, peripheral nervous system, or musculoskeletal system involvement have already been reported and the number of such cases keeps increasing day by day. Although it is still not clear, this infection probably leads to neurological and cerebrovascular events due to hypoxia, inflammation, and hypercoagulation [3].

The presence of reported COVID-19-associated immune-mediated neurological diseases has brought up an autoimmunity phenomenon triggered by this virus. However, neurological complications after recovery from SARS-CoV-2 infection are rare in the current literature. A very rare neurological complication of SARS-CoV-2 infection has been reported as transverse myelitis. Moreover, the development of transverse myelitis following total recovery from infection as a possible prolonged manifestation of COVID-19 has also been recently reported [4]. Here, we present cases of acute longitudinally extensive transverse myelitis (LETM) in two healthy individuals that developed within a month

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after complete recovery following SARS-CoV-2 infection. Could this picture be a new phenomenon induced by triggered autoimmunity?

Case presentations

Case 1

A 44-year-old man with no other previous medical condition was admitted to our neurology clinic in February 2021. Two months before his admission to our clinic, the patient's wife had a COVID-19 infection. The patient had remained in isolation with her but did not provide any polymerase chain reaction (PCR) sample for himself. He had flu-like symptoms, cough, and anosmia like his wife but did not use any medication for these symptoms. Symptoms associated with possible COVID-19 infection had resolved within 10 days. About a month after the resolution of the suspected COVID-19 infection, the patient's complaint of numbness in the bilateral toes started. The patient, whose complaints of paresthesia reached the umbilical level within a week and felt no urinary sensation, was applied to another neurology clinic. He was discharged from this clinic with vitamin B12 repletion, and no pathology was observed in the spinal magnetic resonance imaging (MRI) examination. In the following days, the patient developed bilateral lower extremity paralysis and urinary/fecal incontinence, and eventually, he began to be mobilized with a cane. Subsequently, he lost his ability to walk. The patient applied to our clinic 1 month after the onset of the first complaint. Upon admission, paraplegia was observed in his neurological examination. While bilateral lower limb proximal muscle strength was MRC grade 2 (Medical Research Council scale for muscle strength), bilateral distal muscle strength was 1. There was discriminative hypoesthesia under the umbilicus level. Deep tendon reflexes were pathologically increased in the lower extremities, and bilateral Achilles tendon clonus was present. Bilateral Babinski reflex was positive, and he had diffuse lower extremity spasticity. While brain imaging was normal, thoracal LETM was observed in spinal imaging (Fig. 1). A cerebrospinal fluid (CSF) examination was performed, and no significant diagnostic positivity was present. Additionally, no notable findings were found in the evaluation in terms of infectious and vasculitic processes. On the other hand, serum aquaporin-4 (Aq4) and myelin

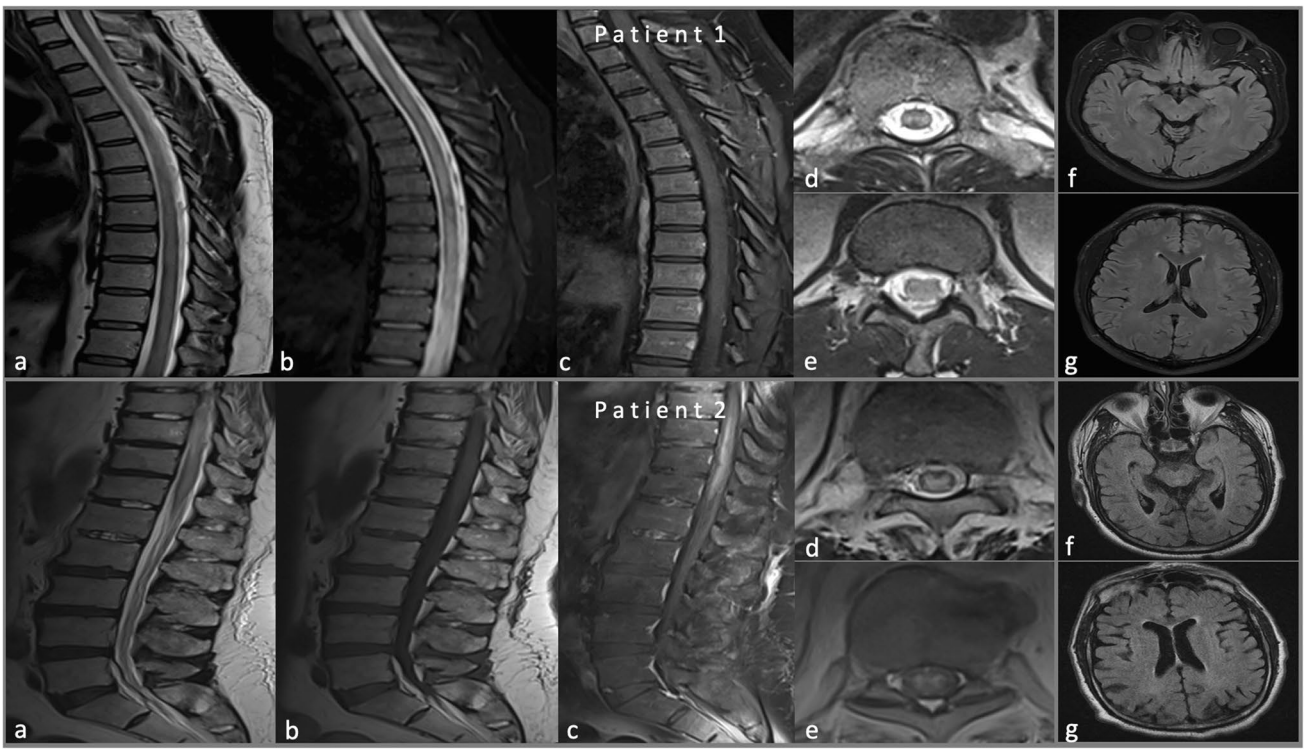

Fig. 1 Spinal and brain MR imaging of the patients. Patient 1 (upper row): sagittal spinal T2W (a), STIR (b), and axial T2W (d, e) images show a T2-hyperintense lesion centrally located and longitudinally extending from T5 to T12. Postcontrast sagittal spinal T1W image (c) does not reveal any contrast enhancement. Axial brain FLAIR (f, g) images reveal normal characteristics. Patient 2 (lower row): sagittal (a) and axial (d) T2W and sagittal pre-contrast T1W MR images demonstrate a T2-hyperintense lesion longitudinally extending along the lower thoracic cord segment involving conus medullaris. Postcontrast sagittal (c) and axial (e) T1W images demonstrate heterogeneous contrast enhancement of the cord lesion. Axial brain FLAIR (f, g) images reveal normal characteristics

oligodendrocyte glycoprotein (MOG) antibodies were also negative. All tests performed for diagnostic evaluation are shown in Table 1. Since the patient's history of COVID-19 was not proven, serum COVID-19 IgG was studied, and it was found to be positive in a high titer (anti-SARS-Cov2 (ECLIA)—82.97). Pulse steroid therapy (1000 mg intravenous methylprednisolone) was administered for 10 days with the diagnosis of COVID-19-associated LETM. After steroid therapy, partial improvement was observed in muscle strength and urinary/fecal incontinences were controlled. Considering that it may affect COVID-associated immune-mediated processes, human intravenous immunoglobulin (IVIG) treatment (0.4 mg/kg/day) was administered for 5 days following steroid therapy. After the treatment, his spasticity decreased, and incontinence resolved. He started to be mobilized with unilateral support and was discharged with an oral steroid reduction plan.

Case 2

A 73-year-old male foreigner, who did not have any health problems other than type 2 diabetes mellitus and did not use any medication additionally to oral antidiabetic agents, was admitted to our neurology clinic in February 2021. Two months before his admission to our clinic, the patient had applied to a hospital with flu-like symptoms and had been diagnosed with COVID-19 infection when the coronavirus RNA nasopharyngeal swab was reported positive, in the region where he lived. He had been followed in home isolation and had not used any additional drugs other than favipiravir and enoxaparin. He had pulled through COVID-19 infection within 10 days without any symptom of lung involvement. Three weeks after the resolution of COVID-19, the patient's complaint of paresthesia in bilateral toes started and subsequently progressed in an ascending way. The patient, whose paresthesia reached the umbilical level within 2 weeks, started to be mobilized with a cane and developed urinary/fecal incontinence; therefore, he applied to a neurology clinic in his region. Spinal and brain MRI was performed in the relevant center. While brain MRI is within normal limits, spinal MRI showed diffuse enhancing signal intensity from distal T8 thoracic segment to the conus spinales (Fig. 1). No significant diagnostic positivity was present in the patient, who underwent CSF examination and was additionally evaluated in terms of infectious and vasculitic processes. The patient was referred to us after 10 days of pulse steroid therapy (1000 mg intravenous methylprednisolone) with the suspicion of transverse myelitis. The patient did not describe any clinical improvement after steroid therapy. Neurological examination of the patient upon admission showed bilateral lower extremity proximal and distal muscle weaknesses (MRC grade 3) and there was a loss of sensation after T10 spinal segment. The patient's urinary and fecal incontinence were still present. For diagnostic evaluation, which is summarized in Table 1, CSF analysis, vasculitic tests, viral infectious parameters, and Aq4 antibody testing were repeated, and additionally, MOG antibody was studied. No significant diagnostic positivity was found. Since the patient had a history of COVID-19 infection, serum COVID-19 IgG antibody testing was performed, in which the anti-spike protein S1 domain targeted SARS-Cov2 IgG (ELISA) (2.23) test was positive. Ten sessions of plasmapheresis were applied to the patient who was presumed to have LETM associated with COVID-19. Clinical improvement was observed after the 3rd session, and the patient was discharged with an oral steroid reduction plan when bilateral lower extremity muscle strength was MRC grade 4 and he had total urinary control.

Table 1 Diagnostic evaluation of patients

Case 1	Case 2
Serum anti-SARS-Cov2 (ECLIA)—82.97	Serum SARS-Cov2 IgG (ELISA)—2.23
Aq4 antibody: negative	Aq4 antibody: negative
Anti-MOG: negative	Anti-MOG: negative
Protein (CSF): 39 mg/dL	Protein (CSF): 58.9 mg/dL
IgG index (CSF): 0.48	IgG index (CSF): 0.51
Oligoclonal band: negative	Oligoclonal band: negative
Infectious markers: negative	Infectious markers: negative
(serum and CSF analysis for Borrelia, Brucella, Syphilis, Tuberculosis, Herpes Simplex virus, Toxoplasma, Varicella Zoster virus, Rubella, Rubeola, Cytomegalovirus, Epstein-Barr virus, Measles and CSF culture*)*	*(serum and CSF analysis for Borrelia, Brucella, Syphilis, Tuberculosis, Herpes Simplex virus, Toxoplasma, Varicella Zoster virus, Rubella, Rubeola, Cytomegalovirus, Epstein-Barr virus, Measles and* CSF culture*)*
Vasculitis markers: negative	*Vasculitis markers: negative*
[serum analysis for rheumatoid factor (RF), anti-nuclear antibody (ANA), Anti-neutrophil cytoplasmic antibodies (ANCA), anti-double stranded DNA (dsDNA), extractable nuclear antigen (ENA) antibodies, angiotensin-converting enzyme (ACE), lupus anticoagulants]	*[serum analysis for rheumatoid factor (RF), anti-nuclear antibody (ANA), Anti-neutrophil cytoplasmic antibodies (ANCA), anti-double stranded DNA (dsDNA), extractable nuclear antigen (ENA) antibodies, angiotensin-converting enzyme (ACE), lupus anticoagulants]*
Thorax CT: no diagnostic finding for collogen tissue diseases	Thorax CT: no diagnostic finding for collogen tissue diseases

Discussion

Transverse myelitis (TM) characterized by acute or subacute onset spinal cord dysfunction due to inflammation is heterogeneous and non-compressive myelopathy. There is a wide variety of potential etiologies. The most common ones can be broadly classified as para-infectious/post-infectious, toxin/drug-induced, paraneoplastic, autoimmune disorders, and acquired demyelinating diseases [5]. Despite all diagnostic evaluations, 60% of TM can still be idiopathic, meaning that the exact pathophysiology of the disease is unknown and varies according to etiology [6].

In our report, we presented two cases of post-infectious myelitis that could be a neurological complication of COVID-19. Given the onset of symptoms in the two confirmed COVID-19 cases, as well as significant improvement with steroids and plasma exchange, this picture is likely to be an autoimmune-mediated response to the novel coronavirus. Since the autoimmune phenomenon triggered by COVID-19 was considered in the foreground of the diagnosis, the differential diagnosis process of the cases from acquired demyelinating diseases should be meticulously carried out. However, visual or neurological signs and symptoms due to brain stem, cerebellar, or hemisphere dysfunction, which are classically seen in demyelinating diseases, were not observed in our cases. Moreover, both immunoglobulin G autoantibodies for Aq4 and MOG and oligoclonal bands that are the immunological distinguishing features of these diseases were not detected. Neuromyelitis optica spectrum diseases (NMOSD) is also one of the diseases to be kept in mind in situations of acute myelitis. According to the international consensus diagnostic criteria for NMOSD without Aq4 antibody, normal features in the brain MRI and failure to provide at least two of the necessary core clinical characteristics (optic neuritis, acute syndromes of brainstem, area postrema, cerebellum, or diencephalon) have led us to avoid the diagnosis of NMOSD [7]. Likewise, no evidence was found regarding the manifestation of autoimmune collagen tissue diseases. After detailed diagnostic evaluation, we assume a post-infectious etiology in terms of secondary immunogenic overreaction in our cases. Similarly, microorganisms, including mycoplasma pneumoniae, Epstein-Barr virus, cytomegalovirus, rhinovirus, and measles, play a role in post-infectious acute myelitis [8]. Nowadays, one possible hypothesis is that infectious organisms are targeted by the immune system, which also attacks the central nervous system (CNS) tissue due to structural similarities between microbial cell wall components and neuronal receptors [9].

Neurological complications throughout SARS-CoV-2 infections were initially based on the theory of the direct viral invasion of the CNS [10]. Later, it was also hypothesized that SARS-CoV-2, which binds strongly to the angiotensin-converting enzyme 2 (ACE2) receptors, can trigger neuronal damage through hypoxic and immune-mediated pathways [11]. Although SARS-CoV-2 genome sequences, which could not be examined for technical reasons in our cases, are often undetectable in CSF, recent studies suggest that blood–brain barrier integrity may be impaired in these patients [12, 13]. Despite the direct viral invasion theory into the CNS, indirect involvement of the CNS via the viral-mediated immune response seems plausible. Autoimmunity mediated by excessive cytokine release, cross-reactivity between CNS components, and viral particles may lead to CNS damage [14]. Recent evidence suggests that induced autoimmunity mediated by SARS-CoV-2 can be responsible for most of the CNS disorders. Furthermore, autoimmunity mediated by the cross-reaction between viral particles and myelin basic protein may be a driving force for neural demyelination resulting in acquired atypical demyelinating diseases [15].

In a paper reviewing the cases, the latency from the onset of COVID-19 symptoms to the first neurological symptoms followed a dual distribution, and 68% of the cases experienced TM-related symptoms over a period of 10 days to 6 weeks after COVID-19 infection [4]. Supporting the literature, our cases have experienced TM-related symptoms in 5 or 6 weeks after COVID-19 infection, respectively. In another review article that compiles the spinal cord disorders caused by the SARS-CoV-2 virus in detail, 33 reported cases were seen. While 17 of them had LETM on neuroimaging, 3 cases were accepted as also part of acute disseminated encephalomyelitis syndrome. While an increase in lymphopenia and/or inflammation markers was observed in more than half of these cases, in a similar number of cases, inflammatory changes occurred in the CSF evaluation [16]. In addition, cases of acute necrotizing myelitis and encephalomyelitis have been published following COVID-19 [17, 18]. Our cases differ with the severe, longitudinally extensive transverse myelitis and anatomically related symptoms with no observation of any inflammatory pattern in CSF analysis. These findings seem important to highlight the atypical course of COVID-19-related LETM cases. Additionally, one of our cases improved with a rapid response to steroid treatment while the other has improved by plasmapheresis revealing individual differences in COVID-19-mediated immunity.

Interestingly, atypical clinical presentations, the response to immune therapies, and the devastating severity of neurological involvement, even in cases without systemic involvement, suggest that an autoimmune phenomenon mediated by the virus may underlie the neurological symptoms. When the whole information obtained is evaluated, it seems to be possible to speculate about an autoimmune phenomenon triggered by COVID-19 infection. Although the individualized

response shown by immunity creates an atypical and variable case spectrum, as the number of cases accumulating in the literature increases, it would create a picture with its own characteristics.

Conclusion

Although the incidence of acute myelitis associated with COVID-19 infection is unknown, similar cases attributing COVID-19 to acute myelitis as a neurological complication continue to be reported. To the best of our knowledge, here, we present two post-COVID LETM with atypical presentations. It seems post-COVID-19 CNS autoimmunity is a possible concern after the initial presentation of COVID-19 infection. More evidence appears to be needed to understand the pathogenesis and subsequent neurological sequelae of active or new infections with SARS-CoV-2.

Declarations

Ethical approval and Informed consent Written consent of the patients have been taken. The article process was carried out in accordance with the Declaration of Helsinki. The presented paper is a case report.

Conflict of interest The authors declare no competing interests.

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