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Short Communication

COVID-19-related encephalopathy presenting with aphasia resolving following tocilizumab treatment

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ABSTRACT

Encephalopathy is emerging as a recurrent complication of COVID-19 yet remains poorly characterized. We report the case of a middle-aged woman with COVID-19-related encephalopathy presenting as expressive aphasia and inattentiveness, subsequently progressing to agitation and marked confusion. Brain MRI and CSF analysis were unremarkable, while EEG showed slowing with frontal sharp waves. Neuropsychiatric symptoms resolved following treatment with tocilizumab.

CNS involvement in COVID-19 may present as a subacute encephalopathy characterized by prominent frontal lobe dysfunction, with language disturbances as first neurological manifestation. Future studies should further investigate the role of tocilizumab in treating COVID-19-related encephalopathy.

1. Introduction

Coronavirus disease 2019 (Covid-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Guan et al., 2020). The disease is characterized predominantly by respiratory symptoms and encompasses a broad spectrum of severities. A subgroup of COVID-19 patients develop cytokine release syndrome (CRS), an aberrant host immune response that may exacerbate lung damage and lead to multiple organ dysfunction (Moore and June, 2020).

Neurological manifestations of COVID-19 are being increasingly reported, including a spectrum of encephalitis with distinguished underlying pathogenic mechanisms. Among well-known entities such as acute disseminated encephalomyelitis, limbic encephalitis and acute necrotizing encephalopathy, SARS-CoV-2 may cause viral encephalitis secondary to CNS invasion and, notably, a type of encephalopathy that appears related to cytokine-mediated neuroinflammation (Piloto et al., 2020; Muccioli et al., 2020; Beach et al., 2020; Koralkin and Tyler, 2020). This has not been clearly phenotyped thus far, however it appears characterized by altered mental status ranging from mild confusion to delirium, language disturbances including akinetic mutism, as well as other various CNS manifestations (Koralkin and Tyler, 2020).

Tocilizumab, an anti-interleukin (IL)-6 receptor antibody, has shown efficacy in treating systemic manifestations of CRS associated with COVID-19 (Price et al., 2020; Xu et al., 2020), yet its role in the management of associated CNS manifestations remains unclear.

Here we report a middle-aged woman with COVID-19-related encephalopathy presenting with expressive aphasia and inattentiveness, subsequently progressing to severe encephalopathy, resolving following treatment with tocilizumab. Written informed consent for publication was obtained from the patient.

2. Case report

An otherwise healthy 47-year-old pediatrician presented with a five-day history of asthenia and rhinorrhea, which developed into ageusia, hyposmia, inattentiveness, and language disturbance characterized by anomia, agrammatism and sporadic semantic paraphasias. These were evident in Italian, the patient’s second language, which she used in her everyday life. In the following days, concentration difficulties progressed and were accompanied by burning pain in the extremities, dry cough, fever, severe frontal headache, and eventually dyspnea, leading to hospitalization 15 days after symptom onset [Fig. 1A]. At admission, she was febrile (38 °C) and had mild respiratory failure, treated with low-flow oxygen therapy.
demonstrated bilateral interstitial pneumonia and a nasopharyngeal swab was positive for SARS-CoV-2. Blood tests showed lymphopenia, thrombocytopenia, and slightly elevated D-dimer, ferritin, LDH, CRP and IL-6 levels. Soon after hospitalization, the patient progressively became agitated and markedly confused, with fluctuating severity. Neurological examination did not uncover any further focal neurological deficits. At the time this was performed, however, the patient’s mental status did not allow a formal testing of language or other neuropsychological functions. EEG revealed slowing of the background posterior dominant rhythm with frontal sharp waves [Fig. 1B]. Brain MRI showed mild T2 hyperintensity in bilateral parietal and posterior periventricular white matter [Fig. 1C]. CSF examination demonstrated 7 leukocytes/μL, normal protein levels, oligoclonal bands (pattern 3) and negative RT-PCR for SARS-CoV-2. CSF and serologic antibodies against neuronal intracellular and cell surface antigens tested negative. She was treated with tocilizumab (400 mg), resulting in marked improvement of her neuropsychiatric symptoms within the first 24 h, and resolution within 2 days. Oxygen-therapy was progressively weaned off, and the patient
was discharged asymptomatic on the 11th hospital day. She only vaguely recalls what happened during the first days of hospitalization. At a follow-up visit performed after two months, neurological examination and EEG were unremarkable, and the patient was asymptomatic.

3. Discussion

Our patient presented with expressive aphasia and inattentiveness as the earliest CNS symptoms, subsequently progressing to marked confusion and agitation. Brain MRI revealed non-specific white matter hyperintensities, ruling out structural lesions which could justify neuropsychological manifestations. The altered mental status might have been caused also by non-convulsive status epilepticus, a clinical condition already associated with COVID-19 (Le Guennec et al., 2020), yet was excluded by the EEG, which showed diffuse slowing with frontal sharp waves, a finding frequently reported in COVID-19-related encephalopathy (Galanopoulou et al., 2020; Pasini et al., 2020). Aphasia was accompanied by manifestations consistent with dysexecutive syndrome and behavioral symptoms, suggesting a frontal lobe dysfunction. The latter is emerging as a recurrent feature of COVID-19-related encephalopathy (Cani et al., 2020; Helms et al., 2020; Koralnik and Tyler, 2020) and it is possible that the language disturbances observed in our patient as well as in previous reports are secondary to this network's dysfunction. CSF analysis showed a slightly increased cellularity and negative PCR for SARS-CoV-2. Even though these findings cannot rule out CNS viral invasion with certainty, we believe more likely an immunomediated para-infectious pathogenic mechanism underlying the neurological manifestations of our patient, also according to the emerging evidence supporting an inflammatory, cytokine-mediated, pathogenesis in a subset of patients with COVID-19-related encephalopathy (Beach et al., 2020; Cani et al., 2020; Muccioli et al., 2020; Pilotto et al., 2020). The relationship between the disclosed oligoclonal bands in the present report and COVID-19 remains unclear.

Our patient developed early neurological manifestations, while respiratory distress was mild and occurred later in the disease course, hence, it is unlikely that hypoxemia significantly contributed to encephalopathy pathogenesis.

Our patient recovered following treatment with tocilizumab, an immunotherapy which has shown efficacy in treating COVID-19-related CRS (Price et al., 2020; Xu et al., 2020). Interestingly, another patient with COVID-19-related encephalopathy with elevated CSF inflammatory markers and concomitant respiratory distress recovered following treatment with tocilizumab (Farhadian et al., 2020).

As COVID-19-related encephalopathy may have a self-limited course even without a specific therapy (Beach et al., 2020; Cani et al., 2020; Bernard-Valnet et al., 2020), it is possible that clinical recovery in our patient occurred spontaneously. However, taking into account the clear relationship in time, neuropsychiatric symptoms may have resolved as a consequence of treatment with tocilizumab. Serum levels of IL-6 increased dramatically following tocilizumab administration, which is to be expected due to formation of tocilizumab-soluble IL-6 receptor complex (Nishimoto et al., 2008). Unfortunately, we were not able to assess IL-6 levels in CSF as well as other cytokines in both serum and CSF, in order to correlate disease course with cytokines levels following tocilizumab treatment.

Considered that the long-term outcome of COVID-19-related encephalopathy is currently unknown and that associated clinical manifestations may be severe, immunotherapy should be considered in these subjects; specifically, tocilizumab may be useful for COVID-19 patients with CRS and concomitant encephalopathy.

4. Conclusion

We showed that COVID-19-related encephalopathy may present as prominent frontal lobe dysfunction, with language disturbances as the first neurological manifestation. In our patient, neuropsychiatric symptoms resolved promptly following treatment with tocilizumab. Whether this therapy may represent an effective treatment option for COVID-19-related encephalopathy, in addition to CRS induced by SARS-CoV-2, should be confirmed in future studies.
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