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Neuropsychiatric presentation of Covid-19-related encephalitis: Case report

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ABSTRACT
Covid-19-related encephalitis is a heterogeneous syndrome characterized by a combination of clinical, laboratory, and imaging features related to inflammation of the brain, where the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is presumably the causative agent. We reported a case of Covid-19-related encephalitis presenting with neuropsychiatric symptoms, including intense agitation. Reverse-transcriptase polymerase-chain-reaction in cerebrospinal fluid was positive for SARS-CoV-2. Our case expands the literature about neurologic manifestations of Covid-19 and emphasizes the possibility of prominent behavioral symptoms as the initial manifestation.

1. Introduction
Covid-19, the infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a range of typical clinical manifestations, including cough, fever, myalgias, gastrointestinal symptoms, and anosmia (Gandhi et al., 2020). Several neurologic manifestations have been described since late 2019, when a global pandemic started, increasing the burden of the disease (Asadi-pooya, 2020; Chen et al., 2021; Hassett et al., 2020). Neuropsychiatric manifestations have also been described, including a range of psychopathologies such as depression, anxiety, psychosis, suicidal ideation, insomnia, and delirium (Nal- leballe et al., 2020; Taquet et al., 2021). Uncommon presentations of Covid-19 with encephalitis were recently reported (Pilotto et al., 2021), including limbic encephalitis (Bhagat et al., 2021; Chiveri et al., 2021). We report Covid-19-related encephalitis, confirmed by reverse-transcriptase polymerase-chain-reaction (RT-PCR) in cerebrospinal fluid (CSF), presenting with severe agitation.

2. Case report
A 52-year-old man was present in an outpatient neurologic office with a 3-day history of acute onset cognitive impairment characterized by impaired attention, forgetfulness, and difficulties with word-finding. Concomitantly, he developed aggressiveness and psychomotor agitation. He also had a new-onset generalized tonic-clonic seizure. He had contact with family members infected with Covid-19 in the previous 15 days. His past medical history was unremarkable. During the evaluation, the patient became agitated, with increased aimless motor activity and verbal and physical aggressiveness. He was unconcerned about the use of a facemask and became distressed when confronted by his family. During the office evaluation, he needed to be restricted to avoid aggression toward the physician. In-hospital investigation with 1.5T MRI revealed a normal-appearance brain imaging (including medial temporal lobe and other limbic structures - Fig. 1). CSF analysis showed a mild lymphocytic pleocytosis. CSF RT-PCR was positive for SARS-CoV-2 (Table 1). The electroencephalogram was normal. After a few days, cognitive impairment and neuropsychiatric features progressed. The patient evolved to a decreased level of consciousness. He developed dyspnea with rapid evolution to severe respiratory failure due to lung injury. The patient died due to pulmonary complications after three days of intensive care unit admission (10 days after the beginning of his illness). An autopsy was not performed.

3. Discussion
We reported a case of encephalitis due to Covid-19 with positive CSF RT-PCR for SARS-CoV-2, in which agitation was the first symptom. Encephalitis is characterized by a combination of clinical, laboratory, and imaging features related to brain inflammation (Graus et al., 2016). Proposed criteria for possible autoimmune encephalitis might be used as
The involvement of the central nervous system in SARS-CoV-2 is characterized by a combination of clinical, laboratory, and imaging features. Proposed diagnostic criteria for limbic encephalitis require abnormal medial temporal lobe imaging (Graus et al., 2016). However, CSF RT-PCR is the gold standard to detect CNS involvement in Covid-19 (Bellon et al., 2020).

SARS-CoV-2 affects the brain through different mechanisms, including direct brain invasion inducing systemic pro-inflammatory cytokines that surpass the blood-brain barrier (cytokine storm). Also, neurotransmitter system dysfunction, brain vascular injury, thrombotic events, and neuronal damage are possible pathophysiological events. All mechanisms may be associated with a myriad of neuropsychiatric symptoms (Boldrini et al., 2021). The finding of positive CSF RT-PCR in our patient is consistent with CNS direct invasion. Several mechanisms have been proposed, including penetration of the olfactory mucosa and transsynaptic migration along the olfactory tract, inflammation-induced breakdown of the blood-brain barrier or entrance via monocytes ("Trojan-horse" mechanism), or via circumventricular organs (midline structures around the third and fourth ventricles, where the capillaries have a wall devoid of the blood-brain barrier) (Boldrini et al., 2021; Paterson et al., 2020; Zubair et al., 2020).

Limbic system involvement probably occurs even in mild to moderate Covid-19 (Douaud et al., 2021). Limbic encephalitis was also reported (Bhagat et al., 2021; Chiveri et al., 2021). Proposed diagnostic criteria for limbic encephalitis require abnormal medial temporal lobe imaging (Graus et al., 2016), which was not present in the reported patient. Therefore, our case cannot be labeled as “limbic encephalitis. Nevertheless, the severe agitation presented by our patient possibly indicated the involvement of the limbic system (Cummings et al., 2015), even without imaging abnormalities in the limbic system, and is in line with other neuropsychiatric manifestations reported in the literature.

4. Conclusion

COVID-19 related encephalitis is a heterogeneous syndrome characterized by a combination of clinical, laboratory, and imaging features related to brain inflammation, where the SARS-CoV-2 is presumably the causative agent. As the pandemic persists and the number of infected subjects increases, knowledge about CNS involvement of the SARS-CoV-2 also increases. Our case report of COVID-19-related encephalitis presenting with prominent neuropsychiatric symptoms (agitation) and a positive CSF RT-PCR for SARS-CoV-2 expands the literature about the relationship between SARS-CoV-2 and CNS involvement.

Author statements

Marco Orsini: Conceptualization, Methodology; Data curation, Writing- Original draft preparation. Fabio Porto: Conceptualization, Methodology; Writing- Original draft, Writing- Reviewing and Editing. Jacqueline Fernandes do Nascimento: Writing- Original draft preparation.

Table 1

| Parameter          | Result      | Reference value   |
|--------------------|-------------|-------------------|
| Color              | Colorless   | Colorless         |
| Aspect             | Clear       | Clear             |
| Total proteins     | 60 mg/dl    | Adults: 15–45 mg/dl |
|                    |             | Adults >60 anos: 15–60 mg/dl |
| Albumin            | 22 mg/dl    | 10–30 mg/dl       |
| Glucose            | 53 mg/dl    | 50–80 mg/dl       |
| Chlorides          | 117 mmol/l  | 115–130 mmol/l    |
| L DH               | 21 U/l      | 0–25 U/l          |
| Glutamine          | 17 mg/dl    | 15–20 mg/dl       |
| Leukocytes         | 8/µl        | 0–5U/µl           |
| Differential cytology |           |                   |
| Lymphocytes        | 50%         | 50% ± 20%         |
| Monocytes          | 12%         | Monocytes: 30% ± 15% |
| Neutrophil         | 4%          | Neutrophils: 2% ± 4% |
| Opening pressure   | 120         | 100–180           |
| Cellularity        | 8 cells/mm3 | 0–4 cells/mm3     |
| Virus              | Sars-CoV-2 Positive       | Negative |
| Mycobacteria       | Negative    | Negative          |
| Fungi              | Negative    | Negative          |
| Protozoa           | Negative    | Negative          |
| Spirochetes        | Negative    | Negative          |

Fig. 1. T2-weighted coronal MRI at the level of amygdalae (A) and hippocampal formations (B) showing typical appearing limbic structures.
