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Posterior reversible encephalopathy syndrome – A pathology that should not be overlooked in the era of COVID-19

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ABSTRACT

Background and objectives: Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) that causes Coronavirus Disease 2019 (COVID-19) may determine a series of neurological complications directly, by invasion of the nervous system or indirectly, secondary to systemic organ failure. Posterior reversible encephalopathy syndrome (PRES) represents a clinical and radiological neurological entity involving predominantly the occipital lobes. PRES was observed in patients receiving cytotoxic drugs, patients suffering from infectious diseases and sepsis, hypertensive emergencies and eclampsia, renal or autoimmune diseases. As more infectious SARS-COV-2 variants are now dominant in most of the Europe, an increasing number of patients is presenting to the Emergency Department.

Materials and methods: Case report of a 38-year-old patient, with previous exposure to SARS-COV-2 presented to the Emergency Department (ED) with generalized tonic-clonic seizures, dyspnea, cortical blindness and aphasia. The patient had been exhibiting fever, cough and shortness of breath in the previous 10 days. He had no relevant medical history and was receiving antibiotics and corticosteroids as prescribed by his general practitioner.

Results: Laboratory findings together with the thoracic computed tomography scan were consistent with the diagnosis of severe SARS-COV-2 pneumonia. The cerebral MRI scans showed bilateral T2-weighted/FLAIR hyperintensities that were suggestive for PRES. The patient was diagnosed with COVID-19 complicated with PRES. He received adequate treatment and the symptoms resolved in 48 h.

Conclusions: This is a rare and interesting case of a patient with PRES and COVID-19 as underlying pathology, in whom rapid diagnosis in the ED and early initiation of appropriate treatment led to full recovery. Immediate extensive work-up in patients with COVID-19 and neurological symptoms proves to be paramount for best outcome. To our knowledge this is the first case of PRES described in a patient with Delta variant of SARS-COV-2.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) represents a clinical and radiological neurological entity with severe complications in 40% of cases. Patients frequently report visual disturbances, but other focal neurological signs and symptoms may be present as well [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) that causes Coronavirus Disease 2019 (COVID-19) may determine neurological complications either by direct invasion of the nervous system or secondary to failure of different organs. Although the virus affects primary the lungs, severe cases are accompanied by multiorgan dysfunction [2]. As more infectious SARS-COV-2 variants are now dominant in most of the Europe, an increasing number of patients is presenting to the Emergency Department.

The aim of this paper is to present a rare case of a young patient with COVID-19 who was diagnosed with PRES during the peak of the pandemic in our country. To establish the etiology of the patient's symptoms different laboratory tests were performed in the ED. It was certified that the patient suffered from SARS-COV-2 infection with subsequent serious complications that required urgent therapeutical measures.

2. Case presentation

A 38-year-old male patient presented to the ED for language impairment and a generalized tonic-clonic seizure. Subtle changes in his

Abbreviations: COVID-19, Coronavirus Disease 2019; CT, Computed tomography; ED, Emergency Department; MRI, Magnetic resonance imaging; PRES, Posterior reversible encephalopathy syndrome; SARS-COV-2, Severe acute respiratory syndrome coronavirus 2.

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behavior had been observed by the family in the last 4 days prior to his presentation to the ED, namely periods of confusion and agitation alternating with periods of somnolence. The patient had been quarantined following exposure to a COVID-19 infected family member in the last 14 days and and for the last 10 days he had fever, cough and shortness of breath for which he had taken antibiotics, corticosteroids and aspirin under the guidance of his primary care physician. The patient had a normal weight and he had medical history of *Helicobacter Pylori* infection, hepatic steatosis, occasional alcohol consumption and no significant medical family history.

At the ED the patient exhibited fluctuating level of consciousness ranging from mild somnolence to agitation, and he was dyspneic, with peripheral oxygen saturation of 90% (corrected using low-flow oxigenotherapy, 1-2 l/min) and blood pressure of 130/80 mmHg. The neurological examination revealed cortical blindness (absent blink to visual threat in all four quadrants of the visual field and present pupillary light reflex) and mixed aphasia (he exhibited no spontaneous speech apart from a swear word that he repeated continuously, did not understand verbal commands and was unable to name any objects during confrontation naming, or to repeat words or phrases, read or write). Meningeal signs were absent.

Serial imaging scans were performed: a non-contrast cerebral CT scan performed immediately after the ED presentation, a contrast enhanced cerebral CT scan performed in the first 8 h of admission and also another non-contrast cerebral CT scan repeated at 3 days after the ED presentation, all of these showed no abnormalities. The thorax CT scan done immediately after presentation showed typical COVID-19 radiological pattern with a total severity score of severe involvement.

Laboratory findings depicted inflammatory syndrome and hypercholesterolemia. The RT-PCR test for SARS-COV-2 from the nasopharingeal swab was positive. A spinal tap was done. The cerebrospinal fluid (CSF) analysis revealed an erythrocyte count of 145/mm^3, leukocyte count of 3/mm^3, proteins 52,4 mg/dl, albumin 30,7 mg/dl, glucose 73 mg/dl. The microbiology examination of the CSF showed no bacteria on Gram and Ziehl-Neelsen stains. The RT-PCR for SARS-COV-2 from CSF was negative.

Due to the unavailability of performing cerebral MRI scans in the first days of his admission, the patient underwent the examination 3 weeks after the resolution of his symptoms. It revealed slight symmetrical T2-weighted/FLAIR occipital hyperintensities (Fig. 1 and Fig. 2), corresponding to vasogenic edema in the resolution phase, suggestive for PRES, as vasogenic edema can persist on cerebreal MRI scans days to weeks after the resolution of symptoms.

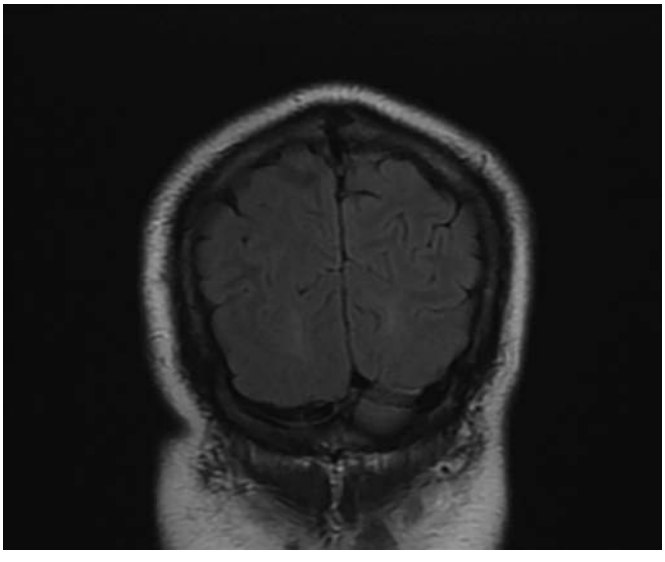

Fig. 1. Cerebral MRI - coronal FLAIR sequence showing slight hyperintensities in the occipital lobes.

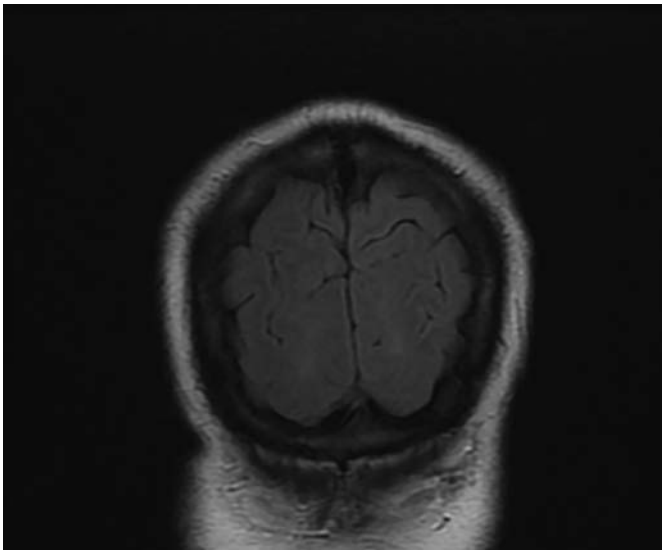

Fig. 2. Cerebral MRI - coronal FLAIR sequence revealing slight hyperintensities in the occipital lobes.

Routine, short-term, electroencephalography (30 min recording) performed after the resolution of symptoms revealed generalized high-amplitude delta and theta waves disrupting the normal posterior-anterior gradient of dominant alpha rhythm. The EEG trace revealed no ictal or interictal epileptiform discharges. The presence of diffuse slowing, theta-delta waves, during wakefulness even though nonspecific (in this case for cortical blindness and/or aphasia), is suggestive for diffuse cerebral dysfunction. This result is in line with a PRES syndrome since the patient only presented seizures at presentation, no more than 24 h but there was a persistence of vasogenic edema on MRI at 3 weeks.

The diagnostic suspected was PRES favored by the COVID-19 infection. The patient was treated with Remdesivir, corticosteroids, antiseizure drugs (Levetiracetam 1000 mg/day), antibiotics and low-molecular-weight-heparin. In 48 h the patient's symptoms resolved and he was discharged and was scheduled for follow-up in order to evaluate if other treatment interventions are needed.

An informed consent was obtained concerning the publication of this case report.

3. Discussion

PRES was observed in patients receiving cytotoxic drugs, or with infectious diseases and sepsis, hypertensive emergencies and eclampsia, renal or autoimmune diseases [1].

Our patient presented with typical acute manifestation for PRES like generalized tonic-clonic seizures and visual impairment, but also with mixed aphasia mimicking a left middle cerebral artery stroke, excluded by the CT and CT angiography scans. All other causes of PRES, except COVID-19, were excluded. There are studies that pinpoint endothelial dysfunction as a crucial factor in the physiopathology of PRES, recent evidence suggesting that SARS-COV-2 directly infects the endothelial cells inducing diffuse inflammation [3]. As there are various patterns of vasogenic oedema involvement of the central nervous system, patients with PRES may present non-specific symptoms. Current literature suggests that 28–94% of patients with PRES present with encephalopathy of varying severity ranging from mild confusion to coma but focal neurological signs like aphasia are documented in only one fifth of the cases. One uncommon presenting symptom which was also observed in our patient is agitation [4].

The link between prior corticosteroid treatment and the development of PRES is yet to be established. Studies pinpoint that as the risk factors for developing PRES include autoimmune disorders, bone

marrow and solid organ transplantation, cancer, sepsis many patients with PRES associate prior corticosteroid treatment (medium range-6 days). It is unclear at this point whether there is a strong association between corticosteroid treatment and the development of PRES because these conditions are already associated with inflammatory endothelial disfunction. Also, corticosteroids are a risk factor for developing hypertension that can precipitate PRES [5]. Moreover there are case reports in literature that describe a rapid resolution of severe PRES symptoms at patients that received corticosteroids [6]. In the case of our patient, he had received corticosteroids 3 days prior to the ED admission, but also during the in-hospital stay due to the severe COVID-19 pneumonia. Our patient did not present hypertension neither at presentation, nor during the in-hospital stay.

Hyperglicemia (with or without diabetes mellitus) has been incriminated in several cases in literature to precipitate PRES due to endothelial dysfunction caused by excessive circulating inflammatory cytokines [7]. Our patient presented with postprandial (approximately 3 h) blood glucose of 130 mg/dl and did not suffer from diabetes. Repeated blood glucose levels and glycated hemoglobin were normal.

Hypoxia can also determine cortical blindness, seizures, altered consciousness and other neurologic deficits due to brain cells ischemia. Exposure to mild hypoxia rapidly induces an increase in cerebral blood flow due to cerebral vasodilation of small arteries and even large intracranial and extracranial arteries when oxygen blood saturation (SaO2) is less than 80% [8]. Our patient monitored daily his blood oxygen saturation at home during his COVID-19 quarantine and admitted that only in the morning before the admission his SaO2 was abnormal, 86%. At ED admission the measured SaO2 was 90%, but it quickly normalized with low-flow oxygenotherapy. Moreover, repeated CT brain scans and the brain MRI did not reveal lesions in the hippocampus, the dorsolateral caudate nucleus and the reticular nucleus of thalamus, areas that are prone to hypoxic ischemia.

In the case of our patient imaging work-up and spinal tap with PCR for SARS-COV-2 performed in the ED excluded most of the neurological complications of COVID-19. COVID-19 patients may present neurological signs and symptoms that are still poorly understood and correspond to numerous pathophysiological mechanisms [9], varying from headache and hyposmia to severe neurologic manifestations secondary to cerebral venous thrombosis, ischemic or hemorrhagic stroke. These manifestations could be divided into five distinct categories: vascular, encephalopathies, inflammatory central nervous system (CNS) syndromes including encephalitis, peripheral nervous system involvement and miscellaneous CNS disorders [2].

Another possible cause for the patient's symptoms could be SARS-COV-2 encephalitis.

There are reported cases of SARS-COV-2 encephalitis with normal CSF exam including negative PCR for SARS-COV-2 [9], but the MRI excluded this diagnosis.

There are no specific diagnostic criteria for PRES. Usually, the clinical presentation along with the presence of risk factors and the absence of other possible causes, supported by the cerebral MRI suggest the diagnosis. In the case of our patient the SARS-COV-2 infection can be considered a possible risk factor, and the rapid resolution of symptoms with treatment and the absence of other brain CT or MRI findings apart from mild bilateral occipital vasogenic edema support the diagnostic of PRES.

For almost 25 years since PRES was first described, no specific treatment was identified except for the treatment of the underlying cause. The extent of the recovery is not very well defined, especially in SARS-COV-2 infected patients, post-mortem brain MRI studies revealing lesions compatible with PRES in patients who did not survive to COVID-19 [10]. Our patient received treatment for COVID-19 with rapid improvement of neurologic symptoms.

4. Conclusion

This is a rare and interesting case of a patient with PRES and COVID-19 as underlying pathology, in whom rapid diagnosis in the ED and early initiation of appropriate treatment led to full recovery. Immediate extensive work-up in patients with COVID-19 and neurological symptoms proves to be paramount for best outcome. To our knowledge this is the first case of PRES described in a patient with Delta variant of SARS-COV-2.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Availability of data and materials

All data were presented in the manuscript.

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Author's contribution

PI: study design, case management, literature research and writing of the manuscript; ACR: study design, case management, literature research and writing of the manuscript, critical revision of the first draft and final approval of the manuscript; OR: case management, literature research; IFB: case management, literature research; RSB: case management, literature research; AF: study design, case management, literature research and writing of the manuscript, critical revision of the first draft and final approval of the manuscript.

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Credit authorship contribution statement

Patricia Ioan: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Athena Cristina Ribigan:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Octaviana Rusu:** Visualization, Investigation, Data curation, Conceptualization. **Ionut Flavius Bratu:** Investigation, Formal analysis, Conceptualization. **Raluca Stefania Badea:** Visualization, Investigation, Formal analysis. **Florina Antochi:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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