CASE REPORT

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) AS A NEUROLOGICAL MANIFESTATION IN SEVERE COVID-19

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November 2020

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Case Report: Posterior Reversible Encephalopathy Syndrome (PRES) as a neurological manifestation in severe COVID-19 infection.

Introduction

The SARS-CoV-2 virus (severe acute respiratory syndrome-coronavirus 2) and the resultant Coronavirus disease 2019 (COVID-19) was first identified in 2019, and has subsequently spread into a world-wide pandemic (1). SARS-CoV-2 uses human cell receptor angiotensin-converting enzyme 2 (ACE2) as cellular entry point. ACE2 is expressed in airway epithelia, lung parenchyma, vascular endothelium, heart, kidneys and small intestine, which explains most of COVID-19 symptoms. As ACE2 is also present in glial cells and neurons of mammalian brain (2), SARS-CoV-2 is therefore considered to have potential neuro-invasiveness that might lead to acute brain disorders. The virus might enter the central nervous system through hematogenous dissemination or neuronal retrograde route, via e.g. olfactory bulbs or medullary neurons (3). The anosmia frequently observed supports this last theory. The neuro-invasiveness is also supported by case reports of meningo-encefalitis, intracerebral hemorrhage, ischemic strokes and secondary acute necrotizing encephalopathy. Central neurological symptoms as headache, stroke, impaired consciousness are also observed in COVID-19 patients (4, 5).

Posterior reversible encephalopathy syndrome (PRES) usually presents with acute impairment in level of consciousness, headache, visual disturbances and seizures. It is usually associated with cortical or subcortical vasogenic edema, involving predominantly the parietal and occipital regions bilaterally (5). The condition is commonly associated with fluctuation in blood pressure, renal failure, autoimmune conditions, infections and sepsis, preeclampsia or eclampsia and certain types of immunosuppressive-cytotoxic drugs (6). The pathogenesis of PRES remains controversial but there are various proposed mechanisms. It is thought to be related to hyper perfusion or vasospasm, with fluid extravasation through the blood brain barrier resulting in cortical or subcortical edema (1). It can be caused by endothelial injury related to abrupt blood pressure changes or direct effects of cytokines on the endothelium (7).

The key to diagnosis of PRES is neuro-imaging. Although computed tomography (CT) imaging allows for rapid assessment. it is not 100% sensitive. MRI is proven superior for diagnosis. Typical MRI findings in PRES are bilateral white-matter abnormalities in vascular watershed areas in the posterior regions of both cerebral hemispheres, affecting mostly the occipital and parietal lobes. Atypical features— including hemorrhage, asymmetrical changes, isolated involvement of the frontal lobes, and cortical lesions are common (8).

Case

A 61-year-old man with a medical history of treated arterial hypertension presented to the hospital 4 days after symptom onset which included shortness of breath and a general fatigue. A nasopharyngeal swab taken by his general practioner tested positive for SARS-CoV-2 nucleic acid. A chest CT scan taken at the emergency department showed bilateral multiple multilobar peripheral ground-glass opacifications highly suggestive for COVID-19 infection (Fig. 1). Due to moderate hypoxic respiratory failure (arterial pO2 of 50mmHg) he was admitted to a dedicated COVID-19 ward. Medical treatment consisted of Amoxicillin-Clavunalic Acid (1g every four hours for five days) and hydroxychloroquine (loading dose of 400mg, 200mg daily for the next four days). Due to increasing need of oxygen and hypoxic respiratory failure he was transferred to the intensive care unit (ICU) at day 5, with the need of mechanical ventilation on day 7. Bacterial respiratory surinfections occurred and antibiotic regimen was gradually upgraded from Cefepim to Pipperacilline-Tazobactam and finally to Meropenem. At day 35 a tracheostomy was performed to facilitate discontinuation of mechanical ventilation. He also developed acute renal failure requiring intermittent veno-venous hemodialysis.

At day 52 days an acute episode of altered consciousness occurred followed by multiple episodes of generalized tonic-clonic insults. He was treated with Valproate 500mg twice daily and Levetiracetam 1200mg once daily. Clinical investigation showed bilateral cortical blindness. A head CT scan showed posterior reversible ischemia, compatible with PRES. An MRI of the brain confirmed the diagnoses and showed confluent T2 hyperintensities without diffusion restriction and flair sequence showing symmetric parieto-occipital white matter edema (Fig. 2). At the time of diagnosis, there was only one case report published of transient cortical blindness in COVID-19 pneumonia, in a Chinese hospital . This was the first case in Europa found in literature (9).

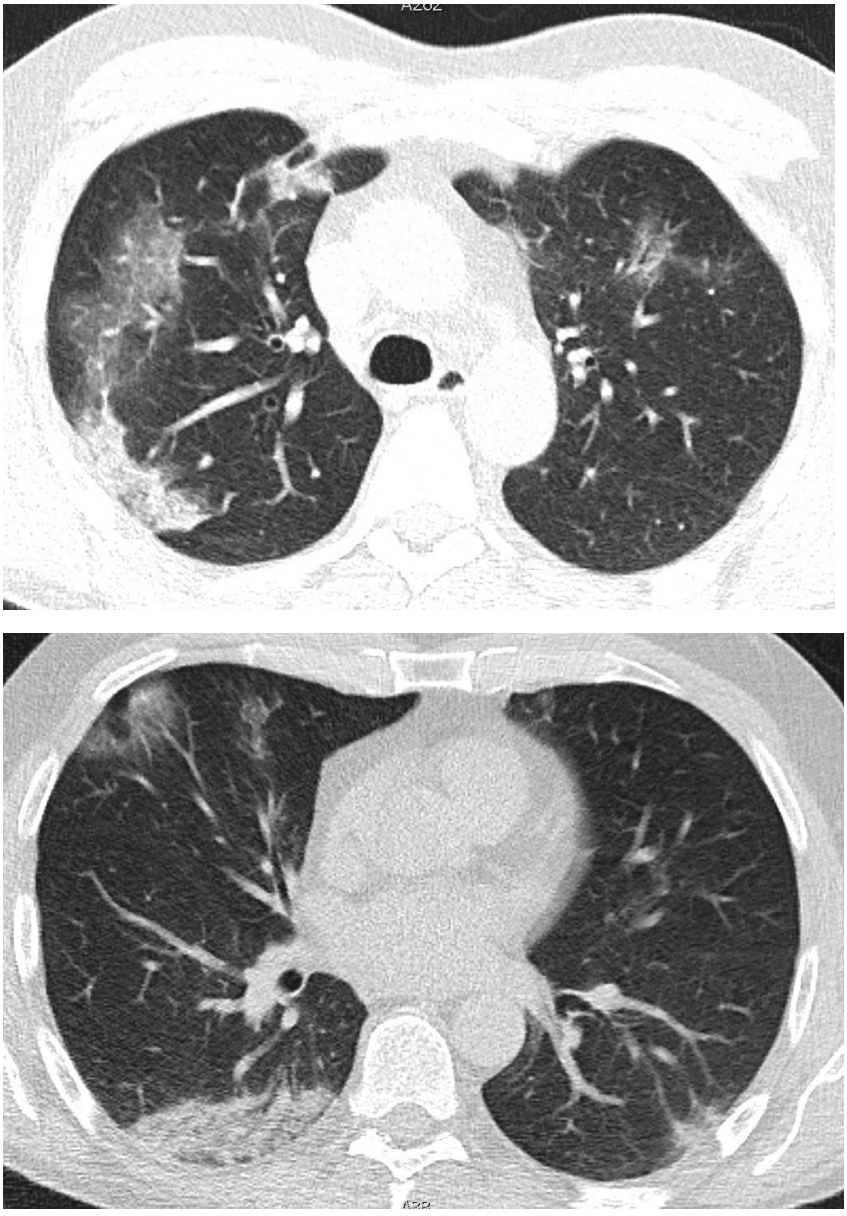
Hypertension and acute renal failure are two important risk factors to develop PRES. In this case report the patient was persistently hypertensive with systolic pressure above 200mmHg for days before the insult. Blood pressure control was managed with Moxonidine, Lisinopril, Losartan and Bisoprolol. The visus disturbances regressed completely within three days. No new incident of seizures under therapy with Levetiracetam occurred.

A follow-up MRI after one month was performed and showed complete regression of the bilateral cortical and subcortical parieto-occipital vasogenic edema.

The patient was discharged on day 96 to a rehabilitation facility with completely regressed neurological symptoms.

Imaging characteristics of the case

Fig 1. CT scan: showing bilateral multiple multilobar peripheral ground-glass opacifications.



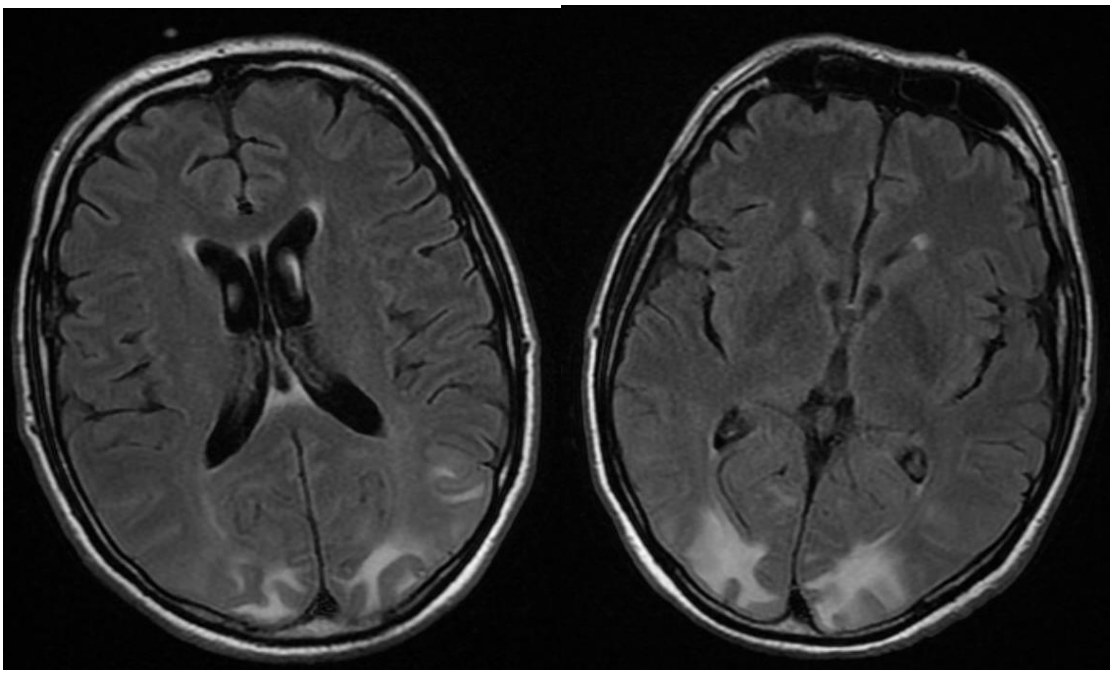


Fig. 2 Axial T2 FLAIR showed hyperintensity involving the subcortical white matter of both occipital lobes and posterior temporal lobe on the left, compatible with PRES.

Discussion

It is well described that SARS-CoV-2 infection is correlated with neurological symptoms (10). Of patients with COVID-19 infection, 57.4% developed some form of neurological symptom. Nonspecific symptoms such as myalgias (17.2%), headache (14.1%), and dizziness (6.1%) were mostly present in the early stages of infection. Anosmia (4.9%) and dysgeusia (6.2%) tended to occur early (60% as the first clinical manifestation) and were more frequent in less severe cases. Disorders of consciousness occurred commonly (19.6%), mostly in older patients and in severe and advanced COVID-19 stages. Myopathy (3.1%), dysautonomia (2.5%), cerebrovascular diseases (1.7%), seizures (0.7%), movement disorders (0.7%), encephalitis (n=1), Guillain-Barré syndrome (n=1), and optic neuritis (n=1) were also reported. Neurological complications were the main cause of death in 4.1% of all deceased study subjects (6).

There are several case reports describing PRES in Covid-19 patients (1, 9, 11). Endothelial dysfunction related to SARS-CoV-2 in combination with hemodynamic instability and immunological activation with release of cytokines, may increase the vascular permeability in the brain tissue. Disruption of BBB may cause vasogenic edema and PRES (1).

There can be an attribution of direct entry and invasion of the SARS-CoV-2 virus in the olfactory bulb and surface ACE2 targets on vascular endothelial cells. This binding may cause an increase in blood pressure along with weakening of the endothelial layer leading to a weakened blood-brain barrier, which may result in dysfunction of the brain's autoregulation of cerebral circulation (12).

In a prospective, monocentric, case series study, the occurrence of structural brain abnormalities in non-survivors of COVID-19 was investigated on post-mortem (<24h) MRI. The postmortem brain MRI demonstrated hemorrhagic and PRES-related brain lesions (7).

The patient described here had a prolonged intubation period with fluctuating blood pressures, which potentially impaired his cerebral autoregulatory threshold and may have therefore been at higher risk of consequences of uncontrolled hypertension such as hypertensive encephalopathy and PRES due to endothelial dysfunction. Regulating the blood pressure and controlling the pneumonia have helped for the full recovery.

In the setting of an emergency department it's important to keep in mind that the neurological disorders, such as seizures, visual impairment, could be the more predominant symptom in COVID-19 infection. At the ward or ICU, diagnosis is mostly highly suspected or confirmed so the measurements are taken. At the emergency department it's important to be alert and think about possible (infectious) diseases in order to protect all health workers with adequate personal protective equipment.

Further research is needed to confirm the mechanisms underlying SARS-CoV-2 invasion and its resultant neurological effects. Due to the potential for SARS-CoV-2 to directly and indirectly affect the nervous system, physicians should be aware of these atypical neurological presentations in COVID-19 patients.

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