COVID-19 encephalitis as a differential diagnosis of a Cyclosporine related Posterior Leukoencephalopathy Syndrome (PRES)

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Abstract

PRES is a rare neurological disease possibly associated with the use of calcineurin inhibitors like cyclosporine A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is responsible for the outbreak of coronavirus disease 19 (COVID-19) and can cause neurological manifestations. We describe a case of CSA-related PRES whose diagnosis was difficult due to concurrent infection with SARS-CoV-2. The 16-year-old patient was known to have corticosteroid-resistant nephrotic syndrome secondary to minimal change disease. CSA was therefore introduced and on the fifth day of treatment, he presented with seizures followed by fever. Biological and MRI data were in favor of SARS-CoV-2 encephalitis. Relief of immunosuppression by discontinuation of CSA was decided and the patient was put on anticonvulsants. After being declared cured of COVID-19, which was without other clinical signs, the CSA was reintroduced but the patient presented with seizures the next day. This allowed us to rectify the diagnosis and relate the seizures to a CSA-related PRES. We concluded that infection with SARS-CoV-2 could be a differential diagnosis of a PRES related to anticalcineurins.

Introduction

PRES is a serious neurological disorder of (sub) acute onset characterized by abnormalities in cerebral white matter. Clinical symptoms may include headaches, visual disturbances, disorders of consciousness, seizures, or focal neurological deficits [1]. PRES develops frequently in the context of cytotoxic medication, (pre) eclampsia, sepsis, renal disease, or autoimmune disorders [1].

Among drugs, PRES may complicate calcineurin inhibitors such as cyclosporine A (CSA). Organ-transplanted patients and those with nephrotic syndrome on this drug have reportedly experienced this complication [2, 3, and 4].

This article reports a unique and challenging case of a 16-year-old boy admitted to our department with steroid-resistant nephrotic syndrome (NS) and COVID-19 in February 2022. SARS-CoV-2 infection misled the diagnosis of CSA-induced PRES.

Case Report

The patient is a 16-years-old Tunisian boy known for nephrotic syndrome related to a minimal change disease diagnosed based on a renal biopsy in October 2021. In February 2022, he was admitted to the Nephrology department for a corticosteroid-resistant NS with severe adverse events of glucocorticoids (Cushing syndrome, glaucoma, and dyslipidemia).On clinical examination, the boy's weight was 75 kg, his height was 1.68m, and he was afebrile and had no respiratory symptoms. His blood pressure was 130/70 mmHg with a heart

rate of 80 beats per minute. He also had lower limb edema related to his nephrotic syndrome. Regarding his corticosteroid nephrotic syndrome, we decided to start CSA treatment at a dose of 3mg/kg/day with progressive tapering of corticosteroids.

On the fifth day of CSA start, the patient presented two short left clonic focal seizures with a duration inferior to two minutes. After one minute, he had a third motor focal onset seizure with secondary generalization and conscious alteration. The recovery of consciousness was after 30 minutes. Apart from a high CRP, biological tests were in the normal range and could not explain these symptoms (Table 1). Intravenous sodium valproate was initiated quickly and we have not objectified a new seizure. The cranial magnetic resonance imaging (MRI) showed leptomeningeal enhancement with a predilection in the cerebellar hemispheres (Figure 1). The cerebrospinal fluid (CSF) analysis shoIntravenouswed normal cellularity with hyperproteinorachia (0.71g/l) (Table 2) and the CSF bacterial culture was negative. In the meantime, the patient experienced sinus tachycardia, with one episode of fever. Therefore, we decided to perform nasopharyngeal RT-PCR for SARS-CoV-2since the patient was in contact with a COVID-19 subject. The test returned positive.

Although the RT-PCR for SARS-CoV-2in the CSF was negative, the data from the MRI and the CSF analysis, along with the positivity of the nasopharyngeal RT-PCR for SARS-CoV-2, led to the diagnosis of secondary encephalitis to SARS-CoV-2infection. As a result, we decided to discontinue CSA, being immunosuppressive, during the infectious period.

For the next ten days, the patient showed no recurrence of the seizure, did not require oxygen therapy, and did not present any new symptoms. After a second nasopharyngeal swab for SARS-CoV-2 that was negative, the patient was declared cured. The analysis of the CSF of a second lumbar punction analysis showed normal cellularity with normal glycorrhachia and proteinorachia. The patient was discharged with a maintenance oral dose of sodium valproate. Two weeks later, the patient had not experienced any recurrence of neurological symptoms and he had a persistent severe nephrotic syndrome. Therefore, we decided to restart CSA treatment. Despite being under an anti-epileptic drug, the patient experienced generalized tonic-clonic seizure one day after the immunosuppressant resumed treatment. This allowed us to rectify the diagnosis and relate the seizures to the CSA. A second cranial MRI (Figure 2) showed a progression of the previous lesions and the appearance of new cortical and subcortical hyperintensities in axial FLAIR- weighted and diffusion in the biparietal and right frontal lobe with an exaggerated meningeal gadolinium enhancement in front of these lesions. Imaging, as well as clinical data and the causal link with the taking of the treatment, the diagnosis of CSA-induced PRES, was retained. As an alternative to CSA, we opted for Rituximab at a dose of 1g per dose (two doses spaced two weeks apart) with good clinical and biological tolerance.

Discussion

Herein we reported the case of a 16-year-old boy whose treatment by CSA for a corticoresistant nephrotic syndrome was complicated by a PRES. The diagnosis of CSA-related PRES was challenging since it was initially mistaken for COVID-19 encephalitis.

The primary pathophysiological process of PRES, first described by Hinchey et al. in 1996 [5], was identified as vasogenic edema that denotes fluid extravasation from intracerebral capillaries [3]. It is believed that the underlying cause of PRES may create a breakdown in cerebral autoregulation, leading to the leakage of fluid into the brain parenchyma. In these patients, either passive over distension of the vessels due to elevations in blood pressure or direct toxic effects on the endothelium [6] blunt the myogenic response.

The consequent symptoms are variable ranging from confusion headache, nausea vomiting, and visual disturbance, to encephalopathy, and seizures associated with transient lesions on neuroimaging [7].

CSA was found to be efficient in decreasing proteinuria in both steroid-dependent and steroid-resistant nephrotic patients and is now largely used in nephrology [8]. The association of PRES with CSA use has been previously described in NS patients, with successful recovery after drug withdrawal [3, 9, and 10]. Although the exact prevalence has not yet been determined**,** 5.7% of pediatric patients with nephrotic syndrome who received cyclosporine developed PRES during the previous series of observations [3]. Cyclosporine

is responsible for a direct endothelial dysfunction resulting in a release of endothelin, prostacyclin, and thromboxane. These factors may cause microthrombi and damage the blood-brain barrier [5]. In the presence of altered permeability, CSA may overcome the blood-brain barrier and enter the brain. In one study, the entrance of CSA into the brain inhibited gamma-aminobutyric acid neurotransmission in rats, resulting in convulsions [11].

It is worth mentioning that NS itself may be a predisposing factor for developing PRES in both adults and children [3]. In addition to CSA, Other factors seen in the nephrotic state could induce vasogenic edema due to decreased intravascular oncotic pressure, increased permeability of intracerebral capillaries, and fluid overload. Furthermore, children with hypertension, high-dose steroid treatments, hypercholesterolemia, high proteinuria levels, and low serum albumin levels are at a higher risk of PRES [13]. Our case had all these risk factors mentioned above. On the other hand, he also presented another possible explanation for seizures and PRES: SARS-CoV-2 infection. Indeed, SARS-CoV-2has recently been admitted to be a potential cause of PRES [14, 15]. There are two possible explanations in this context. Firstly, SARS-CoV-2 is known to cause endothelial dysfunction. Furthermore, the virus binds directly to the angiotensin-converting enzyme 2 (ACE2) receptors causing an increase in blood pressure along with the weakening of the endothelial layer. Consequently, this leads to a weakened blood-brain barrier, which may result in dysfunction of the brain's autoregulation of cerebral circulation [15]. The prevalence of PRES in COVID-19 patients is estimated to be between 1–4% [16].

However, the resumption of seizures directly after reinitiating of treatment made it possible to incriminate CSA as the cause of PRES in the reported case.

Considering all of this, we believe that CSA and SARS-CoV-2 infection may have synergistic neurologic toxic effects in our case. Therefore, this may explain the short period between the treatment initiation and the symptom installation. As reported in the literature, this period can range from one week to as long as 26 months [5, 17]. Our patient experienced neurological manifestations four days after CSA initiation and was diagnosed with COVID-19 on the same day of symptoms onset.

On another hand, we wonder if CSA had a protective effect against SARS-CoV-2 in the reported case. Indeed, although he was immunosuppressed, he did not present with a severe form of infection. That may be explained by the capacity of CSA to inhibit the replication of several different coronaviruses in vitro, as demonstrated by several independent studies [18].

The MRI is the gold standard exam to confirm PRES. It shows high-density signals in the white matter, especially in the occipital or temporal area [7]. This preference distribution may be due to the paucity of sympathetic innervation in this vascular territory [10]. In addition to parieto-occipital involvement, high signal intensity areas may be seen in the frontal lobe in up to 82% of patients [11]. Involvement of the anterior circulations and regions other than the parieto-occipital lobes like the cerebellum (34.2%) is, therefore, common [19]. In this case, occasionally called atypical PRES.

Conclusion

Through this observation, we come to two conclusions. Firstly, infection with SARS-CoV-2 could be a differential diagnosis of a PRES related to anticalcineurins. Nevertheless, it is essential to establish the correct diagnosis because management depends on it. Secondly, CSA would be a protective factor against infection by SARS-CoV-2 and its cessation would not be justified during infection by this virus.

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