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Tacrolimus Associated Posterior Reversible Encephalopathy Syndrome (PRES): About a case

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Abstract

The Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome, it may occur due to a number of causes, including the use of immunosuppressive treatments. It is a rare entity. We report here the occurrence of a PRES syndrome in a patient treated with tacrolimus after liver transplantation, revealed by ocular manifestations associated with intermittent headaches of moderate intensity and tremor in the hands later complicated by a condition epilepticus. The brain scan showed an occipital hematoma in resorption and a lumbar puncture with normal pressure measurement. The brain MRI had objectified on the FLAIR sequence an evocative aspect of reversible posterior encephalopathy in the posterior occipital and parietal territory. Antiepileptic treatment was introduced and tacrolimus was replaced by ciclosporin, given the strong presumption of its involvement in the occurrence of this PRES, with good evolution. The prognosis of PRES is generally favorable under treatment, with a risk of serious sequelae in case of delayed diagnosis justifying that this syndrome must be evoked in front of neurological manifestations in a patient on tacrolimus.

Keywords: PRES syndrome-tacrolimus-calcineurin, Inhibitor-posterior, Reversible encephalopathy syndrome.

INTRODUCTION

The use of Calcineurin inhibitors led to major advances in the field of transplantation with excellent short-term outcome. However, neurotoxicity is among the main effects, and the PRES syndrome is the most severe form.

The posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by neurological symptoms such as headache, convulsions, cortical blindness, focal neurologic deficit, with MRI of the brain often revealing hyperintensities on T2 and FLAIR especially at the parieto-occipital lobes.

We report here one case of PRES syndrome in a patient who is under tacrolimus treatement after liver transplantation. There is no therapeutic consensus of the treatement of this complication. And the pathogenic mechanism remains poorly understood.

Observation

32-year-old patient, followed since 2004 for cirrhosis secondary to Budd Chiari syndrome on agenesis of the inferior hepatic vena cava extended over 12 cm, in ascitic and hemorrhagic decompensation under ligation protocol with multiple hospitalizations for management of a digestive restorative hemorrhage from which the liver transplantation was indicated.

Patient underwent orthotopic liver transplantation on 22/11 / 2017. Prophylaxis of rejection was based on the standard protocol: triple immunosuppression by an association of anticalcineurin (ACN) (tacrolimus (Prograf)), mycophenolate mofetil (Cellcept) (MMF)) and corticosteroids.

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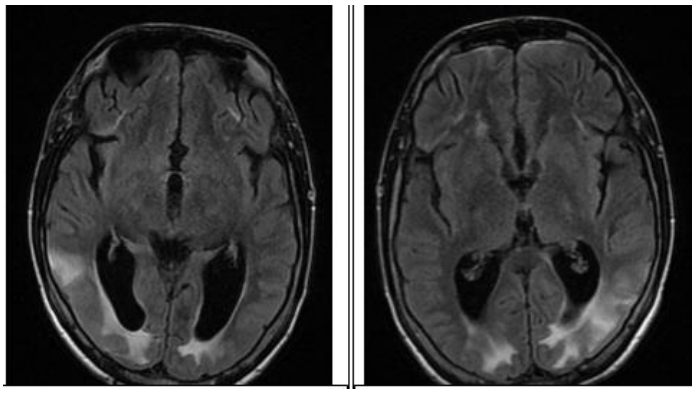
The postoperative course was marked by the occurrence of seizures with frontal syndrome + drowsiness. A cerebral CT showed a parieto-occipital hematoma with cerebral edema without any surgical indication. The patient was put on antiepileptic treatment with a good clinical evolution. During his hospitalization, the patient presented ophthalmic manifestations like diplopia with photophobia and myopia associated with moderate intermittent headache with hand tremor and initially correct blood pressure. Residual tacrolimus dosage was slightly elevated (20ng / ml).

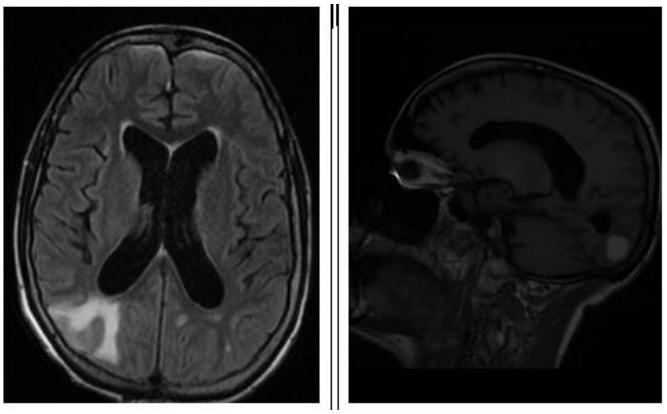
An ophthalmologic examination was done, showing a slightly atrophic papilla probably related to an intracranial hypertension from which the realization of a cerebral CT that showed an occipital hematoma in resorption, and a lumbar puncture with measurement of the pressures was normal. (a correct liver function and a correct ionogram).

The MRI showed high signal foci in the occipital lobes, the left partial lobe evoking posterior reversible encephalopathy syndrome (PRES). The use of ciclosporin was proposed but, in view of the non-availability of the product and the improvement of the neurological signs after, a drop in the dose was made. The patient was declared outgoing under tacrolimus, mycophenolate mfetil1g * 2 / d and under Sodium valproate 500mg * 2 / d.

At 3 months from transplantation,the patient was admitted to the emergency room in a status epilepticus with cluster seizures despite benzodiazepines administrated intravenously at 2 times where he was placed on clonazepam and then on phenobarbital. Because of the profound alteration of consciousness (GCS to 7) and the occurrence of respiratory distress, the patient was intubated and ventilated then a control imaging (CT) was redone showing an increase in hypodensity in the occipital and parietal region. A monitoring of the blood pressure was instituted, objectifying 150/90 and 140/90 mmHg blood pressure figures. Given the strong presumption of involvement of tacrolimus in the PRES syndrome occurrence and the severity of the clinical symptoms, Tacrolimus was replaced by cyclosporine with initiation of corticosteroids while waiting to reach the therapeutic dose of cyclosporine with rapid dose decrease.

Currently, the patient is asymptomatic on cyclosporine (Seizures were controlled with low-dose antiepileptic. 7 months after transplantation, the patient had no more episodes of seizure with correct liver function)





- Photo A, B, C: Fluid-Attirated Inversion Recovery (FLAIR) sequence showing high signal foci in occipital lobes, left parietal lobe suggestive of posterior reversible encephalopathy syndrome (PRES)
- Photo D: T1 sequence showing an occipital hematoma of 17 mm.

Figure 1: Cerebral MRI

DISCUSSION

- Tacrolimus is an immunosuppressive agent commonly used after organ transplantation. It belongs to the group of calcineurin inhibitors, which has been shown to be very effective in preventing acute rejection after solid organ transplantation. However, many side effects have been described, neurotoxicity and nephrotoxicity are its main undesirable effects. The syndrome of reversible posterior encephalopathy (PRES) is the most serious and dramatic consequence of the neurotoxicity of calcineurin inhibitors [1]. Other minor neurological side effects have been reported as insomnia, symptoms visual, headache, tremor, paresthesia and mood disorders are more common, occurring in up to 40% of transplant patients [2].
- The incidence of PRES syndrome following solid organ transplantation was estimated in old studies between (1% and 6%); other more recent studies estimated it at 0.49% [1]. However, Wong *et al* reported that the incidence of tacrolimus-induced PRES is about 1.6% [10].
- The exact pathophysiological mechanism is not yet known and remains controversial at present [12]. Two theories have been developed [14, 15]:
    - The most common theory is that of hypertension exceeding the limits of cerebral autoregulation, resulting in cerebral hyper-perfusion with vascular alteration and development of cerebral edema. This theory is supported by the blood pressure elevation frequently found in PRES and the rapid resolution of signs as early as the management of hypertension. Nevertheless, many PRES syndromes occur without any elevation of blood pressure or with minimal elevation.
    - The second theory favors cerebral vasoconstriction secondary to arterial hypertension or a systemic process. This phenomenon of self-regulation leading to a decrease in cerebral perfusion and therefore vasogenic edema.

The syndrome of reversible posterior encephalopathy brings together a set of nonspecific neurological manifestations: an impairment of consciousness (somnolence, confusion, coma), seizures, visual disturbances, memory problems, nausea and vomiting,Or focal neurologic signs [5].

In imaging, posterior reversible encephalopathy is characterized by abnormalities of the white and the grey matter, which preferentially affect the posterior regions [4, 19]. In computed tomography (CT), the lesion is marked by diffuse hypodensity, In this case, cerebral CT showed hypodensity in the occipital and parietal region (Figure 2).

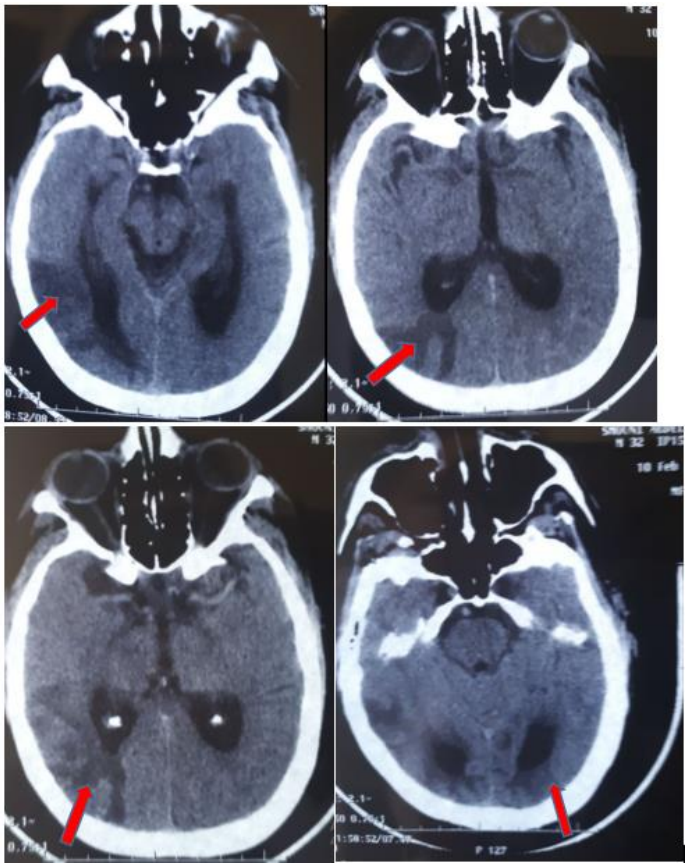


Figure 2: CT scan: showing occipital and parietal hypodensity more marked on the left (red arrow)

At the MRI, the lesions appear in iso signal or hypo signal T1 and hypersignal T2 and FLAIR. There is usually no enhancement after injection of contrast [4].

The distribution of lesions is suggestive of imaging, and is most commonly affected (98%) in the classical posterior region (parietal or occipital lobe). Further localizations can be observed, such as frontal lobes (68%), temporal lobes. (40%) and cerebellar hemispheres (30%) [3]. Complicating forms with cerebral haemorrhages were described in 19% of cases in the form of Subarachnoid haemorrhage or intra-parenchymal haematomas [18], as the case of our patient who had an hematoma who had been shown on imaging (Figure 2photo D).

The diagnosis of reversible posterior encephalopathy is based on a combination of clinical symptoms and imaging findings, particularly on magnetic resonance imaging (MRI) which is considered as the gold standard examination. In our patient, the PRES syndrome was retained on the typical localization of brain MRI lesions (Figure 1) and clinical manifestations on a predisposed ground (organ transplant under immunosuppressant).

Only early diagnosis makes it possible to start a suitable treatment before the installation of irreversible lesions [7]. The PRES syndromes secondary to calcineurin inhibitors may have occurred even with a residual level in the therapeutic range [20]. It can be improved either by lowering the dose of the drug in question or by stopping this medication. Although the switch to another calcineurin inhibitor represents a therapeutic alternative [2, 6], as in our case where the patient was put on ciclosporin in front of the strong presumption of his involvement in the occurrence of this PRES especially that the blood pressure figures not exceed the upper limit of self-regulation of cerebral arterial pressure (150-160 mm Hg). The evolution in the case of our patient was favorable with total regression of visual disturbances and hand tremors as well as control of seizures**.**

A delay in diagnosis and treatment can lead to permanent sequelae that affect the brain tissue, with a risk of very important neurological sequelae [8, 9]. In the majority of patients a complete recovery is obtained but in 10.7% recovery with sequelae has been reported as the persistence of impaired alertness; decreased visual acuity, epilepsy, amnesia, hemiparesis; unedysarthrie; and abnormalities of the visual field [11]. Although the prognosis of PRES syndrome is favorable in the majority of the cases, a mortality rate variable according to the ranges of 11 to 36% (all etiologies taken together) has been reported [13, 16, 18] In cases complicated by the occurrence of convulsive seizures, the interruption of convulsive states is a very important step in the therapeutic management, because patients who have convulsions with repetitions have a higher risk of cerebral ischemia and therefore, to develop irreversible sequelae.The treatment of the state of convulsive illness is based on intravenous benzodiazepines in first intension (clonazepam or diazepam), if the status epilepticus persists with long-acting antiepileptics (phenobarbital or fosphenytoin). In cases of refractory status epilepticus, the use of anesthetic agents (propofol, thiopental or midazolam) may be necessary [17].

CONCLUSION

The posterior reversible encephalopathy syndrome is a recently individualized complication. Its diagnosis is radio-clinical. The prognosis is generally favorable under therapeutic management adapted, with a risk of serious sequelae in the case of delayed diagnosis thus justifying thinking about this syndrome in the case of neurological manifestations in a patient under Tacrolimus with appropriate and early management.

Declaration of interests: The authors declare that they have no conflict of interest in relation to this article.

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