

Atypical Posterior Reversible Encephalopathy Syndrome Imaging on Liver Transplant Patients

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Abstract

The Posterior Reversible Encephalopathy Syndrome (PRES) is a known clinical entity that presents as changes on neurological images (CT/MRI) with concomitant appearance of new onset neurological signs and symptoms. It complicates a diversity of diseases and the use of certain medication, mostly immunosuppressive, that should be taken into account when new clinical manifestations with neuroimaging changes appear on an immunosuppressed patient.

Case report: We report a case of a Liver Transplant recipient patient with Tacrolimus as main immunosuppression, that develops new onset neurological focalization signs and diffuse atypical changes on imaging (CT and MRI/MRA) not according to her signs and symptoms, which improve once the calcineurin inhibitors are removed from her medication scheme.

Conclusion: In any patient receiving calcineurin inhibitors the presence of new onset changes on imaging and neurological manifestations, even if they are not the typical ones, imposes the ruling out of common infectious causes and the rotation of the immunosuppressive medication in expectation of improvement of the clinical picture, which supports the diagnosis of PRES.

Introduction

The earliest definition and description of the Posterior Reversible Encephalopathy Syndrome (PRES) was given in 1996 by Hinchey et al. [1]. On this description it was described a diverse group of clinical-radiological findings such as: headache, paresis, visual disturbances, seizures and consciousness state alterations [2], in conjunction with radiological evidence of bilateral subcortical vasogenic edema that apparently was more common on the posterior areas of the brain. [1,3].

PRES has been diagnosed within several contexts, it is considered a common comorbidity on hypertensive obstetric conditions such as preclampsia and eclampsia, renal diseases, autoimmune conditions, immunosuppressive therapy (calcineurin inhibitors) and hypertensive encephalopathy [4,5]. Tacrolimus and cyclosporin belong to the family of the calcineurin inhibitors and their mechanism of action relies on avoiding the transcription of interleukin-2 (IL-2) [6,7], these medications have some adverse effects such as neurotoxicity, hypertension and nephrotoxicity [7,8]. These adverse effects at the same time are commonly found within the development of PRES without showing causality, which may be explained by the fact that most of the information we have about this pathology relies on observational retrospective studies [1-5].

The neurologic manifestations can present on an acute or sub-acute manner, between the most common ones and in a frequency order there can be observed encephalopathy which can vary from a mild confusion to stupor, seizures, which are generalized tonic-clonic on most of the cases even though partial crises have been reported and there can be presence of status epilepticus, which has a worst

prognosis; constant headache that the patient cannot localize, with poor analgesic response; visual alterations that go from blurry vision to cortical blindness depending on the affected area [9-12]. PRES is mostly reversible however there have been reports of some residual impairment on some patients, most of them due to large hemorrhages or infarctions, even though variables had been evaluated as predictors of the reversibility of this syndrome, it seems to be individual-dependent.

Next we are describing the case of a patient recipient of liver transplant with cadaveric donor on immunosuppressive therapy with tacrolimus and subsequent development of PRES.

Case

The patient is a 55-year-old female previously diagnosed with primary biliary colangitis on cirrhotic decompensated phase, that was subject of orthotopic liver transplantation on June 2015, from a donor with cold ischemia time of 4 h 35 min, with a post-transplant stay of 7 days, without any immediate complication. The patient goes to the emergency service of the Luis Vernaza Hospital on January the 9th of 2016 with right hemiparesis of crural predominance, facial asymmetry, speech difficulties and holocraneal headache. At that moment the patient was 7 months after her liver transplant surgery without major organ complications. On the physical examination the patient seems oriented on time, space and person, with blood pressure of 100/80 mmHg and other vital signs within normal limits. Neurologic evaluation reveals right central facial paralysis, right hemiparesis with strength evaluation of 4/5 on upper limb and 2/5 on inferior limb. A blood sample is taken that shows serum creatinine of 1.4 mg/dL

(Glomerular Filtration Rate by MDR4 of 41.49 mL/min/1.73 m²). A Computed Tomography without contrast is done where hypo densities are seen on white substance without previous hemorrhage or infarction signs; with these results a Magnetic Resonance Image (MRI) of the brain is ordered where there can be appreciated micro infarction on basal ganglia, semioval centers and radiate crown, periventricular leukoaraiosis and demyelination of basal ganglia on T2 and Diffusion Weighted Imaging (DWI) sequences (Figure 1). A Magnetic Resonance Angiography (MRA) of the Willis Polygon is realized where there is no evidence of stenosis, aneurism or arteriovenous malformations.

Two days posterior to the admission a lumbar puncture for Cerebrospinal Fluid (CSF) analysis is realized and Polymerase Chain Reaction (PCR) for Herpes virus, John Cunningham (JC) virus, Toxoplasma gondii and Mycobacterium tuberculosis are realized with negative results for all of them. At this moment Tacrolimus associated PRES is suspected, the patient was receiving 2 mg Orally (PO) Twice a Day (BID) with a serum dosage of 6.8 ng/ml; the immunosuppressant is changed to Cyclosporin at a 50 mg PO BID with serum dosage of

132 ng/ml. Despite the change in the immunosuppressive regimen the neurological manifestations persist, and the dose of cyclosporine is decreased to 25 mg PO BID and prednisone is added at a dose of 20 mg/d to avoid organ rejection.

On day 6 after admission the clinical manifestations persist and the neurological symptoms progress reducing the muscular strength on the upper limb to 1/5 on Daniel's scale, there is instauration of diplopia with divergent strabismus and development of motor aphasia. Cyclosporin is totally suspended and immunosuppression is replaced with Azathioprine 50 mg +Prednisone 20 mg PO once a day. 48 h later the patient is reevaluated with improvement of the dysarthria and the right hemiparesis. Afterwards the patient remains hospitalized for a total of 20 days since her admission through emergency services with total resolution of her symptoms. Currently the patient remains asymptomatic, without any sequel and with current immunosuppressive treatment of Everolimus 0.5 mg PO once daily +Prednisone 5 mg PO once daily.

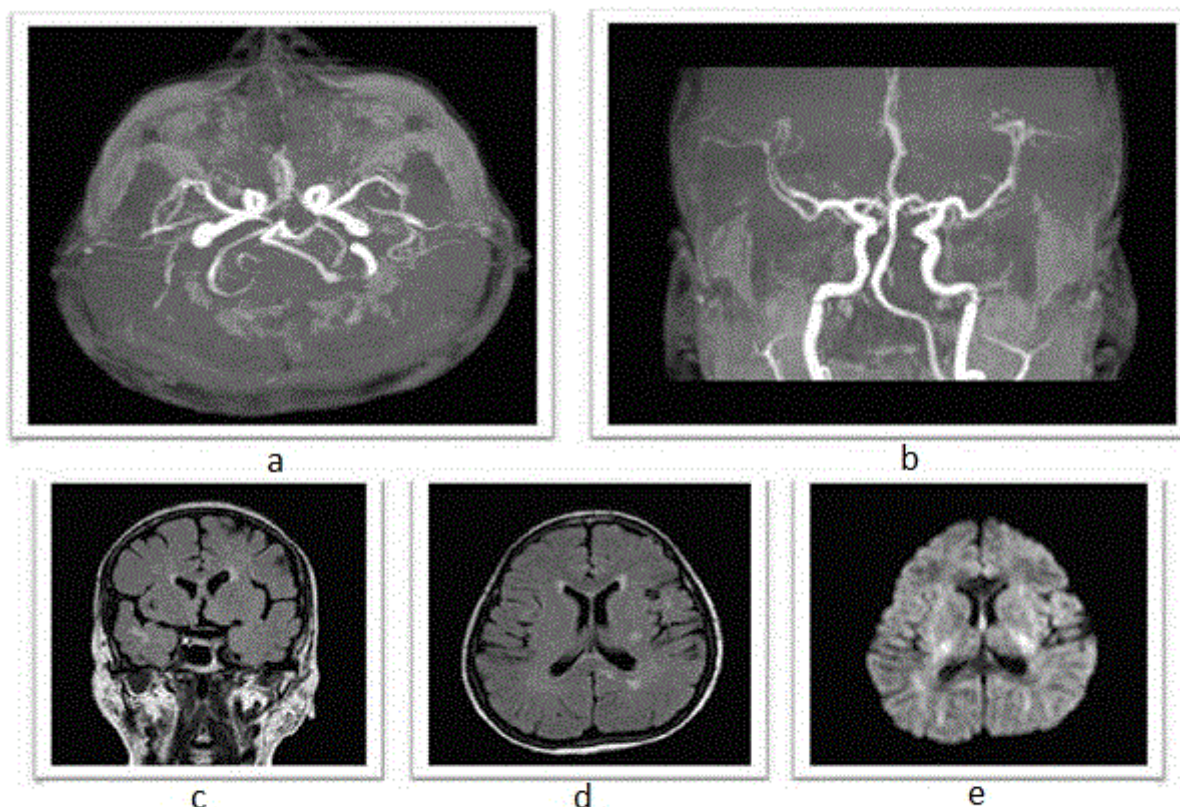


Figure 1: a and b-Magnetic Resonance Arteriography (MRA) showing Circle of Willis patency without stenosis or aneurism; c-Magnetic Resonance Imaging on T2 sequence, coronary cut; Magnetic Resonance Imaging on T2 sequence, axial cut; d- Magnetic Resonance Imaging on DWI sequence, axial cut.

Discussion

The pathophysiology of PRES has not been clearly defined, actually there are several hypothesis that are widely debated between them the

autoregulation of cerebral blood flow dysfunction associated with blood pressure rise that would cause damage to endothelium, that eventually causes fluid extravasation to the interstitial space, cytokine release and subcortical edema production [10]. However on 25% of the

cases there can be seen normal or low blood pressure [4] which suggests that there are individuals more susceptible to abrupt changes of blood pressure than from an elevation of it [10]. Besides hypertension, there has been seen commonly a concomitant renal injury and rise on cellular damage markers such as lactate dehydrogenase (LDH) during PRES.

PRES is considered as the maximum extreme in the spectrum of the neurotoxicity caused by calcineurin inhibitors; this toxicity is thought to be caused by sympathetic stimuli alteration, induction of apoptosis of oligodendrocytes and nitric oxide production inhibition by endothelium [11].

Within the neurologic manifestations there has been described headache that can range from mild to severe, different degrees of visual impairment and partial to generalized seizures. However it is worth notice that the report of focalized neurologic signs range from 0-3%.

When using different imaging studies the MRI is preferred since it let us distinguish from other possible diagnoses, specially the sequence T2, DWI and FLAIR which let us classify the white matter edema in four different patterns described by Legriél et al. being the holohemispheric watershed pattern that courses with bilateral vasogenic edema of the frontal, parietal and occipital lobes. The superior frontal pattern presents edema on the superior sulci. The dominant parietal-occipital pattern that is the one classically described on the first PRES reports, which consist on edema of the parietal and occipital lobe on different degrees. And the partial or asymmetric expression of the primary patterns, where the partial form is the absence of edema on the parietal or occipital area and the asymmetric form that is characterized by the unilateral absence of edema in either of the two lobes previously described [12-15,4,9].

On a solid organ recipient transplant patients presenting with progressive neurological disease there are some common infectious etiologies we are obligated to rule out before thinking on pharmacological induced PRES, such as Herpes virus encephalitis, progressive multifocal leukoencephalopathy (PML) and cerebral toxoplasma reactivation. However, HSV encephalitis is more common on the first month after liver transplant and most of the time it presents with primary skin/mucosae characteristic lesions [16,17]. PML seems as a tentative option given the clinical picture, however this lesion is more common on HIV patients and with a negative PCR test on a CSF analysis, with a specificity of 95%, this diagnosis becomes unlikely [18]. Finally cerebral toxoplasma reactivation would have presented as multiple ring lesions with preference for basal ganglia, once again, this infection is more prevalent on the HIV population and the CSF analysis gave back negative PCR results [19].

Other important factor is the time between the procedure/start of the immunosuppression and the onset of neurologic symptoms, in our case clinical manifestations starts 7 months after the procedure, the literature describes an early onset related with use of CNi in patients after liver transplantation (LTx) usually within 2-3 months post-transplant [20]. despite this information a case of PRES occurring 13 months after LTx with CNi has been reported on 2005 [21] and in a case series of 19 subjects shows 1 patient who develops symptoms after 14 months of treatment with tacrolimus [22].

Our patient is impossible to classify from an imaging point of view on any of the four MRI patterns and common infectious causes have been excluded. Finally due to the total clinical resolution after the treatment modification with withholding of the calcineurin inhibitors medication we reached and the PRES diagnosis.

Conclusion

Even though there is a clearly defined series of radiological signs and neurologic manifestations that usually present during PRES, it is important to remember that in any patient receiving calcineurin inhibitors, the presence of neurologic alterations de novo with changes on imaging studies as MR and the systematic evaluation and elimination of more common causes should raise the concern for PRES, since this is a potentially reversible etiology. In case there may be any doubt about the feasibility of the diagnosis a clinical improvement and a cleaning of the radiologic images posterior to the medication suspension should help support the diagnosis further.

Conflict of Interest

The authors of this case report have no conflict of interest on respect of funding, affiliations or management that could be perceived as source of interest.

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