Reviewer's report

Title: Vasospasm is a significant factor in cyclosporine-induced neurotoxicity: Case report

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Reviewer: Walter Bartynski

Reviewer's report:

The authors describe a case of cyclosporine toxicity where cerebral blood flow characteristics are evaluated by Trans Cranial Doppler (TCD). The manuscript is well written and delivers an important message.

Several issues should be addressed:

Major compulsory revisions:

Case Report: An MR image of the stroke should be provided as well as diffusion image and ADC map. Was follow-up imaging obtained? Was true restricted diffusion present in the entire area of abnormality identified on the brain MR images or was the restricted diffusion only a small portion of the abnormal brain region? Did this region persist as stroke or reverse? It is quite unusual for stroke with true parenchymal ischemic injury and focal symptoms to reverse so rapidly with only decrease in cyclosporine and reduced vasospasm. Could the area of brain abnormality identified on MR be a region of vasogenic edema without parenchymal injury, i.e. PRES vasogenic edema? Imaging should be provided for enhanced reader understanding.

Calcium and Magnesium levels and normal ranges should be provided.

Discussion: Fourth and fifth sentences: While hypertension is commonly seen in the setting of PRES, hypertension exceeding the limits of auto-regulation with forced hyper-perfusion has never been definitively demonstrated. PRES also occurs in the absence of hypertension. Most studies where features of CBF have been evaluated have demonstrated hypo-perfusion in PRES as opposed to hyper-perfusion (see Bartynski AJNR Am J Neuroradiol 2008, 29: 1036-1042 and Bartynski WS AJNR Am J Neuroradiol 2008, 29: 1043-1049. Vasoconstriction or vasospasm has been identified and reversible vasoconstriction has also been demonstrated. The authors should rephrase these summary statements or sentences regarding PRES to be more accurate.

Histology in acute-phase PRES has primarily demonstrated endothelial activation and lymphocytic trafficking. A recent case report of reversible encephalopathy in the setting of cardiac transplantation has also demonstrated VEGF up-regulation, indicating hypoxemia, likely related to reduced brain perfusion (see Horbinski C et al. AJNR Am J Neuroradiol 2009;30:588-590) and likely responsible for the
reversible vasogenic edema in that case. In the authors case report, vasoconstriction that reverses upon withdrawal of cyclosporine, if sustained, could contribute to sustained brain hypoperfusion leading to hypoxemia, VEGF upregulation and PRES vasogenic edema. The authors should discuss the importance of their observation as a potential contributor to the development of PRES vasogenic edema in other instances where cyclosporine is used including stem-cell transplantation and solid organ transplantation.

Minor revisions:

The typical range of cyclosporine depends upon clinical condition treated. How does the range stated for cyclosporine compare with typical treatment blood levels for solid organ transplantation or stem cell transplantation? Typically patients managed with cyclosporine for stem cell transplant run higher blood levels than patients managed after solid organ transplants.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare I have no competing interests.