Agenesis of Bilateral Internal Carotid Arteries in the PHACE Syndrome

We read with interest the paper by Weon et al., in which they described the case of a 14-year-old girl with a complex association of agenesis of the bilateral internal carotid arteries with transcranial collaterals from the external carotid artery, agenesis of the verteobasilar system, hypoplasia of the right cerebellar hemisphere, absence of the inferior cerebellar vermis, and facial capillary hemangioma. PHACE syndrome is a constellation of anomalies that includes posterior fossa abnormalities, hemangiomas, arterial abnormalities, aortic coarctation and cardiac abnormalities, and eye abnormalities.\

The acronym has been subsequently expanded to “PHACES” to include sternal defects, which may be associated in a minority of patients. Among arterial anomalies occurring in patients with PHACE syndrome, Weon et al noted that agenesis of major arteries, such as the internal carotid and vertebral arteries, is usually unilateral and occurs ipsilaterally to the cutaneous lesion.

In a 2001 paper with a coincidentally similar title that was unfortunately not cited by Weon et al, we described 3 patients with PHACE syndrome, one of whom had a complex arterial abnormality bearing some similarities to that described by Weon et al. This patient was a female neonate with bilateral agenesis of the internal carotid arteries, as shown by MR angiography and confirmed by the absence of the carotid canals on the bone window setting of brain CT. Unlike Weon et al’s case, in our case the anterior circulation was reconstituted by a huge basilar trunk via enlarged posterior communicating arteries, whereas the external carotid artery branches did not contribute to the anterior circulation except for the right ophthalmic artery originating from a branch of the right middle meningeal artery. Thus, to the best of our knowledge, Weon et al’s is the second report on bilateral agenesis of the internal carotid arteries in the setting of PHACE syndrome.

Other features of our case included tricuspid atresia, right hemispheric cerebellar cortical dysplasia (until then a novel feature of PHACE syndrome), and a remarkably minor cutaneous expressivity with a capillary hemangioma of the right pinna in the absence of the disfiguring hemifacial hemangioma that is found in most patients with PHACE syndrome. We did not find ophthalmologic abnormalities or sphenoidal defects, and also the other 2 cases from our series, as well as an additional, unpublished case that we recently observed, did not display the full phenotypic spectrum of the syndrome. Thus, we agree with Weon et al that the PHACE syndrome is heterogeneous and that absence of one or more components is the rule. We also believe that all patients with a facial hemangioma (regardless of size) should undergo neuroradiologic, cardiologic, and ophthalmologic investigations to disclose possible associated abnormalities. It is hoped that future research will establish more precise diagnostic criteria and, one hopes, disclose the genetic background to what we believe is not merely an association of findings—etymologically, a syndrome—but rather a true vascular phakomatosis.

References


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Post-transplant Neurotoxicity: What Role do Calcineurin Inhibitors Actually Play?

It is well known that calcineurin inhibitors (CIs; cyclosporine and tacrolimus) may induce severe neurotoxicity even at therapeutic levels. Major central nervous system (CNS) complications induced by CI include headaches, altered mental status (AMS), seizures, cortical blindness, auditory and visual hallucinations, spasticity, paresis, and ataxia. It is interesting that, in their recent article, Besenski et al found AMS, headaches, and seizures as the most common symptoms not only in the kidney transplant recipients (KTR) whom they studied, but also in a group of pretransplant patients.

The pathogenesis of CI-induced CNS toxicity remains unclear. It has not been determined whether the clinical symptoms in KTR treated with CI are due to the direct drug toxicity, hypomagnesemia or hypercholesterolemia, hypertension, or a combination of these. Is the mechanism due to demyelination, ischemia mediated by vascular spasm, or hypertension?

It has been suggested in the literature that subcortical edema is the result of a hyperperfusion insult promoted by endothelial damage with breakthrough of autoregulation in the posterior circulation, which has paucity of sympathetic innervation. MR imaging perfusion studies have shown areas of signal intensity abnormality, whereas diffusion studies have been negative. Endothelial cell damage could be responsible for direct injury to the capillary bed and alteration of the blood-brain barrier, as well as the release of potent vasoconstrictors resulting in vasospasm. Injury to the blood-brain barrier may occur and recent reports note brain enhancement in several patients.

In the series presented by Besenski et al, none of the patients had hypomagnesemia or hypertension, and only 9% had a cholesterol level <120 mg/dL. As the authors stated, this probably contributed to the low incidence of CI CNS toxicity in their study. The authors found posterior reversible encephalopathy syndrome (PRES) in 5% of KTR but also in 4% of the comparison group. It is not clear from this report why the 4% of pretransplant patients had PRES, because they were not hypertensive or taking any neurotoxic medication. PRES can be seen in other conditions such as eclampsia, hypertensive encephalopathy, systemic lupus erythematosus, and thrombotic microangiopathy. Besenski et al’s data suggest that, in KTR, PRES is probably not exclusively caused by direct CI CNS toxicity because the incidence was similar in KTR and in the pretransplant comparison group and in their different groups 1, 2, and 3 (the groups were based on the time interval between transplantation and MR imaging examination). They therefore suggested that the etiology of PRES in KTR is multifactorial and needs further investigation. They did note, however, that statistical power was restricted by the number of patients in their study.
The major finding in this article was that the prevalence of PRES and both acute and chronic changes did not differ significantly in pre- and post-transplant kidney recipients, and, therefore, the authors claimed that their study did not support the previously reported suggestion that those changes were mostly because of CI toxicity because the pretransplant group was not treated with CI. On the other hand, a study by Sheth et al of 10 asymptomatic post-transplant patients found no MR imaging abnormalities, and the authors concluded that lesions visible in patients with clinical neurotoxicity were because of cyclosporin effects and not pre-existing coincidental abnormalities. The other major finding in the paper by Besenski et al was that there was no significant difference in the prevalence of brain abnormalities in early compared with late post-transplant periods when exposure to CI is tapered. This also is in contradistinction to what has been previously published where symptoms and imaging findings have been noted to regress rapidly after discontinuation or reduction in dosage of CI and correction of potentiating factors.

In the future, larger series of cases with appropriate control groups must be studied to obtain statistically significant numbers. Also, further investigation needs to be performed on the mechanism and pathophysiology of CI toxicity, including studies where CI is tapered and serial MR studies are obtained.

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References