Fluorescein Angiographic and Histopathologic Findings of Bilateral Peripheral Retinal Nonperfusion in Nonaccidental Injury: A Case Series

The triad of shaken baby syndrome consists of multilayered retinal hemorrhages, subdural hematomas, and neurologic abnormalities that often occur in the context of an inconsistent history and are commonly accompanied by other inflicted injuries. Retinal hemorrhages are typically seen immediately after initial trauma. Unilateral peripheral retinal nonperfusion as a late sequela to non-accidental injuries (NAI) has recently been described. To our knowledge, bilateral 360° peripheral retinal nonperfusion has only been reported once in a single case, but we report the first case series of relevant clinicopathologic findings demonstrating bilateral peripheral retinal nonperfusion in 3 subjects with NAI.

A computer-generated search of the Bascom Palmer Eye Institute patient database identified fluorescein angiographic (FA) images of 3 subjects with NAI more than 2 months after trauma. Florida Lions Eye Bank Ocular Pathology Laboratory case files from 2000 through 2010 were reviewed to obtain cases of children who had sustained NAI and deceased subjects with NAI. Autopsy eyes had been previously evaluated histopathologically in 3 subjects with NAI and deceased subjects with NAI. Autopsy eyes had been previously evaluated histopathologically and were stained for hematoxylin and eosin, iron, and CD31 to characterize the peripheral retinal vasculature; stained for glial fibrillary acid protein to characterize glial proliferation; and stained for vascular endothelial growth factor (VEGF) receptor to evaluate the potential for peripheral neovascularization. The presence of vascular lumina and patent large vessels and blood vessels) endothelial staining punctate (ie, presumed involuted vasculature; stained for glial fibrillary acid protein to characterize glial proliferation; and stained for vascular endothelial growth factor (VEGF) receptor to evaluate the potential for peripheral neovascularization. The presence of vascular lumina and patent blood vessels and blood vessels was within normal limits for all subjects. No apparent papillary defects were identified. Intraocular pressures were soft to palpation in all subjects. During examination under anesthesia, posterior segment examinations revealed bilateral peripheral retinal nonperfusion and peripheral retinal ischemia in 1 male and 2 female children (age range, 7-24 months) on fundoscopic examination and FA imaging (RetCam II; Clarity Medical Systems Inc). In addition, on fundoscopic examination, significantly attenuated retinal vasculature, mottled retinal pigment epithelium, and pale optic nerves were visualized bilaterally in all subjects.

Report of Cases. Three living subjects with NAI were identified. Anterior segment examination in all subjects was within normal limits. The visual acuity of all subjects was difficult to obtain because of their young age and other comorbidities. Pupils and irises were within normal limits for all subjects. No afferent pupillary defects were identified. Intraocular pressures were soft to palpation in all subjects. During examination under anesthesia, posterior segment examinations revealed bilateral peripheral retinal nonperfusion and peripheral retinal ischemia in 1 male and 2 female children (age range, 7-24 months) on fundoscopic examination and FA imaging (RetCam II; Clarity Medical Systems Inc). In addition, on fundoscopic examination, significantly attenuated retinal vasculature, mottled retinal pigment epithelium, and pale optic nerves were visualized bilaterally in all subjects.

Patient 1. A 2-year-old girl with a history of NAI involving both eyes had recurrent pain in the right eye and atypical seizures that were unresponsive to medical therapy. Computerized tomographic scans revealed left frontal lobe damage, and she was admitted for an examination under anesthesia. Intraoperative FA identified significant bilateral peripheral retinal ischemia without any neovascular process (Figure 1A). Electroretinograms showed marked depression in rod and cones response and a selectively impaired b-wave on a combined rod-cone electretinogram response.

Patient 2. A 7-month-old male infant with a history of NAI and peripheral retinal ischemia in both eyes documented 1 month prior was admitted for an examination under anesthesia. Fundoscopic examination revealed preretinal hemorrhages and a subretinal demarcation line present in both eyes. Intraoperative FA identified significant bilateral peripheral retinal ischemia (Figure 1B).

Patient 3. A 1-year-old boy with a history of NAI with dense vitreous hemorrhage in the right eye was admitted for an examination under anesthesia of both eyes and a 23-gauge pars plana vitrectomy of the right eye. Intraoperative FA revealed extensive ischemia at the posterior pole and periphery in both eyes (Figure 1C).

A subset of 16 autopsy specimens (11 subjects with NAI and 5 control subjects) of children was reviewed. Nine cases (17 eyes) of children who had sustained NAI and lived for at least 2 months were identified. In all cases, there was evidence of previous ocular trauma. Results from the iron stain were negative in the control subjects (Figure 2F) and positive in the NAI cases (Figure 3F). In 4 cases (8 eyes), there was an increased distance of termination of vascular lumina formation from the ora serrata in both the nasal and temporal retina...
Figure 1. Fluorescein angiograms of infants with nonaccidental injuries. A, Patient 1’s right eye has significantly attenuated vasculature for 360° (arrows). B, Patient 1’s left eye with significantly attenuated vasculature for 360° (arrows) and multiple chorioretinal scars throughout the fundus (asterisks) that are visualized throughout the fundus. C, Patient 2’s right eye (inferior temporal view) has truncation of vasculature (arrows) and dot-blot hemorrhages at the edge of the disc (arrowhead) that are visualized at the ora serrata (dagger). D, Patient 2’s left eye (temporal view) has truncation of vasculature (arrows) and dot-blot hemorrhages superior and inferior to the fovea (arrowhead) that are visualized at the ora serrata (dagger). E, Patient 3’s right eye has significantly attenuated peripheral vasculature for 360° (arrows), central vitreous haze due to resolving vitreous hemorrhage (arrowhead), and multiple chorioretinal scars throughout the fundus that are visualized. F, Patient 3’s left eye has significantly attenuated peripheral vasculature for 360° (arrows) as well as extensive chorioretinal scarring temporal to and involving the macula (asterisk).
Figure 3B) compared with control subjects (Figure 2B). The CD31 staining of the peripheral retinal vessels was diminished compared with control subjects with decreased lumen formation and an increase of punctate staining in the mid and far periphery (Figure 2D and Figure 3D). These findings are similar to that seen in the area of peripheral retinal nonperfusion. There was increased glial fibrillary acid protein staining of the neural retina in the cases of NAI (Figure 3E) compared with control subjects (Figure 2E). Vascular endothelial growth factor receptor staining negatively for both control and NAI autopsy specimens.

Comment. Bilateral nonperfusion of the peripheral retinal vasculature has been described in pediatric retinal diseases such as retinopathy of prematurity, familial exudative vitreoretinopathy, Norrie disease, and most recently in persistent fetal vasculature. However, it is a clinical newly recognized finding described in NAI. The link between the biomechanics of NAI to the bilateral peripheral retinal nonperfusion in chronically shaken children is not clearly understood. It is possible that vitreoretinal traction coupled with rotational and acceleration-deceleration forces may lead to vascular damage and secondary nonperfusion in the areas of tight vitreoretinal adhesion specifically in the peripheral retina. In addition, apparent glial cell activation is present in many of these cases and may play a role in peripheral retinal nonperfusion.

Common ophthalmic findings in shaken baby syndrome include retinal detachment, retinal pigment epithelium tear, and epiretinal membrane. Goldenberg et al and Kiernan et al previously reported the presence of neovascularization and suggested the importance of bilateral laser photocoagulation therapy in subjects with NAI. However, the autopsy specimens studied herein were negative for VEGF receptor and did not demonstrate any evidence of retinal neovascularization. Endothelial progenitor cells have been described to play an important role in VEGF expression for vascular repair in traumatic brain injury, and it is possible that a varied endothelial progenitor cell count may be present in subjects with NAI. It has also been theorized that a loss of luminal endothelial cell polarity can cause an unequal ratio of receptors, influencing the distribution and concentration.
of VEGF.13 With the presumed involuted blood vessels found in our NAI autopsy specimens, it is possible that the distribution of VEGF receptors on the luminal surfaces of the endothelial cells can impact the VEGF ligand distribution in the blood as well as the VEGF signaling efficiency.

Our case series illustrates a clinically significant finding related to shaken baby syndrome, which may be considered in the differential diagnosis of peripheral retinal nonperfusion in children. The findings of peripheral retinal nonperfusion with decreased lumen formation and peripheral involution of blood vessels together is demonstrated in a subset of autopsy specimens of children that sustained NAI, which correlates with the FA findings described. Although the mechanism for vaso-occlusion in this condition is uncertain, children with this type of injury should receive serial fundus examinations and clinicians should consider diagnostic imaging.

Figure 3. Histopathologic features of non-accidental injury eyes. A, Ora serrata–hemosiderin deposition (arrow) is present in the far peripheral neural retina (hematoxylin and eosin, original magnification × 200). B, CD31 (Dako) staining discloses lack of lumen formation and decreased punctate staining at the level of the ora serrata (arrow). C, Hemosiderin deposition (arrow) is present in the midperipheral neural retina (hematoxylin and eosin, original magnification × 200). D, CD31 (Dako) staining discloses focal lumen formation at the midperiphery (arrow) with nonperfusion present peripheral to this area (asterisk) (immunohistochemical stain, original magnification × 200). E, Increased glial fibrillary acid protein (Dako) staining is present within the peripheral neural retina, representing glial activation (immunohistochemical stain, original magnification × 200). F, Presence of old hemorrhage with positive iron stain in the ora serrata (Perls Prussian blue stain, original magnification × 200).

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Retinal Pigment Epithelial Depigmented Lesions Associated With Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem hamartomatous disorder that can occur in nearly every tissue in the body but primarily affects the skin, brain, and eye. Major and minor diagnostic criteria for TSC have been established by the Tuberous Sclerosis Consensus Conference in 1998. A diagnosis of definitive TSC is established by the presence of 2 major features or 1 major feature plus 2 minor features. A diagnosis of probable TSC requires the presence of 1 major feature and 1 minor feature, and a diagnosis of possible TSC requires the presence of either 1 major feature or 2 or more minor features.

The most common eye finding of tuberous sclerosis is the retinal astrocytic hamartoma. Other features include eyelid angiofibroma, iris atrophy, uveal coloboma, and retinal achromatic patch. The retinal achromatic patch is not clearly described, and this could represent a flat astrocytic hamartoma or retinal pigment epithelial (RPE) “punched-out” depigmentation.

The relationship of RPE punched-out depigmentation with TSC is not well recognized. Herein, we analyze the relationship of RPE depigmented lesions with TSC.

Methods. The computer-coded records of all patients evaluated on the Ocular Oncology Service at Wills Eye Institute in Philadelphia, Pennsylvania, were reviewed for TSC (eTable 1) or retinal astrocytic hamartoma between July 1974 and November 2010. Each chart was evaluated for patient and tumor features. The affected eye was evaluated for the presence, multiplicity, location, and basal dimension of retinal astrocytic hamartoma(s) and RPE depigmented lesions.

Statistical evaluation was performed to evaluate the relationship of RPE depigmentation with clinical features of TSC using logistic regression analysis (Table). The specific features of RPE lesions were described.