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LETTER TO THE EDITOR

Noonan syndrome associated with retinal cavernous hemangioma and atypical epiretinal membrane: Case report

Syndrome de Noonan associé à un hémangiome caverneux rétinien et une membrane épirétinienne atypique : à propos d'un cas

Case report

We report the case of a nine-year-old girl with Noonan syndrome (mutation in the *PTPN11* gene), who was referred by her pediatric ophthalmologist after incidental finding of a retinal lesion in the left eye. We noticed hypertelorism on external examination. The best visual acuity was 20/25 in the right eye and 20/32 in the left eye with correction of mild myopia and astigmatism in both eyes. There was no nystagmus or strabismus. Examination of the anterior segment was unremarkable. Fundus examination was normal in the right eye but revealed, in the lower temporal part of the left eye, a vascular lesion with clusters of aneurysms and appearance of grapes typical of cavernous hemangioma of the retina (Fig. 1). Fluorescein angiography was characterized by progressive filling of the retinal hemangioma as well as 360° peripheral diffuse capillary leakage (Fig. 2). The spectral domain optical coherence tomography (SD-OCT) showed from the edges of the macula an aspect of schisis sparing the fovea (Fig. 3A). Because no threatening for the vision, we offered a simple follow-up to the patient. Eight months later, we noticed a drop of vision in the left eye to 20/50 secondary to a moderate vitreous hemorrhage. The comparative SD-OCT showed disappearance of the schisis aspect of the retina (Fig. 3B). Fundus examination did not show any posterior vitreous detachment or retinal tear. The vitreous hemorrhage resolved spontaneously within four months with the restoration of initial visual acuity (Fig. 3C).

By this clinical case, we wish to highlight two points: first, the unknown and probably genetic-mediated association between Noonan syndrome and cavernous hemangioma of the retina; second, the atypical aspect of the epiretinal membrane associated with the hemangioma and its presumed role in the vitreous hemorrhage.

Discussion

To our knowledge, this is the first association between Noonan syndrome and cavernous hemangioma of the retina described. Noonan syndrome is associated with many ophthalmologic manifestations, the most frequent being refractive problems, external abnormalities (hypertelorism, ptosis, and epicanthus), and strabismus [1]. However, there are only a few abnormalities described in the fundus, and they tend to affect the optic nerve. We found only one association with retinal vascular abnormalities, a case of Coats disease [1]. This patient with Noonan syndrome associated with Coats disease has a mutation in the *RAF1* gene, while our patient with Noonan syndrome associated with retinal cavernous hemangioma has a mutation in *PTPN11* gene. Thus there is no common link between these two retinal vascular anomalies and the genotype of Noonan syndrome. However, *PTPN11* gene codes for SHP-2 phosphatase that plays a role in adhesion-dependent activation of the RhoA family of small GTPases, and a study showed that the Noonan syndrome mutation in SHP-2 phosphatase enhances cell motility [2]. Many developmental processes such as heart morphogenesis and vasculogenesis require the precise regulation of motility. The same study suggested that the lymphedema in Noonan syndrome might be induced by the increased motility of endothelial cells. The pathogenesis of the retinal cavernous hemangioma in our case of Noonan syndrome could be the same.

The retinal cavernous hemangioma is in the majority of cases a sporadic condition and a typically isolated

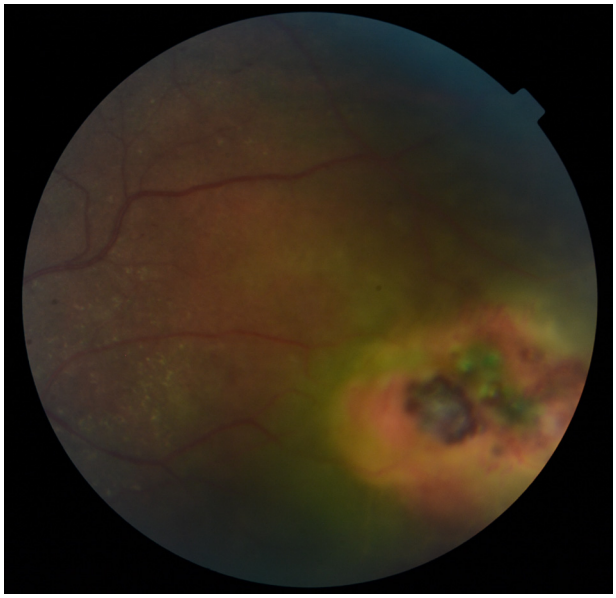

Figure 1. Fundus color photography of the left eye showing in the temporal inferior periphery a cavernous hemangioma of the retina with clusters of aneurysms and appearance of grapes.

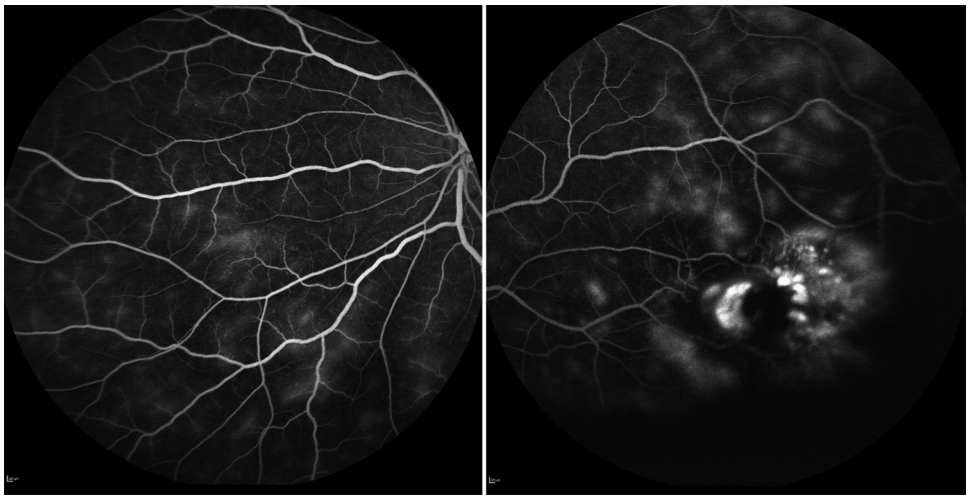

Figure 2. Fluorescein angiography of the left eye showing a peripheral capillary leakage and the filling of the cavernous hemangioma of the retina.

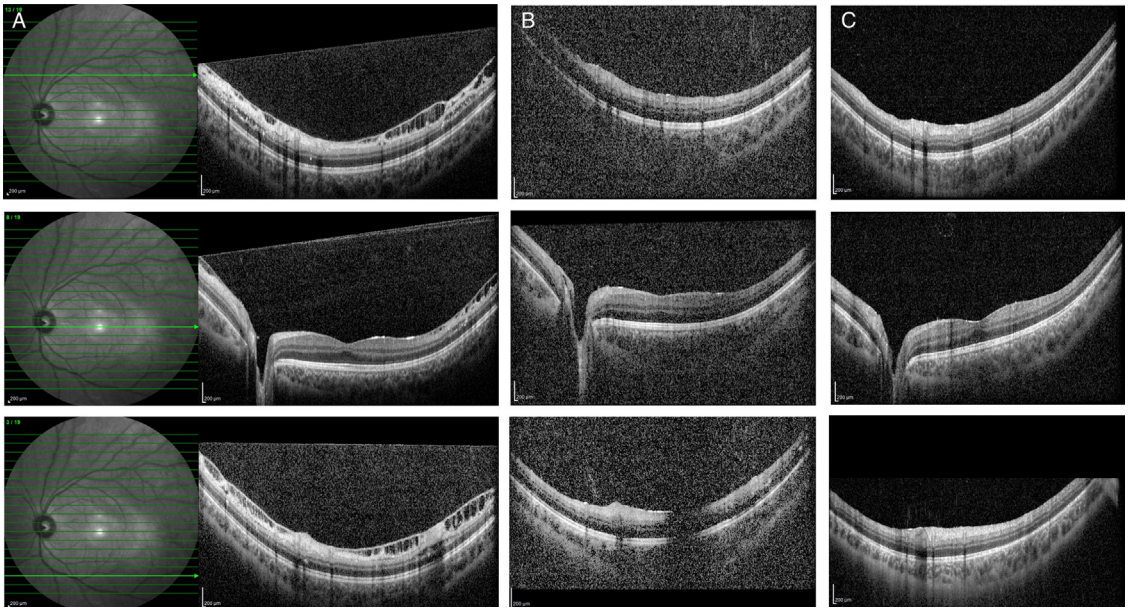

Figure 3. Spectral domain optical coherence tomography of the left eye. A. Before the vitreous hemorrhage, showing the atypical aspect of retinoschisis with fovea sparing. B. During the vitreous hemorrhage, showing the disappearance of the atypical epiretinal membrane and the retinal structure normalization. C. After the resolution of the vitreous hemorrhage.

finding, although some autosomal dominant cases have been described [3]. This form of cavernous hemangioma of the retina associated with autosomal dominant inheritance pattern tends to occur in association with cutaneous hemangioma and central nervous system hemangioma, and is often linked to bilateral hemangioma of the retina [3]. Our patient presents a unilateral form, and the fundus examination of her father was normal. However, a magnetic resonance imagery of the brain was ordered because of the significant morbidity in case of association with central nervous system hemangioma. Fortunately, this examination was normal.

At the first consultation, our patient was asymptomatic as in the majority of cases of retinal cavernous hemangioma. Indeed, it is a vascular tumor most often discovered incidentally at an average age of 21 years. During the follow-up, we noticed a loss of vision caused by a vitreous hemorrhage [3]. This is one of the two major causes of visual disturbance, the second cause being the macular involvement by the tumor. In recent years, SD-OCT has made possible to suspect the role of preretinal membrane contraction in the occurrence of vitreous hemorrhages in the absence of a vitreous detachment [4]. Our clinical case seems to confirm this theory. Indeed, we noticed at the first consultation an atypical aspect of peripheral retinoschisis with fovea sparing, probably secondary to an atypical epiretinal membrane. The onset of vitreous hemorrhage coincides with the disappearance of this atypical retinoschisis. Histologically, the epiretinal membrane in retinal cavernous hemangiomas has been studied and seems to be formed by retinal glial cells, which proliferate on the inner retinal surface after gaining

access through breaks in the internal limiting membrane [5]. It should be noted that, in the majority of cases, vitrectomy is not necessary, due to the spontaneous resolution of vitreous hemorrhage as reported in this clinical case [3]. Treatment is necessary only if there is a significant persistent vitreous hemorrhage or subretinal hemorrhage [3].

Disclosure of interest

The authors declare that they have no competing interest.

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