Five-year follow-up of bilateral choroidal neovascularization secondary to optic nerve head drusen treated with ranibizumab in a nine-year-old girl

Suivi à cinq ans d’une néovascularisation choroidienne bilatérale sur drusées papillaires traitées par ranibizumab chez une enfant de neuf ans

We report the case of a nine-year-old girl who was referred to L’Union Private Hospital (Saint-Jean, Midi-Pyrénées, France) in May 2009 for a recent visual impairment in the left eye secondary to sub-retinal neovascularization associated with optic nerve head drusen (ONHD). She had no relevant ocular or general history.

Visual acuity was limited to 20/200 in the left eye, and was 20/20 in the right eye. Anterior segment and intraocular pressure were normal in both eyes. Fundus examination revealed a bilateral lumpy aspect of the ONH (Fig. 1A/B), which were hyper-autofluorescent leading to the diagnosis of bilateral ONHD (Fig. 1C/D). In the left eye, there was an inter-papillo-macular and elevated grey lesion (Fig. 1B), which showed early hyperfluorescence, and an intense leakage at fluorescein angiography (Fig. 1F). OCT scans showed retinal thickening, sub-retinal hyperreflectivity in the inter-papillo-macular region and sub-retinal fluid in the subfoveal area (Fig. 2A). These findings lead to the diagnosis of choroidal neovascular membrane secondary to ONHD in the left eye.

A single ranibizumab (0.5 mg/0.05 mL) intravitreal injection was administered. One month later, visual acuity was limited to 20/200 and OCT scan showed the decrease of the retinal thickening and the persistence of sub-retinal hyperreflectivity (Fig. 2B). At the two-month follow-up examination, retinal thickening increased anew. The patient underwent a second ranibizumab intravitreal injection in the left eye. The five-month examination revealed visual acuity improvement at 20/40; OCT showed anatomical improvement with the persistence of sub-retinal fibrosis.

In May 2010, the patient presented with a recent visual impairment in the right eye which visual acuity was 20/25. Fundus examination, fluorescein angiography (Fig. 3) and OCT scans showed similar lesions in the right eye as the ones observed in the left eye one year before. The patient underwent a third ranibizumab intravitreal injection (the first in the right eye). Follow-up examinations showed functional and anatomical improvements. In May 2014, visual acuity was 20/20 in the right eye and 20/25 in the left eye. In the Fig. 2C, the latest OCT scan shows the remaining persistence of sub-retinal fibrosis in the left eye.

ONHD is an infrequent condition; its prevalence has been reported to be 0.04% in children [1]. ONHD initially correspond to polysaccharide protein deposits in the optic nerve head: in children, ONHD are frequently non-calcified. Calcium phosphate Ca₃(PO₄)₂ salt [2] eventually deposit leading to the classical ONHD calcified aspect. These deposits increase progressively with age, making ONHD more visible in adults. Although ONHD complications have been well documented, the frequency of sub-retinal neovascularization secondary to ONHD is not defined and its occurrence in children is very rare [1].

The location of the sub-retinal neovascularization associated to ONHD is usually peripapillary, impairing vision by subfoveal location of sub-retinal fluid, haemorrhage or neovascular membrane spreading. Peripapillary neovascularization can be associated to several conditions such as age-related macular degeneration, angioid streaks, multifocal choroiditis, histoplasmosis scars, optic disc abnormalities...[2].

Prognosis of choroidal neovascular membrane secondary to ONHD has improved since the availability of anti-VEGF therapies. Before that, treatment of this vision impairing condition was difficult. Several therapeutic options included observation and spontaneous resolution [3], laser [4,5], dynamic phototherapie [6] or surgical removal [7,8], which had been described as efficient in the long-term for selected cases. However, all of the papers describing these therapeutic options are small series and large series or comparative studies are missing.

Anti-VEGF therapy efficacy in neovascularization associated to ONHD has been reported by several authors [1,9–13]. In their report, Knape et al. performed combined treatment with ranibizumab and laser focal photocoagulation [1]. It must be highlighted that no series has been reported and reported cases were single cases as ours. Moreover, we are unaware of cases of resistance to anti-VEGF therapy in sub-retinal neovascularization associated to ONHD. Some reported cases were treated by a single anti-VEGF intravitreal injection and none received more than 2 injections. This element is in favour of a high sensitivity to anti-VEGF therapy of sub-retinal neovascularization associated to ONHD. Moreover, no long-term recurrence has yet been reported.

In our case, we first observed in the left eye a response, which was secondarily proven to be incomplete. Indeed,
Figure 1. Color fundus photographs (A, B), autofluorescent images (C, D) and fluorescein angiography (E, F) of both eyes presenting with optic nerve head drusen complicated with left choroidal neovascularization in a nine-year-old girl (in 2009). Fundus examination (A, B) and autofluorescence images (C, D) showed classical bilateral aspect of white refractile and hyper-autofluorescent bodies at the surface of the optic nerve head. Fundus examination of the left eye (B) also showed a grey inter-papillo-macular lesion, characterised at fluorescein angiography (F) by early hyperfluorescence and intense leakage, confirming the diagnosis of an associated neovascular membrane in the left eye. The right eye angiography (E) showed blurred borders of the optic nerve head, linked with the drusen, but no hyperfluorescence or leakage.

we did not perform a second intravitreal injection at the first month follow-up examination because, firstly, the patient experienced a functional improvement. Secondly, we observed a significative decrease of retinal thickening despite the persistence of sub-retinal hyperreflectivity that we interpreted as sub-retinal fibrosis. Thirdly, in 2009, little data was available in the international literature on the safety anti-VEGF therapy administered in children and on its
Figure 2. Macular OCT follow-up of peripapillar neovascularization associated with optic nerve head drusen in the left eye. At initial presentation in May 2009 (A), OCT showed retinal thickening, sub-retinal hyperreflectivity in the inter-papillo-macular region (neovascular membrane) and sub-retinal fluid in the subfoveal area. One month later (B), OCT showed anatomical improvement with retinal thickness decrease and subfoveal fluid disappearance but persistence of sub-retinal hyperreflectivity. In 2014, at the five-year examination (C), OCT shows the persistence of the sub-retinal fibrosis as well as an intraretinal cyst. Visual acuity at this stage is 20/25.

Figure 3. Color fundus photography (A), and fluorescein angiography (B) of the right eye in 2010, one year after left eye initial presentation. The fundus image showed lumpy aspect of optic nerve head drusen and a peripapillary grey lesion. The fluorescein angiography images (B) showed hyperfluorescence and intense leakage and confirmed the bilateralization of neovascular membrane associated with optic nerve head drusen in the contralateral eye.

efficacy on sub-retinal neovascularization associated with ONHD. Eventually, the second intravitreal injection in the left eye was decided based on the observation of retinal thickening relapse at the two-month follow-up examination. Thereafter, we observed no recurrence in the long term and, during the follow-up, we progressively observed in the left eye visual acuity improvement probably linked to healing phenomena in the photoreceptors and pigment epithelium layers.

We must highlight that intravitreal injections were performed off-label in a nine-year-old girl. As pediatric population is characterized, on the one hand, by lower drug distribution volume and thus higher drug concentrations, and on the other hand, by physical growth [14], children are more likely to present with adverse effects linked to drug interactions with growth factors homeostasis. Literature on long-term safety of intravitreal anti-VEGF use in children is poor and no systemic complication has ever been reported. In our case, we did not observe any adverse effects of ranibizumab use.

To our knowledge, this is the first very long-term follow-up in the management of sub-retinal neovascularization secondary to ONHD treated by ranibizumab in pediatric population [15].

Literature search

Literature search was performed by using PubMed/Medline for English titles for all available dates. MeSH terms included: optic nerve head drusen, disc drusen, bilateral, bevacizumab, ranibizumab, sub-retinal neovascularization, choroidal neovascularization.

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Disclosure of interest

The authors declare that they have no competing interest.

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