Unusual presentation of more common disease/injury

Treatment of Stargardt disease with dobesilate

Pedro Cuevas,¹ Luis A Outeiriño,² Javier Angulo,¹ Guillermo Giménez-Gallego³¹Departamento de Investigación, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain²Departamento de Oftalmología, Hospital de Día Pío XII, Madrid, Spain³Departamento de Estructura y Función de Proteínas, Centro de Investigaciones Biológicas, CSIC, Madrid, Spain

Correspondence to Professor Pedro Cuevas, pedro.cuevas@hrc.es

Summary

Stargardt disease is a common inherited macular degeneration characterised by a significant loss in the central vision during the first or second decade of the life. Bilateral atrophic changes in the central retina are associated with degeneration of photoreceptors and underlying retinal pigment epithelium, and yellow flecks are extending from the macula. We present a patient with Stargardt disease treated with an intravitreal injection of dobesilate, showing an improvement of visual acuity 4 weeks after treatment

CASE PRESENTATION

On 23 September 2004, a 30-year-old female patient presented with a visual acuity (VA) in both eyes of 0.20 that was diagnosed as caused by Stargardt disease (STGD). The clinical diagnosis was based on the age of the patient and a family clinical record suggesting that the disease is caused by the inheritance of a recessive autosomal gene, the presence of bilateral impairment of central vision, and atrophic macular lesions with the appearance of perimacular and/or peripheral white-yellow lipofuscin flecks. Further clinical examination included the following tests: best corrected VA (BCVA) with manifested refraction by Snellen visual chart, colour fundus photography, fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT). FAF has emerged as the most useful non-invasive imaging tool for evaluation of patients with STGD.¹ By means of FAF imaging, lipofuscin flecks can be clearly visualised as foci of very intense signal. Fundus FAF imaging can also be used to monitor the progression of the disease by demonstrating the development of areas of increased FAF over time. This case reported that the fundus colour photography of both eyes of the patient showed obvious yellowish-white flecks at the macula (figure 1A,B). Aggregates of intense FAF signals were clearly obvious at the macula in the fluorescein angiographies (figure 1a,b).

On 5 December 2011, the patient returned to the clinic with a further severe reduction in VA. BCVA test in both eyes was 0.01 this time and the area presenting flecks and fluorescent aggregates had widen considerably when compared with the previous images, reaching the mid-periphery of the retina (figure 1C,D,c,d), findings indicating the end stage of the disease.^{2 3}

Macular structure and foveolar thickness were assessed by SD-OCT. SD-OCT images were obtained before and after 4 weeks of treatment in equivalent horizontal scans crossing the centre of the fovea. As shown in figure 2A, SD-OCT scans showed a markedly thinned retina in the foveola (69 µm). This reduction in foveolar thickness is an SD-OCT characteristic finding of STGD, and shows a statistically significant correlation with VA loss.^{4 5} Above all, SD-OCT

images depict a notable lumpy hyper-reflectivity, at the retinal pigment epithelium (RPE), with marked discontinuities, which shows strikingly that this retinal layer was thoroughly disorganised at both the foveolar and parafoveolar levels (figure 2A). Highlighted inside an inset, a small hyper-reflective lesion located in the RPE layer is protruding towards the sensorial retina. These sort of small lesions appear to correspond to the accumulation of lipofuscin and are interpreted as SD-OCT images of retinal flecks.⁶

A decision was made to treat the patient with intravitreal dobesilate injection in her right eye. After approval of our Institution Ethical Committee, patient signed an informed consent form, which included a comprehensive description of dobesilate and the proposed procedure. The patient received an intravitreal solution of dobesilate (150 µl) under sterile conditions, following the International Guidelines for intravitreal injections⁷ in her right eye. Dobesilate was administered as a 12.5% solution of diethylammonium 2,5-dihydroxybenzenesulphonate (etamsylate; dicynone Sanofi-Aventis, Paris, France). No ocular side effects were observed upon the administration of dobesilate or during the following days. Four weeks after the treatment there was a significant improvement of the patient's vision (BCVA progressed from 0.01 to 0.30) on spite that fundus photography and fluorescein angiography did not reveal apparent changes (not shown). Figure 2B also shows that no significant changes have occurred in foveolar thickness along this period (73 µm after treatment vs 69 µm at baseline). In contrast, SD-OCT scans performed at that time depicted a considerable reflectivity decrease in foveolar and parafoveolar sites around RPE, and a remarkable recovery of the normal architecture of this retinal layer (figure 2B). Visual improvement was maintained after 2 months of follow-up.

DISCUSSION

STGD, also known as juvenile macular degeneration, is a bilateral and symmetrical central blinding disease similar to age-related macular degeneration (AMD) that occurs in approximately 1 in 8000–10 000 people of any sex and race.⁸ The age of onset of STGD is typically 10–20 years of age and leads in almost all cases to blindness by age

Figure 1 Fundus photography (A and B) and fluorescein angiography (a and b) from the left and right eye, respectively at the first presentation (23 September 2004). Visual acuity was 0.20. Fundus colour photography (C and D) and fluorescein angiography (c and d), from the left and right eye, respectively, of the same patient 7 years after the first presentation (5 December 2011). Note the centrifugal extension of lipofuscin flecks over time. Visual acuity decreased to 0.01.

50.⁹ Stargardt exhibits simple Mendelian transmission and is caused by mutations in the *ABCA4* gene that encodes an ATP-binding flippase located at the rims of rod and cone outer segment discs.¹⁰ Mutations causing STGD have been also located in exon 6 of the *ELOVL4* gene, which encodes a protein involved in fatty acid elongation. All these mutations introduce a premature stop codon, resulting, at the protein level, in the loss of a C-terminal endoplasmic reticulum retention signal that leads to the cellular mislocalisation of the ELOVL4 mutant protein, which, at the same time, sequesters the wild-type protein into stable aggresome-like complexes.¹¹ At the end stage of the disease, the distance VA is stabilised at approximately 0.01.³ No cure or treatment is available.

Ophthalmoscopic examination of Stargardt patients typically reveals bilateral atrophic changes in the macula associated with the degeneration of photoreceptor cells and the underlying RPE. RPE is a retinal monolayer of hexagonal melanin-containing cells that sits on Bruch's membrane, critical for the neurosensory retina homeostasis since it acts as blood-retinal barrier between the vascular choriocapillaries and the neural retina, and phagocytoses the continuously shed photoreceptor outer segments for wasting and

recycling.¹² A characteristic feature of STGD is the presence of yellow-white flecks of lipofuscin. Initially located at the macula, these deposits expanded centrifugally over time² as figure 1 illustrates. During fluorescence angiography lipofuscin absorbs blue excitatory light and emits a characteristic stippled hyperfluorescence.¹³

STGD and AMD are both caused by chronic inflammation of the RPE.¹⁰ In trying to explain the origin of this inflammation, the appearance in these two diseases of two characteristic sorts of aggregates at the RPE, lipofuscin flecks and drusen deposits, respectively, should probably be taken into account. Recently, the presence of amyloids in both sorts of deposits have been described and a parallelism between the formation of drusen and lipofuscin granules and the build-up of Alzheimer's plaques has been proposed.^{14–16} That injections of leupeptin (a thiol proteinase inhibitor) or chloroquine (a general lysosomal enzyme inhibitor) induce in rats the formation of lysosome-associated granular aggregates, which closely resembled those of lipofuscin, further supporting the role of amyloid protein aggregates in the formation of these deposits.¹⁷ Formation of aggresome-like complexes (a sort of amyloid formation) in the case of ELOVL4 mutant

Figure 2 Spectral-domain optical coherence tomography (SD-OCT) scans from the right eye at baseline, showing areas of retinal pigment epithelium (RPE) atrophy (A), and 4 weeks after treatment, showing a more normal RPE layer (B). The SD-OCT scan A shows a small hyper-reflective linear lesion located in the RPE layer (inset). Visual acuity improved to 0.30.

protein causing STGD has been observed.^{11 18} The inflammatory properties of the oligomers, precursors of the formation of the amyloid fibrils, are today widely accepted, and have been proposed as cause of AMD in the case of drusen.^{19–22} The upregulation of glial fibrillar acidic protein (GFAP), a ubiquitous marker of retinal stress and degeneration, was observed in STGD animal models well before phenotypic differences with wild-type mice retinas could be detected, an effect necessarily simultaneous to the build-up of the precursor oligomers of the protein aggregates that later will be observed. Simultaneous to the GFAP accumulation, an overexpression of fibroblast growth factor (FGF) was also detected that maintains such high levels until cone loss (18 months).¹¹

FGF was the first described angiogenic factor.²³ Later on, using in vitro mitogenesis assays, it was described that this protein is a broad-spectrum mitogen; practically all cell lineages derived from the embryonic mesoderm and neuroectoderm are under the control of this growth factor.²⁴ Furthermore, it was also shown that the vasculogenesis induced by vascular endothelial growth factor (the signalling target of many different monoclonal antibodies developed to inhibit the angiogenesis driven by this protein) necessarily requires of the cooperation of FGF.⁵ At the same time FGFs have been detected in most adult tissues derived from these embryonic cell types, sometimes expressed at high levels, trapped in the extracellular matrix, from which they are released by heparanases or other specialised proteins when necessary, as in the case of traumas that cause tissue destruction.^{25 26} Although initially classified as a broad-spectrum mitogen, FGF seems nowadays better considered as an inflammation triggering protein,²⁷ which has been described as a cytokine closely associated with the inflammasome, and related with intraocular inflammatory conditions.^{28 29} Furthermore, as mentioned above, FGF showed an anomalous uprising simultaneous with the first appearance of markers of retina degeneration in STGD.¹¹ Inhibition of FGF appeared thus as a promising pharmacological target to control the inflammation of the RPE in this disease.

As a milestone in developing rational and safe therapies against FGF activities, we have spent important efforts in the development of synthetic inhibitors of FGF. These studies led to the identification of a family of small size chemical compounds, of reasonably potent inhibitors of FGF, headed by gentisic acid. The most effective of them was a compound known in pharmacology as dobesilate, the active principle of doxium, a drug orally administered for more than 35 years for the treatment of diabetic retinopathy with a good safety profile.^{25 30} We have already used intraocular injections of pharmaceutical preparations of ammonium dobesilate in solution to treat successfully other kind of eye inflammatory diseases, associated with big distortions of the retinal layer architecture which recovered a normal-like shape after the treatment in all the cases (figure 2).^{31–34}

Our results may seem in contradiction with those of Haritoglou *et al*,³⁵ who carried out an accurate statistical study to assess the real clinical benefits of oral calcium dobesilate in the treatment of diabetic retinopathy that concluded that the oral administration of dobesilate did not show statistically significant clinical benefits for treating this disease. Perhaps, as discussed in detail in a

previous article, the different administration procedures employed in this last study and in the case reported here are at the root of the outcome differences.³¹ A detailed discussion about the paradox that seems to constitute the fact that the administration of an FGF inhibitor does not cause considerable distortion in adult tissues of mesodermal and neuroectodermal origin, being FGF involved in their homeostasis, was included also in the same article.

Finally, it may result also surprising that BCVA had progressed from 0.01 to 0.30 4 weeks after the treatment, on spite that fundus photography, fluorescein angiography and foveolar thickness did not show apparent changes after this period of time. Nevertheless, this is not a surprising result if the alteration of RPE observed in STGD is consequence of an inflammation caused by precursors of the formation of the amyloid fibrils. Today it is widely accepted that amyloid tangles are some sort inert waste that, except for some mechanical alteration of tissue homeostasis, do not show neither toxic nor inflammatory properties.³⁶ Consequently, improvement of STGD symptoms probably does not require removal of the amyloid plaques but merely to counteract the inflammatory features of the amyloid-precursor oligomers, by blunting the activity of one of the main responsible cytokines of the intraocular inflammation. Our results seem to suggest that the mere recovery of the RPE architecture, by harnessing inflammation, is enough to considerably increase the quality of the vision. Normalisation of the histological features of RPE probably correlates with the recovery of its regular physiological functions. Taking into account that recovery of the RPE architecture did not cause substantial modifications in the fovea, according to fundus photography, fluorescein angiography and foveolar thickness measurement, the vision improvement should probably be mostly attributed to the regularisation of the RPE physiology.

It does not escape us that the treatment described here might be also relevant for the treatment of some local inflammations caused by amyloid-precursor oligomers.

Learning points

- ▶ Stargardt disease (STGD) is a common inherited juvenile macular degeneration.
- ▶ Recently, STGD has been related to chronic retinal inflammation.
- ▶ Proinflammatory activities of fibroblast growth factor have been implicated in the pathophysiology of STGD.
- ▶ Intravitreal dobesilate, an inhibitor of FGF, improves visual acuity in STGD.

Competing interests None.

Patient consent Obtained.

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