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Retinal structure in young patients aged 10 years or less with Best vitelliform macular dystrophy

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ABSTRACT

Purpose: To analyze retinal structure in young patients with Best disease with reference to future gene therapy.

Methods: Retrospective observational spectral domain optical coherence tomography study of 4 patients aged 10 years or less with Best disease.

Results: Findings ranged from subtle thickening at the level of the retinal pigment epithelium-photoreceptor interdigitation line, to subretinal fluid and precipitate-like changes at the level of the photoreceptor outer segments, and further to choroidal neovascularization. The photoreceptor inner ellipsoid layer could be visualized seemingly undisturbed above the vitelliform lesions, except in the case of choroidal neovascularization.

Conclusions: Clinical variability is evident even among young patients aged 10 years or less with Best disease. The earliest structural alterations seem to occur at the level of the retinal pigment epithelium-photoreceptor interdigitation line. The photoreceptor inner segment seems to be unaffected unless choroidal neovascularization develops, which seems promising regarding future gene therapy.

Key words: BEST1, Best vitelliform macular dystrophy, optical coherence tomography, retinal degeneration.

INTRODUCTION

Mutations in the *BEST1* gene can cause a variety of ocular phenotypes ranging from isolated vitelliform macular dystrophy to widespread retinal dystrophy as in autosomal recessive bestrophinopathy and further to widespread ocular manifestations as in autosomal dominant vitreoretinochoroidopathy [1-5]. Among these, the most common manifestation is the classical Best vitelliform macular dystrophy or Best disease, characterized by an autosomal dominant inheritance, variable penetrance and expressivity, mostly reduced electro-oculogram and vitelliform alterations in the macula. The macular changes progress through various stages ranging from normal or previtelliform (stage 0) through vitelliform (stage 2) to fibrosis (stage 4b) or choroidal neovascularization (stage 4c) [1]. The prevalence of Best disease was recently estimated to 1.5/100 000 [6].

Mutations in the *BEST1* gene were incriminated in Best disease by Petrukhin et al. in 1998 [7]. The gene product of *BEST1*, bestrophin, was previously postulated to act as an calcium-sensitive chloride channel in the basolateral cell membrane of the retinal pigment epithelium however a recent study showed that bestrophin is localised in the endoplasmic reticulum membrane, close to the cell membrane [8]. Lack of channel conductance may underlie or contribute to the reduction or absence of a light rise in the electro-oculogram and may be a pathogenic mechanism in *BEST1* associated retinal dystrophy.

In this study we review retinal structural alterations investigated with spectral domain optical coherence tomography (SD-OCT), in young patients aged 10 years of less with Best disease, caused by dominant mutations in the *BEST1* gene. These findings are of particular interest in light of the recent advances in gene therapy in an animal model of vitelliform macular dystrophy, namely canine multifocal retinopathy, for which gene therapy has shown sustained therapeutic effect (Guziewicz K et al. IOVS 2013;54:ARVO E-Abstract 5965) [9]. There may exist a therapeutic window for gene therapy, in the sense of replacing the defective gene product with its wild-type counterpart, before irreversible structural damage occurs, such as fibrosis. Furthermore, considering that later stages of Best disease may be characterized by non-specific outer retinal structural alterations resulting from subretinal fluid and defective phagocytosis of rod and cone outer segments [6], analysis of the earliest stages of this disorder may reveal significant insights into its pathophysiology. For these reasons it may relevant to study natural course manifesting as retinal structure alterations in young patients with Best disease.

METHODS

This retrospective study included 4 patients aged 10 years or less with Best disease identified at the National Low Vision Eye Clinic (Kennedy Center), a national referral center which offers specialized diagnostics and optical rehabilitation in Denmark. Genotypes and some phenotypic aspects including imaging were previously presented by us [6,10,11]. Herein we present an analysis of retinal structure based on previously not published imaging. This was not a systematic evaluation of a treatment or a device. The tenets of the Declaration of Helsinki were followed and all federal or state laws in the countries (Denmark, Israel and Sweden) involved in the study. Institutional review board approval is not granted for retrospective studies in Denmark.

Clinical investigations

Standard clinical examination was performed. Horizontal macular SD-OCT scans were obtained with Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany and Cirrus OCT; Carl Zeiss Meditec, Dublin, US) in both eyes of all patients [6,12,13]. Intravenous fluorescein angiography was performed in 1 of the patients.

RESULTS

Clinical findings

All patients presented at or before age 10 years (Table 1), with findings as presented in Figures 1-4. These ranged from a subtle thickening at the level of the retinal pigment epithelium- photoreceptor interdigitation line as seen in the youngest case (Fig. 2 Bottom), through subretinal fluid and more pronounced accumulations at or above the retinal pigment epithelium (Fig. 3), to choroidal neovascularization membrane and cystoid macular edema as seen in patient IV (Fig. 4 Middle row). Unless there was a choroidal neovascularization membrane, the photoreceptor inner segment ellipsoid line (which is believed to result from an orderly arrangement of mitochondria in the photoreceptor inner segments) could be distinguished in all patients across the macular scans, seemingly unaffected. Furthermore, as seen in patients II and III (Fig. 2 Bottom and Fig. 3 Top), the retinal pigment epithelium-photoreceptor interdigitation line could be visualized above the vitelliform lesion, which seemed to be located external to this level. The vitelliform material seemed to lie above the retinal pigment epithelium as in Fig. 1 Top, however on the other hand it seemed to bulge the retinal pigment epithelium line from below as in Fig. 1 Bottom and Fig. 3 Bottom. In addition, wherever

subretinal fluid was present, the photoreceptor outer segments seemed thickened with precipitate-like alterations extending into the subretinal space (Fig. 3 Bottom and Fig. 4 Bottom).

One patient presented with generalized cystoid macular edema due to choroidal neovascularization membrane (Table 1 and Fig. 4). This was found in the right eye of a 10-year-old patient, heterozygous for *BEST1* p.Asp302Asn. The choroidal neovascularization was treated with a single intravitreal injection of 0.5 mg ranibizumab and photodynamic therapy with verteporfin, leading to resolution of macular edema and improvement of vision, from counting fingers before treatment to 0.2 decimal acuity at follow-up 1 month after treatment (Table 1, Fig. 4 Middle row). However some thinning of the retina and subretinal fibrosis was seen after treatment (Fig. 4 Middle row). The patient received 1 reinjection with 0.5 mg ranibizumab after 8 months, as some remaining paracentral subretinal fluid was suspected to result from further activity in the choroidal neovascularization membrane. At follow-up after 4 years, the best corrected decimal visual acuity in the treated right eye was 0.3, as compared to 1.0 in the untreated left eye. The central retinal thinning and subretinal fibrosis seen with SD-OCT after the first treatment (Fig. 4 Middle row), has remained essentially unchanged throughout follow-up. Furthermore, the subretinal fluid and precipitate-like alterations in the left eye have remained unchanged throughout follow-up (not shown).

DISCUSSION

As for many other hereditary retinal degenerations, Best disease is known for its variable expressivity and penetrance. Even with the constraints imposed by the criteria used in the current study - age equal to or less than 10 years and pathogenic mutations in the *BEST1* gene – clinical variability was evident.

Photoreceptor outer segment layer thickening may be an unspecific consequence of serous neurosensory retinal detachment, as described in central serous chorioretinopathy, and recently in Best disease by us [6,14]. The primary involvement of the retinal pigment epithelium in Best disease seems to lead to a thickening at the level of the retinal pigment epithelium-photoreceptor interdigitation line (as seen in the youngest patient in this series, Fig. 2 Bottom), perhaps as a result of defective phagocytosis of photoreceptor outer segments[6,15]. Subsequently subretinal fluid may develop (as seen in patient III, Fig. 3 Bottom), perhaps resulting from insufficient pumping mechanism of the retinal pigment epithelium, which normally keeps the subretinal space relatively dehydrated. In keeping with this

theory, we were able to visualize the retinal pigment epithelium-photoreceptor interdigitation line overlying a vitelliform lesion which seemed to be located external to this line (Fig. 3, Top). However caution is required as to the interpretation of the sequence of events regarding retinal structural alterations in Best disease and longitudinal studies with regular imaging should be carried out. Choroidal neovascularization may be relatively frequent in young patients with Best disease and was also reported in autosomal recessive bestrophinopathy [16-18]. Optimal treatment of neovascular complications in Best disease is not known, and some of the ensuing fibrosis may have been caused by the use of photodynamic therapy with verteporfin, in addition to the intravitreal injection of ranibizumab. Photodynamic therapy was used in order to avoid the need for multiple intravitreal injections, as each such procedure may require general anaesthesia/sedation in young children.

Limitations of the present study include small sample size, use of 2 different SD-OCT devices for patient IV (Fig. 4) and, except for patient IV, lack of longitudinal data. Furthermore, regarding potential sub-retinal pigment epithelium pathology, as in the lower panels of Figures 1 and 3, this may be better visualized with enhanced depth imaging (EDI) and averaging with the Spectralis machine, which was not carried out in this study.

As far as we are aware, in addition to this study, SD-OCT findings in young patients (equal or less than 10 years old) with Best disease were described previously by others as follows: 1 case (imaging presented) [19], in 2 cases (imaging presented) [3], in 3 cases (1 case with imaging presented) [20], and in 2 cases (imaging presented) [21]. In the study by Querques et al. [20], it seems that after a period of 63 months follow-up, subretinal fluid replaced vitelliform hyper-reflective material located between the photoreceptors and the retinal pigment epithelium, in a patient who presented with the latter finding at the age of 8 years. In another study by Querques et al. [19], an 8 year old case displayed an isolated thickening at the level of the retinal pigment epithelium-photoreceptor interdigitation line, similar to our patient II (Fig. 2 Bottom), a finding which may represent the earliest noticeable structural alteration by SD-OCT in Best disease. In 1 of the 2 cases presented by Bitner et al. [3], a pronounced bilateral thickening at the level of the retinal pigment epithelium-photoreceptor interdigitation line was seen already at the age of 2.5 years. Similar imaging findings were present in 2 patients, one of whom presented in the previtelliform stage, described by Ferrara et al. [21]. Thus the findings presented in the present study are consistent with previous descriptions and add further knowledge regarding the clinical variability of Best disease even before 10 years of age. Recently it has been shown that mutations in the *IMPG* (interphotoreceptor matrix proteoglycan 1) genes (*IMPG1* and *IMPG2*) may cause macular dystrophy,

with vitelliform material located above the retinal pigment epithelium, and with preservation of this epithelium by SD-OCT [22,23]. However onset occurred later than in Best disease, after 30 years of age [22,23].

To conclude, we present retinal structural changes by SD-OCT in young patients with Best disease. Photoreceptors seem to be preserved as demonstrated by intact inner segment ellipsoid layers and distinguishable retinal pigment epithelium-photoreceptor interdigitation lines, unless there is subretinal fluid or choroidal neovascularization. Our results suggest that such patients may be suitable candidates for future gene replacement therapy until at least 10 years of age and perhaps further. In case of the sudden development of a choroidal neovascularization membrane, this should be treated first, and retinal structure should be re-evaluated after treatment. Our data also highlight the importance of obtaining an early genetic diagnosis in patients and young family members, even before the appearance of any clinical symptoms which might be prevented or delayed with future therapies, such as gene therapy for the *BEST1* gene. Further longitudinal study including regular imaging is needed in order to elucidate the earliest pathogenetic sequence of retinal structural alterations in young patients with Best disease.

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c. Contributions to Authors:

Design of the study (PS, DS, SAH, SA, ML).

Conduct of the study (PS, DS, SAH, SA, ML).

Collection, management, analysis, and interpretation of the data (PS, DS, SAH, SA, ML).

Preparation, review and approval of the manuscript (PS, DS, SAH, SA, ML).

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e. Statement: Patrik Schatz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Conflict of Interest statement: All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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FIGURE CAPTIONS

Figure 1. Patient I: Imaging of right and left eyes of a 6 year old patient with the mutation c.275G>A, p.Arg92His in *BEST1*.

Top: Right eye: Spectral domain optical coherence tomography (SD-OCT) shows outer retinal material accumulation (red asterisk) between the retinal pigment epithelium (blue arrow) and the photoreceptors (red arrow shows the photoreceptor inner segment ellipsoid line).

Bottom: Left eye: SD-OCT shows outer retinal material accumulation (red asterisk) between the retinal pigment epithelium (blue arrow) and the photoreceptors (red arrow shows the photoreceptor inner segment ellipsoid line). Compared to the upper panel, the retinal pigment epithelium line cannot be distinguished beneath the vitelliform material, probably due to shadowing from this material. It cannot be excluded that some of the material is located at the level of, or below, the retinal pigment epithelium. In addition, there is thinning of the inner nuclear layer.

Figure 2. Patient II: Imaging of right and left eyes of a 6 year old patient with the homozygous mutation c.936C>A, p.Asp312Glu in *BEST1*.

Top: Right eye: Spectral domain optical coherence tomography (SD-OCT) shows normal retinal layers.

Bottom: Left eye: SD-OCT shows subtle thickening at the level of the retinal pigment epithelium-photoreceptor interdigitation line (red arrows).

Figure 3. Patient III: Imaging of right and left eyes of a 9 year old patient with the homozygous mutation c.936C>A, p.Asp312Glu in *BEST1*.

Top: Right eye: Spectral domain optical coherence tomography (SD-OCT) shows outer retinal material accumulation between retinal pigment epithelium and photoreceptors. The retinal pigment epithelium-photoreceptor interdigitation line seems to be located above the lesion (red arrows).

Bottom: Left eye: SD-OCT shows outer retinal material accumulation at the level of the photoreceptor outer segments, which may represent elongated photoreceptor outer segments (red arrows), subretinal fluid (blue asterisk) and vitelliform material that seems to reside on Bruch´s membrane, or below the retinal pigment epithelium (red asterisk).

Figure 4. Patient IV: Imaging of both eyes of a 10 year old patient with the mutation c.904G>A, p.Asp302Asn in *BEST1*, who received treatment in the right eye with intravitreal injection of ranibizumab and photodynamic therapy with verteporfin due to choroidal neovascularization. Visual acuity in the right eye two months earlier was 0.2 and had decreased to counting fingers at the time of presentation with choroidal neovascularization.

Top row. Right eye. Left: Fundus, middle: 40 second fluorescein angiography (FA) frame and right: eight- minute FA frame, before treatment. Bleeding (blue arrow) and leakage indicate activity from choroidal neovascularization.

Middle row. Right eye. Left panel. Spectral domain optical coherence tomography (SD-OCT) before treatment. Intraretinal cystoid edema. Right panel. Optical coherence tomography 1 month after treatment. Resolution of intraretinal edema. Subretinal fibrosis (blue asterisk) and neuroretinal thinning. Visual acuity 1 month after treatment: 0.2.

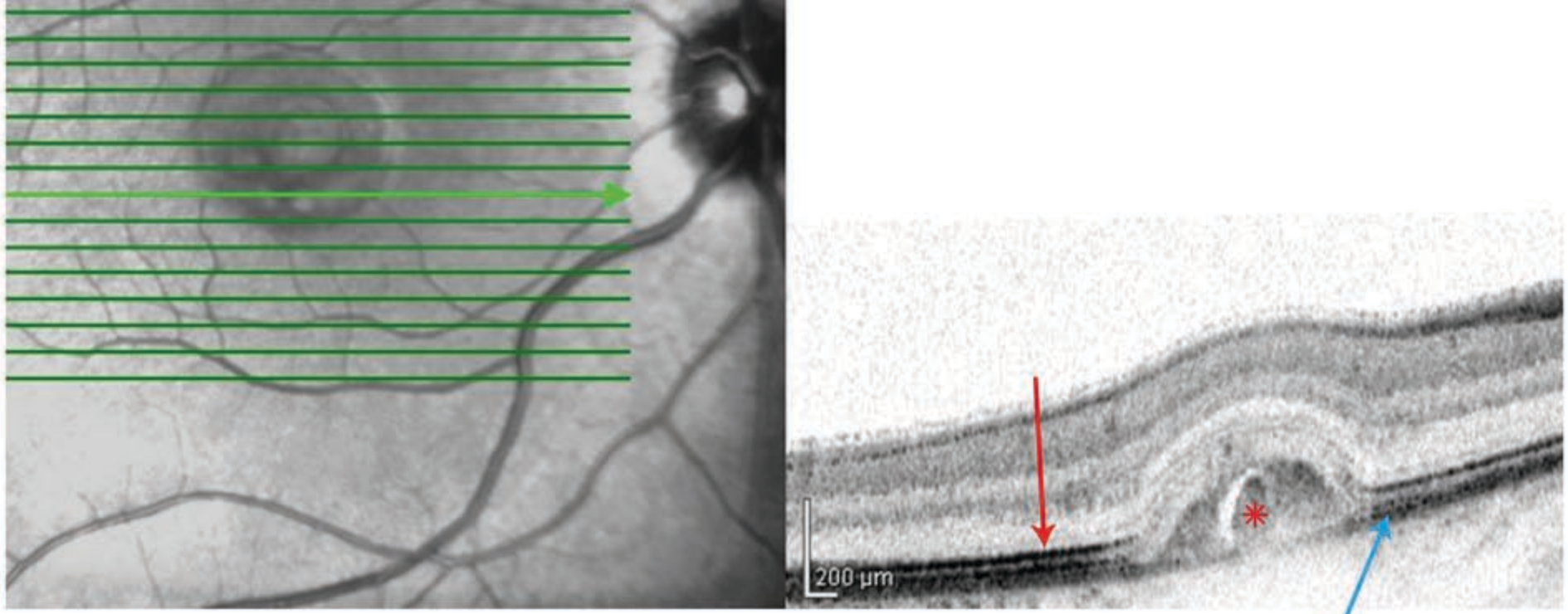
Bottom row: Left eye. SD-OCT shows outer retinal material accumulation at the level of the photoreceptor outer segments, which may represent elongated photoreceptor outer segments (red arrow) and subretinal fluid (blue asterisk).

Table 1. Genetic and clinical data at presentation, and reference for each of the young patients aged 10 years or less with Best disease. Patient I-IV correspond to Figs. 1-4, respectively.

Patient	Gender age	*BEST1* genotype (mutation and effect on protein)	Stage OD, OS	Optical coherence tomography findings OD/OS	Visual acuity at presentation OD, OS	Reference
I	M 6	c.275G>A p.Arg92His	Vitelliform, Vitelliform	Hyperreflective material between the RPE and photoreceptors/Bulging of the RPE	0.8, 0.8	Schatz et al [10].
II	M 6	c.936C>A* p.Asp312Glu*	Vitelliform, Vitelliform	Normal/Thickened RPE-photoreceptor interdigitation line	0.7, 0.7	Schatz et al [10]. Piñeiro-Gallego et al [11].
III	M 9	c.936C>A* p.Asp312Glu*	Vitelliform, Multifocal Vitelliform	Hyperreflective material accumulation between the RPE or BM and the photoreceptors/As for OD and in addition SRF and elongation of the POS	0.5, 0.4	Schatz et al [10]. Piñeiro-Gallego et al [11].
IV	M 10	c.904G>A p.Asp302Asn	Choroidal Neovascularization, Vitelliform	Cystoid macular edema and SRF/SRF and elongation of the POS	0.2, 0.2	Bitner et al [6].

Abbreviations: OD=right eye. OS=left eye. Retinal pigment epithelium=RPE. Bruch's membrane=BM. Photoreceptor outer segments=PO. Subretinal fluid=SRF.

* Homozygous mutation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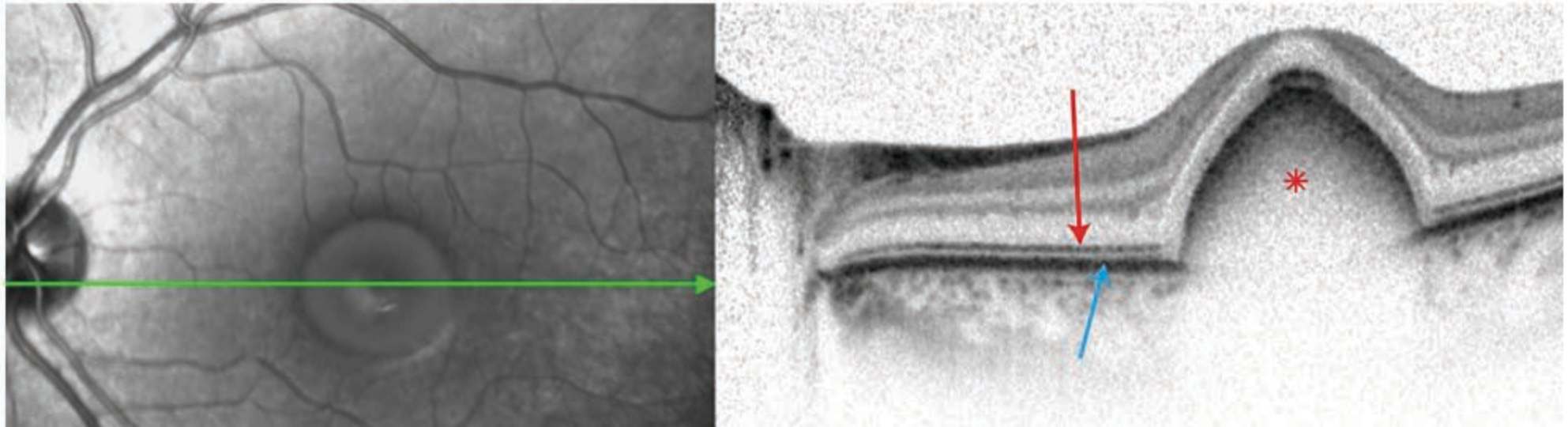

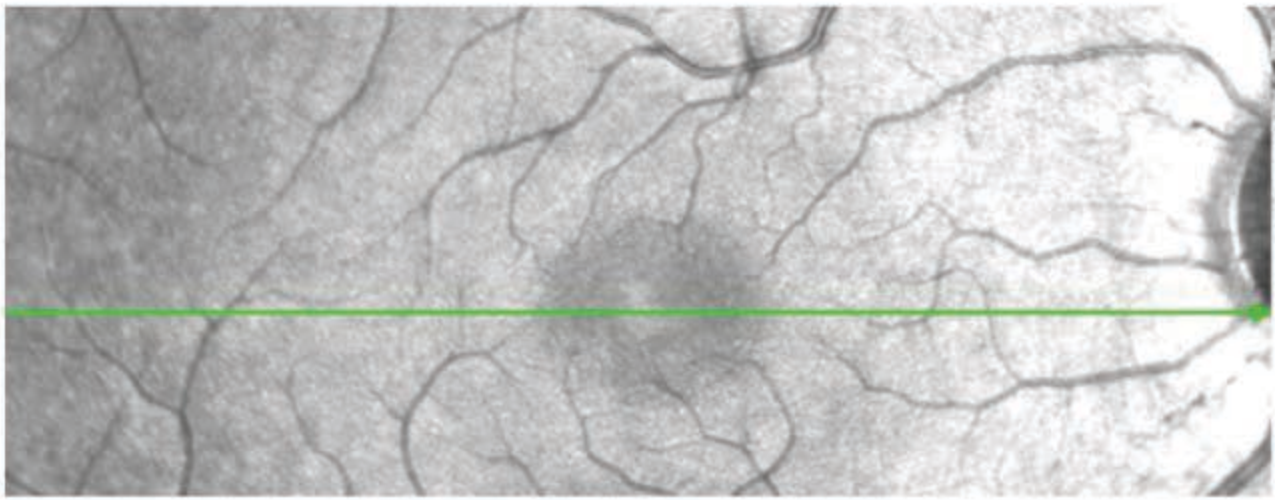

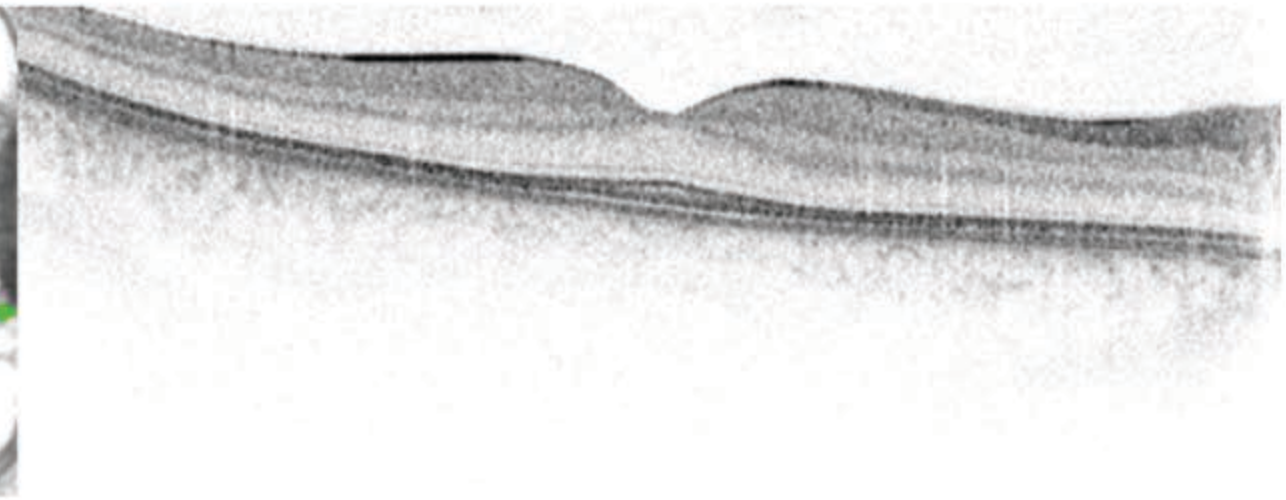

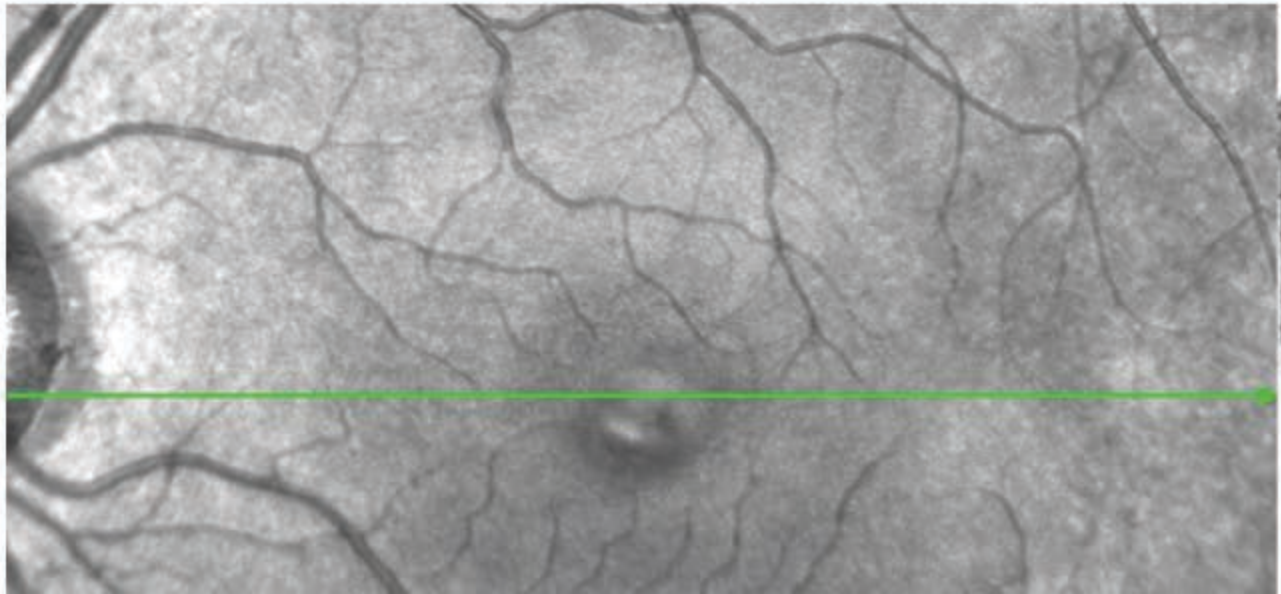

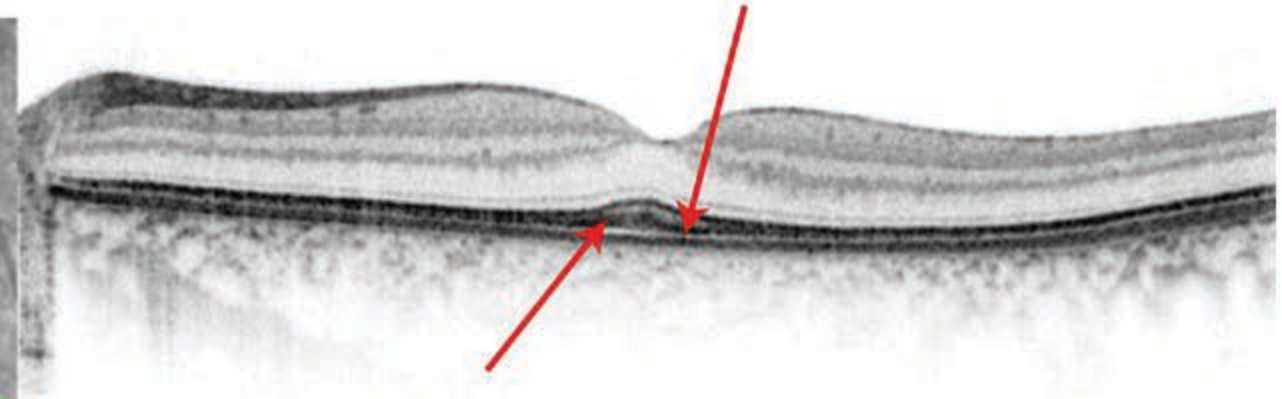

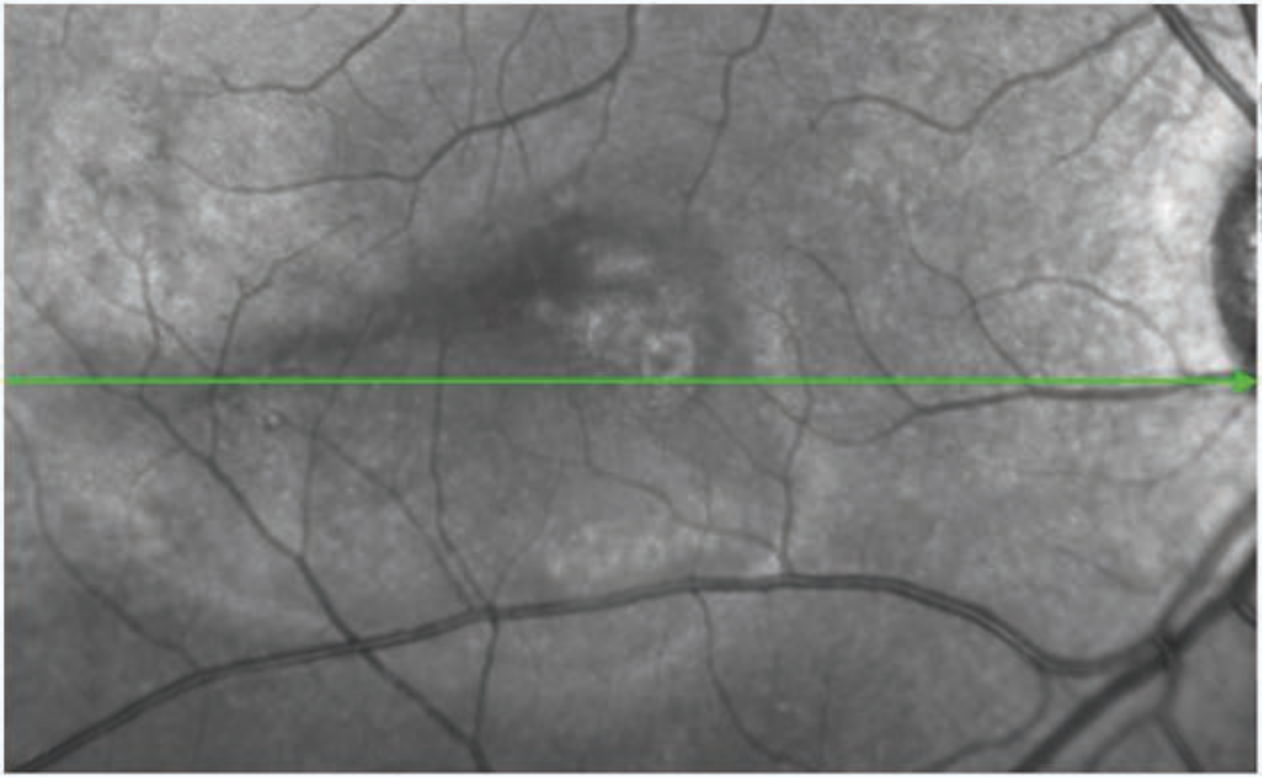

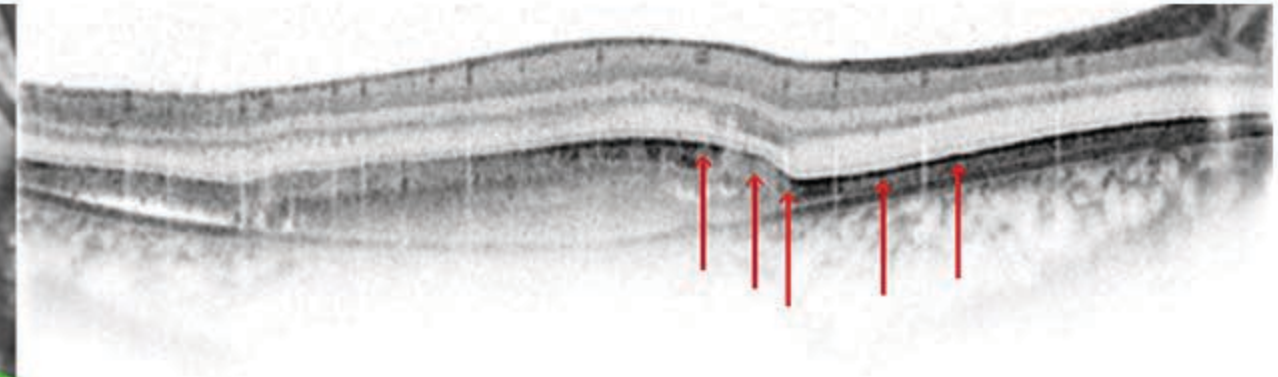

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