Three-dimensional spectral domain optical coherence tomography in Stargardt disease and fundus flavimaculatus

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Introduction

Stargardt disease (STGD) is an autosomal recessive macular dystrophy of childhood, characterised by juvenile onset, rapid progression and a poor visual outcome [1–3]. On the other hand, fundus flavimaculatus (FFM), a Stargardt-like phenotype, is characterised by late onset and slow progression [4]. The disease is usually termed STGD when visual acuity loss begins in the first two decades, while the term FFM is favored when the disease begins at the end of the second or in the third decade. Genetic studies demonstrated that both STGD and FFM are linked with the ABCA4 gene, which encodes an ATP-binding cassette transporter protein that is expressed by rod outer segments. Histological analyses show the accumulation of lipofuscin, a lipid-containing fluorophoric by-product of photoreceptor digestion, within retinal pigment epithelium (RPE) cells [5–9]. Both lead to central macular atrophy and thus loss of central vision (<20/200).

Three-dimensional spectral-domain optical coherence tomography (SD-OCT) is being reported for the first time in Stargardt disease and fundus flavimaculatus.

Materials and methods

The authors confirm adherence to the tenets of the Declaration of Helsinki. After taking a written informed consent, spectral domain optical coherence tomography [Cirrus high definition OCT (Carl Zeiss Meditec Inc.), CA, USA] was performed in cases of Stargardt disease and fundus flavimaculatus.

Case report 1 A 16-year-old male patient presented in the outpatient department of our tertiary care centre with complaints of painless progressive diminution of vision in both the eyes since 4 years. Best corrected visual acuity of the patient was finger counting at 5 m in both eyes. Anterior segment examination was unremarkable in both the eyes. Fundus examination revealed central hypopigmented area of macular atrophy with pigmentary changes, which was surrounded by a transitional zone comprising of two areas inner hyperpigmented area surrounded by outer hypopigmented area (Fig. 1). There was also the presence of hypopigmented polymorphous flecks in both the eyes distributed all over the posterior pole. Fundus also showed wedge-shaped defect along the superior and inferior vascular arcades along with peripapillary thinning of nerve fibre layer. Fluorescein angiography showed dark choroid, and other features corresponded to the fundus findings of three zones—central hypofluorescent area, middle hyperfluorescent and outer hypofluorescent zone around it—with hyperfluorescent polymorphous areas corresponding to flecks, which showed staining in late stages.

SD-OCT revealed hyperplastic RPE in the fovea (Fig. 2a, b). Areas of irregular hyper-reflectivity were observed below the RPE. Irregular residual neurosensory retina was found to be present in the foveal region (Fig. 2b). Photoreceptor layer and external limiting membrane could not be differentiated from each other in the parafoveal region (Fig. 2a). 3D analysis exquisitely demonstrated location of flecks at different layers

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Fig. 1 Coloured fundus photograph in case of Stargardt disease shows the central hypopigmented area of macular atrophy (white arrow). Black arrow shows the transitional zone in different stages of photoreceptor disruption. Blue arrows show widely distributed flecks all over the posterior pole. Pink arrow shows the wedge-shaped defect in the retinal nerve fibre layer

of retina. Characteristic hyper-reflective deposits were present at the level of outer nuclear layer, RPE and also below the

Fig. 2 **a** Advanced macular visualisation shows central atrophic zone with irregular remnant of outer nuclear layer (white arrow). Irregular hyper-reflective areas can also be appreciated below the retinal pigment epithelium. In addition, hyperplastic retinal pigment epithelium can be observed in the foveal region. **b** Magnified view of foveal region shows remnants of neurosensory retina and hyperplastic retinal pigment epithelium

RPE (Figs. 3 and 4). Few flecks present at the level of outer nuclear layer showed anatomical connection with the one present at the level of RPE (Fig. 3). These hyper-reflective deposits corresponded to flecks as corroborated with scanning laser ophthalmoscopy (SLO) image. Furthermore, they were present as irregularities on the RPE map. Central subfield thickness was 103 μm in the right eye and 108 μm in the left eye, whereas macular cube average thickness was 195 μm in right eye and 190 μm in left eye.

Case report 2 A 36-year-old male patient presented in the outpatient department of our tertiary care centre with complaints of painless progressive diminution of vision in both the eyes since 7 years. Best corrected visual acuity of the patient was 20/200 in the right eye and finger counting at 5 m in the left eye. Anterior segment examination was unremarkable in both the eyes. Fundus examination revealed a well-defined central hypopigmented patch corresponded to the macular atrophy, which was surrounded by the transitional zone beyond which was the healthy retina (Fig. 5). The transitional zone consisted of two areas: inner hyperpigmented area surrounded by outer hypopigmented area. Hypopigmented polymorphous flecks were more uniformly distributed along the vascular arcades at the posterior pole. Wedge-shaped defect along the vascular arcades with peripapillary thinning of nerve fibre layer was also observed. Fundus fluorescein angiography showed the classic picture of dark choroid, central hypofluorescent area corresponding to macular atrophy and the hyperfluorescent transitional zone around it, which corresponded to the fundus findings. There was presence of hyperfluorescent polymorphous areas along the arcades corresponding to the flecks. The central hypofluorescent area and flecks showed staining in the late phases.

SD-OCT of both eyes revealed minimal residual neurosensory layer in the foveal region (Fig. 6a, b). The photoreceptor layer and external limiting membrane could not be discerned from each other. There was presence of irregular hyper-reflective areas below the RPE, which were more prominent subfoveal (Fig. 6b). Hyper-reflective deposits were present at the level of RPE only (Fig. 7). These hyper-reflective deposits corresponded to flecks as

Fig. 3 **a** Advanced 3D analysis shows retinal flecks below the retinal pigment epithelium further supported by the magnified view of area within *red dotted circle* (**b**). It also shows fleck at the level of outer nuclear layer, which has anatomical connection with the fleck at the level of retinal pigment epithelium, which can be more precisely appreciated by the magnified view of area enclosed in *red circle* (**c**)

corroborated with SLO image (Fig. 8). Central subfield thickness was 103 μm in the right eye and 93 μm in the left eye, whereas macular cube average thickness was 195 μm in the right eye and 208 μm in the left eye.

In our study, 3D SD-OCT comparative maps at different layers of retina were used to differentiate between STGD

and FFM for the first time (Fig. 9). The three maps on the right (Fig. 9, a1, b1 and c1) were obtained in case of STGD and the one on left (Fig. 9, a2, b2 and c2) in case of FFM. The internal limiting membrane (ILM)-RPE map (Fig. 9, a1 and a2) revealed the presence of two different zones: inner one representing central macular atrophy noted as accentuated foveal depression surrounded by outer transitional zone. The ILM map, however, helped us to differentiate between the two (Fig. 9, c1 and c2). The two zones were

Fig. 4 **a** Independent fleck at the level of outer nuclear layer (*area within black dotted circle*, **b** magnified view) fleck at the level of retinal pigment epithelium (*area enclosed in black circle*, **c** magnified view)

Fig. 5 Coloured fundus photograph shows central macular atrophy (*white arrowhead*) surrounded by the transitional zone (*white arrow*). *Black arrows* show flecks localised along vascular arcades. *Blue arrow* shows defect in the retinal nerve fibre layer

very well defined in the case of FFM as two concentric rings, whereas in STGD, there was presence of only an ill-defined depression at the centre. The RPE further supported

the finding of widespread flecks over the posterior pole of retina in STGD, which were present as irregularities throughout the map, whereas they were localised at the centre in the case of FFM (Fig. 9, b1 and b2).

Fig. 6 **a** Advanced visualisation of macula shows central atrophy with minimal remnant of neurosensory retina in the foveal region (*white arrow*). Irregular hyper-reflectivity more prominent sub-foveal can also be appreciated. **b** Magnified view of foveal region shows minimal remnant of neurosensory retina with enhanced irregular reflectivity in subfoveal region

Discussion

The difference in STGD and FFM remains controversial. Over a period of time after immense research in this field, scientists have come to the conclusion that both are the same entity occurring from mutation in the same gene and differ

Fig. 7 **a, b** Advanced 3D visualisation shows flecks at the level of retinal pigment epithelium further revealed on magnified view of area enclosed in *black circle*

Fig. 8 SLO image with corresponding advanced visualisation of fundus on SD-OCT. A section in the SLO image passing through three prominent flecks shows corresponding hyper reflective deposits on 3D analysis

only in the age of presentation. In the present study, we have discussed two cases: one is a 16-year-old male patient and the other is a 36-year-old male patient, both presented with similar complaint of gradual diminution of vision but duration of history was shorter in the younger patient. The age of presentation and progression in both cases can be correlated with juvenile onset and rapid progression in STGD, whereas they can be correlated with late onset and slower progression in FFM.

Fundus examination in the case of STGD (Fig. 1) showed larger central hypopigmented area surrounded by the transitional zone as compared to FFM (Fig. 6). The central hypopigmented zone corresponded to the central macular atrophy with complete loss of photoreceptor layer and only minimum remnants of ONL as seen in the advanced macular visualisation. The transitional zone may be hypothesised to be the area in the process of photoreceptor disruption. This zone is further divided into two, signifying that the disruption is at different stages resulting in the formation of one hyperpigmented and one hypopigmented region. Three-dimensional SD-OCT imaging for the first time demonstrates this zonal division of hypo- and hyperpigmented

areas. The ILM-RPE (Fig. 9, a1 and a2) maps are, for the first time, being used and revealed two concentric ring like pattern for the two zones in both STGD and FFM. On analysis of single ILM map (Fig. 9, c1 and c2), a differentiating feature was observed; the two zones were much better defined in the case of FFM as compared to STGD. Another distinguishing feature was the presence of hyperplastic RPE in the foveal region in the case of STGD, which was not observed in FFM. Irregular hyper-reflectivity below the RPE was more prominent subfoveal in the case of FFM, which was not observed in STGD.

Flecks were characteristically present in both STGD and FFM. Nature of flecks has also been debated. Klein et al. [10] established the presence of mucopolysaccharide deposits (hyaluronic acid) in retinal cells, whereas Eagle et al. [11] found a massive accumulation of lipofuscin in the RPE cells. Despite some histological reports, the exact location of the retinal flecks within the retinal layers remains controversial. In two separate studies by Voigt et al. [12] and Prato et al. [13], their location has been classified at two different levels—type 1 at the level of RPE and type 2 at the level of ONL. They have related their presence to the disease

Fig. 9 a1, a2 ILM-RPE maps showing the two areas of central macular atrophy and the transitional zone in Stargardt disease and fundus flavimaculates, respectively. b1, b2 RPE maps showing irregularities corresponding to the flecks, more widespread in Stargardt disease (b1) as compared to FFM (b2). The ILM map shows the two zones of central macular atrophy and the transitional zone much more distinct in fundus flavimaculatus as two concentric rings (c1) as compared to Stargardt disease (c2)

progression and have reported that the presence of type 2 lesions were always associated with presence of type 1 lesions. It was speculated that type 2 deposits could be the residual cover of the dome-shaped type 1 lesion as consistent with the natural history of the flecks, which progressively degrade from a well-defined lesion to residual material. Another study by Voigt et al. [14] demonstrated presence of flecks at five different levels group A–E in FFM. Group A lesions were limited to the outer segment (OS) of the photoreceptors, the RPE interdigitations, and the RPE/Bruch membrane complex. Group B showed a protrusion of the hyper-reflective material through the interface of inner segment (IS)/OS of the photoreceptors up to the external limiting membrane. A further protrusion of the hyper-reflective material into the outer nuclear layer was seen in group C lesions. Group D lesions were characterised by an accumulation of the hyper-reflective material limited to the outer nuclear layer. Type E lesions were described as drusen-like retinal pigment detachments. Another study by Verdina et al. [15] showed the absence of isolated flecks at ONL and reported that there was presence of anatomical connection between all the hyper-reflective flecks at the level of ONL with the one present at the level of RPE.

In the present study, three-dimensional SD-OCT imaging provided novel findings showing presence of hyper-reflective flecks not only at the level of RPE and ONL but also at sub-RPE level (Figs. 3 and 4) in the case of STGD. On the contrary in FFM, the presence of hyper-reflective flecks was observed only at the level of RPE (Fig. 7a, b). Thus, in the light of anatomical location of flecks in the different layers of the retina, we can hypothesise that there is simultaneous disruption of outer layers of retina in STGD. In addition, the presence of flecks at the level of ONL, which were anatomically connected to the one at the RPE in STGD, supported the hypothesis of simultaneous disruption of outer layers of retina (Fig. 3c). The distribution of flecks further helps us to conclude that the disease process is widespread in STGD with distribution of flecks all over the posterior pole of retina, whereas in FFM, they were present only along the vascular arcades (Figs. 1 and 5). The RPE map also for the first time shows similar findings with widespread irregularities in STGD, which represented flecks as compared to localised irregularities noted in FFM (Fig. 9, b1 and b2).

Three-dimensional SD-OCT provided novel insight into the in vivo histology and pathogenesis of Stargardt disease and fundus flavimaculatus.

References

1. Stargardt K. Ueber familiäre progressive degeneration in der makulagegend des Auges. Albrecht V Graefes Arch Ophthalmol. 1909;71:534–50.
2. Cibis GW, Morey M, Karris DJ. Dominantly inherited macular dystrophy with flecks (Stargardt). Arch Ophthalmol. 1980;98:1785.
3. Merlin S, Landau J. Abnormal findings in relatives of patients with juvenile hereditary macular degeneration (Stargardt disease). Ophthalmologica. 1970;16:114.
4. Franceschetti A, Francois J. Fundus flavimaculatus. Arch Ophthalmol. 1965;25:505.
5. Birnbach CD, Jarvelainen M, Possin DE, Milam AH. Histopathology and immunocytochemistry of the neurosensory retina in fundus flavimaculatus. Ophthalmology. 1994;101:1211–9.
6. Eagle Jr RC, Lucier AC, Bernardino Jr VB, Yanoff M. Retinal pigment epithelial abnormalities in fundus flavimaculatus: a light and electron microscopic study. Ophthalmology. 1980;87:1189–200.
7. McDonnell PJ, Kivlin JD, Maumenee IH, Green WR. Fundus flavimaculatus without maculopathy: a clinicopathologic study. Ophthalmology. 1986;93:116–9.
8. Steinmetz RL, Garner A, Maguire JJ, Bird AC. Histopathology of incipient fundus flavimaculatus. Ophthalmology. 1991;98:953–6.
9. Lopez PF, Maumenee IH, de la Cruz Z, Green WR. Autosomal-dominant fundus flavimaculatus: clinicopathologic correlation. Ophthalmology. 1990;97:798–809.
10. Klein BA, Krill AE. Fundus flavimaculatus: clinical, functional and histopathological observations. Am J Ophthalmol. 1967;64:3–23.
11. Eagle RC, Lucier AC, Bernadino VB, et al. Retinal pigment epithelial abnormalities in fundus flavimaculatus. Ophthalmol Soc. 1980;84:453–87.
12. Querques G, Leveziel N, Benhamou N, Voigt M, Soubrane G, Souied EH. Analysis of retinal flecks in fundus flavimaculatus using optical coherence tomography. Br J Ophthalmol. 2006;90(9):1157–62.
13. Querques G, Prato R, Coscas G, Soubrane G, Souied EH. In vivo visualization of photoreceptor layer and lipofuscin accumulation in Stargardt's disease and fundus flavimaculatus by high resolution spectral-domain optical coherence tomography. Clin Ophthalmol. 2009;3:693–9.
14. Voigt M, Querques G, Atmani K, Leveziel N, Massamba N, Puche N, Bouzitou-Mfoumou R, Souied EH. Analysis of retinal flecks in fundus flavimaculatus using high-definition spectral-domain optical coherence tomography. Am J Ophthalmol. 2010;150(3):330.
15. Verdina T, Tsang SH, Greenstein VC, Zernant J, Sodi A, Lima LH, Chang S, Allikmets R, Menchini U. Functional analysis of retinal flecks in stargardt disease. J Clin Exp Ophthalmol. 2012;3:6.