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Use of multifocal ERG and OCT for diagnosing Stargardt's disease

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Stargardt's disease (Stargardt's macular dystrophy, juvenile macular degeneration) was originally described by Stargardt in the early 1900s and is known as the most common congenital macular dystrophy, with an incidence of one in every 10,000. Stargardt's disease (STGD) is characterised as a widespread lipofusin storage disease of the retinal pigment epithelium (RPE). Typically, it presents between the first to third decades of life and is associated with a progressive, bilateral decrease in visual acuity leading to legal blindness and central visual acuity of 6/60 to 6/120. Though it is typically associated with an autosomal recessive (AR) inheritance pattern, autosomal dominant (AD) cases have been reported with later onset and less severe acuity loss.[1,2] Classic findings include bilateral macular changes that begin as granular mottling with progression toward a 'beaten bronze' maculopathy. The late stage of the disease is associated with macular atrophic degeneration. Yellow-white flecks in the posterior pole may be noted; they are described as tri-radiating 'fish tail' (pisciform) flecks. Traditionally, Stargardt's disease has been diagnosed through clinical evaluation and fluorescein angiography (IVFA), which demonstrates a dark or 'silent' choroid due to the blockage of the fluorescein by the lipofusin deposition in the RPE. Though fluorescein angiography has been considered the 'gold standard' in verifying the presence of the disease, the characteristic dark choroid pattern is seen in only 85 per cent of patients with Stargardt's disease. There have been reports of patients with autosomal dominant inheritance pattern who fail to demonstrate this classic fluorescein angiography finding.[1,2] Newer and minimally invasive procedures, such as the multifocal electroretinogram (mfERG) and optical coherence tomography (OCT), may aid in diagnosing and managing patients with the disease. These ancillary tests may be used in the event that fluorescein angiography cannot be performed or used in conjunction with traditional fluorescein angiography as a complementary procedure.

Multifocal electroretinography (mfERG) is a minimally invasive procedure that has been shown to be helpful in the diagnosis of Stargardt's disease.[3] Unlike traditional flash electroretinography (fERG), this technology has proved extremely reliable in diagnosing and monitoring various forms of macular dystrophy.[3] In the case of Stargardt's disease, the patient presents with significant variation in presentation; from normal to reduced acuity, minimal to significant fundus findings and normal to slightly reduced full field flash electrophysiological findings. Regardless of the presentation, Stargardt's patients typically have a significant reduction of the foveal response and central approximately 10 degrees in both eyes on mfERG, even early in the disease process with relatively good visual acuity and minimal fundus findings.[3]

In addition to electrophysiology, retinal imaging technology such as OCT has proved effective in correlating structural damage with functional visual loss. The OCT findings of patients with Stargardt's disease include decreased thickness of the retina, most notably in the foveola. The OCT also reveals photoreceptor loss and external nuclear layer changes, as well as abnormalities in the retinal pigment epithelium.[4]

DISCUSSION

Stargardt's disease is generally considered to be an autosomal recessive disease most commonly associated with an abnormality of the ABCA4 gene (ATP-binding cassette). Mutations of this gene have also been reported in association with other inherited diseases such as cone-rod dystrophies, autosomal recessive retinitis pigmentosa (RP), autosomal recessive fundus flavimaculatus and age-related maculopathy.[5,6] Therefore, ABCA4 mutations are

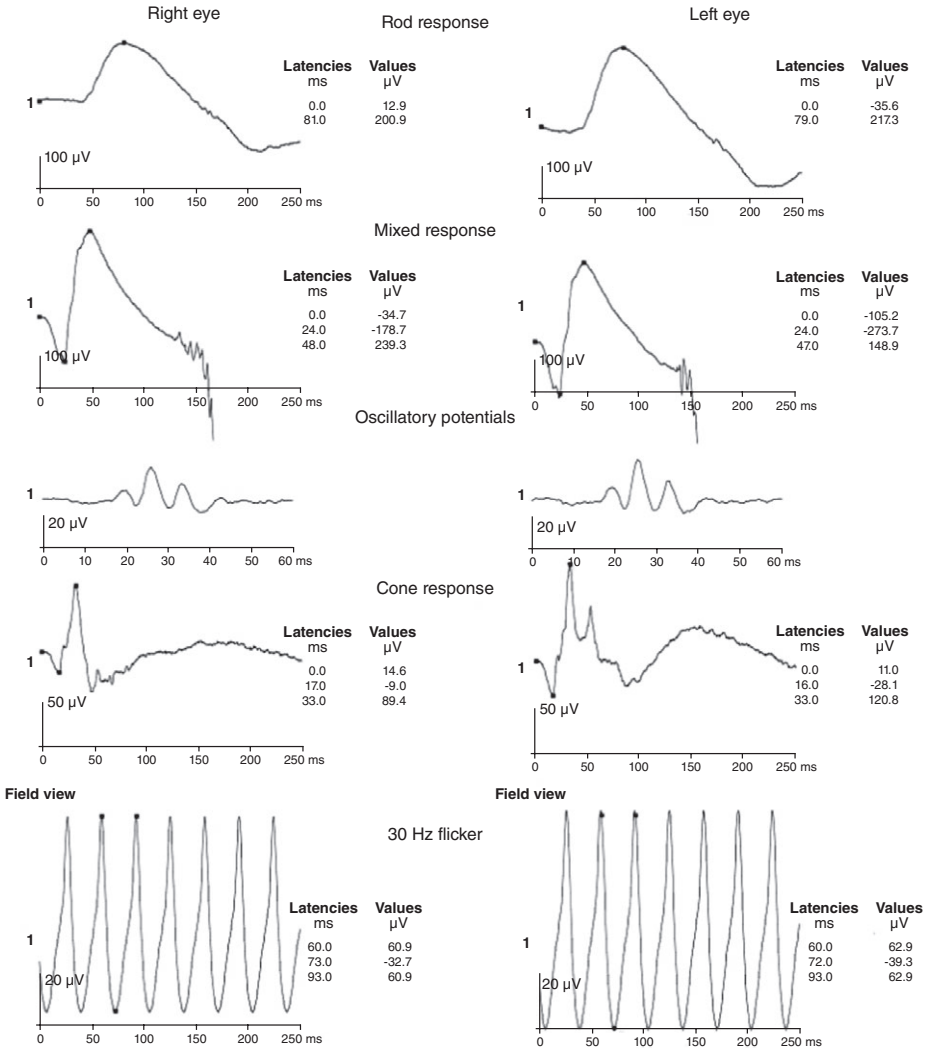

Figure 1. Normal flash ERG of patient with Stargardt's disease presenting with visual acuities (VA) of 'count fingers' OD and 6/9 OS. While a slight attenuation to waveforms can be seen in the OD compared to OS, all measurements for rod and cone responses were robust and well within normal limits.

not only linked to the 'classic' Stargardt's disease but may overlap with various other retinal degenerations.[5] The ELOVL4 gene has been linked with autosomal dominant Stargardt's disease as well as macular degenerations in general.[6]

Electrophysiological testing has been used for years in diagnosing patients with congenital fundus dystrophies, such as retinitis pigmentosa and cone dystrophy. The traditional flash ERG is most helpful in patients with widespread disease or severe fundus involvement. In the case of Stargardt's disease, the retinal degeneration is in the outer retina and most clinical dysfunction involves the macular region. Therefore, historically the flash ERG has not been helpful in establishing this diagnosis[3] (Figure 1). The advent of the multifocal electroretinogram has increased the clinical applications for electrophysiological testing of more localised diseases including Stargardt's disease.

The conventional fast-flicker mfERG is an electrophysiological test similar to flash ERG in that it primarily measures the outer retinal response. The commonly used conventional fast-flicker mfERG stimulus measures only the photopic response and uses mathematical extractions to produce multiple waveforms representing central retinal cone responses. This is in contrast to the flash ERG, which gives a summed, global response of overall outer retinal function and tests both the rod and cone systems. The mfERG uses 61 to 241 hexagon targets (with 103 points being the most commonly used clinically) that alternate between white and black, and maps the central 40 to 50 degrees of the patient's retinal function. By using a slow-flash mfERG (sf-mfERG) testing paradigm, it is possible to look at inner retinal responses by inserting a dark frame between the alternating white to black stimulus, giving what are called multifocal oscillatory potentials.[7] Another way to enhance the inner retinal response is to add a white flash between two dark frames in the sf-mfERG, which is referred to as a global-flash mfERG.[8] While neither slow-flash nor global flash mfERGs is typically used in electrophysiological testing of Stargardt's disease patients, these procedures may become more widespread and add to our Stargardt's disease diagnostic paradigm in the future. No matter which testing paradigm is used, unlike traditional flash ERG, mfERG testing allows for localisation and topographic mapping of small lesions of retinal pathology within the central fundus. In addition, mfERG is particularly useful in patients with normal to minimal fundus changes, where the diagnosis may be clinically challenging on examination.

In patients with Stargardt's disease, the mfERG results typically demonstrate markedly reduced foveal and central retinal function, even in the presence of minimal retinal findings or normal acuity.[3,9] Another mfERG finding consistent with Stargardt's disease is the lack of a marked or progressive delay in the first-order implicit times or latency in contrast to the significant delay usually seen in patients with cone dystrophy[3] (Figure 2). First-order responses are mathematically

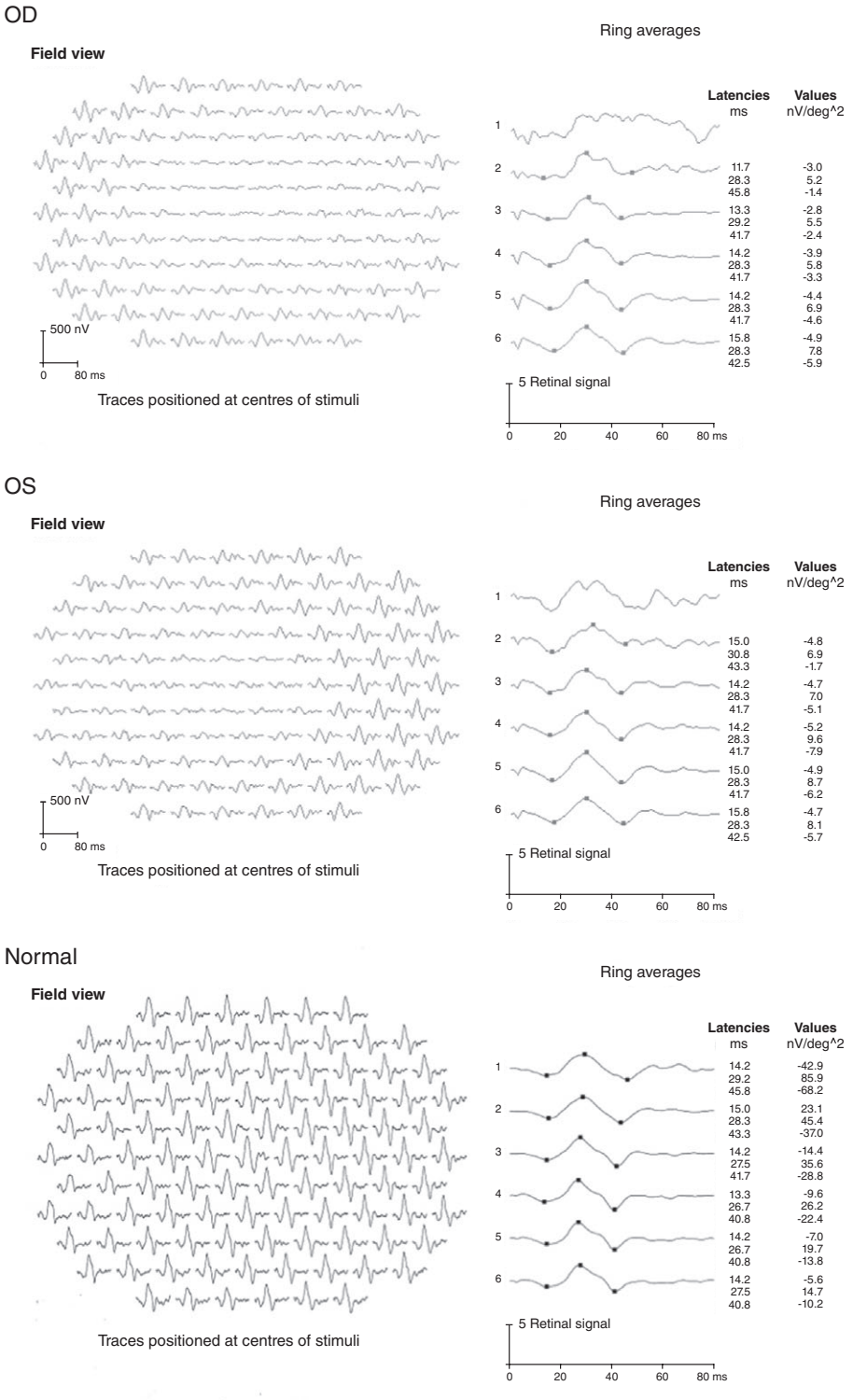

Figure 2. mfERG trace arrays and ring group averages from the patient in Figure 1. Ring averages expand out from the fovea based on retinal eccentricity starting from fovea (ring 1) to the peripheral macula (ring 6). Note that attenuation of the waveform is most marked for ring 1 and by ring 3 has approached our normative database. Also note that there is no significant increase in implicit time between the patient and normal. The finding of a robust flash ERG in this patient is not surprising, based on the cone involvement being primarily limited to the central rings with mfERG testing.

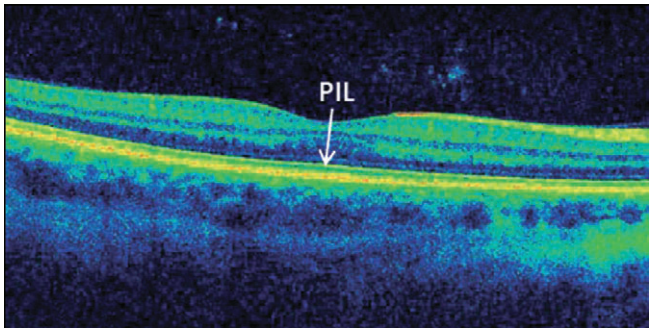

Figure 3A. Spectral domain OCT on a patient with Stargardt's disease with 6/6 visual acuity and an intact photoreceptor integrity line (PIL) (arrow)

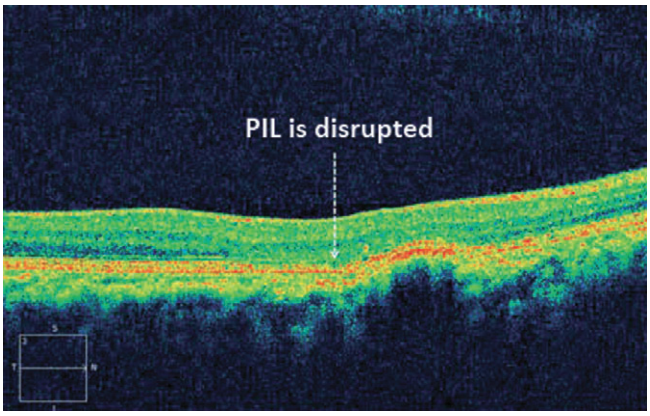

Figure 3B. Spectral domain OCT of the same patient's other eye with significantly reduced visual acuity and a disrupted photoreceptor integrity line (PIL) (arrow)

extracted waveforms that represent the retinal response present in the tested areas (that is, hexagons) each time the bright stimulus is presented. Some patients with Stargardt's disease will show an increased implicit time throughout the mfERG testing area including the peripheral rings, reflecting more widespread retinal damage and usually indicating a worse long-term visual prognosis.[9]

A mfERG staging system developed by Kretschmann and colleagues[3] breaks the results of mfERG testing with Stargardt's disease into five classes:

Class I limits the reduced response to the central 2 rings (approximately 7°)

Class II involves the central three rings (approximately 12°)

Class III involves the entire mfERG testing area (approximately 30°) but with a normal flash ERG

Class IV adds a pathologic flash ERG

Class V, in which the mfERG findings are atypical or absent.

A mfERG that reveals markedly reduced macular amplitude response that approaches normal in the peripheral rings with no significant or just a slight increase in latency (that is, Class II) is the most consistent finding reported on mfERG testing in patients with Stargardt's disease and is not typically seen in other pattern or macular dystrophies.[2,3]

Though the mfERG responses are diminished early in the course of the disease, there is a weak correlation between the mfERG response and visual acuity.[3] For this reason, clinical correlation with other ancillary testing, such as OCT, may help to explain the patient's visual acuity.

Optical coherence tomography is an invaluable tool in the assessment of a number of macular conditions. This diagnostic modality is capable of providing a high resolution cross-sectional image of the retina. Even though OCT has been used in the ophthalmic community for the past decade, we are just beginning to understand its value in the evaluation of a number of retinal diseases. The use of OCT has aided in the evaluation of a number of retinal dystrophies, including retinitis pigmentosa, cone dystrophy, Best's disease and Stargardt's disease. Through detailed images obtained with OCT, clinicians can further evaluate morphologic changes associated with these dystrophies.

In Stargardt's disease, the ability for the OCT to provide a detailed image of the retina has offered new insights into the understanding of the pathogenesis. Stargardt's disease is associated with slow, progressive damage to the RPE cells and overlying photoreceptors, leading to decreased central visual function. In the OCT of a Stargardt's patient morphologic change is depicted as a disorganisation of the retinal layers, thinning of the retinal outer layers and enhanced choroidal reflectivity associated with overlying atrophic retina. Loss of photoreceptors would correlate with a decrease in central visual function. The ability for the new generation OCT (spectral domain) to allow for further visualisation of the inner and outer segment junction of the photoreceptors (photoreceptor integrity line or 'PIL') has enhanced our capability to correlate structure with function. Spectral domain (SD) OCT, with axial resolution of up to three microns, is able to demonstrate an *in vivo* visualisation of the inner segment (IS) and outer segment OS) photoreceptor layers. This unprecedented axial resolution approaches that of conventional histopathology studies.

The outer nuclear layer is a region of low reflectivity, extending from the outer border of the outer plexiform layer to the line of moderate reflectivity formed by the external limiting membrane. The innermost line of high reflectivity under the outer nuclear layer is formed by the junction between the IS and OS of the photoreceptors. This line is known as the IS/OS boundary or photoreceptor integrity line[10] (Figure 3).

Ergun and associates[4] used ultra-high resolution OCT (UHR-OCT) to assess central visual structure and function in Stargardt's disease/fundus flavimaculatus. The purpose of this study was to examine whether UHR-OCT can visualise and quantify transverse photoreceptor loss, in particular focal loss, and compare this with the patient's visual acuity. They concluded that an intact photoreceptor integrity line leads to better visual acuity compared to those patients with a disorganised or absent photoreceptor integrity line.[4]

Querques and co-workers[11] described two types of hyper-reflective deposits on SD-OCT of patients with Stargardt's disease. Type 1 lesions were located within the RPE layer and at the level of the outer segments of the photoreceptors. Type 2 lesions were located at the level of the outer nuclear layer and clearly separated from the RPE layer. Type 1 lesions alone were associated with absence or loss of the photoreceptor layer in the foveal region in all eyes; type 2 lesions were always associated with the presence of type 1 lesions and often associated with loss of the photoreceptor layer within the foveal region.[11]

Witkin and colleagues[10] summarised the correlation of potential OCT abnormalities, particularly the integrity of the IS/OS boundary, with visual function deficits in several diseases in which photoreceptor damage was considered to be the primary site of damage.[10] Therefore, SD OCT can provide important adjunct diagnostic information to assess the status and prognosis of patients with Stargardt's disease.

In the OCT analysis of Stargardt's disease, thickness maps show drastic retinal thinning in the macula. These quantitative measurements not only support the diagnosis but also provide a means for subsequent comparison on follow-up visits. Quantitative measurements provide an excellent objective means to monitor for progression of the disease, which allows the optometric physician to properly educate the patient and formulate a management plan.

CONCLUSION

Multifocal ERG and OCT are non-invasive retinal diagnostic modalities that have emerged in the past decade. We are only beginning to understand their full capabilities in identifying and monitoring structural and functional signs of inherited retinal disease. Future studies and case reports will further demonstrate the value of these ancillary tests in the evaluation of patients with distinct retinal disorders.

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