

Early diagnosis of Stargardt disease with multifocal electroretinogram in children

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Abstract To present two pediatric cases where multifocal electroretinogram (mfERG) was able to establish an earlier diagnosis compared to full field electroretinogram (ERG) Case 1: an 11-year-old boy with reduced visual acuity, pale discs, macular pigmentation with white dots bilaterally. Case 2: a 12-year-old girl with reduced vision in her right eye, slight pallor of the right optic disc, intense pigmentation at both maculae and scattered punctate lesions throughout the peripheral fundi. Both had been investigated with electrodiagnostic tests according to the International Society of Clinical Electrophysiology for Vision protocol. Full-field ERGs for both children showed normal responses. Case 1: mfERG revealed a severe reduction in function in the inner 20°. Case 2: mfERG showed attenuated responses in each eye. Clinical examination and mfERG were consistent with Stargardt disease. mfERG is applicable to children and is a sensitive tool for early diagnosis of retinal dystrophies.

Keywords Multifocal electroretinogram · Macular dystrophy · Stargardt disease · Pediatric

Abbreviations

EDTs	Electrodiagnostic tests
EOG	Electrooculogram
ERG	Electroretinogram
FVEPs	Flash visual evoked potentials
FAF	Fundus autofluorescence
FFA	Fundus fluorescein angiography
ISCEV	International Society of Clinical Electrophysiology of Vision
mfERG	Multifocal electroretinogram
PERGs	Pattern electroretinograms
PRVEP	Pattern-reversal visual evoked potentials
RPE	Retinal pigment epithelium
SNR	Signal-to-noise ratio
STGD	Stargardt disease

Introduction

Stargardt disease (STGD) was first described by Stargardt [1] who was an ophthalmologist in Berlin in 1907 and he used this term to describe patients who show an atrophic macular area surrounded by some or many yellowish ill-defined flecks.

STGD is an autosomal recessive inherited macular dystrophy. In 1997 it was discovered that mutations in the *ABCA4* gene on the short arm of chromosome 1 can cause STGD as well as fundus flavimaculatus, retinitis pigmentosa and some cone rod dystrophies

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[2]. Patients usually report between the ages of 6 and 20 years with bilateral gradual symmetrical diminution of vision.

Fundus fluorescein angiography (FFA), electroretinography and color vision tests are important methods of examination to facilitate diagnosis in the early stages. FFA in early cases shows a central ovoid zone of hyperfluorescence, mostly surrounded even in the early stages by some hyperfluorescent flecks. In these cases there is often ‘choroidal silence’ because of an increased filtering action of the retinal pigment epithelium (RPE). Retinal capillaries are then more clearly visible than normal. Electroretinogram (ERG) responses tend to be within normal limits, although they can be reduced in cases with extensive peripheral involvement particularly later in the disease process [3]. The electrooculogram (EOG) also tends to be within normal limits but can be reduced in patients with extensive involvement or in advanced cases.

In the early 1990s the multifocal electroretinogram (mfERG) was developed as a means by which to record the topography of retinal function [4]. The resulting mfERG can be presented both as a 3D topographic map of function and an array of localized ERGs from each region [5]. Whilst the 3D topographic map gives a graphically intuitive demonstration of retinal function, the International Society of Clinical Electrophysiology of Vision (ISCEV) recommends the individual traces are presented to verify adequate signal-to-noise ratio (SNR). The difficulty in detecting localized defects within the full-field ERG occurs with normal variation; currently the minimum response amplitude for normal to our standard flash in the light with a gold foil electrode is 80 μV although responses as large as 200 μV are routinely recorded. This means that 5–20 % of the retina may not be working even though the full-field ERG could still fall within normal limits. A further advantage of the mfERG technique is not only does it offer an assessment of local retinal function in absolute terms, but in relative terms also. This allows comparison of the macula which has a higher density of cones and higher signal density, against more peripheral retinal area with less cones and a smaller signal. The central macular response is always larger in normals and the ratio of response between central response and peripheral is less variable given a more sensitive and specific test allowing so called ‘ring ratios’ to identify subtle changes of retinal function [6].

Our aim is to present two pediatric cases with STGD, who had retinal abnormalities detected with a reduced mfERG protocol without changes to the full-field ERG.

Case presentations

Case 1

An 11-year-old boy was referred to the Department of Pediatric Ophthalmology at Alder Hey Children’s Hospital because of markedly reduced vision in both eyes discovered at secondary school. He also had a 2-year history of reading difficulties. On examination his visual acuity was 6/60 and N48 in the right eye and 6/38 and N18 in the left eye and absent color vision as he only managed the test plate using Ishihara color plates. He had bilateral temporal pallor of his optic nerve heads and bilateral macular pigmentation which was an indicator of a possible macular dystrophy. His fundus showed white lesions in the mid-periphery bilaterally (Fig. 1). His Goldman visual fields were entirely normal apart from difficulties with the central visual field to a small target. He was registered as partially sighted. He had no family history of any ocular disease. A differential diagnosis of retinitis pigmentosa or STGD was proposed. FFA and fundus autofluorescence (FAF) photographs (Fig. 2) were taken in order to conclude the diagnosis. Electrodiagnostic tests (EDTs) were performed according to the ISCEV protocol [7–10]. A magnetic resonance imaging scan of the brain was negative.

His initial electrophysiological examination showed that his ERGs were within normal limits (Fig. 3) although his pattern electroretinograms (PERGs) were reduced. Pattern-reversal visual evoked potentials (PRVEP) were undetectable although clear but delayed flash visual evoked potentials (FVEPs) were recorded. EOGs were performed after field testing, which is not ideal as the previous light adaptation impacts on the Arden ratio; equivocal responses were recorded with Arden ratios of 1.7 in the right eye and 1.59 in the left eye (lower limit of normal is 1.7 for this laboratory). mfERGs were then recorded to just 19 hexagons using a short m-sequence [11]. mfERGs revealed a severe reduction in function in the inner 20° (Fig. 4). In Fig. 4 the green graph line represents a central ring of <2.5 radius, the red graph line



Fig. 1 Fundus photographs of Case 1 showed temporal pallor of the optic nerve heads, macular pigmentation, and white lesions in the mid-periphery bilaterally (OD, *right eye*; OS, *left eye*)

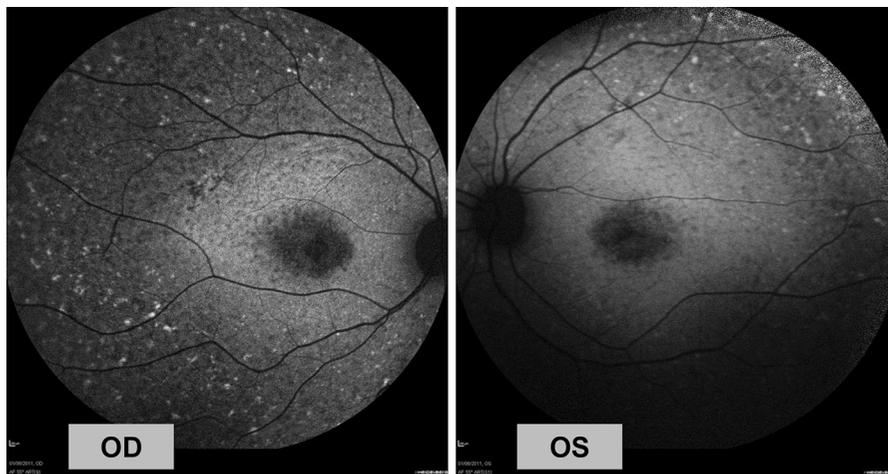


Fig. 2 Fundus autofluorescence (FAF) photographs of Case 1 (OD, *right eye*; OS, *left eye*)

represents a second ring of 2.5–10 radius and the yellow graph line represents a third ring of 10–20 radius.

The clinical examination of his eyes, together with the photographs and the EDTs were consistent with the clinical diagnosis of STGD with macular involvement affecting the central vision. He was referred for genetic testing to confirm STGD. He was also reviewed by an endocrinologist because of the delay in his growth and puberty, which was diagnosed as isolated growth hormone deficiency and was being treated with growth hormones.

After 1-year follow-up his visual acuity was further reduced to 1/24 in the right eye and 1/15 in the left eye and he was therefore registered as severely visual impaired. He was assessed for low vision aids and

supplied with monocular magnifiers. After another 1-year follow-up his vision was further reduced to 1/30 in the right eye and 2/30 in the left eye and his reading vision was <N48 in the right eye and N48 in the left eye.

Case 2

A 12-year-old girl was referred to the Department of Pediatric Ophthalmology at Alder Hey Children's Hospital because of reduced vision which was discovered during a school eye test. On examination she achieved 6/18 in the right eye and 6/12 in the left eye. Her color vision was also affected as she only managed half of the plates on the Ishihara color vision test. She had abnormal retinal appearance, slight pallor

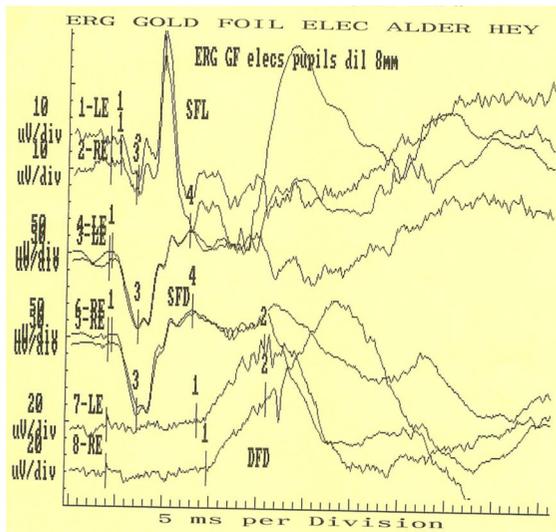


Fig. 3 Full field electroretinogram (ERG) of Case 1 was entirely within normal limits (*RE* right eye, *LE* left eye; SFL, standard flash in the light; SFD, standard flash in the dark; DFD, dim flash in the dark)

of the right disc compared to the left, more intense pigmentation on both maculae than would be expected and scattered punctate hypopigmented lesions throughout the peripheral fundi (Fig. 5). There was no family history of visual impairment. Her Goldman visual field examination appeared normal. A preliminary diagnosis of STGD was made. Again to establish this diagnosis, FFA, FAF photographs and EDTs were undertaken including short-sequence mfERG. Testing was conducted with skin electrodes [12] which have smaller signal than the goldleaf or thread electrodes [13], as the girl could not tolerate an electrode touching her sclera. Her EDTs showed normal cone and rod responses from each eye (standard flash 3 cd/s/m², photopic background light 30 cd/m², 20 min dark adaptation and dim flash 0.01 cd/s/m²) in her full-field ERGs (Fig. 6). Her PERGs were attenuated. Her PRVEPs were reduced and delayed, while her FVEPs were recorded but delayed. mfERG showed severe attenuation in responses in the inner 10° and even the outer ring was delayed in latency (Fig. 7).

Her ocular examination, photographs and the electrophysiological testing were consistent with the clinical diagnosis of STGD with macular involvement. Genetic testing was requested which confirmed her diagnosis.

Discussion

STGD is a complex retinal degenerative disease with variable disease presentation and progression. The progression of vision loss in autosomal recessive STGD is usually rapid in childhood and young adulthood, but may be unpredictable and often does not correlate with the severity of fundus lesions. The visual impairment in STGD is related to the extent of scotoma (blind spot) in the central visual field.

Fundus photographs of early disease range from a beaten-bronze appearance to atrophy, often presenting with characteristic yellow-white flecks at the level of RPE. Histology shows the accumulation of lipofuscin, a lipid-containing fluorophoric by-product of photoreceptor digestion, inside the RPE [2]. FAF is used to visualize lipofuscin which originates from the RPE layer. Abnormally increased FAF suggests RPE dysfunction with increased accumulation of lipofuscin, while decreased FAF indicates RPE atrophy and photoreceptor death. FFA of STGD often shows a characteristic dark choroid superimposed by non-homogenous hyperfluorescent regions in the posterior pole [14].

Both pediatric patients appeared with pale optic nerve heads, macular pigmentation, and white scattered punctate lesions throughout the peripheral fundi bilaterally. FAF of our cases showed a hypo-autofluorescent area of the posterior pole and hyper-autofluorescent lesions in the mid-periphery. FFA in our pediatric patients showed a characteristic dark choroid surrounded by hyperfluorescent regions in the posterior pole and the periphery.

Recently scientists found that in ABCA4-associated retinal degenerations retina-tracking microperimetry can be used to measure macular function at specific retinal locations with a predictable and acceptable reliability [15]. The retinal function can also be assessed by ERG, although this is often normal in STGD. A patient at the end stages of STGD may demonstrate generalized and profound depression of both scotopic and photopic ERG responses [16]. Atrophic lesions contribute to diminished ERG amplitudes, so the presence of an atrophic lesion is probably a manifestation of a more aggressive form of the disease. Based on the electrophysiological attributes three patterns of function loss are recognized in patients with STGD—loss of macular function alone, or combined with loss of either generalized cone

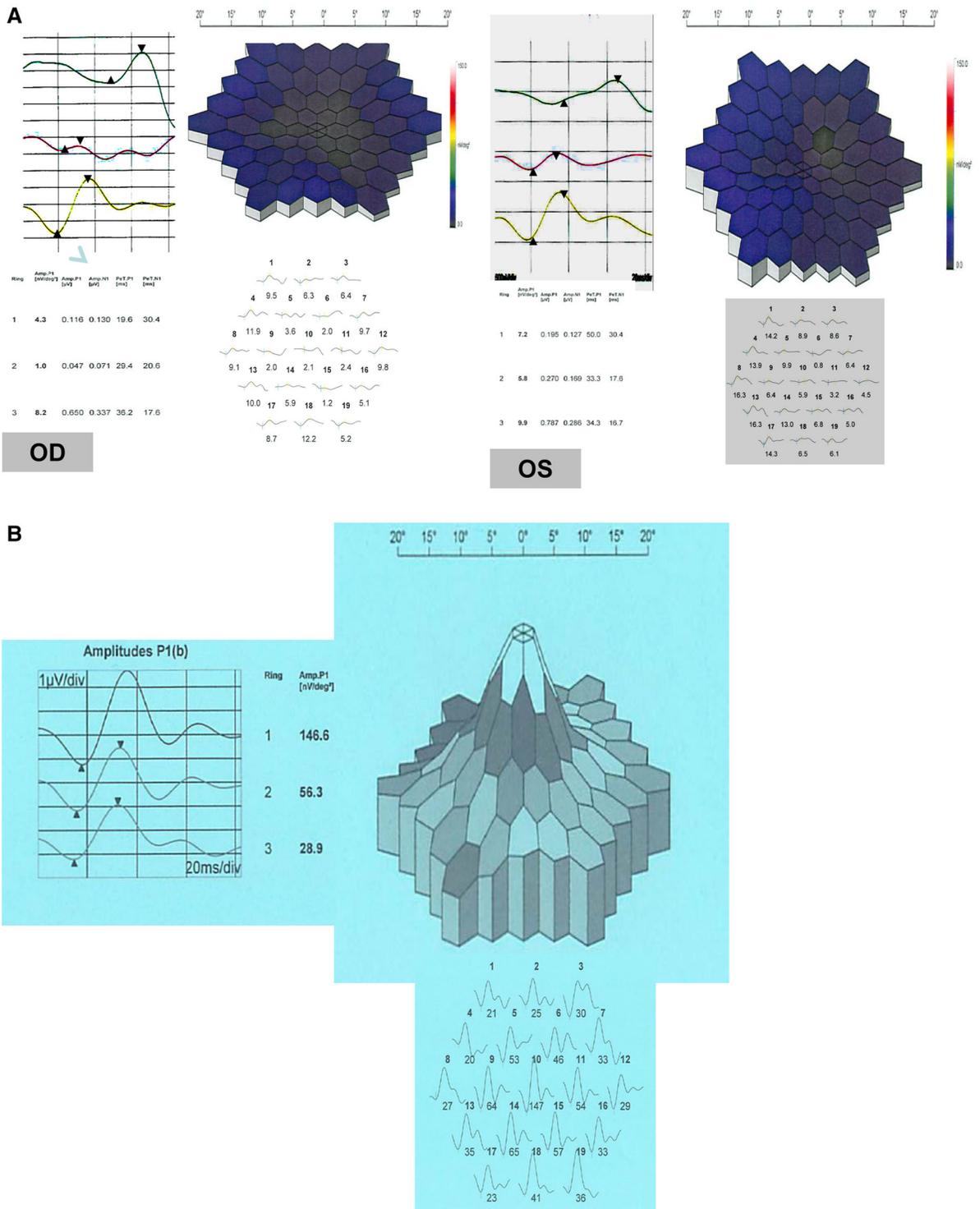


Fig. 4 Multifocal electroretinograms (mfERGs) revealed a severe reduction in function in the inner 20° bilaterally (OD, right eye; OS, left eye) (a) Case 1, (b) representative normal). Arrowheads indicate P1 peaks

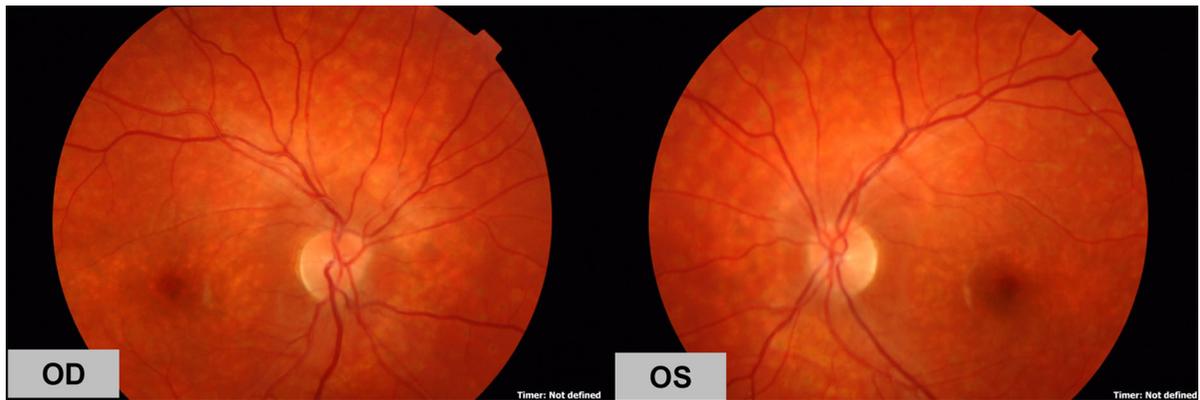


Fig. 5 Fundus photographs of Case 2 showed slight pallor of the *right* disc compared to the *left*, intense pigmentation at both maculae and scattered punctate hypopigmented lesions throughout the peripheral fundi (OD, *right* eye; OS, *left* eye)

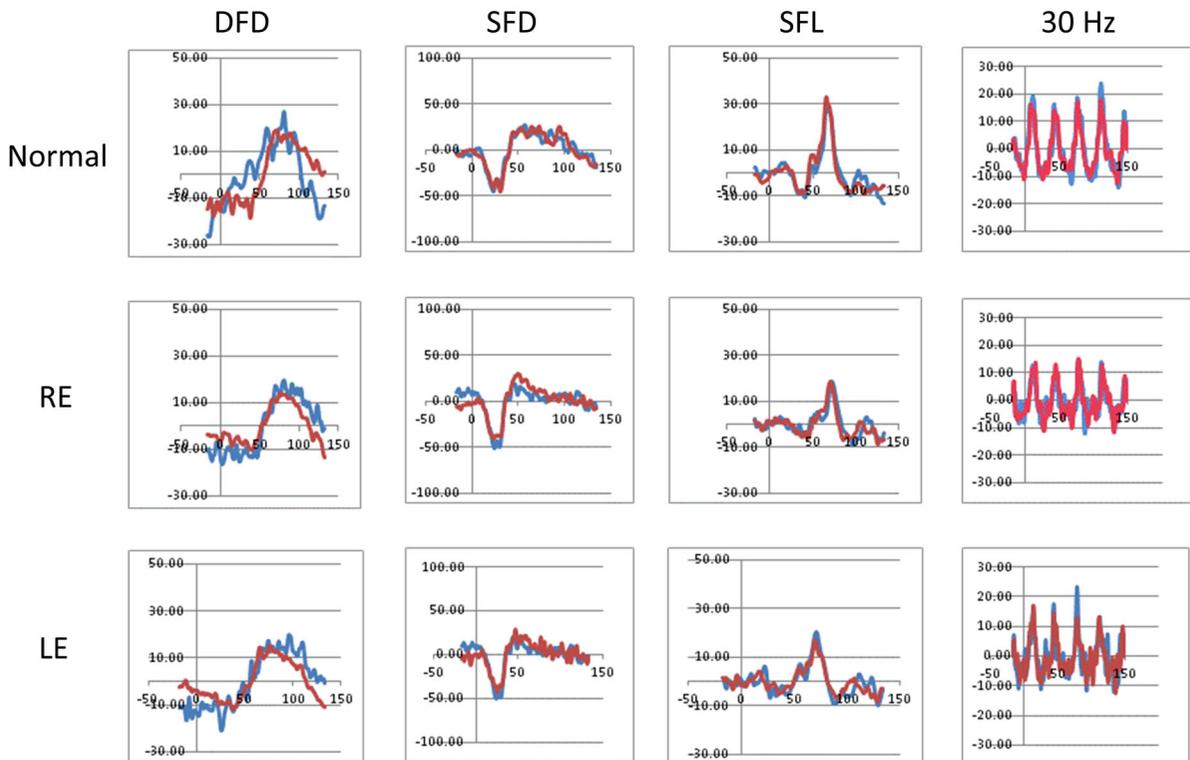


Fig. 6 Full-field electroretinogram (ERG) of Case 2 was normal (RE *right* eye, LE *left* eye, SFL standard flash in the light, SFD standard flash in the dark, DFD dim flash in the dark)

function, or generalized cone and rod function [17]. PERG provides an objective measure of central retinal function. Usually PERG in STGD is not detectable, and it can be markedly abnormal even with clinically well-preserved maculae and good visual acuity [18].

Since its original description mfERG has rapidly become a useful clinical tool [19]. It is possibly most

associated with detecting foveal and/or macular dysfunction [20]. Although its ability to determine the topography of response has led to its use in describing retinal function in retinitis pigmentosa [21], choroideremia and in detecting subtle localized defects which would be missed by full-field ERGs [22]. Drug toxicity can be screened with mfERG, which has the

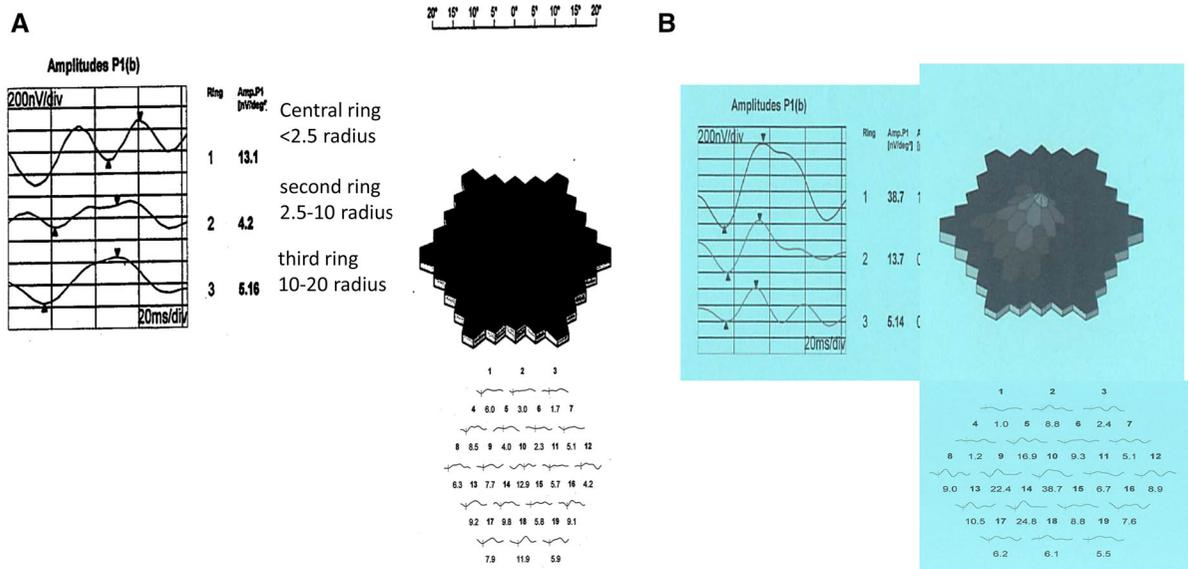


Fig. 7 Multifocal electroretinograms (mfERGs) with skin electrode showed severe attenuation in responses in the in the inner 10° and even the outer ring was delayed in latency. **a** Case

2, b representative normal mfERG with skin electrode). *Arrowheads* indicate P1 peaks

ability to detect a retinal change even if this change is restricted to a small area [23]. The success of treatments have also been objectively monitored with mfERG [24],

The mfERG is a widely used assay to evaluate the topography of cone-mediated function in the central retina. In mfERG, small areas of the retina are stimulated simultaneously and local contributions to a massed electrical potential are extracted from a continuously recorded ERG. Under photopic conditions the local waveforms appear biphasic, with negative and positive deflections. mfERG has the ability to detect local retinal abnormalities that would not be detected by conventional ERGs. As a result mfERG has become a popular electrophysiological tool to assess cone-mediated function in retinal disorders including STGD [25]. The use of mfERG can be limited by the loss of foveal fixation in these patients. The most notable feature of the response topographies for the STGD subject is the severely depressed, or completely absent, central peak consistent with significant central functional defects as observed in STGD patients [12]. mfERG not only assesses whether there is central dysfunction but the area of dysfunction can be gauged by determining the number of stimulating hexagons that have reduced responses.

Despite this clinical utility, few reports have been presented in pediatric cases. This may be due to the difficulty in obtaining a good SNR from the small retinal areas and the need for good patient cooperation over a prolonged period of time. We have reported on two cases tested with a reduced protocol mfERG where only 19 hexagons were presented instead of 103. This means that on average, five times the signal can be gathered from each area; so achieving the same level of SNR requires fewer averages which means less time for the child fixating. With a sclera electrode (gold leaf) which is easily tolerable particularly with an anesthetic drop, only 2 runs (47 s each) are necessary to acquire adequate SNR from each eye. Furthermore, it is no longer necessary to increase the size of the hexagon precise fixation in children with poor vision as the central hexagon is relatively large at 2.5° radius. This relatively large target and previous work identifying the central retina response tends to be slower in humans [26] and should therefore reduce the risk of misdiagnosing poor fixation as a maculopathy.

Both pediatric patients had normal cone and rod responses from each eye in their ERGs, although their PERGs were reduced. Their PRVEPs and their FVEPs were delayed. EOGs were on the low level of normal but within normal limits. mfERGs revealed a severe

reduction in function in the inner 20° in the boy, while severe attenuation in responses in the inner 10° and even the outer ring was delayed in latency in the girl. In both cases the PERG was suspiciously small; in adults this would be strong evidence of macular dysfunction assuming no optic abnormalities. PERGs are technically challenging due to their small signals, and blinking and loss of fixation can be confounding factors particularly in paediatrics. These difficulties can be further increased if the subject cannot tolerate a skin electrode. Even in normals, as demonstrated in Case 2 the SNR can be poor and the salient features difficult to distinguish above the ongoing electrical noise. A second test of macular function can confirm and support the findings in the original test. Fixation can be accessed from the mfERG result as central macular responses are larger and later than peripheral [26] so inadequate fixation can be identified if a peak is off center with a prolonged latency. Further technical problems such as poor contact if there are clear responses from peripheral test areas. The mfERG not only indicates whether there is dysfunction but can determine the extent and location of dysfunction making objective assessment of progression more accurate.

mfERG results considered in conjunction with ERG, clinical examination and history helps in obtaining a complete picture of retinal function and can help in making an earlier diagnosis in retinal dystrophies. We have demonstrated how mfERG with a reduced number of hexagons and recording time can be an effective screen for macular pathology.

Conflict of interest No authors have any financial/proprietary interests to disclose.

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