Multifocal electroretinogram contributes to differentiation of various clinical pictures within a family with Bardet–Biedl syndrome

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Abstract

Purpose To demonstrate the use of the multifocal electroretinogram (mfERG) in addition to the full-field electroretinogram (ERG) in defining varying clinical pictures in children within a family with Bardet–Biedl syndrome (BBS).

Methods All members from a family generation underwent a detailed history and examination before proceeding to a detailed ERG in accordance with the International Society of Clinical Electrophysiology for Vision protocol and a rapid, low-resolution mfERG. Of the sibling pair, the 13-year-old boy showed reduced vision and atypical maculopathy and the 10-year-old sister showed normal vision and atrophic maculopathy. Parents had normal ocular examination.

Results The male sibling had reduced rod and cone full-field ERG responses with a relatively spared central response from the mfERG suggesting central macular sparing. In contrast, for the female sibling, the ERG was normal for the cone pathway although reduced for rod pathway, with mfERG showing central involvement. The mother had rod responses at the lower end of normal range, a normal cone pathway, and a normal mfERG. The father showed a normal ERG and mfERG.

Conclusion The mfERG is a useful adjunct to full-field ERG in the paediatric population and in family studies.

Eye (2014) 28, 1136–1142; doi:10.1038/eye.2014.150; published online 4 July 2014

Introduction

Bardet in 1920 described a patient with retinopathy, polydactyly, and congenital obesity,¹ while Biedl in 1922 added the fourth and fifth cardinal features, mental retardation and hypogenitalism, of the disorder² now known as the Bardet–Biedl syndrome (BBS). Schachat *et al* reviewed BBS and related disorders and suggested that at least four of the five cardinal features, of which retinopathy must be one, must be present to establish the diagnosis conclusively.³ Renal abnormalities are considered as the most common of non-ocular abnormalities and as the sixth cardinal feature of BBS. Molecular genetic linkage analysis has identified 15 genomic loci, 15 genes, and 2 modifying loci. BBS1 is considered as the major locus among white Bardet–Biedl patients.

In the early 1990s, the multifocal electroretinogram (mfERG) was developed as a means by which to record topographic retinal activity.⁴ The resulting mfERG can be presented both as a 3D topographic map of function, and as an array of localized electroretinograms (ERGs) from each region.⁵ The technique has many clinical applications,⁶ although it has not been widely used clinically in the paediatric population because the tests are time consuming and require considerable patient cooperation and special equipment.

The purpose of the paper is to present the usefulness of the mfERG in addition to the full-field ERG in defining varying clinical

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Received: 19 July 2013
 Accepted in revised form: 24 May 2014
 Published online: 4 July 2014

pictures in children within a Caucasian family with BBS.

Patients and methods

A 13-year-old boy was referred to the Department of Paediatric Ophthalmology at Alder Hey Children's Hospital for a second opinion. His ocular examination revealed slightly reduced visual acuity of 6/7.5 from each eye, myopia, normal near visual acuity, and colour vision, while his main concern was of getting used to the dark. Fundus examination showed normal optic discs, attenuated vessels, and atrophic patches in his maculae (Figure 1a). Both eyes showed peripheral retinal fine pigmentary stippling and chorioretinal atrophy. His visual fields showed mild peripheral visual field defect in the right eye and a slightly more advanced visual field defect in the left eye. On questioning, his past medical history (PMH) revealed the surgical removal of an extra digit on the left foot at 1 year of age.

Owing to suspicion of retinal dystrophy for him, all the other members of the family (female sibling 10 years of age and both their parents were questioned in detail about their PMH) underwent a detailed ocular examination. The female sibling described no visual symptoms, had normal visual acuity from each eye, but on examination also had signs of maculopathy with mild retinal vessel attenuation (Figure 1b), normal optic discs, and visual fields. An extra right toe, additional finger on the right hand, and a small finger with a nail on the left hand had been surgically removed in early childhood. The father was asymptomatic, had normal PMH and ocular examination. The mother had normal ocular examination, and had difficulty adapting to the dark.

Both siblings and their parents underwent full-field standard ERGs that were conducted to International Society of Clinical Electrophysiology for Vision standard⁷ and mfERGs were recorded rapidly with a short m-sequence and a reduced number of hexagons in keeping with a paediatric concentration span.⁸ With this short sequence it is possible to run the entire sequence twice in about 2 min, which gives adequate signal to noise (SNR) in most cases. The traditional long sequence tends to take 8 or 16 min to run once. Then this has to be repeated for each eye. By reducing the number of hexagons from 61 to 19, the central hexagon is larger, and the likelihood of accurate fixation is improved within this central hexagon for subjects with imprecise fixation. Also, increasing the hexagon in size would cause the retinal area tested by each hexagon to be larger, which gives a larger signal tending to make it quicker to collect a recording of adequate SNR. Running the short sequence drastically reduces the time an electrode has to

be in contact with the eye and the time that they need to maintain steady fixation. These are important considerations in a paediatric population or in cases of BBS who may have learning difficulties and reduced attention spans.

In addition, we use a slow stimulus mfERG and there is a marked change in latency between the central hexagon and ring 2, which facilitates an assessment of quality of fixation that is of paramount importance in paediatric cases with limited concentration.⁹

Results

The male sibling had a reduced rod and cone pathway ERG, with the rod pathway worse than the cone (Figure 2), whereas his mfERG showed central sparing (Figure 3a), making it possible for him to achieve a visual acuity of 6/9. The female sibling had cone responses acceptable as normal, with rod pathway responses about 50% of the lower limit of normal for amplitude (Figure 4), whereas her mfERG suggested a subtle macular change demonstrated by an attenuated central hexagon response (Figure 3b). A normal delay in latency between the central hexagon and ring 2 demonstrated adequate fixation.⁹ The father's ERG showed normal responses. The mother's showed that her cone pathway responses were within normal limits but her rod pathway responses at the low end of normal range. Both parents had a normal mfERG.

On the annual follow-up visit, the visual acuity of the male sibling was 6/9 in the right eye and 6/18–6/12 in the left eye, whereas the visual acuity of his sister was decreased to 6/9 from each eye. Six months later both siblings and their parents were referred to a human molecular geneticist. The results revealed that both siblings and their mother had mutation on the *BBS1* gene. Both siblings have been transferred back to the General Hospital for their follow-ups.

Discussion

This case series suggests that the mfERG can help differentiate between the different clinical pictures of BBS. The male sibling demonstrated the more traditional central sparing in the presence of reduced rod and cone pathway responses. The female sibling (3 years younger) maintained a good VA at presentation with reduced central responses on mfERG testing. In the annual follow-up assessment both siblings' vision was marginally decreased. In rod–cone dystrophies, years rather than months are needed to see whether there is a clear deterioration in visual acuity.¹⁰

The central hexagon response of the mfERG of the male sibling's LE (~ 40 nV/deg²) was noticeably reduced

Figure 1 (a) Fundus photographs of the male sibling showed attenuated vessels and atrophic maculopathy. (b) Fundus photographs of the female sibling showed signs of maculopathy with mild retinal vessel attenuation (OD: right eye, OS: left eye).

Figure 2 Full-field electroretinograms (ERGs) of the male sibling showed diminished responses of both rod and cone pathway with rod pathway more severely affected. RE, right eye; LE, left eye; DFD, dim flash in the dark; SFD, standard flash in the dark; SFL, standard flash in the light.

Figure 3 (a) Multifocal electretinograms (mfERGs) of the male sibling showed central sparing. (b) Mf ERG of the female sibling suggested a subtle macular change with an attenuated central hexagon amplitude response.

Figure 4 Full-field electroretinograms (ERGs) of the female sibling showed normal cone responses, with rod pathway responses about 50% of the lower limit of normal for amplitude. RE, right eye; LE, left eye; DFD, dim flash in the dark; SFD, standard flash in the dark; SFL, standard flash in the light.

compared with the RE (~ 60 nV/deg²) (Figure 5). The RE vision was to drop from 6/7.5 to 6/9, while LE vision fell further from 6/7.5 to between 6/12 and 6/18. The female sibling on initial presentation had normal VA but an abnormal central mfERG, on follow-up the VA had deteriorated to 6/9. This may suggest mfERG has some prognostic value regarding visual outcome.

Visual fields are likely to be affected first in some cases, which can make navigation difficult. Often the full-field ERG will not be affected if the area of photoreceptor loss is small, nor does it help to differentiate between central and peripheral loss and the dramatic impact this has on visual quality.¹¹

Both siblings had atrophic maculopathy with attenuated retinal vessels, although the male sibling had also peripheral retinal fine pigmentary stippling and chorioretinal atrophy. Apart from pigmentary retinopathy, children with BBS almost always have other associated abnormalities such as polydactyly, congenital obesity, mental retardation and learning difficulties, hypogenitalism, hypertension and renal disease, and delayed or absent puberty. Pigmentary retinopathy is reported in almost all of the cases with changes in the ERG. The retinopathy in BBS differs in most patients from typical retinitis pigmentosa, in that usually the

fundus shows little pigmentary dispersion until later stages. Macular lesions and atrophy of the retinal pigment epithelium or choriocapillaris often develop as the disease progresses.¹² When detectable, the ERG may show a rod-cone loss or, in some cases, even within the same family, a cone-rod loss pattern, the latter of which has led authors to call the retinal dystrophy in BBS a 'cone-rod retinal degeneration'.³ Both siblings were born with polydactyly, seemed to control their weight well, and go through puberty normally as demonstrated by their pubic hair appearance and the rest of their gender characteristics. Both seemed to have dyslexic tendencies and struggled at school being near the bottom of the class. The female sibling had kidney reflux in the past that led to scarring of her left kidney.

The mother while having a normal set of ERGs and mfERGs, did have dark-adapted ERGs at the lower limit of normal, which may suggest the carrier status. Kim *et al* concluded that the presence of a functional abnormality on mfERG testing in a BBS family member with a normal retinal examination should suggest the presence of a carrier state for the BBS. However, the authors added that a normal mfERG result would not by itself rule out carrier status, which is in agreement with our findings.¹³ Cox *et al*¹⁴ showed that the primary

Figure 5 Multifocal electroretinograms (mfERGs) of the male sibling showed reduced central hexagon response from the LE compared with the RE (RE: right eye, LE: left eye).

defect in carriers of BBS appeared to be proximal to the outer segments, most likely before the rod–bipolar cell synapse confirming primary involvement of the rod pathway.

Conclusions

The mfERG is a useful adjunct to the full-field ERG in the paediatric population and in family studies. mfERG results considered in conjunction with ERG, clinical examination, and family history help in obtaining a complete clinical picture that helps in determining subsequent individual prognosis and counselling. In this series, the male sibling had a smaller central mfERG in the LE (~ 40 nV/deg²) compared with the RE (~ 60 nV/deg²), at time of recording VA was 6/9 also detected early macular changes in function before visible structural changes. Within BBS it is established that presenting features can differ as can the visual fields. In this family, the mfERG has identified two quite disparate presentations with the male sibling having the more traditional central sparing but his sister having a reduction of central visual function and reduced

dark-adapted full-field ERG, both of which can be explained by the phenotypic variability of BBS.

What was known before

- Although mfERG has many clinical applications, it has not been widely used clinically in the paediatric population because the tests are time consuming, and require considerable patient cooperation and special equipment.

What this study adds

- mfERG is a useful adjunct to full-field ERG in the paediatric population and in family studies. mfERG in addition to full-field ERG helps in defining varying clinical pictures in children within a Caucasian family with BBS.

Conflict of interest

The authors declare no conflict of interest.

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