CLINICAL STUDY

Electrophysiological findings in Stargardt's–fundus flavimaculatus disease

P. STAVROU, P.A. GOOD, G.P. MISSON, E.E. KRITZINGER

Abstract

Purpose **To determine the incidence of electrophysiological abnormalities in patients with Stargardt's–fundus flavimaculatus (STGD/FFM) disease.**

Methods **A retrospective review was carried out of the hospital records of 46 patients who had undergone a scotopic, single flash photopic and 30 Hz electroretinogram (ERG), pattern ERG (PERG) and electro-oculogram (EOG).**

Results **Patients were classified in two groups: those with flecks ($n = 26$) and those without flecks ($n = 20$). The incidence of abnormalities (amplitude and/or latency) for the two groups was: PERG, 90% and 98%; 30 Hz ERG, 55.8% and 50%; scotopic ERG, 38.5% and 27.5%; and single flash photopic ERG, 26% and 16%, respectively. EOG abnormalities occurred significantly more frequently in the group with flecks compared with the group without flecks: 69% and 42.5% respectively ($p < 0.025$). Furthermore, in the group with flecks the group mean scotopic ERG b-wave, 30 Hz ERG b-wave and PERG (P50) amplitude were significantly lower than in the group without flecks ($p < 0.01$).**

Conclusions **The most consistent electrophysiological abnormality in STGD/FFM is the reduction of the PERG. However, EOG, 30 Hz ERG, scotopic and photopic ERG abnormalities can also frequently occur. ERG and EOG abnormalities occur more often in the presence of flecks.**

Key words Electro-oculogram, Electroretinogram, Flecks, Fundus flavimaculatus, Macular dystrophy, Stargardt's

In 1909, Stargardt first described a bilateral, hereditary macular dystrophy characterised by atrophic-appearing macular lesions that were eventually surrounded either partially or completely by a ring of soft white flecks.[1] In 1963, Franceschetti introduced the term 'fundus flavimaculatus' to describe a disorder characterised by ill-defined, white-yellow spots or 'flecks' in the deeper retinal layers of the posterior pole, with or without macular degeneration.[2] Patients without atrophic-appearing macular lesions were described as having a 'pure form' of fundus flavimaculatus.[3,4]

Deutman[5] noted that Stargardt's disease had a central onset, whereas in fundus flavimaculatus the yellow-white spots were present at the posterior pole before the fovea was affected. Subsequently, various authors reporting on large groups of patients demonstrated marked overlap in the fundus appearance of these two disorders. It was therefore suggested that they should be grouped under the term Stargardt's–fundus flavimaculatus disease (STGD/FFM).[6–8] This classification is used throughout this paper.

STGD/FFM is the most common macular dystrophy. Its inheritance is usually autosomal recessive, although dominantly inherited cases[8,9] have also been described. It usually presents in the first two decades of life with impaired central vision. There is no associated nystagmus, photophobia or night blindness. The clinical course is slow visual deterioration over a period of years. There appears to be no gender, racial or ethnic predilection.

The electrodiagnostic findings are variable and depend on the stage of the disease. The reported incidence of flash electroretinogram (ERG) abnormalities ranges from 0 to 78%.[4,6–8,10,11] The most frequently described ERG abnormality is a decrease in the b-wave amplitude, usually with a normal implicit time.[7,12] Abnormalities of the pattern ERG (PERG) have also been reported.[7,13] The electro-oculogram (EOG) is described as normal in more than half of cases, while there have been individuals with abnormal EOG and normal ERG.[6,7]

In this study we investigated this apparent heterogeneity of electrophysiological findings. Scotopic ERG, single flash photopic ERG, 30 Hz ERG, PERG and EOG were performed in a group of patients with STGD/FFM, who were subdivided according to the presence or absence of flecks.

Patients and methods

Patients

The hospital records of 46 consecutive patients who were diagnosed as suffering from STGD/

P. Stavrou
P.A. Good
G.P. Misson
E.E. Kritzinger
Birmingham & Midland Eye Centre
Birmingham, UK

Mrs P. Stavrou, FRCS Ed ✉
Birmingham & Midland Eye Centre
City Hospital NHS Trust
Dudley Road
Birmingham B18 7QU, UK
Tel: +44 (0)121 554 3801

FFM between 1987 and 1996 at the Birmingham & Midland Eye Centre were retrospectively reviewed. There were 29 male and 17 female patients, mean (±SD) age 27.2 (±13.4) years (range 6–64 years). Thirty-nine patients were Caucasian and 7 were Asian. The patients were classified into two groups: those with flecks and those without flecks. The two groups were similar for sex and race distribution. The mean age (±SD) of the two groups was also similar: 27.4 (±13.1) years and 27.0 (±13.3) years for the groups with and without flecks respectively.

Visual acuity

Thirteen of the 46 patients (28.3%) had a visual acuity in the better eye of 6/12 or better. Three of these 13 patients had a visual acuity of 6/6 in each eye. Another 13 patients had a visual acuity in the better eye between 6/12 and 6/24. The remaining 20 patients (43.4%) had a visual acuity of 6/36 or less. Four patients had asymmetry in visual acuity of more than 5 lines on the Snellen chart.

Heredity

Autosomal recessive inheritance was suggested in 9 patients; 6 patients represented three sibling pairs, 2 patients gave a history of an affected sibling and 1 patient gave a history of parental consanguinity. Each sibling pair manifested a similar fundus appearance.

Fundus appearance

All 46 patients had macular changes while 26 patients also had perifoveal and/or posterior pole flecks. The macular appearances included diffuse foveal reflex, pigment mottling and atrophy, tapetal sheen or beaten-bronze reflex, choroidal atrophy and bull's-eye pigmentary changes. All patients showed symmetrical macular changes even when a marked difference in visual acuity between the two eyes was noted. Patients with flecks exhibited white to deep yellow, round or pisciform-shaped lesions limited to the posterior pole and posterior equatorial regions. Pigmentary lesions were rare.

The electrophysiological findings (ERG, PERG and EOG) in the patients with STGD/FFM were compared with those of a control group of 30 healthy volunteers matched for sex and age. There were 20 male and 10 female subjects, mean age 30.2 years (range 10–60 years). The group mean maximal scotopic ERG, single flash photopic ERG, 30 Hz ERG, PERG and EOG results were analysed by unpaired Student's *t*-test. Incidences for each test parameter were compared by chi-squared analysis of proportion.

Methods

ERG

The ERG was recorded according to the ISCEV standardisation protocol[14] employing Ganzfeld stimulation and Burian-Allen contact lens electrodes referred to an outer canthal Ag/AgCl electrode. Recordings were made with the pupils dilated with guttae tropicamide 1%. A Nicolet CA1000 or Nicolet Spirit clinical averager was used to record the data. Frequency band-pass filtering was set at 1–1000 Hz.

Scotopic stimuli, recorded after 20 min of dark adaptation, consisted of a standard flash of 2.8 foot-lambert-second/flash (ft-L-s/flash). Five averages were obtained with a 10 s interstimulus duration. Our laboratory normal range for the standard maximal flash ERG amplitude is 290–550 μV and the normal range for the standard maximal flash scotopic b-wave latency is 37–43 ms. Single flash photopic responses were recorded using a 18 ft-L-s/flash stimulus with a background illumination of 20 ft-L. Recordings were made after light adaptation (30 ft-L) for 5 min. Ten averages were obtained at a rate of 1 per second. Our laboratory range for the single flash photopic response is 70–200 μV. There are no laboratory normal values for photopic b-wave implicit time.

Responses from 30 Hz cone stimulation were obtained using a background Ganzfeld illumination of 20 ft-L and a stimulus intensity of 3.5 ft-L/flash. One hundred averages were taken at a rate of 30 flashes per second. Measurements of the peak-to-peak ERG b-wave amplitude and implicit time were obtained. Our laboratory normal range for 30 Hz cone b-wave amplitude is 25–120 μV and for 30 Hz cone b-wave implicit time is 26–33 ms. Scotopic (maximal flash) oscillatory potentials were recorded using off-line digital filtering (100-2000 Hz) of the scotopic b-wave.

Values were considered abnormal if they fell outside our laboratory normal range. The values of all control subjects were within this normal range.

Pattern ERG (PERG)

Pattern ERGs were obtained according to the ISCEV standardisation protocol[14] using a high-contrast (> 90%) black and white checkerboard of 0.5 and 1 cycle per degree reversing at a rate of 4 Hz. One hundred and fifty averages were obtained for each stimulus parameter and repeated 3 times. A 50 μV artifact rejection was employed. Electrodes consisted of a carbon-fibre electrode referred to an Ag/AgCl electrode sited at the lateral canthi. Filter band-pass was 1–250 Hz. Peak-to-peak N35 to P50 and P50 to N95 measurements were made from each response. The N95 component was expressed as the ratio of P50/N95. Our laboratory normal range for P50 is over 1.9 μV and for the P50/N95 ratio, below 0.8.

EOG

The EOG was recorded from Ag/AgCl skin electrodes on the inner and outer canthi of each eye. After 5 min of light adaptation with a photopic illumination of 30 ft-L on a Ganzfeld screen, 30° ocular movements between two red target lights were recorded for a total of 12 min in the dark. This was followed by 10 min of light adaptation

using 30 ft-L Ganzfeld illumination. The ocular movements were recorded, every 2 min throughout the test, using a Medelec Sensor clinical averager with a band-pass filter of 1–250 Hz. The Arden index was calculated by dividing the average of the two largest values in the light by the average of the two smallest values after 10–12 min in the dark. Our laboratory normal range for the EOG is 170–280%.

Results

STGD/FFM with flecks

Scotopic ERG

Thirteen of the 52 eyes with flecks (25%) had a reduction of the scotopic b-wave amplitude while another 7 eyes (13.5%) showed b-wave delay. The group mean scotopic b-wave amplitude was significantly lower than both the mean value of the controls ($p < 0.01$) and the mean value of patients without flecks ($p < 0.01$). The group mean scotopic b-wave implicit time was significantly longer than the mean value of the controls ($p < 0.01$) but not significantly longer than the mean of patients without flecks. The oscillatory potentials were not selectively reduced.

Single flash photopic ERG

Thirteen of the 52 eyes with flecks (26%) had a reduction of the single flash photopic b-wave amplitude. The group mean single flash photopic b-wave amplitude was significantly lower than both the mean value of the controls ($p < 0.01$) and the mean value of the patients without flecks ($p < 0.01$).

30 Hz ERG

Eighteen of the 52 eyes with flecks (34.6%) had a reduction of the 30 Hz ERG amplitude, while another 11 eyes (21.1%) had a delay of the cone b-wave. The group mean 30 Hz ERG amplitude was significantly lower than both the mean value of the controls ($p < 0.01$) and the mean value of the patients without flecks ($p < 0.01$). The group mean 30 Hz implicit time was significantly longer than the mean value of the controls ($p < 0.01$) but not significantly different from the mean of patients without flecks.

PERG

Forty-seven of the 52 eyes with flecks (90%) had a reduction of the P50 component of the PERG. The group mean P50 amplitude was significantly lower than both the mean value of the controls ($p < 0.01$) and the mean value of patients without flecks ($p < 0.01$). The group mean P50/N95 ratio was not significantly different from the mean of the patients without flecks or the control group mean. None of the patients in whom PERG was present had an abnormal P50/N95 ratio.

Fig. 1 shows the scotopic, 30 Hz and pattern ERG in two patients with flecks and a normal control.

EOG

Thirty-six of the 52 eyes with flecks (69%) had a subnormal EOG. The group mean Arden index was significantly lower than that of the controls ($p < 0.01$) but not significantly different from that of patients without flecks. The incidence of EOG abnormalities was significantly higher in patients with flecks compared with those without flecks ($p < 0.025$).

STGD/FFM without flecks

Scotopic ERG

Eight of the 40 eyes without flecks (20%) had a reduction of the scotopic b-wave amplitude while another 3 eyes (7.5%) showed delay of the b-wave. The group mean scotopic b-wave amplitude was significantly lower than the mean value of the controls ($p < 0.01$), but significantly higher than that of patients with flecks ($p < 0.01$). The group mean scotopic b-wave implicit time was significantly longer than the mean value of the controls ($p < 0.01$), but not significantly different from that of patients with flecks. The oscillatory potentials were not selectively reduced.

Single flash photopic ERG

Six of the 40 eyes without flecks (16%) had a reduction of the single flash photopic b-wave amplitude. The group mean single flash photopic b-wave amplitude was not significantly lower than the mean value of the controls but was significantly higher than that of the patients with flecks ($p < 0.01$).

30 Hz ERG

Fourteen of the 40 eyes without flecks (35%) had a reduction of the 30 Hz ERG amplitude, while another 6 eyes (15%) showed delay of the cone b-wave. The group mean 30 Hz amplitude was significantly lower than the mean value of the controls ($p < 0.01$). The group mean 30 Hz implicit time was significantly longer than the mean value of the controls ($p < 0.01$). There was no significant difference in amplitude and implicit time of the 30 Hz ERG between patients with flecks compared with those without flecks.

PERG

Thirty-nine of the 40 eyes without flecks (98%) had a reduction of the P50 component of the PERG. The group mean P50 amplitude was significantly lower than the mean value of the controls ($p < 0.01$), but significantly higher than that of patients with flecks. The group mean P50/N95 ratio was not significantly different from that of either the group with flecks or the control group. None of the patients in whom PERG was present had an abnormal P50/N95 ratio.

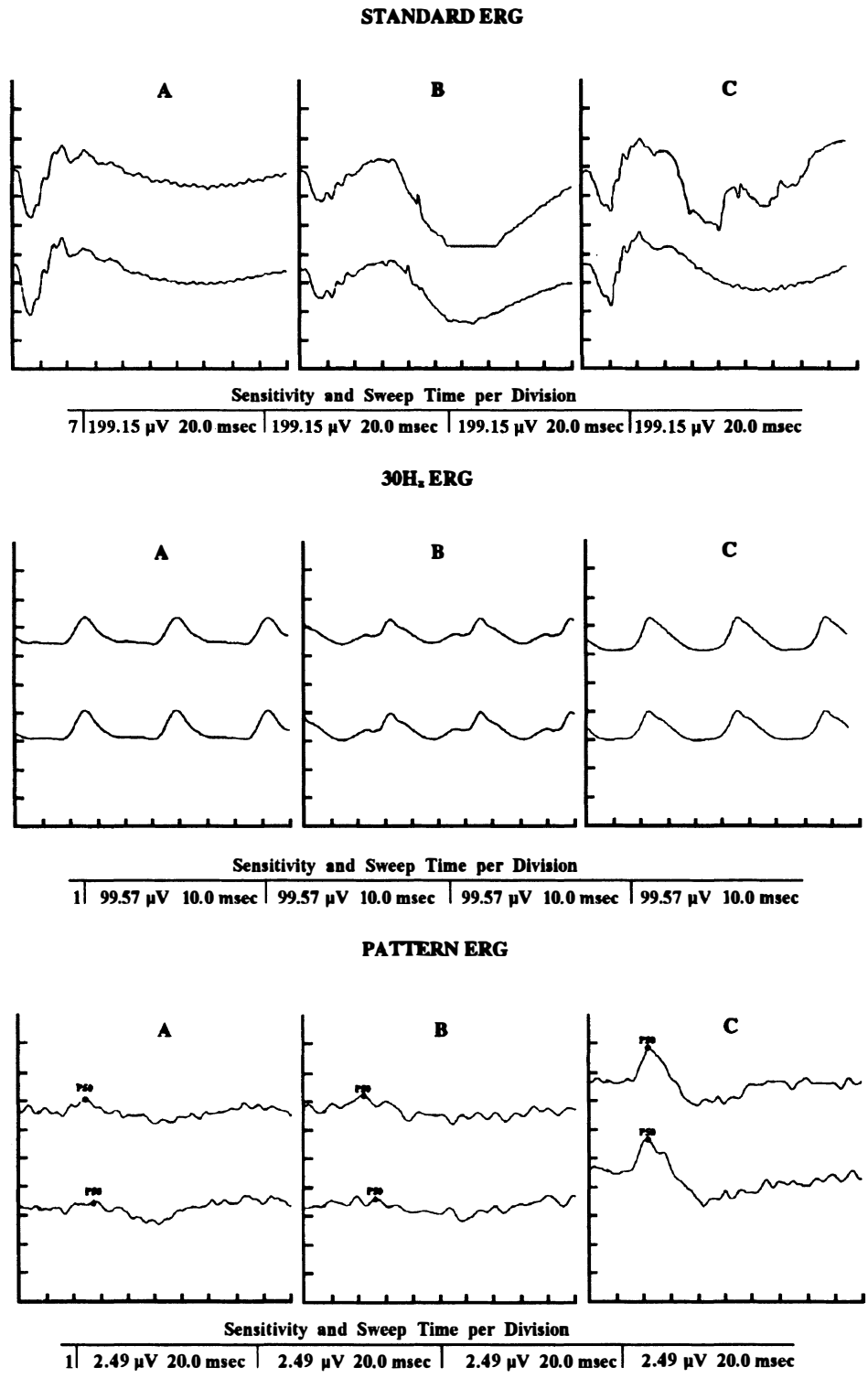

Fig. 1. *Flash (standard scotopic and 30 Hz) and pattern ERG in two patients (A and B) with STGD/FFM with flecks. The visual acuity was similar and in the range 6/24–6/36. Top traces are from the right eye and bottom traces are from the left eye. Flash (standard scotopic and 30 Hz) and pattern ERG from a normal control (C) are also shown. Patient A: a 28-year-old man. Scotopic and 30 Hz ERG: normal. Pattern ERG: markedly reduced (P50: 1.3 µV right, 0.8 µV left; normal > 2.2 µV). EOG: right 148%; left 150%; reduced. Patient B: an 18-year-old man. Scotopic ERG: slightly reduced a- and b-wave amplitude and delayed b-wave. 30 Hz ERG: normal amplitude but delayed. Pattern ERG: markedly reduced (P50: right 1.1 µV, left 0.6 µV). EOG: right 180%, left 200%; normal.*

EOG

Seventeen of the 40 eyes without flecks (42.5%) had subnormal EOG. The group mean Arden index (±SD) was significantly lower compared with that of the controls ($p < 0.01$).

A summary of all results is given in Table 1 and Fig. 2.

Discussion

There has been marked variation in the reported incidence of electrophysiological abnormalities in STGD/FFM. This may be due to different stages of the disease having been studied in different series and possible incorrect diagnosis of photoreceptor dystrophies

Table 1. *Mean ERG and EOG values (SD in parentheses) in patients with STGD/FFM with and without flecks*

Investigation	STGD/FFM with flecks (n = 52 eyes)	STGD/FFM without flecks (n = 40 eyes)	Control (n = 60 eyes)
Scotopic ERG amplitude	283.3 (83.8)*†	341.5 (74.81)*	381.6 (43.7)
Range	170–480	220–465	310–490
Scotopic ERG latency	44.4 (4.17)*	43.7 (4.20)*	40.20 (2.61)
Range	38.5–47.27	37.6–48.4	37–45
Photopic ERG amplitude	71.8 (36.3)*†	104.1 (39.8)	120.5 (27.0)
Range	43–130	52–180	85–165
30 Hz ERG amplitude	40.12 (20.5)*†	48.39 (23.9)*	54.15 (10.93)
Range	15.6–79.8	18–72.4	32–77
30 Hz ERG latency	31.15 (2.07)*	30.48 (2.29)*	29.20 (1.80)
Range	28.2–34.47	28–35.7	26–32.1
PERG (P50) amplitude	0.61 (0.67)*†	1.09 (0.72)*	2.85 (0.54)
Range	0–3.4	0–3.8	2.2–4.1
PERG (P50/N95 ratio)	0.68 (0.14)	0.58 (0.13)	0.66 (0.12)
Range	0.54–0.8	0.48–0.75	0.4–0.77
EOG	154.9 (45.24)*	167.6 (39.13)*	192.4 (30.2)
Range	116–270	126–270	166–305

EOG values are expressed as a percentage, latency values in milliseconds and amplitude values in microvolts. Statistical analysis was by unpaired t-test.
*$p < 0.01$: STGD/FFM with or without flecks compared with controls.
†$p < 0.01$: STGD/FFM with flecks compared with STGD/FFM without flecks.

as STGD/FFM. In this study, patients with both early and advanced STGD/FFM were examined. The results were analysed in two groups according to the presence or absence of flecks.

The incidence of scotopic ERG b-wave amplitude abnormalities was similar in patients with and without flecks at 20% and 25% respectively. The incidence of scotopic ERG b-wave latency abnormalities was also similar in patients with and without flecks at 13.5% and 7.5% respectively. Single flash photopic ERG amplitude abnormalities occurred in 26% of eyes with flecks and 16% of eyes without flecks. Thirty hertz ERG b-wave amplitude abnormalities occurred in 35% of patients with and without flecks. Thirty hertz ERG b-wave latency abnormalities occurred in 21% of patients with flecks and 15% of patients without flecks. Thus, reduction of cone responses was slightly more prevalent in the group with flecks. The 30 Hz ERG b-wave amplitude was always greater than 50% of laboratory normal values, and any value less than that should be considered as indicating a photoreceptor dystrophy

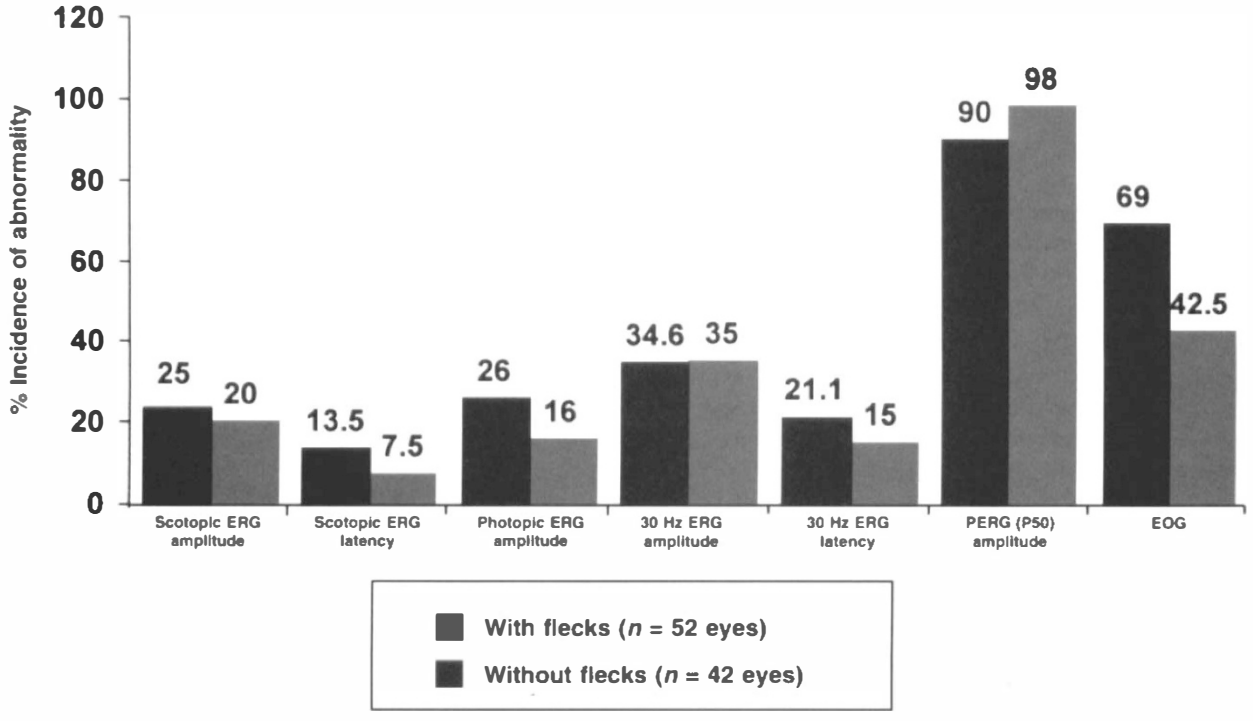

Fig. 2. *Electrophysiological findings in STGD/FFM.*

rather than STGD/FFM. There was no selective reduction of oscillatory potentials in either group.

Reduction of the amplitude of the P50 component of the PERG was similar in patients with and without flecks at 90% and 98% respectively. This is not surprising as the PERG is reduced in any type of macular disease. The slightly higher incidence of abnormality in patients without flecks may be related to the fact that some of these patients had only mild macular changes and exhibited fundus flavimaculatus. The P50/N95 component was not selectively reduced in either group studied.

The incidence of EOG abnormalities was significantly higher in patients with flecks (69%) compared with patients without flecks (42%; $p < 0.025$).

It is interesting that, in the group with flecks, although the ERG b-wave amplitudes were never less than 50% of normal values, and usually within the upper quartile of the abnormal range, the group mean b-wave amplitude was significantly lower to both rod and cone stimulation compared with the group without flecks. The group mean PERG amplitude was also significantly lower in the group with flecks. Furthermore, the incidence of EOG abnormalities was significantly higher in the group with flecks. These findings are similar to those of a previous study.[15] The similar age of the two groups suggests that they represent subgroups with a different electrophysiological evolution rather than the natural history of the disease (with the flecks appearing later in life).

Whilst histopathological studies suggest widespread abnormalities at the level of the photoreceptor/retinal pigment epithelium (RPE),[9,16,17] a recent study has identified a mutation of a rod photoreceptor-specific ATP-binding transporter protein gene (ABCR) in some cases of recessive STGD/FFM.[18] Thus at least some cases of STGD/FFM are a primary dystrophy of the rod photoreceptor, rather than the RPE as previously thought. As the ERG primarily reflects photoreceptor function, our findings of ERG abnormalities may reflect this underlying pathology, although a preferential involvement of the rod (scotopic) responses might be expected.

The EOG abnormalities represent abnormalities in the photoreceptor/RPE unit.[19] The severity of abnormality correlates clinically with the flecks, the presence of which indicates more widespread RPE involvement. The PERG abnormalities are assumed to be non-specific findings and correlate with the extent of macular involvement.

STGD/FFM remains clinically and electrophysiologically heterogeneous and this may represent either manifestations of different genetic abnormalities or, as in the case of the clinical manifestations of mutations of the peripherin/RDS gene,[20] phenotypic heterogeneity.

This study emphasises the importance of careful quantitative measurements of electrodiagnostic data and their comparison with a control group. It is interesting to note that an ABCR mutation has also been described in some cases of age-related macular degeneration (ARMD).[21] Whilst it is usually assumed that the ERG is normal in ARMD, it is possible that careful quantitative analysis of the responses under standardised conditions may identify subtle changes that could be of value in the classification of this common blinding condition.

References

1. Stargardt K. Über familiäre, progressive Degeneration in der Makulagegend des Auges. Graefes Arch Clin Exp Ophthalmol 1909;71:534–50.
2. Franceschetti A. Ueber tapeto-retinale Degenerationen in Kindesalter. In: von Sautter H, editor. Entwicklung und Fortschritt in der Augenheilkunde. Stuttgart: Enke Verlag, 1963:107–20.
3. Franceschetti A, Francois J. Fundus flavimaculatus. Arch Ophthalmol 1965;25:505–30.
4. Klien BA, Krill AE. Fundus flavimaculatus: clinical, functional and histopathologic observations. Am J Ophthalmol 1967;64:3–22.
5. Deutman AF. The hereditary dystrophies of the posterior pole of the eye. Assen, The Netherlands: Van Gocum, 1971:100–71, 300–23.
6. Hadden OB, Gass JDM. Fundus flavimaculatus and Stargardt's disease. Am J Ophthalmol 1976;82:527–39.
7. Noble KG, Carr RE. Stargardt's disease and fundus flavimaculatus. Arch Ophthalmol 1979;97:1281–5.
8. Cibis GW, Morey M, Harris DJ. Dominantly inherited macular dystrophy with flecks (Stargardt). Arch Ophthalmol 1980;98:1785–9.
9. Lopez PF, Maumanaa IH, de la Cruz Z, Green WR. Autosomal-dominant fundus flavimaculatus: clinicopathologic correlation. Ophthalmology 1990;97:798–809.
10. François J. Juvenile makulardegenerationen. Klin Montasbl Augenheilkd 1979;175:715–34.
11. Fishman GA. Fundus flavimaculatus: a clinical classification. Arch Ophthalmol 1976;94:2061–7.
12. Aaberg TM. Stargardt's disease and fundus flavimaculatus: evaluation of morphologic progression and intrafamilial coexistence. Trans Am Ophthalmol Soc 1986;84:453–87.
13. Arden GB, Carter RM, MacFarlan A. Pattern and Ganzfeld electroretinograms in macular diseases. Br J Ophthalmol 1984;68:878–84.
14. Marmor MF, Arden GB, Nilson SEG, Zrenner EZ. Standard for clinical electroretinography. Arch Ophthalmol 1989;107:816–9.
15. Moloney JBM, Mooney DJ, O'Connor MA. Retinal function in Stargardt's disease and fundus flavimaculatus. Am J Ophthalmol 1983;96:57–65.
16. Eagle R Jr, Lucier AC, Bernardino VB Jr, Yanoff M. Retinal pigment epithelial abnormalities in fundus flavimaculatus: a light and electron microscopic study. Ophthalmology 1980;87:1189–200.
17. McDonnell PJ, Kivlin JD, Maumenee IH, Green WR. Fundus flavimaculatus without maculopathy. Ophthalmology 1986;93:116–9.
18. Allikmets R, Singh N, Sun H, Shroyer NF, Hutchinson A, Chidambaram A, *et al*. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nature Genet 1997;15:236–46.
19. Marmor MF, Zrenner E. Standard for clinical electro-oculography. Arch Ophthalmol 1993;111:601–4.
20. Weleber RG, Carr RE, Murphey WH, Sheffield VC, Stone EM. Phenotypic variation including retinitis pigmentosa, pattern dystrophy and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/RDS gene. Arch Ophthalmol 1993;111:1531–42.
21. Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, *et al*. Mutation of the Stargardt disease gene (ABCR) in age related macular degeneration. Science 1997;277:1805–7.