Documenta Ophthalmologica **73**: 395–404, 1990.

The electroretinogram in Stargardt's disease and fundus flavimaculatus

PIERRE LACHAPELLE,[1,2] JOHN M. LITTLE & MARIE SYLVIE ROY

[1]Department of Ophthalmology, McGill University – Montreal Children's Hospital, Montreal, Quebec, Canada H3H 1P3; [2]Department of Neurology & Neurosurgery, McGill University – Montreal Children's Hospital, Montreal, Quebec, Canada H3H 1P3; [3]Department de Psychologie, Université de Montréal, Montréal, Québec, Canada H3C 3J7

Received and accepted 13 December 1989

Key words: Stargardt's disease, fundus flavimaculatus, electroretinogram, oscillatory potentials

Abstract. A retrospective study was performed comparing the ERG results of 15 patients with Stargardt's disease and fundus flavimaculatus. Patients with fundus flavimaculatus had "fish-tail" lesions with or without macular changes, while the Stargardt's group had macular atrophy without fish-tail flecks. The mean visual acuity was 20/200 for the Stargardt's patients compared with a mean of 20/80 for the fundus flavimaculatus patients. The Stargardt's photopic and scotopic amplitudes were respectively 33% and 34% of normal, while the fundus flavimaculatus values were less impaired at 58% and 64% of normal.

Introduction

Since their original description, Stargardt's disease (SD) and fundus flavimaculatus (FFM) have triggered numerous studies aimed at further characterizing the two retinal diseases. Originally, Stargardt described a hereditary, bilateral, macular degeneration seen in seven children. A follow-up examination of one of Stargardt's patients, performed more than 40 years after the original study, revealed the presence of macular and perimacular flecks extending beyond the arcades. These flecks were reported absent in Stargardt's original drawings [1]. In 1962, Franceschetti described a progressive, autosomal recessive, retinal condition characterized with subretinal yellow flecks, which were associated, in 50% of the cases, with macular changes similar to those seen in Stargardt's disease. Franceschetti named the condition fundus flavimaculatus [2, 3]. As recognized by Franceschetti, if the flecks are localized at the posterior pole with macular involvement it becomes almost impossible to clinically distinguish FFM

from SD. This has led some investigators to consider these two retinal disorders as reflecting the same disease process [4, 5] for which Deutman suggested the eponym "Stargardt's flavimaculatus" as a more accurate identification [6]. This view is also supported by Fishman [5] in his staging of FFM, with stage 1 identifying FFM patients in whom the retinopathy is strictly limited to the macula, a condition similar to that originally described by Stargardt.

On the other hand there are numerous studies in which SD and FFM appeared to have been successfully segregated that report differences between the two retinal conditions. Moloney and associates [7] reported that psychophysical and electrophysiological (especially electrooculogram) tests were more impaired in FFM. They also reported that the age of onset was significantly lower in FFM. Foveal densitometry measurements by van Meel and van Norren [8] also indicated a difference between FFM and SD, where the former was found to be closer to normal while the latter yielded markedly abnormal results. However, most of these studies did not provide the necessary information on how the diagnosis was made and at what stage was the disease process. The purpose of this study was to investigate if there are electroretinographic (ERG) differences between SD and FFM. We reviewed ERG charts from the last three years and considered only those that had been labelled as SD, FFM, or Stargardt's flavimaculatus. Our findings indicate that, while both conditions yielded lower than normal ERGs, those obtained from SD patients were more severely impaired.

Materials and methods

This study was conducted in a semi-double blind fashion. We reviewed our ERG charts (last three years) to identify those cases that had been diagnosed as SD, FFM, or Stargardt's flavimaculatus. A total of 15 patients were considered. The patients were then subdivided into two groups according to their fundus findings at the time of examination and on examination of the fundus photographs. The first group consisted of six patients in whom typical "fish-tail" lesions could be observed with or without macular changes. This group was referred to as FFM. The second group consisted of nine patients with macular atrophy but without the fish-tail flecks. The peripheral retina could, however, show evidences of flecks (not pisciform in shape) or region of mottling of the retinal pigment epithelium (RPE). The latter group of patients were referred to as Stargardt's disease. Once the two groups had been clearly delineated, the ERGs and (oscillatory potentials) (OPs) were

analyzed for possible differences. The data were compared also with an age-matched control group (20 subjects).

The mean age was 26 years (range 9–40) for the SD group and 24 years (range 6–47) for the FFM patients. The mean visual acuity was 20/200 for the SD patients (range 20/70–20/400) and 20/80 (range 20/20–20/200) in the FFM group. ERGs were recorded by means of a corneal contact lens electrode (Medical Workshop Inc.) placed on the anesthetized cornea (proparacaine HCl 0.5%), with reference and ground electrodes placed on the forehead and earlobe respectively. The pupils were maximally dilated (phenylephrine HCl 10% and cyclopentolate HCl 1%) and the media were clear. A Ganzfeld stimulator of 45 cm in diameter, illuminated at 30 cd/m^2 (rod saturating background) and equipped with a Grass PS22 photostimulator, was used to evoke the ERGs with intensities of I-16 (10 $cd \cdot sec \cdot m^{-2}$) in light adaptation, I-1 (1 $cd \cdot sec \cdot m^{-2}$) in dark adaptation, and I-1 + 1.5 ND filter (0.03 $cd \cdot sec \cdot m^{-2}$) also in dark adaptation. Subjects were dark-adapted for 15 minutes, and light-adapted ERGs were recorded prior to the dark-adaptation period to avoid the light readaptation effect previously reported [9]. ERGs and OPs were recorded simultaneously with the following recording bandwidths: 1–1000 Hz (3 db attenuation) and 100–1000 Hz (3 db attenuation) obtained with the Grass P-511 AC amplifiers (analog amplifiers). Peak time and amplitude measurements were performed according to methods previously described [9, 10].

Results

Figure 1 illustrates the typical fundus features used to distinguish SD (top) from FFM (bottom). In SD the pathology was, in most cases, limited to the macular region (atrophy, "beaten-bronze" appearance), although some patients showed evidences of peripheral involvement (i.e., non-pisciform flecks, RPE mottling). Patients with FM all showed the typical fish tail-shaped lesions, while the macular changes were similar to those seen in SD. None of our patients had the form of FFM in which peripheral flecks are seen in the absence of macular involvement.

Representative light-adapted and dark-adapted ERGs in SD and FFM are illustrated in Figures 2 and 3 respectively. Amplitude and peak time measurements are summarized in Table 1. In SD the amplitude of the light-adapted and the dark-adapted ERGs were significantly lower than normal ($p < 0.05$). On average, the light-adapted ERG was 33% of normal amplitude while the dark-adapted ERG was 34% and 32% of normal amplitudes for intensities 1 $cd \cdot sec \cdot m^{-2}$ and 0.03 $cm \cdot sec \cdot m^{-2}$ respectively

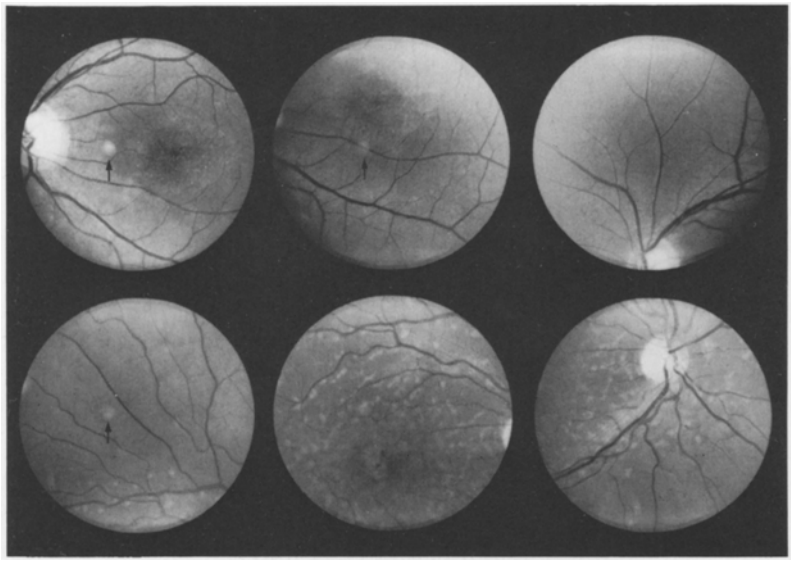

Fig. 1. Fundus photographs of the left eye of a patient with Stargardt's disease (top) showing an atrophic macular region (left), the inferior temporal region (middle), and the superior region (right). The bottom set of pictures illustrate the right eye fundus of a patient affected with fundus flavimaculatus. The inferior nasal region (right), the atrophied macular region (center), and superior temporal region (left) all show the typical fish-tail-shaped lesion characteristic of fundus flavimaculatus. Small arros (top left and center pictures, bottom left) point at a camera artifact.

(Table 1). In all patients but one (patient 4) the light-adapted ERG b-wave peak time was significantly ($p < 0.05$) delayed, but the dark-adapted ERG b-wave was delayed in only one patient (patient 2, Fig. 2).

Although the ERGs recorded from FFM patients were significantly ($p < 0.05$) larger than those obtained from SD patients, they were still significantly ($p < 0.05$) lower than normal. On average, the light-adapted ERG b-wave was 58% of normal while the dark-adapted ERG b-wave was 64% of normal at intensity $1\,cd{\cdot}sec{\cdot}m^{-2}$ and 70% of normal at $0.03\,cm{\cdot}sec{\cdot}m^{-2}$. The timing of the light-adapted ERG b-wave was normal in all the cases studied, while the dark-adapted ERG was delayed in only one patient and only for intensity $0.03\,cd{\cdot}sec{\cdot}m^{-2}$ (Fig. 3, tracing B 4).

Since in SD the light-adapted ERG is the most affected (when both the peak time and the amplitude are considered) and in FFM both light- and dark-adapted ERGs appear equally attenuated, electroretinal potentials evoked in light-adapted conditions appear to yield valuable information in the differential diagnosis between SD and FFM. As shown in Figure 2, all

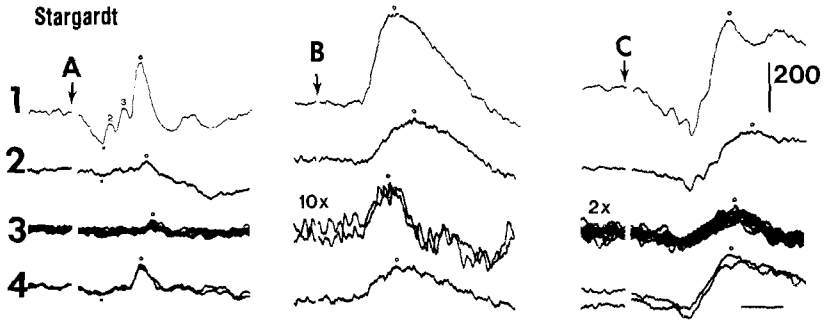

Fig. 2. Light-adapted (A) and dark-adapted (B, C) ERGs recorded from patients affected with Stargardt's disease. The intensity of stimulation used was 10 cm·sec·m^{-2} (A), 0.03 cd·sec·m^{-2} (B) and 1 cd·sec·m^{-2} (C). Tracings A-1, B-1, and C-1 illustrate those recorded from a normal subject. Vertical arrows indicate flash onset. The small squares point at the peak of the a-wave, the small dots the peak of the b-wave. Tracings 2, 3, and 4 (A, B, C) were obtained from three Stargardt's disease patients. The recordings illustrated represent single-sweep responses. In tracings 3 (A, B, C) and 4 (A, C) multiple sweeps are superimposed.

Calibration: Horizontal 20 msec (A, C), 40 msec (B); Vertical 200 μV except for B-3 20 μV and C-3 100 μV.

but one SD patient had significantly ($p < 0.05$) delayed light-adapted b-wave and all patients in the FFM group (Fig. 3) had normal light-adapted b-wave peak time.

To further separate the two groups, light-adapted OPs evoked to the same

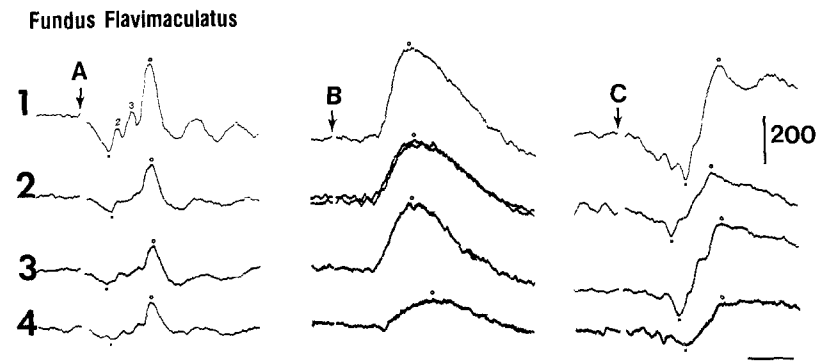

Fig. 3. Light-adapted (A) and dark-adapted (B, C) ERGs recorded from patients affected with fundus flavimaculatus. The intensity of stimulation used was 10 cd·sec·m^{-2} (A), 0.03 cd·sec·m^{-2} (B), and 1 cd·sec·m^{-2} (C). Tracings A-1, B-1, and C-1 illustrate that recorded from a normal subject. Vertical arrows indicate flash onset. The small squares point at the peak of the a-wave while the small dots identify the peak of the b-wave. Tracings 2, 3, and 4 (A, B, C) were obtained from three fundus flavimaculatus patients. The recordings illustrated represent single sweep responses. Two responses are superimposed in tracing B-2.

Calibration: Horizontal 20 msec (A, C), 40 msec (B); Vertical 200 μV.

Table 1. Peak time and amplitude b-wave measurement and oscillatory potential (mean ± standard deviation).

Test	Normals ($N = 20$)	Fundus flavimaculatus ($N = 6$)	Stargardt's disease ($N = 9$)
Photopic ($10\,cd{\cdot}sec{\cdot}m^{-2}$)			
Amplitude	340 ± 60	198 ± 38 (160–260)	112.9 ± 62.2 (50–220)
Peak Time	32 ± 1	32.7 ± 0.5 (32–33)	35.75 ± 2.6 (32–40)
Scotopic ($1\,cd{\cdot}sec{\cdot}m^{-2}$)			
Amplitude	500 ± 80	322 ± 84.4 (200–420)	174 ± 103.6 (60–280)
Peak Time	47 ± 3	45.8 ± 3.3 (42–50)	48.9 ± 3.5 (44–56)
Scotopic ($0.03\,cd{\cdot}sec{\cdot}m^{-2}$)			
Amplitude	390 ± 70	273.3 ± 74.8 (130–350)	123.6 ± 85.3 (20–200)
Peak Time	75 ± 4	77.6 ± 7.1 (72–90)	78.7 ± 6.2 (70–90)
OP_2 (msec)	15.04 ± 0.6	16.01 ± 0.43	18.24 ± 0.84

intensity ($10\,cd{\cdot}sec{\cdot}m^{-2}$) were also examined (Fig. 4). Special attention was given to the peak time of OP_2. Although in both groups the peak time of OP_2 was significantly delayed ($p < 0.05$) when compared with normals, in SD the peak time of OP_2 is delayed by almost 5 standard deviations (average data: Fig. 4) and in FFM the peak time of OP_2 is within 2 standard deviations of the normal mean value. The peak time of OP_2 was delayed in all SD patients examined, even the one in which a normal light-adapted ERG b-wave peak time was found (Fig. 4, tracing B-4). In contrast, the peak time of OP_2 in some FFM subjects was within the upper limit of the 1 standard deviation from normal, which might explain why, on average, they yielded a significant difference from normal value. Furthermore, as exemplified in Figure 4, the amplitude of OP_2 was also much lower in SD.

Discussion

Although our study was performed on a limited number of individuals, in both conditions (SD and FFM) the light- and dark-adapted ERGs are significantly lower than those obtained from our age-matched control group. Some of our findings might be explained by our relatively small

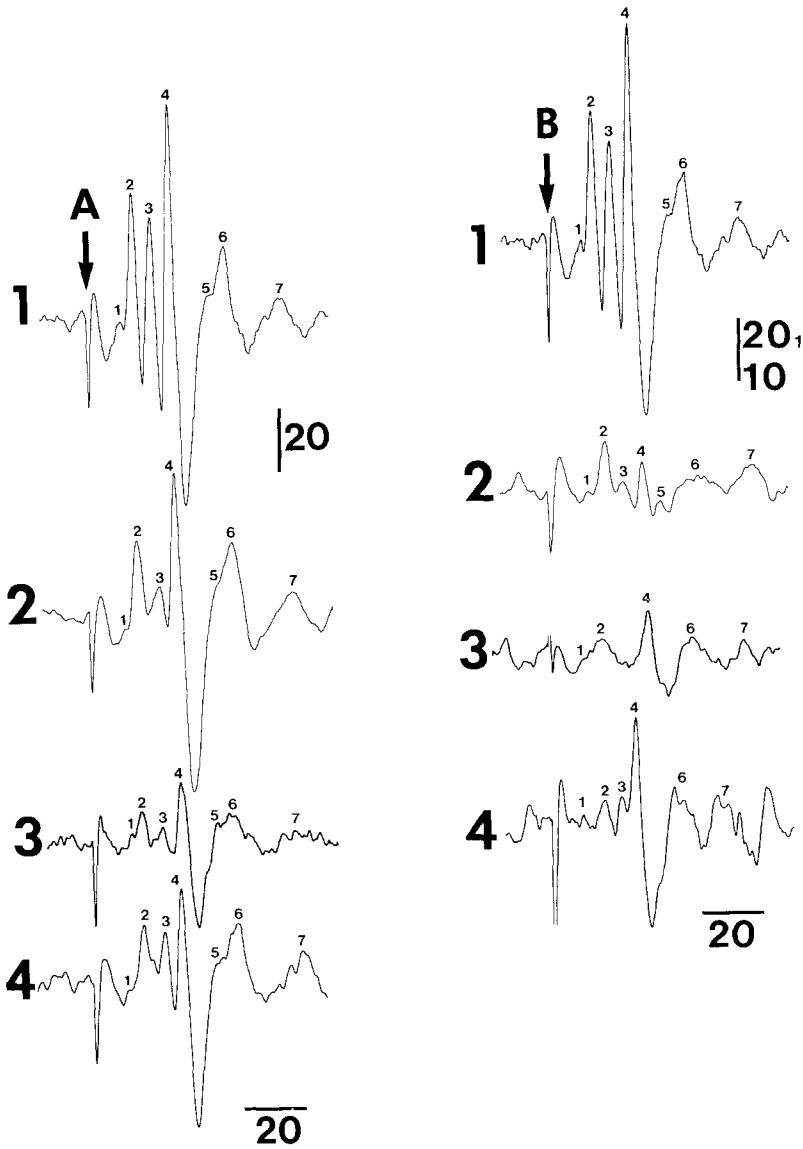

Fig. 4. Light-adapted oscillatory potentials recorded from patients affected with fundus flavimaculatus (A) and Stargardt's disease (B). Tracings A-1 and B-1 were obtained from the same normal as that illustrated in Figures 2 and 3 (tracing A-1). The OPs were obtained from the same patients illustrated in Figures 2 and 3 and disposed in the same order. Vertical arrows indicate flash onset. Note the delayed OP_2 in the Stargardt's disease group (tracings B-2, B-3, and B-4) while OP_2 is of normal timing in fundus flavimaculatus (tracings A-2, A-3, and A-4). The recordings represent an average of 16 flashes presented at an interstimulus interval of 1.3 seconds. The intensity of the flash was of $10\,cd{\cdot}sec{\cdot}m^{-2}$.

Calibration: Horizontal 20 msec; Vertical 20 μV (A, B-1), 10 μV (B-2, B-3, B-4).

sample size. For instance, although on average the b-wave amplitudes were lower than normal in FFM, the amplitude ranges (given at Table 1) indicate that some FFM subjects had b-wave amplitudes falling within 1 standard deviation from the normal mean (especially dark-adapted b-waves). In contrast, even when the amplitude ranges are considered, none of our SD patients had b-wave amplitudes falling within 1 standard deviation from the normal mean. Clearly, our Stargardt patients stand out as those with the most impaired electroretinal signals.

At first our findings may appear to contrast with previous reports. Noble and Carr [4] reported ERG anomalies in only eight of the 50 patients tested, without saying if they were SD or FFM. Van Meel and van Norren [8] reported abnormal ERGs in two of their six SD patients, while their two FFM subjects had normal ERGs. In their study Hadden and Gass [11] reported seven of 36 patients with abnormal ERGs, but no information is given on which of the two conditions yielded the abnormal electroretinal signal. In contrast, Klein and Krill [12] reported that 20 of their 24 patients had abnormal ERGs. The most consistent ERG anomaly that they reported was that it took more time to reach the normal dark-adapted b-wave amplitude. They showed that the amplitude of the dark-adapted b-wave was abnormal (lower than normal) at 17 minutes of dark-adaptation in 17 of 24 patients, while it was abnormal in only two of 24 patients if measurements were obtained after 45 minutes of dark adaptation. A similar finding is also acknowledged by Fishman [5], who also noted a delay in reaching normal dark-adapted values in some of his patients from stage 2 on. Patients in the later stages (stages 3 and 4) had definitely abnormal ERGs (both photopic and scotopic). Moloney and associates [7] also reported abnormal photopic and scotopic ERGs in their SD and FFM patients. They also reported abnormal OP amplitudes.

On the basis of such reports we think that our findings also could be explained by our ERG protocol. Our photopic ERGs were obtained prior to dark adaptation and are therefore not influenced by the dark-adaptation process. It was previously shown [9, 13] that if photopic ERGs are recorded after dark adaptation, one needs to wait 15–20 minutes in order for the cone system to fully recover. Recording the photopic ERGs prior to the dark-adapted condition overcomes the effect that dark adaptation appears to exert on the photopic system [9] and more than probably allows for a more accurate evaluation of the cone function. Unfortunately, most papers written on FFM or SD did not clearly specify when the photopic ERGs were obtained. Second, we obtained our dark-adapted ERGs after 15 minutes of dark adaptation rather than the more widely used 30 minutes. As clearly shown by Klein and Krill [12], the scotopic ERG in FFM is abnormal after

17 minutes of dark adaptation, while it is normal after 45 minutes of dark adaptation. Use a shorter period of dark adaptation thus allows one to better identify scotopic anomalies, especially in conditions where the dark adaptation process is slowed down by pathologies. A longer period of dark adaptation might fail to reveal these anomalies. Finally, although in both anomalies the timing of OP_2 was longer than normal, the average OP_2 peak time is delayed by almost 5 standard deviations from the normal mean in SD, while the peak time of OP_2 is well within 2 standard deviations in FFM. The timing of OP_2 in SD is delayed even in the one subject where the corresponding photopic b-wave showed normal timing.

Our intention was to examine if, on the basis of ERG findings, SD and FFM could be considered as two separate entities. It is difficult at this time to make a clear statement. Our ERG results could be interpreted as reflecting different stages of one disease process, in a fashion similar to that proposed by Fishman [5]. Those patients that we labelled as FFM would fall in stage 2 of Fishman's nomenclature, while those that we labelled as SD would fall in stages 3 and 4. If one segregates these patients on the sole basis of presence or absence of typical fish-tail flecks, however, then those with the pisciform flecks appear more normal (from an ERG basis) than those without. More research, especially long-term follow-ups of our FFM subjects, is needed in order to see if, as suggested by Fishman [5], they will progressively evolve to more impaired electroretinal signals.

Acknowledgments

This work was supported by a grant-in-aid from the McGill University – Montreal Children's Hospital Research Institute and the Medical Research Council of Canada (Ma-8649). This is publication 90004 from the McGill University – Montreal Children's Hospital Research Institute. Thanks are due to Ms June Paterson and Danuta Rylski for proof-reading the manuscript and to Ms Michelle McKerral for typing.

References

1. Blacharski PA. Fundus flavimaculatus. In: Newsome DA, ed. Retinal dystrophies and degenerations. New York: Raven Press, 1988.
2. Franceschetti A. A special form of tapetoretinal degeneration: fundus flavimaculatus. Trans Am Acad Ophthalmol Otolaryngol 1965; 69: 1048–53.
3. Franceschetti A, François J. Fundus flavimaculatus. Arch Ophthalmol 1965; 25: 505–30.
4. Noble KG, Carr RE. Stargardt's disease and fundus flavimaculatus. Arch Ophthalmol 1979; 97: 1281–5.

5. Fishman GA. Fundus flavimaculatus: a clinical classification. Arch Ophthalmol 1976; 94: 2061–7.
6. Deutman AF. The hereditary dystrophies of the posterior pole of the eye. Springfield, Illinois: Charles C. Thomas, 1971; 100–71.
7. Moloney JBM, Mooney DJ, O'Connor MA. Retinal function in Stargardt's disease and fundus flavimaculatus. Am J Ophthalmol 1983; 96: 57–65.
8. van Meel GJ, van Norren D. Foveal densitometry as a diagnostic technique in Stargardt's disease. Am J Ophthalmol 1986; 102: 353–62.
9. Lachapelle P. Analysis of the photopic electroretinogram recorded before and after dark adaptation. Can J Ophthalmol 1987; 22: 354–61.
10. Lachapelle P, Molotchnikoff S. Components of the electroretinogram: a reappraisal. Doc Ophthalmol 1986; 63: 337–48.
11. Hadden OB, Gass JDM. Fundus flavimaculatus and Stargardt's disease. Am J Ophthalmol 1976; 82: 527–39.
12. Klein BA, Krill AE. Fundus flavimaculatus. Am J Ophthalmol 1967; 64: 3–23.
13. Gouras P, MacKay CJ. Growth in amplitude of the human cone electroretinogram with light adaptation. Invest Ophthalmol Vis Sci 1989; 30: 625–30.

Address for correspondence: Dr. P. Lachapelle, Dept. of Ophthalmology, The Montreal Children's Hospital, 2300 Tupper Street, Montreal, Quebec H3H 1P3, Canada.