

# Electroretinogram abnormalities in nonanterior childhood uveitis

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## ABSTRACT.

**Purpose:** A major point of concern in uveitis is the development of irreversible retinal changes after inflammation. In this study, we assess how nonanterior childhood uveitis affects retinal function using full-field electroretinography (ERG).

**Methods:** Cross-sectional study. ERGs of 63 uveitis eyes (33 children) were measured according to extended International Society for Clinical Electrophysiology of Vision (ISCEV) protocols. ERG abnormalities were investigated in relation to the following clinical parameters: demographics, uveitis characteristics, including severity of inflammation, treatment, best corrected visual acuity (BCVA), cystoid macular oedema (CME) on optical coherence tomography and fluorescein angiography score.

**Results:** The ERG showed abnormalities in 34 eyes (54%). The most frequent ERG abnormalities were prolonged implicit times of the cone b-wave (37%;  $n = 23/63$ ) and an abnormal 30-Hz flicker response (implicit time and/or amplitude) (33%;  $n = 21/63$ ). Factors associated with these ERG abnormalities were CME ( $p = 0.021$ ) and 3+ vitreous cells ( $p = 0.021$ ). BCVA in eyes with and without these ERG abnormalities did not statistically differ and was relatively good (median: 0.05 LogMAR, IQR: 0.00–0.15 LogMAR).

**Conclusion:** The ERG is frequently affected in childhood uveitis indicating a global retinal dysfunction. ERG abnormalities seem to be associated with a more severe posterior segment inflammation and a younger age. If an association between ERG abnormalities and long-term visual outcome can be made in the future, these early ERG findings during the course of childhood uveitis have significance for treatment strategies.

**Key words:** electrophysiology – electroretinography – ERG – inflammation – paediatric – uveitis

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## Introduction

Nonanterior, noninfectious uveitis is a serious disease with unilateral blindness developing in up to 19% of children,

despite intensive immunomodulating treatment. This blindness is often caused by complications such as cystoid macular oedema (CME) and glaucoma (de Boer et al. 2006; Hettinga et al. 2014; Kalinina Ayuso et al. 2011).

In addition, after a prolonged course of inflammation, patients with uveitis may develop thinning of the retina with ‘retinal dystrophy-like’ changes and dragged disc vessels (de Smet et al. 2011; Hettinga et al. 2014; Moschos et al. 2014).

To gain a better understanding of the effects of uveitis on retinal function, a full-field (Ganzfeld) electroretinogram (ERG) can be used. The ERG objectively measures retinal function and may therefore provide useful additional information to imaging techniques.

Electroretinography (ERG) abnormalities have been described in various uveitis entities. Particularly in birdshot chorioretinopathy (BSCR) (Moschos et al. 2014; Tzekov & Madow 2015), the ERG is used for monitoring disease activity and treatment, but it may also be useful in other uveitis entities (Zacks et al. 2002; Holder et al. 2005; Moschos et al. 2014). However, there are few studies on ERG abnormalities in childhood uveitis, and knowledge is still lacking on the effects of uveitis on retinal function in children (Shamshinova et al. 1992).

In this study, we retrospectively analysed ERG abnormalities in children with a noninfectious and nonanterior uveitis. We correlate their ERG abnormalities to clinical parameters and investigate the value of the ERG as an additional tool to objectively assess retinal damage in childhood uveitis.

## Materials and Methods

### Study population

We included 33 patients (63 eyes) with a noninfectious, nonanterior uveitis. The

median age at diagnosis was 8.9 years (range: 3.5–14.6 years). All patients were seen at the ophthalmology department of the University Medical Centre Utrecht (UMC Utrecht). Here, we perform an ERG as part of the clinical workup if no obvious underlying cause for uveitis is found, to exclude a retinal dystrophy (Hettinga et al. 2016). In case of doubt regarding the ERG abnormalities, such as reduction in amplitudes, DNA was tested for retinal dystrophy mutations, which was negative ( $N = 3$ ). Furthermore, none of the patients had alterations suggestive of a retinal dystrophy on their latest optical coherence tomography (OCT) and/or visual fields. All patients had an ERG examination between May 2015 and December 2016.

The uveitis diagnosis was based on the Standardization of Uveitis Nomenclature (SUN) criteria (Jabs 2005) and made by an ophthalmologist specialized in uveitis. Electroretinograms and their medical charts were retrospectively reviewed.

This study was conducted in compliance with the ethical principles of the declaration of Helsinki. Ethical approval was requested and obtained from the Medical Ethical Research Committee of the UMC Utrecht. Depending on the age of the patients, we obtained consent from the patients themselves, or their parents or both.

### ERG analysis

The ERGs were measured incorporating the International Society for Clinical Electrophysiology of Vision (ISCEV) standards (McCulloch et al. 2015). Dawson–Trick–Litzkow (DTL) electrodes were used as corneal electrodes. An Espion E3 System with ColorDome Stimulator (Diagnosys LLC, Cambridge, UK) was used for flash stimulation.

We measured an extended ISCEV series, consisting of stimulus strengths that increase with approximately 0.5 log units and range from 0.0001 to 30.0 cds/m<sup>2</sup> for the dark-adapted ERG (DA; rod and combined rod–cone) and from 0.3 to 10.0 cds/m<sup>2</sup> for the light-adapted ERG (LA; cone), including a 30-Hz flicker response (LA; cone).

The ERGs of patients were compared to healthy controls with the same age range as uveitis patients (5–22 years) ( $n = 50$ ). These ERGs were measured with the same equipment and protocols

and provided by the Rotterdam Eye Hospital and Bartiméus (Bartiméus Diagnostic Centre for complex visual disorders, Zeist). An ERG was considered abnormal if amplitudes were below the 2.5th percentile, or implicit times were above the 97.5th percentile or both.

We categorized the ERG abnormalities based on the measuring conditions [LA 0.3–10.0 cds/m<sup>2</sup> (cone response), 30-Hz flicker response (cone response), DA 0.0001–0.01 cds/m<sup>2</sup> (rod response) or DA 3.0–30.0 cds/m<sup>2</sup> (combined rod–cone response)] and which part of the response was abnormal (a-wave, b-wave, amplitudes or implicit times). We did not classify DA 0.03–1.0 cds/m<sup>2</sup>, as stimulus strengths lay between rod and combined rod–cone responses.

All ERGs could be used for analyses. It is our experience that in a child-friendly environment, it is possible to measure an ERG properly, even in small children.

### Clinical parameters

Medical records were reviewed for age, gender, medical history and age at onset of uveitis [defined as age at the date of diagnosis by a (referring) ophthalmologist]. Using the outpatient visit closest to ERG measurement, with a maximum of 2.5 months, we recorded for each eye: laterality and localization of uveitis, best corrected visual acuity (BCVA), cell grade in the anterior chamber, cell grade in the vitreous, flare (Jabs 2005), posterior synechiae, corneal clarity, lens clarity, snowballs, snow banking, vasculitis, optic disc hyperaemia or swelling, and CME, either present on OCT (Zeiss, Cirrus HD OCT 5000) or fluorescein angiography (FA).

An experienced ophthalmologist (JdB) scored FAs using the fluorescein angiographic scoring system of the Angiography Scoring for Uveitis Working Group (ASUWOG; Tugal-Tutkun et al. 2010). We looked at the FA made before or up to 2.5 months after the ERG was made, for statistical analysis. If more than one FA was made, we used the FA with the highest overall score as an indicator of structural damage of previous severity of inflammation.

We recorded per patient treatment with systemic steroids, methotrexate (MTX), mycophenolate mofetil and adalimumab, and we recorded per eye the frequency of administered periocular corticosteroid injections.

### Statistical analysis

For statistical analysis, spss version 21.0 (SPSS Inc., Chicago, IL, USA) was used. Electroretinography abnormalities were investigated in relation to clinical parameters.

We performed all analyses twice, once using all 63 uveitis eyes and once using only one eye per patient. We performed this second analysis as an alternative for paired sampling analyses. For this second analysis, we included the eye with the worst BCVA in case of a bilateral uveitis. If BCVA was the same in both eyes, a random eye was selected per patient.

Pearson chi-square test or the likelihood ratio was applied for categorical variables, and a Student t-test or a Mann–Whitney  $U$  test was applied for continuous variables. Spearman rank correlation coefficient was used to find possible correlations between variables. We considered p-values below 0.05 as statistically significant. All tests were two-tailed.

## Results

### Patient characteristics

Most patients (91%; 30 out of 33) had a bilateral uveitis; 49% of the patients were male. Intermediate uveitis was seen in 64% of the patients and panuveitis in 36% of patients. In three patients, uveitis was associated with Blau syndrome, a rare hereditary disorder with a classical triad of arthritis, dermatitis and uveitis associated with a NOD2 mutation (Sarens et al. 2018). In the other 30 patients, no underlying cause was found.

### ERG analysis

The ERG was abnormal in 35 (56%) eyes (21 patients, two with unilateral uveitis) (Table 1). In line with this, when looking at the specific ERG parameters as continuous variables, uveitis patients did decidedly worse than healthy controls in all cone, 30 Hz, rod and combined rod–cone responses, with the exception of the rod implicit times (Figs. 1 and S1–S7).

The most frequently found ERG abnormality (24 eyes; 38%) was a prolonged implicit time of the cone b-wave, which was most pronounced at the lower stimulus strengths (0.3 and

**Table 1.** Electroretinogram abnormalities of uveitis eyes (*n* = 63).

		Eyes with ERG abnormalities, <i>n</i> (%)
Overall		35 (56)
Single flash cone*		27 (43)
A-wave	Amplitude	4 (6)
	Implicit time	2 (3)
B-wave	Amplitude	9 (14)
	Implicit time	24 (38)
30-Hz flicker response <sup>†</sup>		21 (33)
Through	Implicit time	7 (11)
Peak	Amplitude	17 (27)
	Implicit time	12 (19)
Single flash rod <sup>‡</sup>		8 (13)
A-wave	Implicit time	2 (3)
	B-wave	Amplitude
	Implicit time	0
Single flash combined rod-cone <sup>§</sup>		15 (24)
A-wave	Amplitude	11 (18)
	Implicit time	2 (3)
B-wave	Amplitude	7 (11)
	Implicit time	1 (2)

ERG = electroretinography.

\* Light adapted 0.3–10.0 cds/m<sup>2</sup>

<sup>†</sup> Light-adapted cone response.

<sup>‡</sup> Dark adapted 0.0001–0.01 cds/m<sup>2</sup>.

<sup>§</sup> Dark adapted 3.0–30.0 cds/m<sup>2</sup>.

1.0 cds/m<sup>2</sup> LA). In addition, responses showed abnormal waveforms with less steep slopes of both the ascending and descending limb of the b-wave (Fig. 2).

The second most frequently found ERG abnormality (21 eyes, 33%) was an abnormal 30 Hz flicker response, consisting of a reduction in amplitude, or a prolonged implicit time or both (Fig. 2).

In 16 eyes (25%), both the implicit times of the cone b-wave were prolonged and the 30 Hz flicker response was abnormal. In five eyes, the 30 Hz flicker response was abnormal, while the implicit times of the cone b-wave were within normal values, and in eight eyes, the 30 Hz flicker response was within normal values while the implicit times of cone b-waves were prolonged. No statistically significant differences were found in the b/a wave ratios of the cone ERG between uveitis and age-matched controls.

Besides abnormalities in the cone b-wave and 30 Hz responses, abnormalities in the rod (0.0001–0.01 cds/m<sup>2</sup> DA) and combined rod-cone (3.0–30.0 cds/m<sup>2</sup> DA) responses were found in eight eyes (13%) and 15 eyes (24%), respectively. Six eyes (10%) only had abnormalities in the dark-adapted

ERG, without ERG abnormalities in the light-adapted ERG.

**Statistical analysis of ERG abnormalities in relation to clinical parameters**

We analysed whether clinical parameters were significantly different between uveitis eyes with and without ERG abnormalities. Here, we classified the ERG as abnormal if the implicit time of the cone b-wave was prolonged, or the 30 Hz flicker response was abnormal or both (Table 2). We used these ERG abnormalities, since they had a typical appearance, occurred frequently and are both cone-mediated.

Two clinical parameters were statistically significantly different between eyes with and without these ERG abnormalities in both the analysis using all uveitis eyes and the analysis using only one eye per patient. These were CME and 3+ vitreous cells (Table 2). There was no significant correlation between these two variables (Spearman’s rho correlation coefficient = 0.259; *p* = 0.056).

No statistically significant differences were observed between the two groups with regard to treatment or in the inflammation activity on FA score. Interestingly, we also found no statistical differences in BCVA, which was relatively good in both groups (0.05 and 0.05 LogMAR) (Table 2). Furthermore, no statistically significant differences were observed between clinical parameters and rod and combined rod-cone abnormalities.

**Discussion**

In this study, more than half of the eyes with nonanterior childhood uveitis showed ERG abnormalities. The light-adapted ERG was most frequently affected, showing a prolonged cone b-wave implicit time, particularly at lower stimulus strengths, and abnormal 30-Hz flicker responses. Two clinical parameters were statistically significantly associated with these ERG abnormalities: CME and 3+ vitreous cells.

All eyes with CME had abnormal cone ERGs. Although cones are densely packed in the macula (Osterberg 1935; Jonas et al. 1992), macular dysfunction alone contributes only minimally to the full-field cone (Dawson & Maida 1984; Khan et al. 2018; Robson et al. 2018). The abnormal ERG in the children with

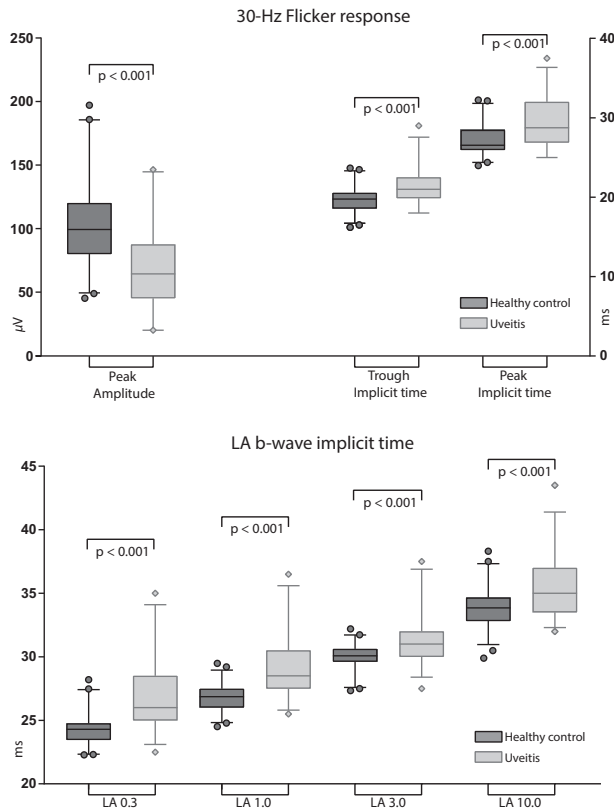
CME therefore indicates a global retinal dysfunction and not only macular dysfunction (Robson et al. 2018).

A correlation between visual acuity and outer retinal function (represented by the a-wave) has been described, which is in line with our study in which we found a relatively good VA and few a-wave abnormalities (Maheshwary et al. 2010; Iannetti et al. 2012). However, a correlation between VA in inner retinal function (represented by the b-wave) as found in birdshot uveitis was not confirmed in our study on childhood uveitis (Sobrin et al. 2005). This discrepancy between birdshot and childhood uveitis may be due to a disease-specific inflammatory mechanism or to the duration of disease.

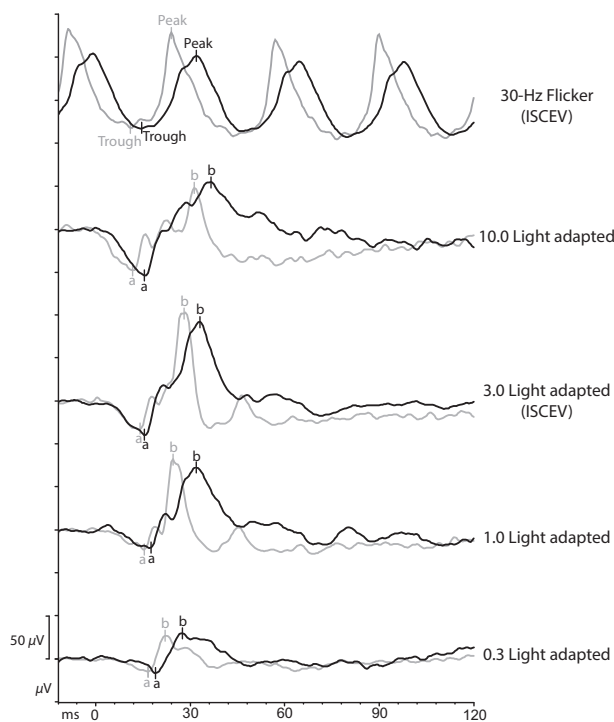
Besides eyes with CME, all eyes with 3+ vitreous cells also showed ERG abnormalities, indicating that more severe inflammation frequently results in retinal dysfunction.

The prolonged b-wave implicit time and the abnormal 30 Hz flicker response indicate an abnormal inner retinal transmission dysfunction from photoreceptors to bipolar cells (Robson et al. 2018). This abnormal signal transmission could be caused by an increased interneuronal distance secondary to an increased permeability of the blood-retinal barrier, caused by inflammation (Noma et al. 2014). Although the prolonged cone b-wave and the 30 Hz flicker response indicate inner retinal dysfunction, amplitudes were mostly normal, as were b/a wave ratios. In addition to the abnormal cone ERGs, we also found some abnormalities in the dark-adapted ERG. Although it may be interesting to investigate these abnormalities in more detail, in this study, we decided to focus on the more profound and more frequent abnormalities of the cone ERG. Here, we saw a consistent and recognizable pattern in the prolonged cone b-wave implicit time and the abnormal 30 Hz flicker response.

Our study is the first one that describes ERG changes in childhood uveitis by using an extended ISCEV-based protocol, with a greater range of stimulus strengths than the ISCEV standard protocol. The abnormal timing in the cone b-wave, which we found in our study, was most profound at lower stimulus strengths (0.3 cds/m<sup>2</sup> LA and 1.0 cds/m<sup>2</sup> LA) and therefore may not have been discovered by using the standard protocol only.



**Fig. 1.** Boxplots of the implicit time of the cone b-wave and the 30-Hz flicker response of patients compared to healthy controls from the same age category (5–22 years,  $n = 50$ ). For statistical analysis, a Mann–Whitney  $U$  test was used.



**Fig. 2.** Representative example ( $n = 1$ ) of a light-adapted (LA) electroretinogram (ERG) of a patient with uveitis (black) and an ERG of age-matched control (grey). The cone b-wave implicit times of the uveitis patient are prolonged; this is most pronounced at the lower stimulus strengths (LA 0.3  $\text{cds}/\text{m}^2$  and 1.0  $\text{cds}/\text{m}^2$ ). The 30 Hz flicker response of the uveitis patient is abnormal as well, with reduced amplitudes and prolonged implicit times.

Previous reports on intermediate uveitis and childhood uveitis mostly describe abnormalities in amplitudes but rarely describe implicit times (Cantrill et al. 1981; Ikeda et al. 1989; Tetsuka et al. 1991). Shamshinova et al. found a subnormal ERG response in 75% of eyes in childhood uveitis, including all anatomic subtypes. Electrorretinography abnormalities were more frequently seen when the macula was affected and in nonanterior uveitis (Shamshinova et al. 1992).

In accordance with our findings, abnormalities of the 30 Hz flicker response in intermediate uveitis have been described. However, abnormal implicit times of the combined rod–cone response have also been reported, whereas we mostly found abnormal cone b-wave implicit times (Cantrill et al. 1981). Other studies on intermediate uveitis mainly describe differences in ERG amplitudes and do not mention implicit times (Ikeda et al. 1989; Tetsuka et al. 1991).

There are several limitations to this study. Due to the retrospective design and limited sample size, weak associations may not have been found. Since paediatric uveitis is not a common entity, we were unable to include more patients. Additionally, we were unable to correct for paired eyes, which would have been preferable since most patients had a bilateral uveitis. We were unable to perform a generalized estimating equation (GEE), since we had a complete separation of data in multiple variables, including CME and the amount of vitreous cells. By using only one eye per patient, we would have discarded almost half of the limited amount of data. Therefore, we decided to perform and present both the analysis with all eyes and the analysis with only one eye per patient.

We did not find statistically significant associations with ERG abnormalities and FA scores in both analyses. We also could not correlate ERG abnormalities to visual field defects, as visual fields were only assessed in a minority of children and were often made a long time before the ERG was performed.

Considering the current findings and previous reports, we emphasize that in nonanterior childhood uveitis, the global inner retinal function is frequently affected. Even though ERG abnormalities in intermediate and childhood uveitis have been reported in the past,



**Table 2.** Clinical characteristics of uveitis eyes in relation to electroretinogram abnormalities.

	Eyes with ERG abnormalities <sup>†</sup> n = 29	Eyes without ERG abnormalities <sup>†</sup> n = 34	p-value all eyes	p-value worst eye <sup>‡‡</sup>
Male	16 (55)	14 (41)	0.267	0.565
Age in years <sup>‡,§</sup>	11.4 (9.5–13.2)	14.8 (11.9–15.8)	0.016*	0.067
Duration of uveitis in years <sup>‡,§</sup>	1.7 (0.7–6.4)	3.4 (1.5–7.3)	0.267	0.908
Blau syndrome	1 (3)	5 (15)	0.112	0.438
History of CME	17 (59)	12 (36)	0.080	0.309
3+ vitreous cells <sup>§,¶</sup>	7 (24)	0	0.001**	0.026**
3+ cells in anterior chamber <sup>§,¶</sup>	2 (7)	0	0.075	0.266
CME <sup>§</sup>	7 (24)	0	0.001**	0.021**
Hyperaemic optic disc <sup>§</sup>	9 (31)	3 (9)	0.023*	0.173
Vitreous haze <sup>§,¶</sup>	8 (28)	7 (21)	0.516	0.602
BCVA in LogMAR <sup>‡,§</sup>	0.10 (0.00–0.40)	0.05 (0.00–0.11)	0.127	0.133
Oral prednisone	21 (72)	28 (82)	0.345	0.602
Methotrexate	11 (38)	17 (50)	0.337	0.246
Adalimumab	5 (17)	7 (21)	0.735	0.805
Mycophenolate mofetil	12 (41)	12 (35)	0.620	0.948
Peribulbar steroid injections	15 (52)	15 (44)	0.547	>0.999
FA total score <sup>‡,††</sup>	11.0 (5.0–17.0)	8.0 (1.8–12.0)	0.108	0.461
FA capillary leakage score <sup>‡,††</sup>	5.0 (0–10.0)	2.0 (0–5.3)	0.148	0.265
FA CME <sup>‡,††</sup>	17 (65)	13 (43)	0.137	0.309
FA vasculitis <sup>‡,††</sup>	16 (59)	19 (63)	0.752	0.466
FA optic disc leakage <sup>‡,††</sup>	23 (85)	23 (76)	0.413	0.391

BCVA = best corrected visual acuity; CME = cystoid macular oedema; ERG = electroretinography; FA = fluorescein angiography; LogMAR = logarithm of minimal angle of resolution; n = number.

\* Significant in one of two analysis.

\*\* Significant in both analyses.

† ERG abnormalities are defined as prolonged implicit times of the light-adapted (0.3–10.0 cds/m<sup>2</sup>) cone b-wave and/or abnormalities of the 30 Hz flicker (amplitudes/implicit times).

Data are given as number (%) unless otherwise stated.

‡ Data given as median (IQR).

§ Present at closest outpatient visit to ERG measurement.

¶ As described by the Standardization of Uveitis Nomenclature classification.

†† FAs with the highest score were used for the calculation of FA scores as described by The Angiography Scoring for Uveitis Working Group.

‡‡ Only one eye per patient was used, in case of bilateral uveitis, eyes with the worst BCVA were selected, when BCVA was the same; eyes were selected at random.

ERG outcomes were not investigated in relation to clinical parameters as shown in our study. We recommend using an extended ISCEV protocol to detect early and subtle retinal dysfunction. If an association between ERG abnormalities and long-term visual outcome can be made in the future, these early ERG findings during the course of childhood uveitis have significance for treatment strategies. Since ERG abnormalities occur when BCVA is still relatively good, further studies should focus on the effects of this retinal dysfunction on long-term visual outcome.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**Figure S1.** Boxplots of the amplitude of the rod and combined rod-cone a-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S2.** Boxplots of the amplitude of the rod and combined rod-cone b-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S3.** Boxplots of the implicit times of the rod and combined rod-cone a-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S4.** Boxplots of the implicit times of the rod and combined rod-cone b-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S5.** Boxplots of the amplitude of the cone a-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S6.** Boxplots of the amplitude of the cone a-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).

**Figure S7.** Boxplots of the implicit time of the cone a-wave of patients compared to healthy controls from the same age category (5-22 years,  $n = 50$ ).