Acta Ophthalmologica

Electroretinogram abnormalities in non-infectious uveitis often persist

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ABSTRACT.

Purpose: **In uveitis, a prolonged implicit time of the cone b-wave is a characteristic electroretinogram (ERG) abnormality. We investigated whether this can improve or deteriorate over time and which clinical factors are associated with change.**

Methods: **Prospective cohort study. Patients with a non-infectious uveitis were included. An ERG was measured in the first year of uveitis onset and a follow-up ERG one year later. Changes in the implicit time of the cone b-wave were investigated in relation to clinical parameters including the following: demographics, uveitis characteristics, treatment, best-corrected visual acuity, optical coherence tomography parameters and fluorescein angiography scores.**

Results: **Of 98 eyes (63 patients), 40 showed a prolonged cone b-wave on the first ERG, which improved in 10 eyes. Eyes with an improved ERG more often had a panuveitis with initially a higher incidence of cells in the anterior chamber during the first ERG, which resolved at the time of their follow-up ERG. Five of the 58 eyes with a normal first ERG had a deteriorated follow-up ERG. These eyes had more frequently an active uveitis at the time of the follow-up ERG. Of the 78 eyes with a stable cone b-wave, 16 had a quiescent inflammation during follow-up. There were no differences in age or treatment.**

Conclusion: **In most patients with non-infectious uveitis, ERG abnormalities appear to be irreversible, even when the inflammation becomes quiescent. However, some ERGs improved, which was associated with reduction in inflammation of the anterior chamber due to panuveitis. In contrast, a worsened ERG was associated with a persistence of inflammation.**

Key words: electrophysiology – electroretinogram – electroretinography – ERG – uveitis

The corresponding author is a member of the Dutch Ophthalmological Societies.

Acta Ophthalmol. 2020: 98: 627–633

doi: 10.1111/aos.14401

Introduction

Uveitis comprises of a group of multiple diseases with an inflammation of the uvea and its adjacent structures, including the retina (Thorne et al. 2016). If this inflammation is severe, it can be treated with immune-modulating drugs. However, despite intensive treatment strategies with these medicines, vision loss can still develop (Suttorp-Schulten & Rothova 1996). This vision loss can be the result of several complications of intraocular inflammation.

Well-known complications are macular oedema, cataract and glaucoma (Forooghian et al. 2009). However, retinal atrophy and loss of retinal function may also occur. Recently, we described a characteristic type of ERG abnormality in uveitis: a prolonged cone b-wave, which was seen in all anatomical subtypes including anterior uveitis. This prolonged cone b-wave was associated with a more severe inflammation of both present and past (Brouwer et al., 2019a,2019b).

So far, it is unknown to what extent ERG abnormalities in uveitis are reversible. We found that the prolonged cone b-wave could still be present in eyes in which inflammation had become inactive at the time of ERG recording. However, there are reports of ERG abnormalities that improve in uveitis. For instance, in birdshot chorioretinitis (BSCR) the ERG can normalize after treatment (Holder et al. 2005; Elbaz et al. 2017). On the other hand, in Behçet disease, the ERG does not improve, even when the inflammation becomes quiet (Hamza et al. 2016). In other uveitis entities, such as in AMPPE, MEWDS and AZOOR, the ERG may either improve or deteriorate over time (Sieving et al. 1984; Jacobson et al. 1995; Li & Kishi 2009).

To gain more insights into factors that may contribute to either an improvement or a worsening of retinal function in uveitis patients, we investigated changes in the ERG over time in

relation to clinical factors such as anatomical localization and diagnosis, severity of inflammation and treatment.

Methods

Design and patient population

This is a 1-year follow-up study of a prospective cohort study which describes the retinal function of uveitis patients by using the ERG (Brouwer et al., 2019a,2019b). Inclusion criteria for this follow-up study were as follows: a non-infectious uveitis and a disease duration of less than 1 year at the time of inclusion for the previous study. The results of the first ERGs were part of a larger cohort study which was previously described (Brouwer et al., 2019a,2019b). The diagnoses which were included are as follows: Behçet disease, birdshot, chorioretinitis, human leucocyte antigen -B27 associated uveitis, Vogt–Koyanagi–Harada disease, sarcoidosis and uveitis of unknown cause.

We included 72 patients (114 uveitis eyes) for this follow-up study. Of the initial 80 patients who had an ERG in the first year of onset of uveitis, four no longer wanted to participate, three were referred back to another hospital and one moved to another country.

All patients were ≥18 years of age, mentally competent and gave informed consent to participate. Patients were seen at the University Medical Centre Utrecht, a tertiary referral centre for uveitis. Patients with juvenile idiopathic arthritis, diabetic retinopathy, retinal dystrophy, family history of retinal dystrophy, myopic degeneration or severe media opacities were excluded. Ethical approval was requested and obtained from the Medical Ethical Research Committee of the University Medical Centre Utrecht. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

ERG analysis

Electroretinograms (ERGs) were performed on the same day as an outpatient clinic visit when uveitis activity was assessed. Electroretinograms (ERGs) were measured according to an extended protocol, with more flash strengths than the standard International Society for Clinical Electrophysiology of Vision (ISCEV) protocol (McCulloch et al. 2015). The flash strengths increase with approximately 0.5 log units steps and range from 0.0001 to 30.0 cds/m^2 (12 flash strengths) for the dark-adapted ERG (DA) and from 0.3 to 10.0 cds/m^2 (4 flash strengths) for the light-adapted ERG (LA) and include a 30 Hz flicker response as well.

We used Dawson–Trick–Litzkow (DTL) electrodes as active electrodes and an Espion E3 system with ColorDome stimulator (Diagnosys LLC, Cambridge, UK) for flash stimulation. Full details of the ERG measurement procedure, as well as our reference values, were previously described (Brouwer et al., 2019a,2019b).

In this study, we focus on changes in the implicit time of the cone b-wave, but other aspects of the ERG were investigated as well. The implicit time of the cone b-wave is correlated to the peak implicit time of the 30 Hz flicker response (Spearman's rho coefficient 0.620 - 0.814 $p < 0.001$ (Brouwer et al., 2019a,2019b). Because the prolonged cone b-wave was the most frequent and characteristic ERG abnormality in uveitis that we observed in our previous study, we focused on differences in the cone b-wave.

To our knowledge, there are no internationally accepted criteria to define whether an ERG has improved or worsened, but only criteria to describe whether an ERG is normal or abnormal (in- or outside reference values). In this study, we used the difference in milliseconds (ms) of the implicit time of the cone b-wave of first ERG minus the follow-up ERG to define whether the ERG was stable, improved or worsened. Because pupil size affects the implicit time of the cone b-wave, we excluded eyes with a pupil size difference >1 mm between the first and follow-up ERG.

To determine how many ms the implicit time needed for change to be defined as significantly changed, we used data of a previous study where we measured a LA ERG twice in 200 uveitis patients, to assess the effects of DTL position on the ERG (Brouwer et al., 2019a,2019b). The DTL position had an effect on amplitudes, but not on implicit times of the ERG. Because this study was in essence a repeated measurement study, we used the difference in implicit time between the two ERGs of each eye to determine a normal repeatability distribution. We defined improvement as a reduction in cone b-wave implicit time of ≥2 SD of this distribution (2.7, 1.7, 1.6 and 1.3 ms for the 0.3, 1.0, 3.0 and 10.0 cds/m^2 flashes, respectively) in at least two consecutive flash strengths. We defined worsening as an increase in implicit time with ≥2SD in at least two consecutive flash strengths. We defined the ERG as stable if the implicit time of the first and second ERG was within 95% of the repeatability distribution (<2 SD). Figure 1 shows examples of a patient with a worsened implicit time (A) and of a patient with an improved implicit time of the cone b-wave (B).

Because the focus of this manuscript is on the implicit time of the cone b-wave of the ERG, the terms stable, improved or worsened ERG mean a stable, improved or worsened implicit time of the cone b-wave, respectively.

Clinical parameters

Medical records were reviewed for age, gender, medical history, uveitis diagnosis and anatomical localization of uveitis. On each of the two outpatient clinical visits, we recorded for each eye the BCVA and graded uveitis activity according to the SUN criteria (Jabs 2005). We also noted the presence of possible media opacities and other factors which might influence the ERG such as: posterior synechiae, corneal clarity, lens clarity, vitreous haze and pupil size.

Also, we recorded per patient if they were treated at the time of ERG recording with systemic steroids, disease-modifying anti-rheumatic drugs (DMARDS) (i.e. methotrexate (MTX), azathioprine, mycophenolate mofetil, mycophenolate sodium, or cyclosporine) or biologicals (adalimumab or infliximab).

We scored fluorescein angiograms (FA) which were performed within 3 months to the time of ERG recordings as an indication of the severity of inflammation. Fluorescein angiograms were scored by an experienced ophthalmologist (JdB) who was blinded regarding the ERG results, using the fluorescein angiographic scoring system of the Angiography Scoring for Uveitis Working Group (ASUWOG) (Tugal-Tutkun, Herbort & Khairallah 2010). This FA scoring system scores individual aspects of an FA, which are added up to a final FA score. This FA score, which is the summation of each

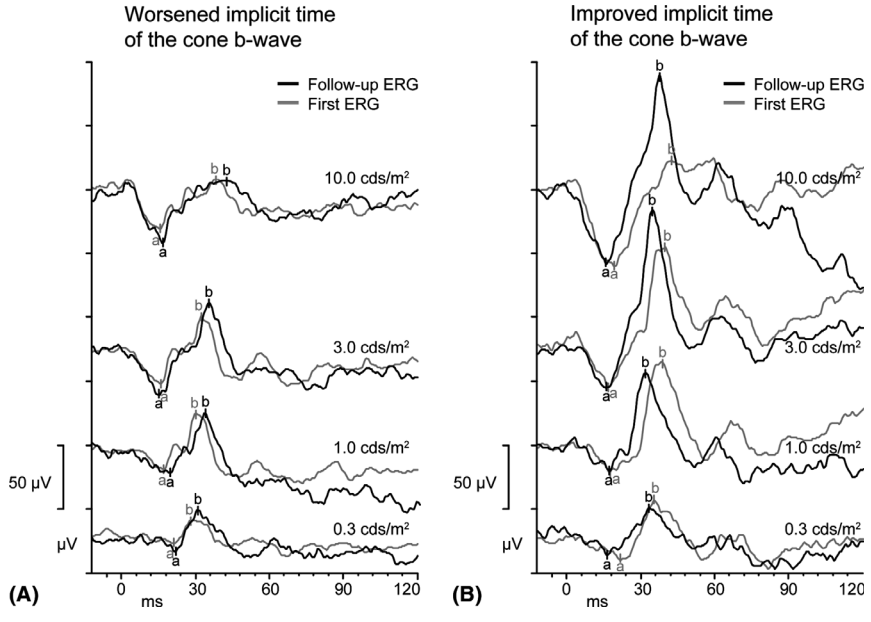

Fig. 1. Example of changes in the implicit time of the cone b-wave. Examples of a patient with a worsened (A) implicit time of the cone b-wave and of a patient with an improved implicit time of the cone b-wave (B). The first ERG is printed in grey and the follow-up ERG a year later in black.

of these individual sub-scores, helps to quantify the magnitude of retinal inflammation. In our previous study, eyes with a higher FA score more frequently had a prolonged cone b-wave (Brouwer et al., 2019b). If FAs were performed on the same day as the ERG, there was at least an hour between the FA and ERG (Azarmina, Moradian & Azarmina 2012).

To determine whether cystoid macula oedema (CMO) was present, we used optical coherence tomography (OCT) (Zeiss, Cirrus HD OCT 5000) scans of the same day as the ERG. We defined an active uveitis as the presence of cells in the anterior chamber and/or a vitritis of ≥1+ cells and/or a fluorescein angiograms (FA) score of >1.

Statistical analysis

For statistical analysis, R version 1.1.456 (© 2009-2018 RStudio, Inc.) was used. Electroretinogram (ERG) changes between the first and the follow-up ERG were investigated using the paired t-test or Wilcoxon paired sample test, depending on the distribution of data. Data distribution was evaluated with qq-plots, histograms and Shapiro-Wilk test. All significances were two-tailed. We considered p-values < 0.05 as statistically significant.

Next, we investigated whether eyes that had a prolonged cone b-wave during the first ERG could improve, or worsen even more in the follow-up ERG. Also, we investigated whether eyes that had an implicit time that was within our reference values could worsen in the follow-up ERG. These outcomes were then investigated in relation to clinical parameters using Pearson chi-square test or Fisher's exact test for categorical variables, and a Student t-test or a Mann–Whitney *U* test for continuous variables, depending on the distribution of data.

For patient-specific characteristics such as age, one eye per patient was analysed. For patients with a bilateral uveitis where both eyes had the same cone b-wave outcome (i.e. both uveitis eyes stable, improved and worsened), one eye was selected at random. If the cone b-wave outcome differed between uveitis eyes of the same patients, the eye with the changed cone b-wave outcome (i.e. improved or worsened) was selected for analysis of patient-specific variables such as age or diagnosis. None of the patients had one eye which improved and one that worsened.

Results

ERG results

Sixteen eyes of nine patients were excluded from further analysis, because the pupil size difference was >1 mm between the two ERGs and a disparity in pupil size can cause a change in b-wave implicit time that is independent of retinal pathology. Of these excluded eyes, 2 eyes showed an improvement, 1 eye worsened and 13 eyes had no significant difference in the implicit time of the cone b-wave.

On a group level, the implicit times of the cone b-wave were not statistically significantly different between the first and the follow-up ERG (see Table 1). The ERG changed significantly in 20 eyes: in 10 eyes the implicit time improved and in 10 eyes it worsened, based on our cut-off values (see Fig. 1 for examples).

There was no predominant flash strength at which this change in implicit time was most prominent. In other ERG parameters (see Table S1), there were also no consistent significant changes between the first and the follow-up ERG. There was a significant correlation between the peak implicit time of the 30Hz flicker response and a prolonged cone b-wave of both the first (Spearman's rho = 0.739, $p < 0.001$) and follow-up ERG (Spearman's rho = 0.695, $p < 0.001$).

Table 1. Results of implicit time of the cone b-wave of the first and follow-up electroretinogram.

Implicit time cone b-wave, median [IQR]		1st ERG (<1 year of diagnosis)	Follow-up ERG (<1 year later)	p-value
cds/m²	0.3	27.00 [25.50, 30.50]	27.00 [26.00, 30.38]	0.544
	1.0	29.25 [28.00, 31.00]	29.25 [28.00, 31.00]	0.960
	3.0	31.50 [30.62, 33.50]	32.00 [31.00, 33.50]	0.760
	10.0	35.50 [35.00, 37.50]	35.75 [35.00, 37.00]	0.510

Results of the first and follow-up ERG of the different flash strengths (cds/m²) of the implicit time of the cone b-wave of 98 uveitis eyes. Eyes with a pupil size difference >1 mm between the first and the follow-up ERG were excluded. Results of the other ERG parameters are shown in Table S1. p-values were tested with the paired Wilcoxon signed-rank test (no normal distribution of data). All significances were two-tailed.
ERG = electroretinogram, IQR = interquartile range, cds/m² = candela seconds/squared metres.

Table 2. Patient characteristics of different outcomes of the implicit time of the cone b-wave.

	Prolonged cone b-wave first ERG				Normal cone b-wave first ERG		
	Improved during FU ERG (n = 8)	Stable during FU ERG (n = 16)	Worsened during FU ERG (n = 4)	p-value	Stable during FU ERG (n = 30)	Worsened during FU ERG (n = 5)	p-value
Age†, median [IQR]	60.97 [54.40, 67.00]	59.21 [52.13, 67.91]	51.58 [44.92, 61.43]	0.694	35.10 [25.26, 52.26]	49.56 [40.45, 53.93]	0.239
Male gender, N (%)	6 (37.5)	5 (62.5)	1 (25.0)	0.492	11 (36.7)	3 (60.0)	0.369
Bilateral uveitis, N (%)	11 (68.8)	5 (62.5)	2 (50.0)	0.863	14 (46.7)	3 (60.0)	0.658
Localization, N (%)				0.241			0.119
Anterior	0	1 (12.5)	0		1 (3.3)	0	
Intermediate	2 (12.5)	1 (12.5)	0		1 (3.3)	2 (40.0)	
Posterior	7 (43.8)	5 (62.5)	4 (100.0)		18 (60.0)	2 (40.0)	
Panuveitis	7 (43.8)	1 (12.5)	0		10 (33.3)	1 (20.0)	
Daignosis, N (%)				0.364			0.555
Unknown cause	9 (56.2)	6 (75.0)	1 (25.0)		8 (26.7)	3 (60.0)	
Chorioretinitis	1 (6.2)	0 (0.0)	1 (25.0)		10 (33.3)	1 (20.0)	
Sarcoidosis	2 (12.5)	2 (25.0)	0		6 (20.0)	0	
Birdshot	2 (12.5)	0 (0.0)	2 (50.0)		2 (6.7)	1 (20.0)	
VKH	1 (6.2)	0	0		0	0	
Behcet	0	0	0		1 (3)	0	
Systemic medication 1st ERG, N (%)	8 (50.0)	3 (37.5)	3 (75.0)	0.514	14 (46.7)	1 (20.0)	0.365
Systemic medication 2nd ERG, N (%)	11 (68.8)	4 (50.0)	3 (75.0)	0.551	4.46 (6.76)	1.10 (1.42)	0.502
Time start systemic medication, median [IQR]‡	5.57 (5.95)	4.93 (6.25)	2.86 (3.43)	0.777	1.73 [1.46, 1.92]	1.65 [1.40, 1.86]	0.576

Patient characteristics and treatment of uveitis patients with different outcomes of the implicit time of the cone b-wave. In case of a bilateral uveitis, one eye per patient was analysed. When both uveitis eyes had the same cone b-wave outcome (i.e. both uveitis eyes stabile, or both improved or both worsened), one eye was selected at random. If the cone b-wave outcome differed between uveitis eyes in patients with a bilateral uveitis, the eye with the changed cone b-wave outcome (i.e. improved or worsened) was selected for analysis of patient-specific variables such as age or diagnosis. None of the patients had one eye with an improved ERG and one eye with a worsened ERG.

1st = first, 2nd = second, ERG = electroretinogram, FU = follow-up, IQR = interquartile range, N = number.

† In years.

‡ Time in months between the onset of uveitis and the start of systemic medication.

ERG changes in relation to clinical parameters

Table 2 shows possible associations between changes in the ERG and patient characteristics as well as treatment. Regarding age, gender, anatomical localization and uveitis diagnosis, there were no differences in changes in the implicit time of the cone b-wave.

We also observed no statistically significant differences in treatment between patients with a different ERG outcome. However, more patients that had an improved follow-up ERG were treated with systemic medication after the first ERG. In contrast, one of the patients with a worsened ERG ceased systemic medication between the first and follow-up ERG.

There was no significant association between the duration of uveitis and start of systemic medication with either an improvement or a worsening of the ERG. However, patients with an abnormal first ERG started systemic medication later compared to patients with a normal first ERG (median uveitis duration on months of 1.2 versus 2.9, respectively, p = 0.382). This difference was not significant, and overall patients with an abnormal first ERG were treated more often with systemic medication. Also, we observed no differences based on uveitis diagnosis.

Table 3 shows possible associations for an improved implicit time of the cone b-wave and uveitis characteristics. Eyes with an improved implicit time more often had a panuveitis with cells in the anterior chamber during the first ERG. This inflammation in the anterior chamber was resolved during the second ERG in all improved eyes.

Table 4 shows possible associations between a worsening of the implicit time of the cone b-wave in eyes with an initial normal ERG and uveitis characteristics. Eyes that had a worsened ERG more frequently had an active uveitis during the second ERG. This activity was mostly due to a vitritis, which was often not present during the first ERG. Besides vitritis, BCVA of these eyes was on average also slightly worse during the first ERG, but improved during the follow-up ERG.

Eyes with an improved ERG had more frequently media opacities and/or a small pupil size during the first ERG, whereas eyes with a worsened ERG had these findings more frequently during the second ERG.

Table 3. Uveitis activity and vision of eyes (40) with a prolonged cone b-wave during their first electroretinogram.

	Uveitis activity and vision of eyes with a prolonged cone b-wave at their first ERG							
	At time of first ERG[†]				At time of follow-up ERG[‡]			
	Improved at time of FU ERG (n = 10)	Stable at time of FU ERG (n = 25)	Worsened at time of FU ERG (n = 5)	p-value	Improved at time of FU ERG (n = 10)	Stable at time of FU ERG (n = 25)	Worsened at time of FU ERG (n = 5)	p-value
Active, N (%)[$]	9 (90)	20 (80)	4 (80	0.847	4 (40)	9 (36)	4 (80)	0.210
BCVA, median [IQR]	0.12 [0.01, 0.22]	0.15 [0.05, 0.40]	0.15 [0.10, 0.52]	0.598	0.36 [0.04, 0.52]	0.15 [0.00, 0.40]	0.22 [0.15, 0.52]	0.566
Flare, N (%)	1 (10)	0	0	0.375	0	2 (8)	1 (20)	0.464
Cells anterior chamber, N (%)	5 (50)	3 (12)	0	0.030	0	0	1 (20)	0.125
Anterior uveitis	1 (10)	0	0		0	0	0	
Panuveitis	4 (40)	3 (12)	0		0	0	1 (20)	
Vitritis, N (%)	5 (50)	11 (44)	2 (40)	>.999	3 (30)	6 (24)	3 (60)	0.291
Anterior uveitis	1 (10)	0	0		0	0	0	
Intermediate uveitis	1 (10)	0	0		0	2 (8)	0	
Posterior uveitis	3 (30)	5 (20)	2 (40)		2 (20)	4 (16)	3 (60)	
Panuveitis	0	6 (24)	0		1 (10)	0	0	
CME on OCT, N (%)	4 (40)	8 (32)	2 (40)	0.894	0	5 (20)	2 (40)	0.155
Mean deviation VF, median [IQR]	−15.1 [−15.1, −15.1]	−3.7 [−6.2, −1.5]	−4.9 [−7.5, −4.2]	0.462	−2.1 [−2.4, −1.9]	−4.4 [−7.5, −2.8]	−7.5[−7.7, −5.1]	0.212
FA score 3mnd, median [IQR]	12.5 [6.8, 17.3]	6.0 [3.8, 9.5]	1.5 [0.8, 2.3]	0.095	11.0 [7.8, 12.5]	2.0 [1.5, 6.0]	20.0 [10.5, 20.0]	0.424
Media opacities and/or small pupil size N (%)[¶]	8 (80)	5 (20)	0	<0.001	6 (24.0)	5 (63)	5 (100)	0.001

Clinical characteristic during the first and FU ERG of eyes with a prolonged cone b-wave during their first ERG. Eyes with a pupil size difference >1 mm between the first and the follow-up ERG were excluded. Statistical testing was done with Fisher's exact test in case of categorical variables and Mann–Whitney U test in case of continuous variables. All tests were two-tailed. Data are presented as N (%), unless otherwise specified

CMO = cystoid macula oedema, ERG = electroretinogram, FA = fluorescein angiography, FU = follow-up, IOL = intraocular lens, IQR = interquartile range, N = number, OCT = optical coherence tomography, VF = visual field.

[†] <first year of uveitis activity.

[‡] >1 year later.

[$] Defined as the presence of cells in the AC and/or a vitritis of ≥1+ cells and/or a FA score of >1.

Defined as opacities of the lens/IOL and/or vitreous opacities and/or a pupil size of <6 mm.

Table 4. Uveitis activity and vision of eyes (58) with a normal implicit time of the cone b-wave during their first electroretinogram.

	Uveitis activity and vision					
	At time of first ERG[†]			At time of follow-up ERG[‡]		
	Stable during FU ERG (n = 53)	Worsened during FU ERG (n = 5)	p-value	Stable during FU ERG (n = 53)	Worsened during FU ERG (n = 5)	p-value
Active, N (%)[$]	22 (44)	2 (40)	>.999	7 (13.7)	3 (60)	0.035
BCVA, median [IQR]	0.00 [−0.08, 0.05]	0.05 [0.05, 0.10]	0.120	−0.05 [−0.08, 0.05]	0.00 [0.0, 0.00]	0.531
Flare, N (%)	1 (2)	0	>0.999	2 (4)	0	>0.999
Cells anterior chamber, N (%)	5 (10)	0	>0.999	1 (2)	0	>0.999
Anterior uveitis		0		0	0	
Panuveitis		0		1 (2)	0	
Vitritis, N (%)	9 (18)	2 (40)	0.259	3 (6)	2 (40)	0.058
Anterior uveitis	0	0		0	0	
Intermediate uveitis	2 (4)	2 (40)		0	1 (20)	
Posterior uveitis	2 (4)	0		3 (6)	0	
Panuveitis	5 (9)	0		0	1 (20)	
CME on OCT, N (%)	6 (12)	0	>0.999	1 (2)	1 (20)	0.166
Mean deviation VF, median [IQR]	−1.3 [−2.8, −0.3]	−1.6 [−1.8, −1.3]	0.802	−1.5 [−2.5, −0.4]	−1.1 [−1.4, −0.8]	0.683
FA score 3mnd, median [IQR]	1.5 [0.0, 4.5]	1.0 [0.0, 2.5]	0.654	0.0 [0.0, 1.5]	0.0 [0.0, 0.0]	0.568
Media opacities and/or small pupil size N (%)[¶]	7 (14)	2 (40)	0.184	12 (25)	1 (20)	>0.999

Clinical characteristic during the first and FU ERG of eyes with a normal implicit time of the cone b-wave during their first ERG. Eyes with a pupil size difference >1 mm between the first and the follow-up ERG were excluded. Statistical testing was done with Fisher's exact test in case of categorical variables and Mann–Whitney U test in case of continuous variables. All tests were two-tailed. Data are presented as N (%), unless otherwise specified.

CMO = cystoid macula oedema, ERG = electroretinogram, FA = fluorescein angiography, FU = follow-up, IOL = intraocular lens, IQR = interquartile range, N = number, OCT = optical coherence tomography, VF = visual field.

[†] <first year of uveitis activity.

[‡] >1 year later.

[$] Defined as the presence of cells in the AC and/or a vitritis of ≥1+ cells and/or a FA score of >1.

[¶] Defined as opacities of the lens/IOL and/or vitreous opacities and/or a pupil size of <6 mm.

It is important to note that most of the eyes did not show significant ERG changes. In 78 eyes (80%), the implicit time was stable, of which 25 eyes had a prolonged implicit time. Almost two third of these (16 eyes) had no signs of an active inflammation during the follow-up ERG.

Tables S2 and S3 give an overview of the different aspects of the FA score. There were no differences in these individually scored aspects of the FA between eyes with a different ERG outcome.

Table S4 shows the correlation matrix between statistically significant clinical factors, duration of uveitis, age and treatment. Although many factors are statistically significant, all of the associations are weak (rho < 0.5).

Discussion

This study highlights that a prolongation of the implicit time of the cone b-wave occurs early on in the non-infectious uveitis and often persists. Only in a minority of cases, it can improve or deteriorate in the course of the disease. Improvement was mostly seen in eyes in which the inflammation became more quiescent, whereas a worsening was seen in eyes with a persistent inflammation. The delayed cone b-wave is probably due to an impaired photo-transmission to the bipolar cells. It remains speculative if this ERG abnormality is the first sign of evolving photoreceptor damage.

Although these findings indicate that it is important to treat the inflammation in uveitis adequately and early, we found no differences between the groups based on type of treatment. This might be due to several factors including variation between treatment strategies, as well as the effects of responders versus non-responders.

In eyes with an improved ERG, the inflammation in the anterior chamber had become quiescent. The majority of these patients had a panuveitis. It is likely that the improvement of the inflammation in the anterior chamber was associated with an improvement of the posterior segment, which should be the subject of further studies.

In most eyes, the ERG abnormalities were irreversible, even without signs of active inflammation at the time of the follow-up ERG. Because we measured the first ERG in the first year of onset of disease, it indicates that the retinal damage can occur early on in the disease process. Patients with an abnormal first ERG started systemic treatment on average later than those with a normal first ERG. Furthermore, patients with an improved ERG were using systemic medication more often at the time of the follow-up ERG compared to the first ERG. Although these results showed a trend, the differences were not significant. One explanation could be that the patients in this study may represent a group with a more severe disease course, because this study was performed in a tertiary referral centre.

Apart from the severity of inflammation, eyes with an improved ERG had more frequently media opacities or a small pupil size during their first ERG. In the light-adapted ERG, implicit times increase when the intensity of the flash strength becomes stronger. Media opacities or a small pupil size can reduce the retinal illuminance of the stimulus flash leading to changes in b-wave implicit time of non-pathologic origin (Brouwer

et al., 2019a,2019b). Therefore, it is possible that the improved implicit time of the cone b-wave may even be underestimated due to the improvement of media opacities. Effects of changes in pupil size were addressed by excluding eyes with a pupil size difference >1 mm.

Because the implicit time of the cone b-wave in uveitis over time has not previously been studied, it is not possible to make comparisons with literature. However, there are some reports of follow-up ERG's in birdshot uveitis that show that the 30 Hz flicker response can improve after systemic treatment with corticosteroids, but not in all cases (Holder et al. 2005). Furthermore, other ERG parameters than the 30 Hz flicker response can be permanently affected in birdshot uveitis (Oh, Christmas & Folk 2002; Tzekov & Madow 2015).

In the current study, we could only replicate that the 30 Hz flicker response improved in the minority of the birdshot patients after the start of systemic treatment, possibly because 6 out of 7 of the included birdshot patients already used systemic medication at the time of the first ERG. In these patients, the implicit time of the 30 Hz flicker response did improve in 4 out of 14 eyes, whereas the implicit time of the cone b-wave did not improve.

Some studies state that a change of >30% in amplitude is necessary to define improvement or deterioration, based on Berson's study on decline in retinitis pigmentosa (RP) (Berson et al. 1985). However, the ERG in RP is generally much more severely affected than in uveitis, where the amplitude often does not change significantly. Most studies that report on follow-up results of the ERG in uveitis do not specify how improvement is defined (Sieving et al. 1984; Jacobson et al. 1995; Holder et al. 2005; Li & Kishi 2009; Hamza et al. 2016), for instance, which aspect of the ERG changed during follow-up. In our study, we observed that the different parameters of the ERG may behave quite differently. For uveitis monitoring, we found that the implicit time of the cone b-wave is the most sensitive parameter.

In summary, this study demonstrates that a prolonged implicit time of the cone b-wave often persists in uveitis. In a minority of cases, this loss of retinal function can improve if the inflammation becomes less active. This emphasizes the importance to treat the inflammation adequately and early in uveitis. Further research is needed to investigate to which extent the implicit time of the cone b-wave can be used as a prognostic marker in uveitis.

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Received on November 20th, 2019.
Accepted on February 21st, 2020.

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We would like to thank all patients for participating in the study. The authors were supported by the following foundations: Dr. F.P Fischer Stichting, and Bartiméus Fonds that contributed through UitZicht (the Netherlands). The funding organizations had no role in the design or conduct of this research. They provided unrestricted grants. A.H. Brouwer, N.H. ten Dam., R. Wijnhoven and M.M. van Genderen have no financial disclosures. G.C. de Wit is employed as a medical physicist at Bartiméus, a Low Vision Institute in the Netherlands. Furthermore, he is a sole proprietor; with his company Optical Diagnostics (http://www.opticaldiagnostics.com), he develops and sells ophthalmic software products and does sometimes consulting work. J.H. de Boer was payed by Abbvie for lectures. We thank J. Ossewaarde-van Norel and L. Ho (University Medical Centre Utrecht) for their help in recruiting patients to participate in this research, D. Gültzau, Y. Burgers and M. Ballast (University Medical Centre Utrecht) for their help in recording the ERGs, F. Riemslag and H. Talsma (Bartiméus Diagnostic Centre for complex visual disorders, Zeist) for giving additional electrophysiological advice and S. Risseeuw (University Medical Centre Utrecht) for her statistical advice.

The corresponding author is a member of the Dutch Ophthalmological Societies.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 ERG results of the first and follow-up ERG.
Table S2 Fluorescein angiography scores of eyes with a prolonged implicit time of the cone b-wave during their first ERG.
Table S3 Fluorescein angiographic scores of eyes with a normal implicit time of the cone b-wave during their first ERG.
Table S4 Correlation matrix of significant clinical factors, as well as systemic medication, duration of uveitis, and age.