Original Article

# Electroretinogram Changes in the Sound Eye of Subjects with Unilateral Necrotizing Herpetic Retinitis

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**Purpose:** To evaluate electroretinogram (ERG) changes in the contralateral normal appearing eye of patients with unilateral acute necrotizing herpetic retinitis (NHR).
**Methods:** This interventional case series includes subjects with acute unilateral NHR. All patients were treated with intravenous followed by oral acyclovir and systemic steroids. Main outcome measures were changes in a- and b-wave amplitudes of scotopic and photopic full-field ERG in the sound eye, 1 and 3 months after therapy as compared to baseline. Twenty normal subjects served as controls.
**Results:** Forty eyes of 20 patients including 12 male and 8 female subjects with mean age of 44.1±11.5 (range 22 to 66) years were studied. Twenty unaffected eyes were the subject of the current study. The retina in all of these eyes remained intact during the course of the study. In the sound eyes, mean b-wave amplitude of the maximal combined response ERG before initiation of treatment was 229.5±38.8 microvolts which increased to 356.1±34.0 ($P<0.001$) and 365.8±32.7 ($P<0.001$) microvolts 1 and 3 months after treatment, respectively. Corresponding figures for b-wave amplitudes of the cone response ERG were 24.9±6.0, 47.0±12.9 ($P<0.001$) and 52.8±12.7 ($P<0.001$) microvolts, respectively. Visual acuity of all sound eyes remained unchanged throughout the study.
**Conclusion:** Despite normal retinal appearance and intact visual acuity in the sound eyes of patients with NHR, electrophysiological changes were observed. Prompt diagnosis and management of NHR and continuation of medication for 3 months may reverse subclinical ERG changes and reduce the risk of progression to overt clinical disease.

**Keywords:** Necrotizing Herpetic Retinitis; Acute Retinal Necrosis; Electroretinography

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## INTRODUCTION

Necrotizing herpetic retinitis (NHR) may present as the acute retinal necrosis (ARN) syndrome. It is an uncommon but devastating, potentially blinding necrotizing retinitis. Initially reported in the 1970s,[1,2] ARN can affect one or both eyes. It is most commonly observed in immunocompetent subjects but may occasionally occur in immunocompromised patients.[3,4] Herpes virus infection was presumed to be the pathogenic cause in cases in which a temporal relationship between clinical herpetic infection and the onset of retinal necrosis was observed.[5-7] Subsequently, the varicella-zoster virus (VZV), herpes simplex virus (HSV) and Epstein-Barr virus (EBV) were shown to be implicated in the pathogenesis of NHR.[8,9]

Clinical features of NHR include anterior uveitis and vitritis, patchy or confluent areas of

white or cream-colored retinal necrosis initially affecting the peripheral retina and extending posteriorly, and secondary retinal atrophy, which may lead to rhegmatogenous retinal detachment (RD). In the majority of cases, there is an occlusive vasculopathy associated with arteritis and phlebitis involving the retinal and choroidal vasculature.

Without treatment, the second eye gets involved in approximately 20% of NHR patients, usually within 6 weeks of the first eye's involvement.[10]

Although there are a number of reports expressing concern about recovery of visual function following medical treatment in eyes with NHR, electrophysiological function may not satisfactorily recover in parallel.[11] Major causes of poor visual outcome and electrophysiological dysfunction in NHR are RD, optic nerve or macular involvement by ischemic vasculopathy and gliotic changes in the retina.[11]

Few experimental studies have shown concomitant ocular changes following intracerebral inoculation of HSV.[12-16] It is generally assumed that the virus spreads to the eye by retrograde transneuronal transport within the visual pathways.[15,16] Peiffer et al[12] reported that intracerebral inoculation of clinically isolated HSV-1 infection induced bilateral retinal disease in approximately 10% of BALB/c mice. Anderson and Field,[13] on the other hand, reported retinal disease in 60% of mice after intracerebral inoculation of another strain of HSV-1.

Lewis et al[14] described two patients with NHR syndrome whose HSV-1 involvement was confirmed by diagnostic vitrectomy. One of the patients exhibited changes on magnetic resonance imaging (MRI) in both lateral geniculate nuclei in the absence of clinical encephalitis. This unique finding provided indirect support for HSV-1 travel between the brain and retina via the visual pathways.

None of these investigators used electroretinography (ERG) to follow the course of virus-induced disease and changes in the physiological function of the retina. The purpose of present study was to examine ERG changes not only in the involved eye of patients with unilateral NHR but also in the apparently uninvolved eye.

## METHODS

Twenty sound eyes of 20 patients, including 12 male and 8 female subjects with mean age of 44.1±11.5 (range, 22 to 66) years with unilateral NHR were studied. The duration of the disease, estimated from the onset of subjective symptoms to the day of treatment, was less than 7 days in all patients.

Clinical diagnosis of NHR was based on criteria described by the Executive Committee of the American Uveitis Society, which includes one or more focal well demarcated area of retinal necrosis located in the peripheral retina, rapid circumferential progression of necrosis with or without retinal breaks and optic disc swelling, occlusive vasculopathy with arteriolar involvement, and a prominent inflammatory reaction in the vitreous and anterior chamber.[17]

Complete ophthalmologic examination at baseline, 3 days, 1 and 2 weeks post-treatment and monthly thereafter for 3 months included assessment of visual acuity, slit lamp examination, fundus examination (indirect ophthalmoscopy and non-contact 90-diopter biomicroscopy).

All patients received intravenous antiviral treatment (acyclovir, 10 mg/kg three times daily) for 10 days followed by 800 mg oral acyclovir 5 times daily for 3 months.[10] Systemic corticosteroid treatment was instituted after 48 hours of treatment with intravenous acyclovir in all cases. The dosage of oral prednisolone was 1mg/kg/day which was tapered by 10 mg every 3 days. All patients were also treated with aspirin 80 mg daily for 10 days.[10,18]

A complete blood count was obtained, creatinine and blood urea nitrogen (BUN) levels were determined and liver function tests were carried out prior to initiating acyclovir therapy and 10 days thereafter.

Prophylactic laser treatment was applied to the normal retina to seal off the posterior edge of the necrotic retina using 3 consecutive rows of confluent and circumferential laser burns for extensive necrosis or diffuse patchy necrosis. Patches of necrosis were also surrounded by laser scars.

For the purpose of this study full-field ERG of the sound eyes was obtained according to

the methods described by the International Society for Clinical Electrophysiology of Vision (ISCEV),[19] using the Mono Elec 2 system (Metrovision Inc., France).

In all cases, the patients' pupils were fully dilated to a diameter of 8 mm with topical 1% tropicamide and 2.5% phenylephrine under superficial anesthesia with 0.5% tetracaine drop. The ERG jet contact lens electrode was used as the recording electrode and 0.5% methylcellulose was deposited into its concavity. Then the reference electrode was placed in the center of the forehead and the grounding electrode was attached to the ear lobe. Scotopic (maximal combined response) and photopic (cone response) ERGs were recorded after 20 and 10 minutes of dark and light adaptation, respectively. Initial ERGs were obtained at the beginning of medical treatment and the next evaluations were performed 1 and 3 months after therapy. Amplitude of ERG a- and b-waves in maximal combined and cone responses were detected and analyzed. Mean ERG a-and b-wave amplitudes of 20 normal subjects were considered as normal value.

All statistical analysis was performed using SPSS software (version 17.0; SPSS, Chicago, IL, USA). To evaluate changes during the study in each group, we used mixed model adjusted for multiple comparisons by the Bonferroni method. This method was also applied to evaluate differences in the proportion of changes among different types of responses. To compare the results between a- and b-waves, we used the Wilcoxon signed rank test. P-Values less than 0.05 were considered as statistically significant.

## RESULTS

Forty eyes of 20 patients with mean age of 44.1±11.5 (range, 22 to 66) years including 8 (40%) female and 12 (60%) male subjects with NHR were enrolled. All cases had unilateral involvement and the right eye was involved in 11 patients (55%).

Table 1 summarizes demographic and clinical data of the patients. All retinas in the affected eyes were attached in the course of the study but pathological changes like retinal fibrosis and atrophy, combined with diffuse retinal gliosis occurred during follow-up. All sound eyes of these patients remained clinically intact during follow-up.

Twenty normal subjects with mean age of 33.8±13.9 (range, 17–61) years were studied as the control group. In these normal subjects, mean a-wave amplitudes of the maximal combined and cone response ERGs were 193±10.5 and 18.3±2.1 microvolts, respectively which were comparable to the sound eyes of the patients (P=0.94 and P=0.98, respectively). However, mean b-wave amplitudes of the maximal combined and cone responses were significantly higher than the sound eyes, i.e. 397.7±26.0 (P<0.001) and 67.4±6.4 (P<0.001) microvolts, respectively.

In sound eyes, mean a-wave amplitude of the maximal combined response ERG before initiation of treatment was 194.1±15.0 microvolts which remained unchanged at 194.5±20.1 (P>0.99) and 195.5±14.9 (P>0.99) microvolts at 1 and 3 months, respectively. Similarly, mean a-wave amplitude of the cone response ERG was 18±2.3 microvolts which also remained unchanged at 18.3±1.7 (P>0.99) and 18.6±1.3 (P>0.99) microvolts, respectively. However, the sound eyes demonstrated a significant increase in b-wave amplitudes. Mean b-wave amplitude of the maximal combined response ERG before treatment was 229.5±38.8 microvolt which significantly increased to 356.1±34 (P<0.001) and 365.8±32.7 (P<0.001) microvolts 1 and 3 months after treatment, respectively. Mean b-wave amplitude in the cone response ERG was 24.9±6.0 microvolts at baseline, increasing significantly to 47±12.9 (P<0.001) and 52.8±12.7 (P<0.001) microvolts at 1 and 3 months after therapy, respectively.

In the involved eyes, a uniform decrease was observed in both a- and b-wave ampitudes in both the maximal combined and cone response ERGs. Mean a-wave amplitude of the maximal combined response ERG before treatment was 65.5±9.1 microvolts which decreased to 57.8±13.0 (P=0.036) and 46.5±17.6 (P<0.001) microvolts, 1 and 3 months after therapy, respectively. Mean a-wave amplitude of the cone response ERG before treatment was 9±3.5 microvolts which decreased to 8.5±3.6 (P=0.593) and 6.8±3.8 (P<0.001) microvolts 1 and 3 months after

**Table 1.** Demographic and clinical data of the patients together with a- and b-waves ERG amplitudes (microvolts) in the same and sound eyes

| ID | Age | Sex | BCVA | | a-wave | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Maximal combined response | | | | | | Cone response | | | | | |
| | | | | | Sound | | | Same | | | Sound | | | Same | | |
| | | | Sound | Same | Pre | M1 | M3 | Pre | M1 | M3 | Pre | M1 | M3 | Pre | M1 | M3 |
| 1 | 48 | F | 20/20 | CF 0.5 | 175 | 192 | 187 | 66.5 | 52 | 34.4 | 15 | 17 | 19 | 7.4 | 9.1 | 6.5 |
| 2 | 50 | M | 20/20 | CF 0.7 | 180 | 186 | 201 | 72.1 | 65.5 | 49 | 17 | 16 | 17 | 10.5 | 8.5 | 7 |
| 3 | 42 | M | 20/25 | HM | 210 | 195 | 176 | 63 | 56 | 32.4 | 14 | 16 | 16 | 7.5 | 9.1 | 8.1 |
| 4 | 47 | M | 20/20 | HM | 195 | 201 | 166 | 56 | 31 | 32.5 | 15 | 17 | 16 | 7.4 | 6.9 | 6.1 |
| 5 | 22 | M | 20/25 | CF 1 | 169 | 162 | 178 | 61.5 | 42 | 33.3 | 14 | 15.6 | 19 | 6.3 | 6.9 | 3.1 |
| 6 | 52 | F | 20/25 | CF 1 | 215 | 198 | 201 | 81 | 73 | 59 | 18 | 18.2 | 17.9 | 8 | 7.5 | 6.1 |
| 7 | 45 | F | 20/20 | CF 1 | 195 | 175 | 196 | 72 | 68 | 54 | 18 | 18 | 19 | 11 | 8.5 | 6.4 |
| 8 | 28 | M | 20/20 | HM | 186 | 178 | 190 | 59 | 62 | 96 | 20 | 21 | 19 | 8 | 7.1 | 6 |
| 9 | 39 | M | 20/25 | CF 2.5 | 212 | 232 | 199 | 80.4 | 79 | 42.8 | 19 | 18 | 20 | 7.4 | 8.1 | 6.7 |
| 10 | 54 | M | 20/25 | CF 1 | 201 | 197 | 231 | 66 | 59.3 | 48 | 21 | 20 | 19 | 10.2 | 7.4 | 6.3 |
| 11 | 50 | M | 20/20 | CF 0.7 | 196 | 235 | 194 | 72 | 61 | 30.4 | 20 | 19 | 18 | 8.4 | 8 | 5.5 |
| 12 | 32 | M | 20/20 | CF 0.7 | 188 | 196 | 199 | 63 | 39 | 34 | 19 | 18 | 19 | 6.4 | 7 | 4.5 |
| 13 | 40 | F | 20/25 | CF 1 | 214 | 175 | 186 | 72 | 59.8 | 45.8 | 20 | 20 | 18 | 8 | 6.3 | 6 |
| 14 | 56 | F | 20/30 | HM | 169 | 181 | 170 | 59 | 38 | 49 | 21 | 19 | 18 | 7.2 | 8.1 | 6.1 |
| 15 | 52 | M | 20/20 | CF 0.7 | 194 | 186 | 214 | 60.5 | 54 | 49.1 | 16 | 17 | 18 | 6.3 | 7 | 3.9 |
| 16 | 22 | F | 20/25 | CF 1.5 | 212 | 190 | 186 | 73.4 | 69.1 | 35.2 | 17 | 17 | 19 | 8.1 | 4.9 | 5.1 |
| 17 | 40 | F | 20/25 | CF 0.3 | 179 | 158 | 201 | 59 | 59 | 34.6 | 19 | 20 | 19 | 6.2 | 5.9 | 5 |
| 18 | 66 | M | 20/20 | HM | 195 | 214 | 201 | 42 | 46 | 51.2 | 17 | 18 | 20 | 11 | 7.5 | 7 |
| 19 | 55 | F | 20/20 | CF 0.7 | 211 | 167 | 194 | 61 | 51 | 39.2 | 21 | 20 | 21 | 12 | 14.5 | 8.2 |
| 20 | 42 | M | 20/25 | CF 2 | 186 | 192 | 201 | 71 | 81.4 | 89.1 | 19 | 21 | 20 | 22 | 21.5 | 22 |

| ID | Age | Sex | BCVA | | b-wave | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Maximal combined response | | | | | | Cone response | | | | | |
| | | | | | Sound | | | Same | | | Sound | | | Same | | |
| | | | Sound | Same | Pre | M1 | M3 | Pre | M1 | M3 | Pre | M1 | M3 | Pre | M1 | M3 |
| 1 | 48 | F | 20/20 | CF 0.5 | 212 | 345 | 365 | 86.8 | 56 | 14.5 | 32.2 | 58 | 62.6 | 22 | 18.1 | 17.5 |
| 2 | 50 | M | 20/20 | CF 0.7 | 210 | 365 | 370 | 42.5 | 39 | 25 | 24.1 | 63.5 | 65.3 | 19 | 12.1 | 11.4 |
| 3 | 42 | M | 20/25 | HM | 256 | 380 | 382 | 56 | 52 | 31.8 | 25 | 63.4 | 66 | 21.4 | 19.6 | 18 |
| 4 | 47 | M | 20/20 | HM | 198 | 295 | 310 | 46 | 30 | 12.8 | 27 | 59 | 79 | 30 | 20.1 | 19.4 |
| 5 | 22 | M | 20/25 | CF 1 | 208 | 333 | 397 | 66.8 | 62.4 | 58 | 27.4 | 69 | 73.6 | 30.9 | 23.2 | 24.9 |
| 6 | 52 | F | 20/25 | CF 1 | 212 | 370 | 382 | 72 | 35 | 24.5 | 22.3 | 45.9 | 51.4 | 19.5 | 14.5 | 13 |
| 7 | 45 | F | 20/20 | CF 1 | 224 | 398 | 410 | 76 | 24.8 | 41 | 24.4 | 70 | 69 | 22 | 16.4 | 10 |
| 8 | 28 | M | 20/20 | HM | 215 | 410 | 396 | 80.2 | 52 | 41 | 33 | 49.5 | 52 | 30.1 | 19.6 | 13.1 |
| 9 | 39 | M | 20/25 | CF 2.5 | 301 | 384 | 391 | 72 | 69.5 | 63 | 18 | 34 | 40 | 19 | 19.1 | 11.2 |
| 10 | 54 | M | 20/25 | CF 1 | 208 | 360 | 352 | 66.3 | 35 | 22.2 | 21 | 50.1 | 49 | 23 | 11.4 | 11.3 |
| 11 | 50 | M | 20/20 | CF 0.7 | 198 | 301 | 312 | 42.5 | 28 | 19.4 | 22 | 35.4 | 61.5 | 18 | 13.1 | 9.4 |
| 12 | 32 | M | 20/20 | CF 0.7 | 275 | 301 | 310 | 73 | 41.4 | 31 | 29 | 31 | 39 | 16 | 10.1 | 8.1 |
| 13 | 40 | F | 20/25 | CF 1 | 221 | 365 | 325 | 66 | 29.1 | 21.9 | 24 | 40 | 40.5 | 21 | 14 | 13.6 |
| 14 | 56 | F | 20/30 | HM | 199 | 315 | 315 | 72 | 52 | 27.5 | 21.5 | 33.8 | 42.1 | 20 | 15.4 | 14 |
| 15 | 52 | M | 20/20 | CF 0.7 | 205 | 370 | 370 | 49.5 | 31 | 19.5 | 25 | 33 | 44.2 | 16 | 12.1 | 13 |
| 16 | 22 | F | 20/25 | CF 1.5 | 225 | 395 | 343 | 46.1 | 22 | 13.1 | 20 | 36 | 41.4 | 19 | 17.5 | 9.2 |
| 17 | 40 | F | 20/25 | CF 0.3 | 270 | 325 | 343 | 72 | 34.3 | 22.8 | 21 | 50 | 51.6 | 30.4 | 17.2 | 12.8 |
| 18 | 66 | M | 20/20 | HM | 202 | 375 | 314 | 61.5 | 72.1 | 70 | 19.5 | 40.7 | 42 | 19.6 | 12 | 11.8 |
| 19 | 55 | F | 20/20 | CF 0.7 | 210 | 360 | 365 | 48.4 | 23 | 19.5 | 18 | 34 | 41 | 24 | 13.5 | 8.4 |
| 20 | 42 | M | 20/25 | CF 2 | 340 | 375 | 364 | 66.5 | 76 | 83.5 | 43.2 | 43.9 | 43.9 | 36 | 38.9 | 9.0 |

F, female; M, male; OD, Right eye; OS, Left eye; Same, ipsilateral involved eye; Sound, contralateral non-involved eye
Pre, before treatment; M1, month 1; M3, month 3

therapy, respectively. Mean b-wave amplitude of the maximal combined response ERG before treatment in the involved eyes was 63.1±13.3 microvolts which decreased to 43.2±17.1 (P<0.001) and 33.1±20.2 (P<0.001) microvolts 1 and 3 months after therapy, respectively. Mean b-wave amplitude of the cone response ERG before treatment was 22.8±5.6 microvolts decreasing to 16.9±6.3 (P<0.001) and 13.2±4.2 (P<0.001) microvolts, 1 and 3 months after therapy, respectively.

Representative ERG wave changes in one of the patients (#5) in the sound and same (affected) eye are compared to that of a normal subject before initiation of treatment, and 1 and 3 months after therapy in Figures 1A and 1B, respectively.

Tables 2 and 3 compare a- and b-wave amplitudes before and after therapy in the maximal combined and cone response ERGs, respectively; a-and b-wave ERG amplitudes of normal subjects have been detailed in Table 4.

The mean proportion of changes from baseline to months 1 and 3 in a- and b- wave amplitudes with relation to the type of response in the sound and affected eyes are shown in Figures 2 and 3, respectively.

No change was observed in visual acuity of the sound eyes within the study period.

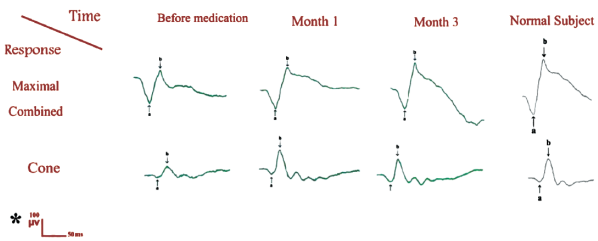


**Figure 1A.** Sound eye tracings: no significant elertroretinographic (ERG) b-wave amplitude could be recorded under scotopic (upper series) and photopic (lower series) conditions before therapy. ERG in the same patient 1 and 3 months after treatment illustrates an increase in b-wave amplitude comparable to a normal subject. No significant change in a-wave amplitude was observed.

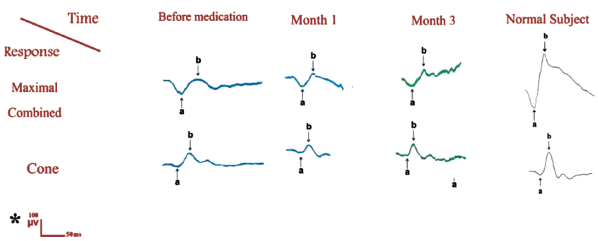


**Figure 1B.** Same (affected eye) tracings: no significant a- and b-wave amplitude could be recorded under scotopic and photopic conditions before, or 1 and 3 months after therapy and all tracings were lower than those recorded from a normal subject.

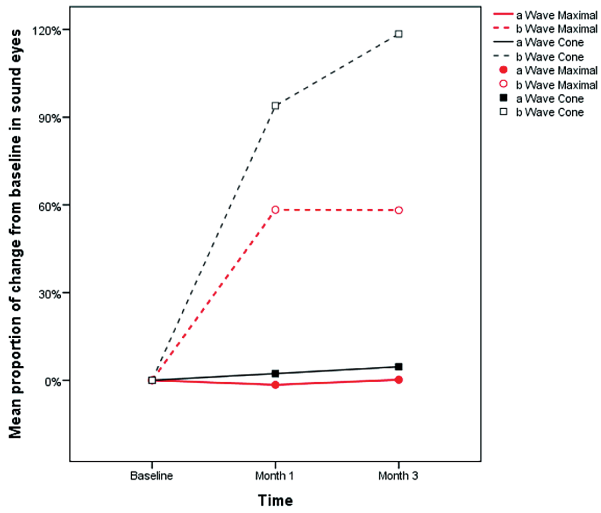


**Figure 2.** Mean proportion of change from baseline in a- and b-wave amplitudes by the type of response in sound eyes. Mixed model analysis (adjusted for multiple comparisons by Bonferroni method) showed a significant increase in b-wave amplitudes under both scotopic and photopic conditions at month 1 which continued to month 3.

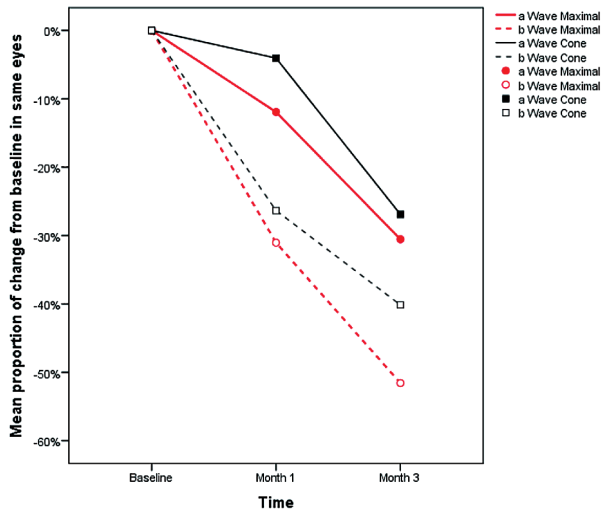


**Figure 3.** Mean proportion of change from baseline in a- and b-wave amplitudes by the type of response in same eyes. Mixed model analysis (adjusted for multiple comparisons by Bonferroni method) showed a significant reduction in mean a- and b-wave amplitudes under both scotopic and photopic conditions at month 1 which continued to month 3.

**Table 2.** Details of a- and b-wave amplitudes (microvolts) of the maximal combined response ERG at baseline, and 1 and 3 months after therapy; changes have been reported in percent values

| Time | a- wave | | | | P* | b- wave | | | | P* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sound | | Same | | | Sound | | Same | | |
| | Mean ± SD (microvolts) | Median (Range) | Mean ± SD (microvolts) | Median (Range) | | Mean ± SD (microvolts) | Median (Range) | Mean ± SD (microvolts) | Median (Range) | |
| Baseline | | | | | | | | | | |
| amplitude | 194.1 ± 15.0 | 195 (169 to 215) | 65.5 ± 9.1 | 64.5 (42 to 81) | <.001 | 229.5 ± 38.8 | 212 (198 to 340) | 63.1 ± 13.3 | 66.4 (42.5 to 86.8) | <.001 |
| Month 1 | | | | | | | | | | |
| amplitude | 194.5 ± 20.1 | 191 (158 to 235) | 57.8 ± 13.0 | 59.2 (31 to 81.4) | <.001 | 356.1 ± 34.0 | 365 (295 to 410) | 43.2 ± 17.1 | 37 (22 to 76) | <.001 |
| change | -3.6 ± 20.7 | -5.5 (-44 to 39) | -7.7 ± 8.9 | -6.9 (-25 to 10.4) | .478 | 126.7 ± 47.5 | 138.5 (26 to 195) | -19.9 ± 16.7 | -22.1 (-51.2 to 10.6) | <.001 |
| P† | >0.99 | | .036 | | | <.001 | | <.001 | | |
| Month 3 | | | | | | | | | | |
| amplitude | 195.5 ± 14.9 | 195 (166 to 231) | 46.5 ± 17.8 | 41 (30.4 to 96) | <.001 | 365.8 ± 32.7 | 364.5 (310 to 410) | 33.1 ± 20.2 | 24.8 (12.8 to 83.5) | <.001 |
| change | -0.5 ± 19.1 | 2.5 (-34 to 30) | -19.1 ± 19.5 | -23.3 (-41.6 to 37) | .005 | 126.4 ± 46.5 | 122 (24 to 189) | -30 ± 20.7 | -33.1 (-72.3 to 17) | <.001 |
| P† | >0.99 | | <.001 | | | <.001 | | <.001 | | |
| change** | 3.1 ± 23.3 | 6 (-41 to 43) | -11.4 ± 16.0 | -12.9 (-36.2 to 34) | .023 | -0.3 ± 27.2 | 5 (-61 to 64) | -10.1 ± 11.6 | -10.5 (-41.5 to 16.2) | .100 |
| P† | >0.99 | | .001 | | | >0.99 | | .009 | | |

* Based on Wilcoxon Singed Rank test

** change comparing 3 and 1 month values

† Based on Mixed model, adjusted for multiple comparison based on Bonferroni method

**Table 3.** Details of a- and b-wave amplitudes (microvolts) of the cone response ERG at baseline, and 1 and 3 month after therapy; changes have been reported in percent values

| | a- wave | | | | P* | b- wave | | | | P* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sound | | Same | | | Sound | | Same | | |
| | Mean ± SD (microvolts) | Median (Range) | Mean ± SD (microvolts) | Median (Range) | | Mean ± SD (microvolts) | Median (Range) | Mean ± SD (microvolts) | Median (Range) | |
| Baseline | 18 ± 2.3 | 18.5 (14 to 21) | 9 ± 3.5 | 8 (6.2 to 22) | <.001 | 24.9 ± 6.0 | 24.1 (18 to 43.2) | 22.8 ± 5.6 | 21.2 (16 to 36) | .108 |
| Month 1 | | | | | | | | | | |
| amplitude | 18.3 ± 1.7 | 18 (15.6 to 21) | 8.5 ± 3.6 | 7.5 (4.9 to 21.5) | <.001 | 47 ± 12.9 | 44.9 (31 to 70) | 16.9 ± 6.3 | 15.9 (10.1 to 38.9) | <.001 |
| change | 0.3 ± 1.3 | 0.1 (-2 to 2) | -0.5 ± 1.7 | -0.5 (-3.5 to 2.5) | .089 | 22.1 ± 12.8 | 18.9 (0.7 to 45.6) | -6 ± 4.1 | -5.8 (-13.2 to 2.9) | <.001 |
| P† | >0.99 | | .593 | | | <.001 | | <.001 | | |
| Month 3 | | | | | | | | | | |
| amplitude | 18.6 ± 1.3 | 19 (16 to 21) | 6.8 ± 3.8 | 6.1 (3.1 to 22) | <.001 | 52.8 ± 12.7 | 50.2 (39 to 79) | 13.2 ± 4.2 | 12.8 (8.1 to 24.9) | <.001 |
| change | 0.6 ± 2.1 | 0.5 (-3 to 5) | -2.2 ± 1.4 | -2 (-4.6 to 0.6) | .001 | 27.9 ± 13 | 25.5 (0.7 to 52) | -9 ± 4.2 | -7.8 (-17.6 to -3) | <.001 |
| P† | .470 | | <.001 | | | <.001 | | <.001 | | |
| change** | 0.3 ± 1.5 | 0.5 (-2 to 3.4) | -1.7 ± 1.5 | -1.4 (-6.3 to 0.5) | .004 | 5.7 ± 6.8 | 4.6 (-1.1 to 26.1) | -2.6 ± 3.0 | -1.5 (-8.3 to 1.7) | <.001 |
| P† | >0.99 | | <.001 | | | .044 | | .006 | | |

* Based on Wilcoxon Singed Rank test

** change comparing 3 and 1 month values

† Based on Mixed model, adjusted for multiple comparison based on Bonferroni method

**Table 4.** Details of ERG a- and b-waves amplitudes (microvolts) in normal subjects

| ID | Age | Sex | Eye | Maximal combined response | | Cone response | |
|---|---|---|---|---|---|---|---|
| | | | | a-wave | b-wave | a-wave | b-wave |
| 1 | 22 | M | OD | 179.0 | 381.0 | 15.0 | 56.0 |
| 2 | 18 | M | OS | 176.0 | 392.0 | 18.0 | 62.0 |
| 3 | 29 | F | OD | 199.0 | 375.0 | 16.0 | 61.5 |
| 4 | 40 | F | OD | 201.0 | 402.0 | 15.0 | 59.0 |
| 5 | 31 | M | OS | 196.0 | 364.0 | 21.0 | 66.0 |
| 6 | 19 | F | OS | 202.0 | 375.0 | 19.0 | 71.0 |
| 7 | 23 | F | OD | 199.0 | 380.0 | 21.0 | 66.0 |
| 8 | 31 | M | OD | 186.0 | 345.0 | 18.0 | 63.5 |
| 9 | 29 | F | OD | 213.0 | 385.0 | 19.0 | 70.0 |
| 10 | 17 | M | OS | 196.0 | 403.0 | 20.0 | 69.0 |
| 11 | 46 | F | OD | 211.0 | 375.0 | 18.0 | 66.0 |
| 12 | 61 | M | OS | 198.0 | 410.0 | 16.0 | 70.0 |
| 13 | 44 | M | OS | 189.0 | 334.0 | 19.0 | 68.0 |
| 14 | 19 | M | OD | 186.0 | 412.0 | 16.0 | 59.0 |
| 15 | 32 | M | OS | 183.0 | 391.0 | 15.0 | 66.0 |
| 16 | 59 | F | OD | 176.0 | 404.0 | 19.0 | 72.0 |
| 17 | 40 | M | OS | 189.0 | 325.0 | 21.0 | 69.0 |
| 18 | 18 | M | OD | 201.0 | 401.0 | 20.0 | 81.0 |
| 19 | 47 | F | OS | 190.0 | 345.0 | 19.0 | 79.0 |
| 20 | 50 | M | OS | 189.0 | 394.0 | 21.0 | 74.0 |
| Mean | 33.8 | | | 193.0 | 379.7 | 18.3 | 67.4 |
| SD | 13.9 | | | 10.5 | 26.0 | 2.1 | 6.4 |

M, male; F, female; OD, right eye; OS, left eye

## DISCUSSION

In the current study, not only both scotopic and photopic ERG a- and b- wave amplitudes were reduced in eyes with NHR, but also b-wave amplitude in both scotopic and photopic ERGs was diminished to subnormal levels in the contralateral normal appearing eyes indicating dysfunction of Muller and bipolar cells of the retina.[20,21]

In the sound eyes, scotopic and photopic ERG b-waves were decreased in amplitude at initiation of treatment but gradually reached higher levels 1 and 3 months thereafter. The amplitude values improved significantly at month 1 and reached normal levels at month 3. The presence of normal a-wave amplitudes before initiation of treatment and at months 1 and 3 indicate lack of dysfunction in the photoreceptor cell layer.[20] Visual acuity of these eyes remained unchanged throughout the study period.

The exact mechanism of reduced ERG b-waves in the contralateral uninvolved eye of patients with NHR is not clear. It has been hypothesized that dissemination and accumulation of virus and virus–specific antigens on the optic nerve and inner nuclear layer of the sound eye by synaptically related neurons induces dysfunction of different inner retinal cell layers reflected in b-wave changes of the ERG.[16,20-24]

Regarding the route and dissemination of herpes virus from the involved eye through the central nervous system, optic nerve and retina of the other eye, several mechanisms have been described.[15,16,22-25]

Von Szily[15] reported that inoculation of herpes simplex virus (HSV) type-1 into the anterior chamber (AC) of rabbits or mice leads to anterior segment inflammation with sparing of the ipsilateral retina, but severe contralateral necrotizing retinitis. Furthermore, tracing experiments showed that HSV travels from the injected AC to the ipsilateral ciliary ganglion along parasympathetic fibers of the oculomotor nerve subserving pupillary constriction.[16] From there, virus spreads to the ipsilateral suprachiasmatic nucleus (SCN) of the hypothalamus and then travels to the contralateral optic nerve and retinal inner nuclear layer.[22-24] Regillo et al,[26] on the other hand demonstrated marked circulatory

and blood flow velocity changes in the central retinal artery and ischemia in inner retinal layers of eyes involved with the NHR syndrome. Few experimental studies have shown that intra-visual cortex inoculation of herpes simplex virus type-1 induced bilateral ERG changes with physiologic and morphologic retinal changes in 62.3% of infected animals of which, 91% were bilateral.[11,21] In contrast, inoculation of the same viral titers into the frontal lobe induced retinal alteration in only 13.3%.[21] Initially, there was a decreased in b-wave amplitude and retinal sensitivity, and necrotic changes in ganglion cells and nuclei in the inner nuclear layer of both retinas.[21] Moreover, immunoperoxidase staining of brain sections demonstrated virus-specific antigens on glial cells in the lateral geniculate and suprachiasmatic nuclei, bilaterally.[21,27]

In another study, Matsuo et al[11] reported that the amplitude of ERG a-wave on initial examination was significantly higher in NHR patients with good visual outcome, but diffuse retinal arteritis on initial examination was accompanied by reduced ERG amplitudes, especially in b-waves.

As Mizota et al[21] described earlier, intra-visual cortex inoculation of HSV-1 in BALB/c mice induces physiologic and morphologic retinal changes in both eyes. They also showed that initial ERG changes consisted of reduction in b-wave amplitude without alteration in a-waves. There was also depression of retinal sensitivity indicating an alteration in physiologic characteristics of inner retinal layer cells.[21]

In the current study, ERG b-wave amplitude in sound eyes of patients with apparently unilateral NHR was lower than that of normal subjects before starting therapy and gradually improved to higher levels at month 1; finally this improvement was complete at month 3, suggesting that even in clinically normal appearing eyes, functional disorders may exist in inner retinal layers.[21] Improved ERG b-wave, which occurred one month after treatment, reflects recovery of inner retinal layers.[20] In addition, lack of a-wave amplitude alterations in our study reflects intact outer retinal layers.

In conclusion, ipsilateral necrotizing herpetic retinitis seems to cause reduction of ERG b-wave amplitudes in contralateral normal appearing eyes; these alterations usually recover 3 months after acyclovir therapy to normal levels. Ophthalmologists should be aware of this phenomenon in patients with NHR which may lead to contralateral vision loss and should consider this disorder an urgent condition requiring immediate treatment in the hope to prevent sight-threatening consequences of the NHR syndrome.

**Conflicts of Interest**

None.

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