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ORIGINAL ARTICLE



Electroretinogram as an Early Diagnostic Biomarker for Acute Retinal Necrosis: A Multicenter Comparative Study

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ABSTRACT

Purpose: Acute retinal necrosis (ARN) is a rare but severe ocular condition that often results in significant visual impairment or blindness. We aimed to determine whether ARN exhibits a distinct electroretinogram (ERG) waveform compared with other infectious and non-infectious uveitis forms.

Methods: This retrospective observational multicenter study included a total of 73 patients; 21 with ARN, 9 with bacterial endophthalmitis, 16 with other types of infectious uveitis, and 27 with non-infectious uveitis. Full-field electroretinography was performed at the initial examination to evaluate retinal function. Additionally, initial and post-treatment visual acuity were recorded. The a- and b-wave amplitudes were measured and compared between the groups.

Results: Patients with ARN had significantly reduced a- and b-wave amplitudes than the other types of infectious and non-infectious uveitis at the first visit ($p < 0.01$). Receiver operating characteristic analysis showed that an a-wave amplitude reduction of more than 73% discriminated ARN from other infectious uveitis with 75% sensitivity and 90% specificity (area under the curve [AUC] = 0.84), while a reduction greater than 49% discriminated ARN from non-infectious uveitis with 89% sensitivity and 76% specificity (AUC = 0.83). Pre-treatment visual acuity was the strongest predictor of visual prognosis.

Conclusions: ERG response is significantly reduced in the early stages of ARN. Therefore, ERG may serve as a valuable diagnostic tool for ARN, particularly when specialist examination or definitive diagnosis based on clinical findings is delayed. Given that early treatment improves the prognosis of ARN, this finding highlights the critical role of early diagnosis in preventing vision loss.

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Acute retinal necrosis (ARN) poses a significant challenge in ophthalmology owing to its rapid onset and severe retinal destruction, often resulting in significant visual loss. Initially identified in the early 1970s by Urayama and colleagues ARN is a severe condition that progresses from acute panuveitis to widespread necrotizing retinitis, often resulting in retinal detachment.¹ This condition is primarily caused by various strains of the human herpes virus and can affect individuals across all demographics, including those with no underlying immune deficiencies.^{2,3} The American Uveitis Society has established specific clinical criteria for ARN diagnosis, highlighting its rapid progression, circumferential spread, and intense intraocular inflammatory response.^{4,5}

Polymerase chain reaction (PCR) technology has transformed the understanding and diagnosis of uveitis by enabling the detection of a broad spectrum of pathogens from minimal intraocular fluid samples using a multiplex PCR system.^{6,7} This advancement has facilitated the precise identification of ARN-related pathogens, predominantly herpes simplex virus

(HSV)-1, HSV-2, and varicella-zoster virus (VZV).^{7,8} The widespread adoption of PCR has prompted a reevaluation of ARN's diagnostic criteria to include virological tests, significantly enhancing diagnostic accuracy and understanding of this disease.⁸

However, PCR testing is not universally available, and results may take several days to obtain. Clinically, ARN is characterized by retinal exudative plaques, retinal vasculitis with vascular occlusions, and vitreous opacities. However, distinguishing ARN from fulminant sarcoidosis, other forms of viral uveitis, or cytomegalovirus (CMV) retinitis can be challenging, particularly when vitreous opacity obstructs fundus visualization. Given the need for rapid diagnosis and timely treatment, exploring alternative diagnostic modalities, such as ophthalmic imaging or electrophysiological testing, is essential for identifying or confirming ARN.

Electrophysiological examination has become a cornerstone for objectively assessing retinal function. Although these tests have been proven invaluable in diagnosing inherited retinal

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diseases by identifying characteristic electrophysiological patterns, their application in examining ARN remains limited. The lack of extensive electroretinogram (ERG) studies specific to ARN suggests a potential gap in our understanding of its electrophysiological impact compared with other retinal conditions.

This study aimed to assess whether electrophysiological testing can distinguish ARN from other types of ocular inflammation and determine the potential for visual recovery. This study bridges that gap by exploring how ARN alters retinal electrophysiological function and comparing these changes to those observed in other inflammatory ocular diseases to pave the way for more targeted diagnostic and therapeutic strategies.

Materials and methods

Patients

This multicenter, retrospective clinical cohort study evaluated consecutive eyes subjected to ERG measurements for uveitis from April 2017 to June 2023 across three Japanese institutions: Osaka University (Osaka Prefecture, western Japan), Nagoya University (Aichi Prefecture, central Japan), and Tohoku University (Miyagi Prefecture, eastern Japan). A total of 73 patients (41 men and 32 women) were enrolled in this study. Twenty one patients were clinically diagnosed with ARN (10 men and 11 women), 9 with bacterial endophthalmitis (7 men and 2 women), 16 with other infectious uveitis, 5 with CMV retinitis (3 men and 2 women), 5 with fungal endophthalmitis (2 men and 3 women), 2 with HTLV-1 (1 man and 1 woman), 1 with HSV-1 associated iritis (1 man), 1 with VZV-associated iritis (1 man), 1 with toxoplasmosis (1 man), 1 with VZV-associated iritis + toxoplasmosis (1 man), and 27 with non-infectious uveitis (Table 1).

Ethics statement

This study was approved by the Institutional Review Board of all participating institutions (Osaka University, Nagoya University, and Tohoku University). In compliance with the Health Insurance Portability and Accountability Act of 1996, the study also strictly adhered to the principles outlined in the Declaration of Helsinki.

Diagnosis

Disease diagnoses were established based on clinical observations and laboratory findings. The diagnostic approach used included slit-lamp examinations, optical coherence tomography, angiographic assessments such as fluorescein angiography and indocyanine green angiography, and PCR analysis of aqueous humor or vitreous sample. Additional diagnostic measures were blood tests and radiological examinations, based on the suspected disease etiology.

Specifically, ARN was diagnosed based on the established criteria derived from the literature.^{5,8} In all patients with suspected ARN, the presence of herpes virus was confirmed using PCR analysis, underscoring the virus' pivotal role in the

disease's pathogenesis. In patients with infectious uveitis beyond ARN, a combination of PCR, culture tests, and serological assays were employed to accurately identify the causative pathogen and establish a definitive diagnosis. Although ARN can occasionally be caused by other viruses, such as CMV, Epstein-Barr virus (EBV), or adenovirus, the Standardization of Uveitis Nomenclature (SUN) Working Group criteria specifically define ARN as PCR-confirmed infection by either VZV or HSV. Therefore, ARN cases included in this study were strictly limited to those with PCR-confirmed VZV or HSV infection. Conversely, the diagnoses of non-infectious uveitis were made according to the established diagnostic criteria for each respective condition, as outlined by recognized clinical guidelines.^{9–13} Patients who did not meet the diagnostic criteria for either infectious or non-infectious uveitis were categorized as having an unknown etiology. The unknown group included patients presenting with intraocular inflammatory cells but without characteristic fundus lesions, as well as those exhibiting vitreous opacity suggestive of intraocular lymphoma. Extensive diagnostic testing, including PCR assays and cytokine analyses, revealed no definitive findings. ERG testing was therefore performed to objectively evaluate the integrity of the retina.

Sample collection and PCR

Anterior chamber fluid was obtained in a minimally invasive manner, with approximately 200 μ L collected using a Nipro aqueous humor pipette (Nipro, Japan).¹⁴ The procedure was performed during outpatient examinations or surgical interventions, following strict aseptic techniques to prevent contamination and ensure patient safety.

In patients requiring vitreous fluid, approximately 1.5 mL sample was carefully extracted prior to the infusion of intraocular fluids during vitrectomy. A 200- μ L aliquot was allocated for PCR examination. DNA extraction was performed using a fully automated nucleic acid extraction system, magLEAD 6gC. A 50- μ L aliquot was extracted from 400 μ L of the sample for DNA extraction, which was used for each PCR analysis. The assay was performed to detect HSV-1 (HHV-1), HSV-2 (HHV-2), VZV (HHV-3), Epstein-Barr virus (HHV-4), (HHV-5), HHV-6, HTLV-1, toxoplasma, and treponema syphilis. The first step involved qualitative PCR using the QuantStudio 5 (Thermo Fisher Scientific, Waltham, USA). If the qualitative PCR results were positive, we proceeded to the second step, quantitative PCR, using the QuantStudio 5 with specific primers and probes (Shimadzu Corporation, Kyoto Japan). To calculate quantitative values, a calibration curve was prepared with standards at three concentrations (106, 104, and 102 copies/ μ L), and the number of copies in the sample was determined.

Classification of the retinal involvement zones

Retinal involvement was categorized into three distinct zones based on anatomical landmarks. Zone 1 was defined as the region located within 1,500 μ m of the optic nerve head or within 3,000 μ m of the fovea. Zone 2 extended from the outer border of Zone 1 to the equator. Zone 3 encompassed

Table 1. Baseline characteristics of the study patients.

Disease	Age	Gender	Type of cd	Disease	Age	Gender	Type of cd	Disease	Age	Gender	Type of cd
Bacterial endophthalmitis (E. Coli)	80	M	LE-4000	CMV retinitis	40	M	LE-4000	Sarcoidosis	48	M	LE-4000
Bacterial endophthalmitis (MRSA)	73	M	RETeval	CMV retinitis	43	M	LE-4000	Sarcoidosis	30	M	LE-4000
Bacterial endophthalmitis (Atypical mycobacteria)	65	F	LE-4000	CMV retinitis	63	F	LE-4000	Sarcoidosis	30	M	RETeval
Bacterial endophthalmitis (E. Coli)	77	M	RETeval	CMV retinitis	72	F	LE-4000	Sarcoidosis	65	F	LE-4000
Bacterial endophthalmitis (MRSA)	89	M	RETeval	CMV retinitis	42	M	LE-4000	Behçet	73	M	LE-4000
Bacterial endophthalmitis (Group A Streptococcus)	59	F	RETeval	Fungal endophthalmitis	67	F	LE-4000	Behçet	36	M	LE-4000
Bacterial endophthalmitis (S. epidermitis)	76	M	RETeval	Fungal endophthalmitis	87	M	RETeval	Lens induced uveitis	37	M	LE-4000
Bacterial endophthalmitis (unknown 16S positive)	64	M	LE-4000	Fungal endophthalmitis	79	M	LE-4000	Lens induced uveitis	45	F	LE-4000
Bacterial endophthalmitis (MRSA)	87	M	RETeval	Fungal endophthalmitis	64	F	RETeval	DM iritis	53	M	LE-4000
				Fungal endophthalmitis	36	F	LE-4000	HLA-B27 AAU	44	F	RETeval
				HTLV-1 related uveitis	46	M	RETeval	MEWDS	19	F	LE-4000
				HTLV-1 related uveitis	57	F	RETeval	PVR(unknown uveitis)	20	F	RETeval
				HSV-1 iritis	51	M	RETeval	Non infectious post operative uveitis	77	F	RETeval
				VZV iritis	77	M	LE-4000	IV related uveitis	70	M	RETeval
				VZV iritis + Toxoplasma related uveitis	68	M	LE-4000	Unknown vasculitis	40	F	LE-4000
				Toxoplasma related uveitis	68	M	LE-4000	Unknown vasculitis	71	F	LE-4000
								Unknown uveitis	55	M	RETeval
								Unknown uveitis	77	F	RETeval
								Unknown uveitis	76	F	LE-4000
								Unknown uveitis	30	F	LE-4000
								Unknown uveitis	61	M	RETeval
								Unknown uveitis	73	M	RETeval
								Unknown uveitis	63	M	LE-4000
								Unknown uveitis	66	M	LE-4000
								Unknown uveitis	74	M	RETeval
								Unknown uveitis	83	F	RETeval
								Unknown uveitis	50	F	LE-4000

Abbreviations: ARN, acute retinal necrosis; CMV, cytomegalovirus; MEWDS, multiple evanescent white dot syndrome; DM, diabetes mellitus; MRSA, methicillin-resistant Staphylococcus aureus; HTLV-1, human T-cell leukemia virus type 1; HSV, herpes simplex virus; VZV, varicella-zoster virus; PVR, proliferative vitreoretinopathy; cd, ERG recording device.

the retinal area peripheral to the equator, extending anteriorly up to the ora serrata (Table 2).¹⁵

ERG examination

ERGs were performed in 16 patients with ARN, 9 with proven bacterial endophthalmitis, 16 with infectious uveitis due to other causes, and 27 with non-infectious uveitis. The ERG method, including traditional ERG and RETeval,^{16–18} was employed to measure retinal potentials. This examination was conducted in accordance with the standardized protocol established by the International

Society for Clinical Electrophysiology of Vision.¹⁶ The typical ERG waveforms for each disease are shown in Figure 1.

ERGs were recorded using contact lens electrodes with the LE4000 system (Tomey, Nagoya, Japan) or skin electrodes using the RETeval system (Mayo Corp., Inazawa, Japan). In cases where the corneal condition, postoperative endophthalmitis, ARN, or other emergent ocular diseases prevented the use of contact lens electrodes, the skin-electrode method (RETeval) was preferred. The light-adapted 3.0 ERG (LA 3 ERG) was performed with a luminance of 30 cd·m⁻² under mydriatic conditions, induced using 0.5% phenylephrine and 0.5% tropicamide eye drops, following 20 minutes of light adaptation. For the

Table 2. The characteristics of ARN patients.

Disease	Age	Gender	zone	VO	Lens	Arteritis
ARN	64	F	1	3+	cataract	present
ARN	79	M	2	3+	IOL	present
ARN	90	M	3	4+	IOL	dense vitreous opacity (N.V)
ARN	83	F	2	2+	IOL	present
ARN	87	F	3	4+	IOL	dense vitreous opacity (N.V)
ARN	57	F	3	2+	IOL	absent
ARN	75	M	3	1+	cataract	absent
ARN	68	F	2	4+	cataract	present
ARN	44	M	1	3+	cataract	present
ARN	15	M	2	3+	clear	present
ARN	61	F	1	0.5+	cataract	present
ARN	18	M	1	1+	clear	present
ARN	14	F	3	3+	cataract	present
ARN	39	M	3	1+	cataract	absent
ARN	42	M	1	3+	cataract	present
ARN	57	F	1	2+	cataract	present
ARN	53	F	3	3+	clear	present
ARN	72	M	2	3+	cataract	present
ARN	60	F	1	1+	cataract	present
ARN	84	F	1	3+	cataract	present
ARN	74	M	2	2+	cataract	present

Abbreviations: ARN, acute retinal necrosis; VO, vitreous opacity; IOL, intraocular lens; N.V, no view.

skin electrode method, silver plate electrodes were utilized. The active, reference, and ground electrodes were positioned on the lower eyelid, lateral canthus, and earlobe, respectively.

In standard ERGs, the noise threshold was set at 10 μ V. For REteval, which has a lower noise level of 7 μ V, the threshold for the lowest a-wave potential was set at 7 μ V. The change in a- and b-waves in the affected eye was calculated as a percentage of the contralateral eye, using the contralateral eye as the control.

Treatment of ARN

Following the diagnosis of ARN, intravenous acyclovir was initiated at a dose of 15 mg/kg/day. Simultaneously, intravenous betamethasone was administered at a dose of 8 mg/day. The acyclovir therapy was maintained for two weeks, after which the dosage was tapered to 10 mg/kg/day. The corticosteroid regimen involved the administration of intravenous betamethasone for 1 week, followed by a transition to oral prednisolone at a dose of 1 mg/kg/day. The prednisolone dosage was then gradually tapered according to the clinical response. All patients presenting with retinal detachment underwent combined phacoemulsification with intraocular lens implantation (if necessary), pars plana vitrectomy, and an encircling scleral buckle procedure.

Statistical analysis

Statistical comparisons between the ARN group and each disease group were performed using a one-way analysis of variance test with the Kruskal–Wallis test for the a-wave, a- and b-wave latencies, pre-treatment visual acuity, and post-treatment visual acuity. A *p* value of < 0.05 was considered significant. The performance of the a- and b-wave potentials and their cutoff points were assessed using the receiver

operating characteristic (ROC) curve analysis. The area under the curve (AUC) was used to evaluate the classification models. All analyses were performed using Prism 10 software version 10.0.2 (Graph Pad Software, San Diego, CA). In the ARN group, multivariate analysis was conducted to identify the factor—a-wave potential, a-wave latency, b-wave potential, b-wave latency, or pretreatment visual acuity, lesion extent (zone), vitreous opacity, age—most strongly associated with post-treatment visual acuity. Due to the inclusion of ordinal data, Spearman's rank correlation coefficient was used to evaluate the associations between postoperative visual acuity and the following clinical parameters: preoperative visual acuity, ERG parameters, zone, vitreous haze severity and age. Statistical analysis was performed using JMP Pro 17 (SAS Institute Inc., Cary, NC, USA).

Results

Potential of both a-wave and b-wave in each disease

Eyes with ARN and bacterial endophthalmitis demonstrated a marked absence of discernible a-wave (Figure 2a) or b-wave (Figure 2b). The a-wave potential in the ARN at the time of initial diagnosis was compared with that in other disease entities. A typical ERG in CMV retinitis demonstrated well-preserved a-waves and b-waves; in sarcoidosis, a hyper-normal waveform was observed, with significantly enhanced a-wave and b-wave amplitudes, characteristic of uveitis.

Differences in a and b-wave amplitude between ARN patients and the other infectious and non-infectious uveitis cases

Patients with ARN and bacterial endophthalmitis demonstrated the greatest reduction in a- and b-wave potentials; those with bacterial endophthalmitis showing more variable results (ARN vs. another infectious uveitis: *p* = 0.001, vs.

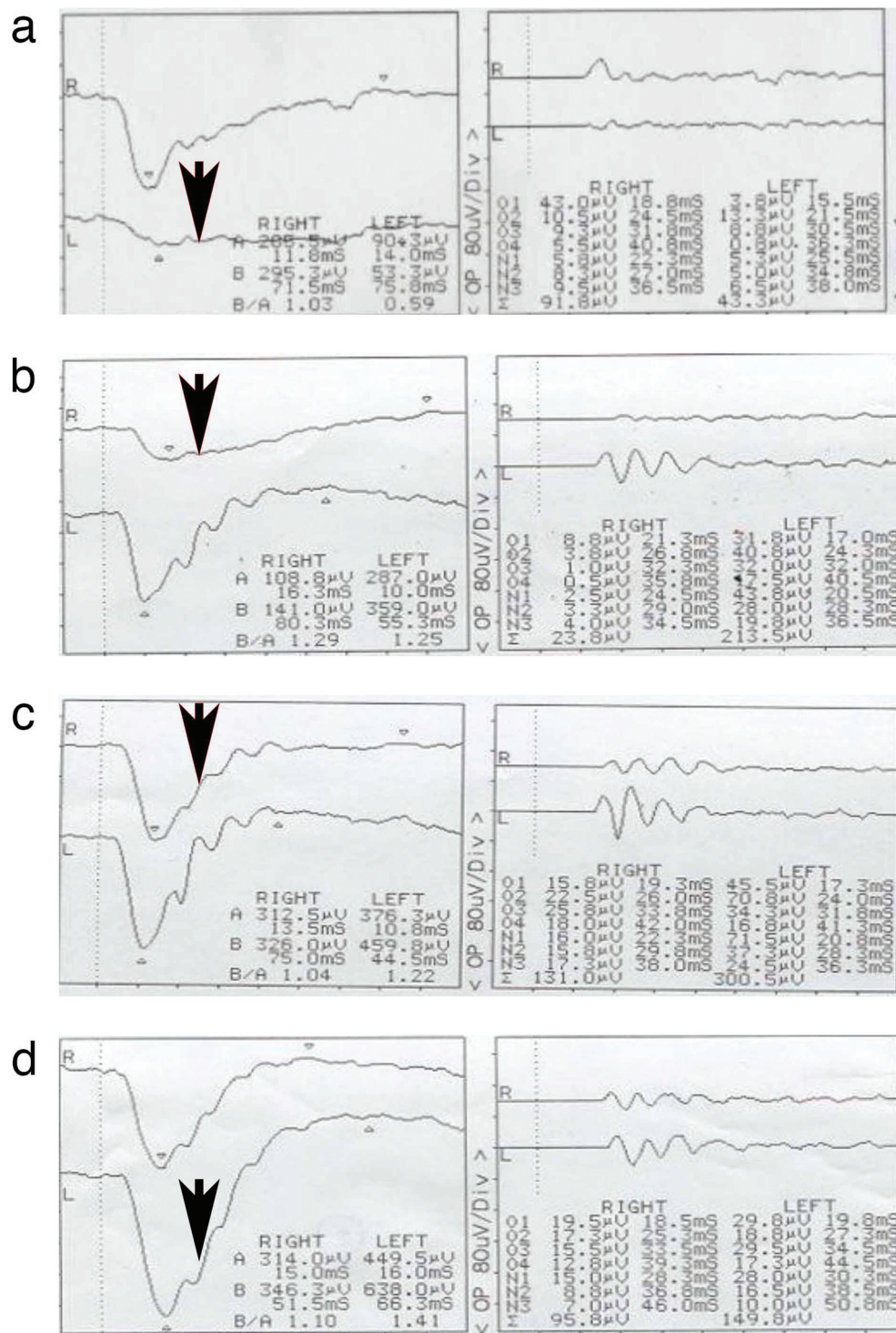


Figure 1. Typical examples of ERG waveforms. Typical ERG waveforms in each group are depicted (arrow). In ARN (a) and bacterial endophthalmitis (b), a marked absence of discernible a-waves or b-waves is present; the arrow indicates the curve of the affected eye. Conversely, CMV retinitis demonstrates well-preserved a-waves and b-waves (c). Sarcoidosis exhibits a hyper-normal waveform (d). The left column presents the peak amplitude of the flash ERG response, whereas the right column displays the oscillatory potentials. ARN, Acute retinal necrosis; CMV, cytomegalovirus; ERG, electroretinogram.

non-infectious uveitis: $p = 0.001$). Bacterial endophthalmitis did not show a significant difference in a-wave amplitude compared with the other two uveitis conditions. For b-wave potentials, the b-wave amplitude in the affected eye of patients with ARN did not differ from that in the group with bacterial endophthalmitis but was significantly

lower compared with other infectious and non-infectious uveitis at the initial examination (ARN vs. another infectious uveitis: $p = 0.005$, ARN vs. non-infectious uveitis: $p = 0.001$). Bacterial endophthalmitis did not show a significant difference in b-wave amplitude compared with the other uveitis conditions (Figure 2b).

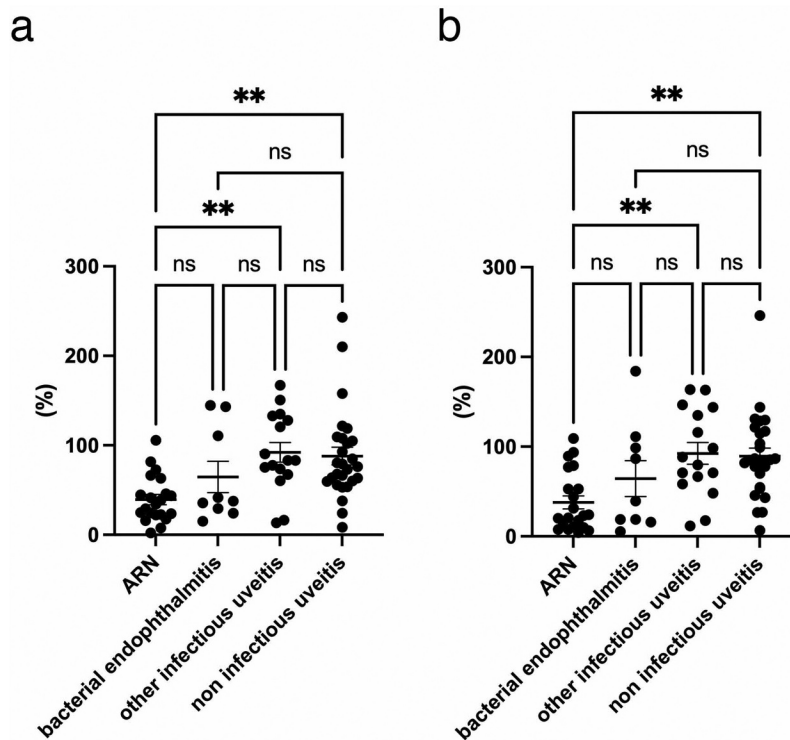


Figure 2. a- and b-wave potentials in each disease group. The values are quantified by dividing the a-wave potential of the affected eye by the a-wave potential of the unaffected (non-diseased) eye (a). When a-wave potentials are compared, the mean rank values are 21.52 for ARN, 32.44 for bacterial endophthalmitis, 47.94 for other infectious uveitis conditions, and 44.07% for non-infectious uveitis. $**p < 0.01$. The ns indicates no significant difference. In the comparison of b-wave potentials, the mean rank values are 22.10 for ARN, 33.0 for bacterial endophthalmitis, 45.74 for other infectious uveitis conditions, and 44.74% for non-infectious uveitis (b). $**p < 0.01$. ns indicates no significant difference. ARN, Acute retinal necrosis.

Pre- and post-treatment visual acuity

A comparison of pre-treatment visual acuity among the four groups revealed no significant differences in initial visual acuity between the ARN group and other three groups. However, eyes with bacterial endophthalmitis exhibited significantly worse initial vision compared with those with other forms of infectious or non-infectious uveitis (Figure 3a). Post-treatment visual acuity was analyzed, and the ARN group demonstrated a significant improvement (Figure 3b). By contrast, no significant difference was observed in the incidence of bacterial endophthalmitis or other infectious uveitis (Figure 3c, d), whereas a significant difference was noted in the incidence of non-infectious uveitis (Figure 3e).

Furthermore, visual acuity outcomes were adjusted to account for cases in which retinal detachment occurred during the treatment period. Only two patients with ARN exhibited a decline in visual acuity from baseline, whereas all other patients demonstrated an improvement from the initial examination. Both patients were not treated by a uveitis specialist initially and underwent surgery immediately after their initial assessment. In one patient, an incomplete vitrectomy resulted in the development of proliferative vitreoretinopathy in Zone 1 during the treatment course, necessitating a second surgical intervention (data not shown). A multivariate analysis identified pretreatment visual acuity as the strongest predictor of posttreatment visual prognosis in ARN (Spearman's $\rho = 0.7084$, $p = 0.0003$).

Difference in a-wave intensity between patients with ARN and those with other infectious or non-infectious uveitis

As the initial visual acuity was not a diagnostic marker for ARN, the potential of a-wave as a diagnostic marker for ARN at the time of initial examination was evaluated. The a-wave amplitude in patients with ARN was significantly reduced compared with that in both the infectious and non-infectious uveitis groups. To distinguish ARN from other infectious uveitis conditions, an ROC curve was generated based on the a-wave amplitude at the initial examination, yielding an AUC of 0.84. A reduction in the a-wave amplitude by more than 73.09% (affected eye/control eye) was highly indicative of ARN, with a sensitivity of 75% and a specificity of 90.5% (Figure 4a). Similarly, to differentiate ARN from non-infectious uveitis, an ROC curve was generated, yielding an AUC of 0.83. A reduction in the a-wave amplitude by more than 49.48% was strongly suggestive of ARN, with a sensitivity of 88.89% and a specificity of 76.19% (Figure 4b).

The diagnostic utility of the b-wave amplitude at the initial examination was similarly investigated, comparing ARN with other infectious and non-infectious uveitis conditions. When comparing ARN to other types of infectious uveitis, the ROC curve derived from the b-wave amplitude yielded an AUC of 0.81. A reduction in the b-wave amplitude of the affected eye by more than 55.57% compared with the control eye resulted in a sensitivity of 81.25% and a specificity of 76.19% for diagnosing ARN (Figure 4c). Additionally, when comparing ARN from non-infectious uveitis, an ROC curve analysis of

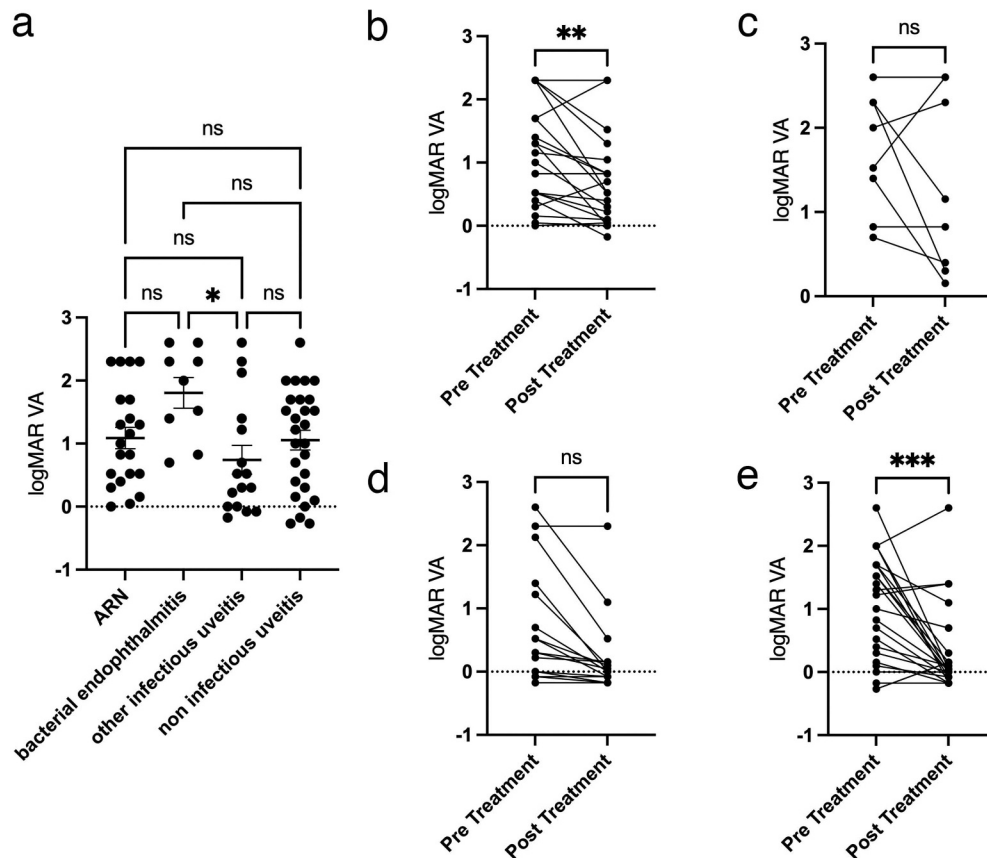


Figure 3. Pre- and post-treatment visual acuity. The visual acuity before and after treatment was compared. No significant difference in initial visual acuity is detected between bacterial endophthalmitis, other infectious uveitis conditions, non-infectious uveitis, and ARN (a). Visual acuity comparison between bacterial endophthalmitis and other groups showed a significant difference, with other-infectious uveitis and non-infectious uveitis demonstrating worse visual acuity compared with bacterial endophthalmitis. When post-treatment visual acuity is analyzed, the ARN group demonstrated a significant improvement (b). By contrast, no significant difference is observed in bacterial endophthalmitis or other infectious uveitis (c, d), whereas a significant difference is noted in non-infectious uveitis (e). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. ns indicates no significant difference. ARN, Acute retinal necrosis.

b-wave amplitudes at the initial examination yielded an AUC of 0.83. A reduction in the b-wave amplitude in the affected eye by more than 77.43% compared with that in the control eye resulted in a sensitivity of 70.37% and specificity of 80.95% for diagnosing ARN versus non-infectious uveitis (Figure 4d). These findings suggest that a high degree of specificity and sensitivity in diagnosing ARN can be achieved by assessing the relative decrease in a-wave and b-wave amplitudes.

Discussion

This study conducted an in-depth analysis of ERG findings and visual acuity outcomes across a spectrum of ocular diseases, with a particular emphasis on ARN. A diverse cohort of 73 patients, including those with bacterial endophthalmitis, infectious uveitis, and non-infectious uveitis, was enrolled to examine the diagnostic value of a- and b-wave potentials in ERG, particularly in differentiating ARN from other ocular conditions.

The findings revealed a significant decrease in a-wave potentials at the initial presentation in patients with ARN compared with those with other forms of uveitis, except for bacterial endophthalmitis. Additionally, b-wave potentials were markedly lower in patients with ARN.

When comparing visual acuity before and after treatment, ARN generally demonstrated a poorer outcome compared with those in other types of uveitis, except for bacterial endophthalmitis. This finding highlights the significant impact that VZV or HSV infection has on retinal cells and visual function, distinguishing ARN from other inflammatory eye diseases. However, despite ARN's relatively poor visual prognosis, the data indicate a notable improvement in visual acuity following appropriate and timely treatment. Multivariate analysis revealed a strong correlation between pre-treatment visual acuity and post-treatment visual prognosis. By contrast, bacterial endophthalmitis is characterized by a more consistently poor visual prognosis. The initial visual acuity in bacterial endophthalmitis exhibited significant variation, as did the outcomes. In bacterial endophthalmitis, bacterial toxins likely cause extensive retinal damage before treatment, leading to irreversible vision loss. Interestingly, although the ERG waveform in ARN can resemble that observed in bacterial endophthalmitis, the more favorable recovery of visual acuity in ARN suggests that the extent of retinal damage, particularly in regions critical for vision, may be less severe. This finding underscores the importance of early and appropriate intervention in ARN to optimize visual recovery.

Previous studies have reported ERG changes in patients with ARN as isolated events, typically showing slight

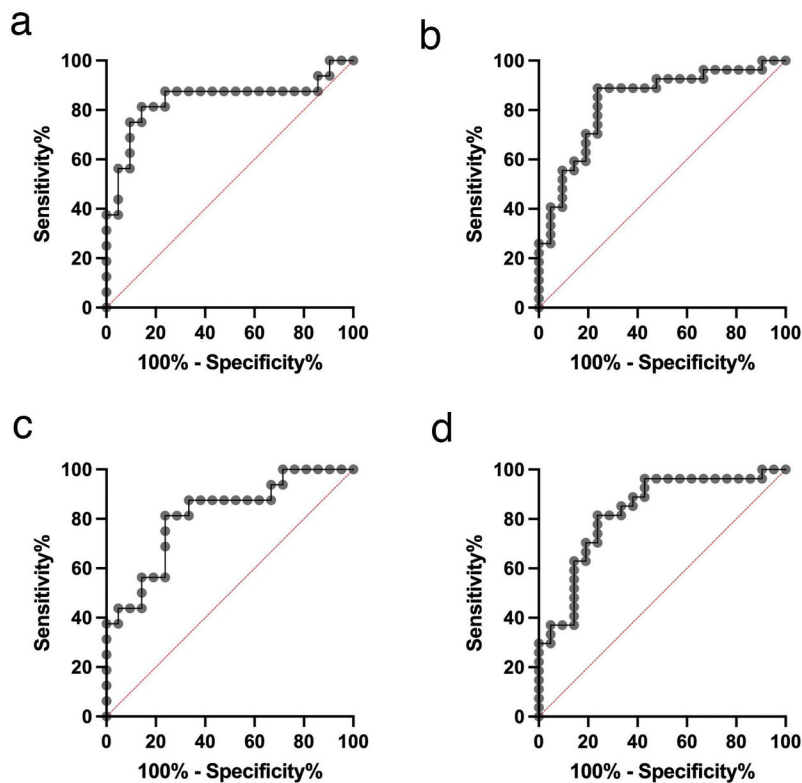


Figure 4. ROC curve between patients with ARN and those with other infectious or non-infectious uveitis conditions. To differentiate between ARN and other forms of infectious uveitis, the area under the curve (AUC) for the a-wave potential is 0.84. In cases of ARN, an a-wave potential ratio (affected/control eye) of more than 73.09% demonstrated a sensitivity of 75.00% and a specificity of 90.48% (a). A similar approach is adopted to differentiate ARN from non-infectious uveitis, yielding an AUC of 0.83 for the a-wave potential, with a threshold of more than 49.48% (affected/control eye). This approach yielded a sensitivity of 88.89% and a specificity of 76.19% (b). The AUC for distinguishing ARN from other infectious uveitis is 0.81 for the b-wave potential, with a b-wave potential ratio (affected/control eye) of more than 55.57% achieving a sensitivity of 81.25% and a specificity of 76.19% (c). When comparing ARN with non-infectious uveitis, the AUC for the b-wave potential was 0.83, with a threshold of more than 77.43% (affected/control eye), resulting in a sensitivity of 70.37% and a specificity of 80.95% (d). ARN, Acute retinal necrosis; CMV, cytomegalovirus; ERG, electroretinogram.

reductions in a- and b-wave potentials.^{19–22} However, Ducker et al. documented patients who developed fulminant ARN with absent a- and b-wave potentials, a finding consistent with the dramatic reductions observed in our study.²³ This research is important because it is the first to document ERG alterations in 21 patients with ARN.

The ERG is a vital diagnostic tool that measures the electrical responses of retinal cells to light stimuli.²⁴ Although vitreous opacities, cataract formation and macular complications such as ERM can significantly affect visual acuity, these factors are unlikely to have a significant effect on ERG amplitudes because the ERG primarily measures global retinal function rather than localized optical perturbations or opacities within the ocular tissues. The a-wave reflects photoreceptor (rod and cone) function,²⁵ whereas the b-wave is generated by inner retinal cells, particularly bipolar and Müller cells.²⁶ In several cases initially presenting with severe anterior segment inflammation, such as postoperative uveitis, HLA-B27-associated acute anterior uveitis, lens-induced uveitis, sarcoidosis, ABD, or herpetic iridocyclitis, posterior segment evaluation by ophthalmoscopy was significantly limited. Consequently, these patients could not be reliably diagnosed based solely on clinical examination at the initial visit. Therefore, ERG was performed as an objective method to evaluate retinal function and detect potential posterior segment involvement, thereby aiding accurate early diagnosis. In

patients with ARN, the significant reduction in a-wave amplitude likely results from direct viral invasion and subsequent immune-mediated damage to photoreceptors.²⁶ Our study's attempt to evaluate oscillatory potentials was hindered by non-recordable waveforms in ARN, suggesting extensive inner retinal damage. The pronounced reduction in a-wave potential serves as a valuable diagnostic marker, distinguishing ARN from other types of uveitis. The application of ROC curve analysis to differentiate ARN from other types of uveitis based on the a-wave potential at the initial examination emphasizes the diagnostic utility of ERG in clinical practice. This damage may be attributed to elevated inflammatory cytokine levels, coupled with the lack of oxygenation of the inner retinal layer due to occlusive vasculitis, which is common in ARN. The cytokine levels measured in vitreous samples of patients with ARN were higher than those in patients with non-infectious uveitis, such as sarcoidosis.²⁷ Although we did not measure intraocular cytokines in this study, previously published data indicate significantly elevated vitreous concentrations of interleukin-6 (IL-6), interferon-gamma (IFN- γ), and interleukin-10 (IL-10) in ARN compared with other types of uveitis.²⁸ Among these cytokines, IL-6 and IFN- γ are known to exhibit neurotoxic and pro-inflammatory effects on retinal tissues. Elevated IL-6 levels can cause disruption of the blood-retinal barrier, enhance leukocyte infiltration, and amplify inflammatory responses, potentially exacerbating

retinal injury.^{29,30} IFN- γ , a representative Th1 cytokine, has been linked to direct photoreceptor damage and retinal inflammation in animal models of autoimmune uveoretinitis.^{31,32} Although IL-10 generally serves as an anti-inflammatory mediator, its increased levels may reflect a regulatory response attempting to control the inflammation associated with these pro-inflammatory cytokines, suggesting a complex cytokine imbalance in ARN.²⁸ Previously, occlusive retinal arteritis has been proposed as the primary mechanism underlying retinal damage and visual impairment in ARN.¹⁵ However, the cytokine hypothesis, supported by existing evidence,²⁸ provides an alternative or complementary mechanism whereby cytokine-driven neurotoxicity and inflammation directly contribute to ERG abnormalities and retinal degeneration. Thus, cytokine imbalance, particularly elevated IL-6 and IFN- γ , might synergistically exacerbate retinal damage alongside the established vascular mechanisms. Therefore, immediate antiviral treatment is crucial to prevent further retinal damage.⁵

Although our study provides valuable insights, it has some limitations. The relatively small sample size, particularly when categorized by disease type, may limit the generalizability of the findings. Additionally, the heterogeneity within the different groups introduces complexity to our results. We also employed two different methods to measure the ERG results, which could raise concerns. However, our approach focused on comparing relative reductions in potential rather than absolute values, thus maintaining the validity of our findings. Both ERG measurement methods have broad clinical applications. The traditional ERG is essential for detailed retinal examinations, whereas the RETeval system offers a quick and practical alternative, particularly in screening scenarios or when patient compliance is challenging.¹⁶

Future research should focus on longitudinal studies to explore the progression of ERG findings in patients with ARN and their correlation with clinical outcomes over time. Investigating the underlying mechanisms of retinal damage in patients with ARN and bacterial endophthalmitis could further elucidate the pathophysiological similarities observed in our study. Expanding the sample size and including a broader range of infectious and non-infectious uveitis conditions would enhance the robustness and applicability of the findings.

In conclusion, this study underscores the distinct electrophysiological signature of ARN, characterized by a profound attenuation of a- and b-wave potentials. These findings not only reinforce the diagnostic and prognostic value of ERG in ARN but also emphasize its critical role in guiding timely and targeted therapeutic interventions. By providing deeper insights into the impact of ARN on retinal function, this study advances the early recognition and appropriate management of ARN, ultimately improving visual outcomes, particularly in patients with residual visual acuity at the time of diagnosis.

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Author contributions

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