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Original Article

Association Between Prognosis of Acute Retinal Necrosis and Retinal Involvement

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Abstract

Objectives: The aims of this study were to describe the clinical presentation and treatment modalities of acute retinal necrosis (ARN) and to evaluate complications and clinical outcomes according to the extent of retinal involvement at initial presentation.

Materials and Methods: The medical records of 52 patients diagnosed with ARN were reviewed and 48 were included in the study. Patients were categorized into two groups according to the extent of retinitis at presentation: retinal involvement of 1-2 quadrants (Group A) or 3-4 quadrants (Group B).

Results: The mean age of the 14 women and 34 men at presentation was 51.3±13.6 years (range: 27-78). There were 40 unilateral and 8 bilateral cases. There were 11 eyes (19.6%) in Group A and 45 eyes (80.4%) in Group B. Eleven patients (22.9%) had a history of herpes simplex virus/varicella-zoster virus infection. One patient in Group A and 11 patients in Group B had received local or systemic corticosteroid therapy without concomitant antiviral treatment before referral. The median follow-up period was 29 months (range: 1-209) in Group A and 8.5 months (range: 0.75-209) in Group B. Mean visual acuity (VA) at presentation was 0.42±0.55 LogMAR (range: 0-2.0) in Group A and 1.28±0.95 LogMAR (range: 0-2.9) in Group B ($p<0.05$). The presence of endothelial keratic precipitates at presentation was significantly different between two groups ($p=0.021$). Retinal detachment (RD) occurred in 1 eye (9.1%) in Group A and 30 eyes (66.7%) in Group B ($p<0.001$). Optic disc pallor was seen in 36.4% (4/11) of eyes in Group A and 71.1% (32/45) of eyes in Group B ($p=0.033$). Other ocular complications were not significantly different between two groups. Mean final visual acuity was 0.29±0.41 LogMAR in Group A and 1.61±0.90 LogMAR in Group B ($p<0.05$).

Conclusion: The extent of retinal involvement at presentation affects visual outcomes and this shows the importance of early diagnosis and early initiation of antiviral treatment.

Keywords: Acute retinal necrosis, viral retinitis, antiviral agents, varicella-zoster virus, herpes simplex virus, retinal detachment

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Introduction

Acute retinal necrosis (ARN) is a clinical syndrome characterized by foci of necrotizing retinitis that start in the peripheral retina and tend to spread rapidly to the posterior pole, with associated retinal arteritis, papillitis, vitritis, and anterior uveitis.[1] It is caused by herpes family viruses and can occur in immunocompetent individuals regardless of age or sex.[2,3,4]

ARN is diagnosed based on clinical examination findings. Polymerase chain reaction (PCR) analysis of anterior chamber fluid or vitreous samples can be used to confirm the diagnosis and identify the causative pathogen.[5,6,7] Systemic (intravenous [IV]/oral) and/or intravitreal antiviral agents are used in treatment.[8,9,10]

Despite effective antiviral therapy, patients may have poor final visual acuity (VA).[2,3] Areas of necrosis that regress with retinal atrophy often cause secondary retinal detachment (RD), a complication which negatively affects visual prognosis. However, Hillenkamp et al.[11] reported in their study that vision loss may be associated with retinal ischemia and optic atrophy rather than RD.

This study examined the clinical findings and treatment of patients diagnosed with ARN and aimed to evaluate the relationship between the extent of retinal involvement at initial presentation and the patients' complications and final VA.

Materials and Methods

We retrospectively analyzed the clinical records of 52 patients who presented to the Department of Ophthalmology of İstanbul University, İstanbul Faculty of Medicine between September 1998 and February 2018 and were diagnosed with ARN. The research followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of İstanbul Faculty of Medicine. Informed consent was obtained from all patients before the treatment.

The diagnosis of ARN was made clinically by a single clinician (İ.T.T.) according to the diagnostic criteria established by the American Uveitis Committee.[1]

The patients' clinical records were examined in terms of demographic characteristics, ocular and medical history, ocular findings at initial presentation and during follow-up, laboratory test results, treatments applied, and complications. Human immunodeficiency virus (HIV) and syphilis serology were investigated in all patients, and PCR analysis of intraocular fluid was performed in patients who presented after 2011.

In each examination, patients underwent complete ophthalmologic examination including best corrected VA (BCVA), biomicroscopic examination, intraocular pressure measurement by applanation tonometry, laser flare photometry (LFP) (KOWA FC-2000 or FM-700, Kowa Company, Ltd, Tokyo, Japan), and fundus examination, as well as spectral-domain optical coherence tomography. Statistical analysis was performed by converting BCVA assessed by Snellen chart to logarithm of the minimal angle of resolution (LogMAR) values. Patients with VA at the level of counting fingers, hand movements, light perception, and no light perception were assigned LogMAR values of 2.0, 2.3, 2.6, and 2.9, respectively.[12,13]

The infectious diseases department was consulted for the patients' IV antiviral therapy. All patients received IV acyclovir (10-15 mg/kg every 8 hours; Zovirax injection, GlaxoSmithKline SpA, Verona, Italy) or IV ganciclovir (5 mg/kg every 12 hours; Cymevene injection, F.Hoffmann-La Roche Ltd, Basel, Switzerland) plus topical corticosteroid (CS) (prednisolone; Pred forte 1% eye drops, Allergan Pharmaceuticals, Westport, Ireland) and mydriatic drops. Systemic CS (prednisolone; Prednol tablet, Gensenta Pharmaceuticals, Istanbul, Turkey) was added to treatment according to the patients' clinical findings. Intravitreal ganciclovir (Cymevene injection) or foscarnet (Foscavir injection, Pfizer, New York, USA) was administered to patients with severe involvement at the time of admission, insufficient improvement or progression of retinal necrosis under IV antiviral therapy. After IV therapy, treatment was continued with oral acyclovir (Aklovir tablet, Sandoz Pharmaceuticals, Kocaeli, Turkey) or valacyclovir (Valtrex tablet, GlaxoSmithKline SpA, Istanbul, Turkey). Antiviral prophylaxis was initiated in all patients.

The patients were divided into two groups according to the extent of necrotizing retinitis at initial presentation: 1-2 quadrants of necrotizing retinitis (Group A) or 3-4 quadrants of necrotizing retinitis (Group B). The extent of retinal involvement was assessed by a single clinician from a fundus photograph or detailed fundus drawings. The two groups were compared in terms of duration of complaints, initial VA, ocular findings at presentation, LFP values, disease progression, final VA, and ocular complications (RD, cataract, epiretinal membrane, cystoid macular edema, glaucoma, neovascularization, and optic disc pallor). The data were statistically analyzed using chi-square, Mann-Whitney U, Fisher's exact, and t tests, with p values <0.05 considered statistically significant.

Results

Of the 52 patients with ARN, we excluded 4 patients who were diagnosed with late-stage total RD at presentation or were not followed up. Fifty-six eyes of the remaining 48 ARN patients were included in the study.

Nine patients (18.8%) were referred to our clinic with the diagnosis of ARN and 9 patients (18.8%) were referred to our clinic with other diagnoses. Thirty patients (62.4%) presented to our clinic first. The mean age at presentation of the 14 women and 34 men in the study was 51.3±13.6 years (range: 27-78).

Presenting complaints were vision loss (89.6%), red eyes (47.9%), and ocular pain (33.3%). The mean time from symptom onset to presentation to our clinic was 15.4±11.8 days (range: 4-60). Eleven patients (22.9%) had a history of herpes simplex virus (HSV)/varicella-zoster virus (VZV) infection (herpes labialis in 2, herpetic encephalitis in 5, herpetic keratitis in 1, herpetic iridocyclitis in 1, and shingles in 2 patients). While 45 patients were immunocompetent, 2 patients with cancer and 1 patient with renal transplant were receiving immunosuppressive therapy. None of the patients had HIV infection.

Involvement was unilateral in 40 patients and bilateral in 8 patients. Five patients had involvement in both eyes at initial

presentation, whereas 3 patients developed involvement in the fellow eye during IV antiviral therapy (on days 4, 6, and 12). While 2 of the 3 patients with fellow eye involvement during antiviral therapy were not receiving steroid treatment, one patient developed fellow eye involvement 1 day after steroid treatment was added to the antiviral treatment.

Based on the extent of necrotizing retinitis at initial presentation, 11 eyes (19.6%) were included in Group A (Figure 1) and 45 eyes (80.4%) were included in Group B (Figure 2). Of the 8 patients with bilateral involvement, 5 had one eye in Group A and the other in Group B while 3 patients had both eyes in Group B. Therefore, Group B involvement was present in at least one eye of a total of 42 patients.

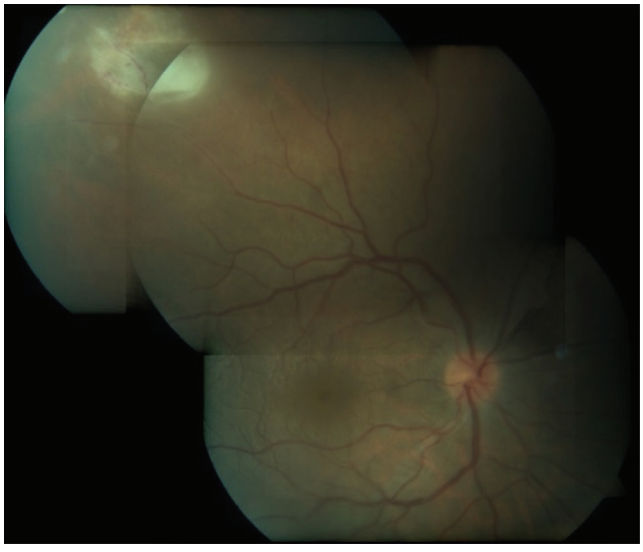

Figure 1. Color fundus photograph of a patients with retinal necrosis in one quadrant (Group A)

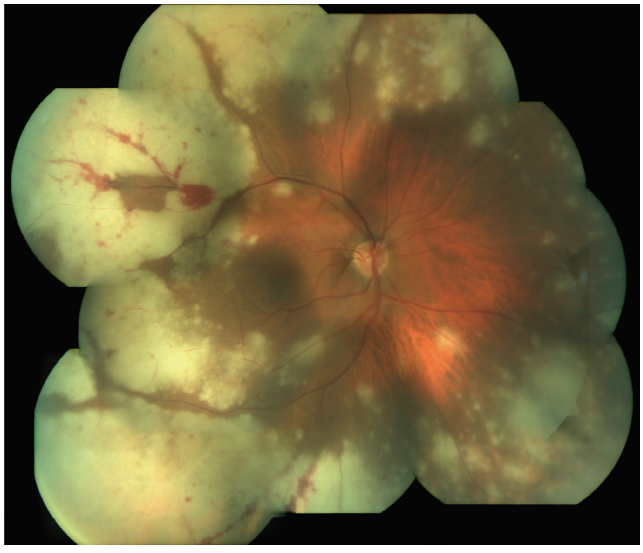

Figure 2. Color fundus photograph of the patient with retinal necrosis in four quadrants (Group B)

Nine patients who were referred with the diagnosis of ARN were receiving systemic antiviral treatment for 1-3 days at the time of presentation. Before presenting to our center, 11 patients (1 patient in Group A and 10 patients in Group B) received 16-1000 mg systemic CS for 3 to 90 days without antiviral therapy, and 3 patients in Group B also received a local depot CS injection. Of a total of 12 patients (1/6 patients in Group A, 16.6%; 11/42 patients in Group B, 26.2%; p>0.05) who received systemic and/or local CS therapy, CS was used for the treatment misdiagnosed noninfectious uveitis in 9 and accompanying systemic disease in 3 of the patients.

The mean duration of complaints was 15.3±13.5 days (range: 5-35) in Group A and 15.4±11.8 days (range: 4-60) in Group B (p>0.05).

Median follow-up time was 29 months (range: 1-209) in Group A and 8.5 months (range: 0.75-209) in Group B. Thirty-two patients (66.7%) were followed for at least 6 months and 24 patients (50%) for at least 1 year.

Mean BCVA at initial presentation was 0.42±0.55 LogMAR (range: 0-2.0) in Group A and 1.28±0.95 LogMAR (range: 0-2.9) in Group B (p<0.05). Mean LFP values at presentation were 73.5±83 photons/millisecond (ph/ms) (median: 46.3, range: 5.6-255) in Group A and 135.7±153 ph/ms (median: 79.9, range: 8.1-551) in Group B (p=0.409).

The patients' ocular findings at initial presentation are shown in Table 1. The only statistically significant difference between the two groups was in the prevalence of keratic precipitate (p=0.021).

PCR analysis of anterior chamber fluid was performed in 24 patients (50%). PCR was positive in a total of 17 patients, including 12 patients (50%) with VZV, 4 patients with HSV-1, and 1 patient with both HSV-2 and VZV. One patient who was positive for HSV-1 was in Group A and the other 16 patients with positive PCR were in Group B (2 VZV-positive patients with bilateral involvement had one eye in Group A and the other eye in Group B). PCR was negative in 7 patients (1 in Group A and 6 in Group B). In patients with negative PCR, diagnosis was confirmed by response to treatment; resampling was not performed.

In 38 patients, necrotizing retinitis was controlled with IV acyclovir in a median of 16.2 days (range: 4-28). Four patients with extensive retinal involvement who were immunosuppressed (2 patients with renal dysfunction receiving immunosuppression therapy by recommendation of the infectious diseases department and 2 patients who were immunosuppressed due to systemic disease) received IV ganciclovir treatment for a median of 22.5 days (range: 10-28) starting at presentation. Six patients who had extensive retinal involvement at initial presentation and persistent retinal necrosis after a median of 40.3 days (range: 22-43) of IV acyclovir treatment (even without progression) were switched to IV ganciclovir treatment. Of 4 patients who had elevated renal function tests (blood urea nitrogen and creatinine) while receiving IV acyclovir, the dose was reduced in 2 patients (10 mg/kg every 12 hours), while IV therapy was discontinued and oral valacyclovir was initiated in the other 2 patients. In

these 4 patients, renal function tests returned to normal with oral or reduced-dose IV antiviral therapy and good hydration, and no worsening of the retinal necrosis was observed. Intravitreal foscarnet and/or ganciclovir injections were administered in addition to IV antiviral therapy to 3 eyes (27.3%) in Group A and 26 eyes (57.8%) in Group B. A single intravitreal injection was performed in 10 eyes, while 19 eyes received multiple intravitreal injections (median: 4.6 injections). Forty-three patients (89.6%) received systemic CS therapy in addition to IV antiviral therapy. Prednisolone was initiated a mean of 12.6±8.4 days (range: 2-33) after IV antiviral therapy at a median dosage of 32 mg/day (range: 16-64 mg). One patient developed bilateral involvement the day after starting prednisolone 32 mg/day on day 5 of IV antiviral therapy, and the prednisolone was discontinued. Time to complete resolution of the retinal necrosis was 28.2±16.7 days (range: 13-58) in Group A and 32±15.2 days (range: 11-78) in Group B, with no statistically significant difference between the two groups (p>0.05).

At the end of IV antiviral therapy, mean LFP values were 32.2±21.7 ph/ms in Group A and 69.4±59.4 ph/ms in Group B (p=0.027).

Ocular complications developed by the patients are shown in Table 2. RD was detected in 55.4% (31/56) of all eyes, with a median time between diagnosis and RD development of 75.5 days (range: 13-330). One eye in Group A with a retinal tear and localized RD at the edge of the tear was treated with barrier retinal argon laser photocoagulation. Twenty-five eyes in Group B with RD were treated with vitreoretinal surgery and silicone injection, and anatomic success was achieved. Vitreoretinal surgery could not be performed in a total of 6 eyes (4 of which presented after developing advanced vitreoretinal proliferation and were deemed inoperable, and 2 because the patient refused the procedure), and phthisis bulbi developed in the 3 eyes that were followed. Silicone removal was performed in 6 patients (6 eyes) at a median of 16 months (range: 3-36). A second vitreoretinal surgery and silicone injection were performed in 1 patient who had silicone removal at 3 months and developed recurrent RD and in 2 eyes of 2 patients who developed fibrous

Table 1. Ocular findings at initial presentation

Ocular findings at presentation	All eyes (n=56) n (%)	Group A (n=11) n (%)	Group B (n=45) n (%)	p value
Conjunctival hyperemia	34 (60.7)	5 (45.5)	29 (64.4)	0.169
Keratic precipitates	52 (92.9)	8 (72.7)	44 (97.8)	**0.021**
Anterior chamber reaction	52 (92.9)	10 (91)	42 (93.3)	0.357
Iris nodule (Koeppe)	3 (5.4)	1 (9.1)	2 (4.4)	0.594
Iris transillumination	2 (3.6)	0	2 (4.4)	0.643
Posterior synechia	6 (10.7)	2 (18.2)	4 (8.9)	0.335
Vitritis	48 (85.7)	8 (72.7)	40 (88.9)	0.241
Vitreous haze	15 (26.8)	2 (18.2)	13 (28.9)	0.381
Elevated IOP	14 (25.0)	1 (9.1)	13 (28.9)	0.167
Optic disc inflammation	26 (46.4)	7 (63.6)	19 (42.2)	0.174
Retinal hemorrhage	43 (71.7)	6 (54.5)	37 (82.2)	0.065
Occlusive arteriolitis	33 (55)	4 (36.4)	29 (64.4)	0.088
Macular edema	12 (20)	4 (36.4)	8 (17.8)	0.162
Macular involvement	3 (5)	0	3 (6.7)	0.512
Retinal detachment	1 (1.8)	0	1 (2.2%)	0.804

IOP: Intraocular pressure

Table 2. Distribution and comparison of ocular complications by group

Ocular complications	Number of Group A eyes (%) (n=11)	Number of Group B eyes (%) (n=45)	p value
Retinal detachment	1 (9.1)	30 (66.7)	**0.001**
Cataract	2 (18.2)	16 (35.6)	0.273
Cystoid macular edema	3 (27.3)	18 (40.0)	0.726
Epiretinal membrane	8 (72.7)	19 (42.2)	0.072
Glaucoma	1 (9.1)	5 (11.1)	0.518
Optic disc pallor	4 (36.4)	32 (71.1)	**0.033**
Phthisis bulbi	0	4 (8.9)	0.309
Neovascularization (iris/retina)	0	4 (8.9)	0.309

Table 3. Mean best-corrected visual acuity (BCVA) values of the groups at initial admission and follow-up			
BCVA values (LogMAR), mean ± SD	**Group A**	**Group B**	**p value**
Initial	0.42±0.55	1.28±0.95	**0.001**
1 week	0.61±0.74	1.30±0.88	**0.015**
1 month	0.33±0.41	1.04±0.95	**0.001**
3 months	0.31±0.34	1.44±0.91	**<0.001**
Final	0.29±0.41	1.61±0.90	**<0.001**
SD: Standard deviation			

proliferation. One eye developed phthisis bulbi despite revision surgery and silicone reinjection. Prophylactic barrier retinal laser photocoagulation was performed in 1 eye of 1 patient.

Cataract developed in 18.2% (2/11) of the eyes in Group A and 40% (18/45) of the eyes in Group B. Cataract occurred after vitreoretinal surgery in 15 eyes in Group B.

Among the other complications, the only significant difference between the two groups was in the prevalence of optic disc pallor (p=0.033).

Comparison of the groups' mean BCVA values at initial presentation and during follow-up is shown in Table 3. The mean BCVA values of group A were significantly better than group B at all visits (p<0.05). The change in mean BCVA at week 1 and month 1 was statistically significant in Group A (p=0.029). In Group B, the change between 1 and 3 months and between values at initial presentation and final visit were found to be statistically significant (p=0.002 and p=0.003, respectively).

Compared to eyes with 1-2 quadrants of retinal involvement, eyes with 3-4 quadrants of retinal involvement at presentation had significantly higher prevalence of keratic precipitates and lower BCVA at initial presentation, and significantly higher rates of RD and optic disc pallor during follow-up, resulting in low VA and high LFP values.

Discussion

This retrospective study evaluated the clinical features, treatments, and outcomes of patients with ARN. Studies have reported that ARN is more common in the 20-60 age range and in the male sex.[14,15] In this study, the age range of the patients was 27-78 years, and involvement was found to be male-predominant (71.2%). It has been reported that patients present most frequently with complaints of vision loss.[16] Similarly, 89.6% of patients in our study complained of vision loss at presentation.

Takase et al.[17] reported a history of HSV/VZV infection in 5 (3.4%) of 149 patients diagnosed with ARN (herpes encephalitis in 1, herpes zoster infections in 4 patients), and the most common ocular finding at presentation was anterior chamber reaction and the presence of keratic precipitates (97%). We observed a higher rate of previous HSV/VZV infection in the present study (22.9%; herpes labialis in 2, herpetic encephalitis in 5, herpetic keratitis in 1, herpetic iridocyclitis in 1, and shingles in 2 cases). Sungur et al.[18] reported keratic precipitates, anterior chamber reaction, and vitritis at presentation in all 13 patients diagnosed with ARN. Similarly, in our study the most common ocular findings at initial presentation were anterior chamber reaction and keratic precipitates, which were detected in 92.9% of the eyes. When the ocular findings were evaluated according to the extent of retinal involvement, keratic precipitates were more common in the group with 3-4 quadrants of retinal involvement.

We divided the patients in this study into two groups according to the prevalence of necrotizing retinitis at presentation (1-2 quadrants or 3-4 quadrants of necrotizing retinitis) and compared their complication rates and outcomes. Meghpara et al.[19] divided 25 eyes with ARN into 3 groups (<25%, 25-50%, and >50% retinal involvement) and reported that 44% of the patients had <25% retinal involvement, 32% had 25-50% retinal involvement, and 24% had >50% retinal involvement. Khochtali et al.[20] detected <25% retinal involvement at presentation in 41.7%, 25-50% retinal involvement in 25%, and >50% retinal involvement in 33.3% of 12 eyes with ARN. In our study, extensive retinal involvement was detected in 80.4% of the eyes at initial presentation. We attribute the high prevalence of extensive retinal involvement with the higher rates of late diagnosis and delayed treatment in our patient group. Especially the fact that they received CS before antiviral treatment because of misdiagnosis may have contributed to the rapid spread of retinal necrosis. However, there was no significant difference between the two groups in terms of symptom duration before presentation. Therefore, extensive peripheral retinal involvement may be asymptomatic and not associated with symptom duration.

PCR analysis of anterior chamber fluid was performed in 25 patients (48.1%) and was positive for VZV in 13 patients (52%) in this study. Our results showed that VZV is the most common cause of ARN, similar to other studies.[11,21,22] Wong et al.[23] compared the clinical characteristics of patients with ARN caused by HSV and VZV, and although both groups had comparable initial VA, the group with VZV ARN was found to have lower final VA and a higher rate of RD. Of the 24 patients in our study who had PCR analysis of anterior chamber fluid, VZV was detected in 12, HSV-1 in 4, and both HSV-2 and VZV in 1 patient. One of the HSV-1-positive patients was in group A and 3 patients were in group B, whereas all VZV-positive patients were in group B.

Baltinas et al.[24] compared IV acyclovir and oral valacyclovir therapy in patients with ARN and reported a median IV treatment duration of 10 days (range: 7-12). Palay et al.[8] reported

treating ARN patients with IV acyclovir at a dose of 1500 mg/m^2/day for 7-10 days. In the present study, IV antiviral therapy was administered for longer than in other studies. Thirty-eight patients received IV acyclovir for a median of 16.2 days (range: 4-28), 4 patients received IV ganciclovir for a median of 20.8 days (range: 10-28), and 6 patients received IV acyclovir for a median of 40.3 days (range: 22-43) followed by IV ganciclovir due to persistent retinal necrosis. All patients continued with oral antiviral treatment after IV treatment. Retinal necrosis regressed completely after a mean of 31.3 days (range: 11-78) after the start of antiviral therapy. Our median duration of antiviral therapy may have been longer than in other studies because of the extent of retinal involvement at presentation.

Previous studies have reported the risk of RD development as 50-80%.[2,18,25,26] In their study, Meghpara et al.[19] found that eyes with >25% retinal involvement had a higher risk of developing RD, all eyes with >50% retinal involvement had optic nerve involvement at initial presentation, and greater extent of retinal involvement, which is also related to RD and optic nerve involvement, was associated with lower VA. Khochtali et al.[20] reported a high risk of RD development in eyes with >50% retinal involvement. In both studies, RD was not detected in any eye with <25% retinal involvement. Similarly, we observed that RD occurred at a higher frequency in the group with 3-4 quadrants of retinal involvement (66.7%). Unlike other studies, an eye in our study with 1 quadrant of retinal involvement developed RD, but unlike the group with extensive retinal involvement, the RD was localized and could be treated with retinal argon laser photocoagulation.

There was no significant difference between the two groups in terms of optic disc inflammation at the time of admission (Group A: 7/11, Group B: 19/45), and optic disc pallor was detected during follow-up in 36.4% (4/11) of the eyes in Group A and 71.1% (32/45) of the eyes in Group B ($p<0.05$). Unlike in the study by Meghpara et al.,[19] we found that eyes with 1-2 quadrants of retinal involvement also showed optic disc inflammation at initial presentation, but none had optic disc pallor. In the group with 3-4 quadrants of retinal involvement, eyes without optic disc inflammation at presentation also developed optic disc pallor over time. This suggests that the extent of retinal involvement at the time of admission is associated with the development of RD and optic disc pallor.

Studies have shown that VA worsens as the extent of retinal involvement increases.[19,20] Similarly, in this study, the group with 1-2 quadrants of retinal involvement had better mean BCVA than the other group at all visits, and 3-4 quadrants of retinal involvement was found to be associated with poor visual prognosis.

Study Limitations

PCR analysis of anterior chamber fluid could not be performed in all patients because it had not been widely adopted in our country early in the study period. Studies conducted with PCR analysis of anterior chamber fluid samples from all ARN patients may be useful in determining the relationship between widespread involvement of the pathogen and the prognosis of the disease and responses to treatment.

Conclusion

In conclusion, ARN is an ophthalmological emergency that requires immediate treatment after diagnosis. Delayed diagnosis and especially the administration of CS before starting antiviral therapy allow the retinal necrosis to spread. As greater extent of retinal involvement at presentation is associated with increased risk of complications and unfavorable visual prognosis, early diagnosis and prompt initiation of antiviral therapy are critical in terms of final vision.

Ethic

Ethics Committee Approval: İstanbul University, İstanbul Faculty of Medicine Ethics Committee, 2021/95-81693.

Informed Consent: Informed consent forms were obtained from all.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A.C., Z.C., M.O., N.K., İ.T.T., Concept: N.A.C., M.O., İ.T.T., Design: N.A.C., M.O., İ.T.T., Data Collection or Processing: N.A.C., M.E.G., Z.C., E.A., Analysis or Interpretation: N.A.C., M.E.G., Z.C., E.A., Literature Search: N.A.C., M.E.G., Writing: N.A.C., M.E.G., Z.C., E.A., M.O., N.K., İ.T.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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