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RETINAL DISORDERS

Association of retinal detachment with age 50 years or younger at onset in patients with acute retinal necrosis

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Abstract

Background Due to the guarded prognosis of acute retinal necrosis (ARN), it is relevant to develop a strategy to early categorize those patients in a higher risk of worse outcomes. The purpose of this study is to describe clinical features and predictive factors for retinal detachment (RD) in patients with ARN.

Methods Retrospective observational case series of 34 adult patients (38 eyes) with ARN examined between January 2005 and July 2015 in the National Eye Institute (Bethesda, USA), the Department of Ophthalmology, University of Chile (Santiago, Chile), and APEC (CDMX, Mexico).

Results A total of 16 males and 18 females with a mean age at presentation of 44.5 ± 16.8 years were included. Twenty-seven patients (79.4%) received intravenous acyclovir as first-line treatment, and 7 patients received either oral antiviral (4 patients) or oral plus intravitreal antiviral (3 patients). All subjects were treated with prednisone, with a mean initial dose of 57.7 ± 16.3 mg per day. Seventeen patients (50.0%) developed retinal detachment. An association of retinal detachment with age at onset was observed ($p = 0.04$), with patients younger than 50 years presenting a higher risk (OR = 14.86, $p = 0.0009$). Additionally, patients in this higher risk group had more inflammation in both anterior chamber and vitreous ($p = 0.04$ and 0.03, respectively). No other predictive factor for retinal detachment was found in the present study.

Conclusions RD represents an important complication in patients with ARN. Younger patients may be at higher risk of this complication, possibly secondary to the presence of a higher level of inflammation.

Key Messages:

- Rhegmatogenous retinal detachment (RD) may develop in up to 75% of patients with acute retinal necrosis(ARN) and it is one of the most important predictive factors of severe vision loss.
- RD was associated with age at onset. Patients with ARN aged 50 years or younger presented an increased risk of this complication.
- Patients with age 50 or younger had more degree of inflammatory findings at disease presentation, in both anterior chamber and vitreous.

Keywords Acute retinal necrosis · Predictive factors · Retinal detachment · Younger age

Background

Acute retinal necrosis (ARN) is an uncommon condition [1], characterized by intense intraocular inflammation and coalescent areas of retinal necrosis. It represents an emergency

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due to the high probability of rapid progression in the absence of appropriate early treatment [2].

Although a specific therapy is currently available, poor visual prognosis and severe complications have been extensively reported in patients with ARN [3, 4]. In this regard, rhegmatogenous retinal detachment (RD) resulting from retinal breaks in or near areas of necrosis may develop in up to 75% of these patients [5], and it is one of the most important predictive factors of severe vision loss [3, 6, 7], emphasizing the importance of such complications in this subset of patients.

Prophylactic laser retinopexy has been used for the prevention of RD in patients with ARN. However, there is no strong evidence that supports the efficacy of this treatment in reducing the risk of RD [8, 9]. The addition of intravitreal therapy to the standard treatment with systemic antiviral agents has shown a significant decrease in the RD rate [7, 10]. In addition, a greater rate of RD in ARN caused by the *Varicella zoster* virus (ARN-VZV) has been described [7].

In the present retrospective study, we evaluated functional outcomes and potential predictive factors for complications in patients with ARN, with an emphasis on RD.

Methods

A multicenter retrospective study of patients with diagnosis of ARN was conducted. Information was gathered from the database of the Department of Ophthalmology, University of Chile (Santiago, Chile), the National Eye Institute (NEI), National Institutes of Health (Bethesda, USA), and the Inflammatory Eye Disease Clinic, Asociacion para Evitar la Ceguera (APEC) (CDMX, Mexico), from January 2005 to July 2015.

All patients were seen under an Institutional Review Board–approved protocol at their respective clinics and the Ethics Committee of the University of Chile approved the study. The protocol fulfilled the tenets of the Declaration of Helsinki.

The inclusion criteria comprised the diagnosis of ARN, according to the criteria published by the American Uveitis Society [2, 11].

Patients were excluded if an alternative disease (i.e., syphilis, tuberculosis, toxoplasmosis) could explain the clinical manifestations diagnosed during the evaluation, or if fewer than 3 months of follow-up data in our institutions were available.

The following information were retrieved from the clinical records: age, gender, ocular findings at diagnosis (best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy (including AC cells and vitreous haze), and ophthalmoscopy under mydriasis), laboratory investigations (PCR analysis of intraocular fluids), treatment strategy (type, doses, and duration), length of follow-up, and complications, especially RD. In addition, the following information from 3-month and 6-month visits were evaluated: BCVA, intraocular inflammation parameters (AC cells, flare, and vitreous haze), recurrences, and complications. Initial or first-line therapy was defined as management indicated at the baseline diagnostic evaluation. Patients with persistent intraocular pressure above 21 mmHg were referred to a glaucoma specialist for complete evaluation and follow-up in order to perform a diagnosis of glaucoma or ocular hypertension.

BCVA cutoffs of 20/50 or less (low vision) and 20/200 or less (legal blindness) were used according to the recommendations of the SUN report [12].

Descriptive statistics were calculated for the whole cohort and groups, including calculating positional and dispersion parameters. Univariate analyses were performed using the non-parametric Mann–Whitney test and Fisher's exact test as appropriate. Cutoff for the higher RD risk age group was calculated using the receiver operating characteristic (ROC) curve, considering the point with the highest Youden's Index in order to maximize the sensitivity and the specificity. p values < 0.05 were considered statistically significant. Statistical analyses were accomplished using Prism 6 software (GraphPad Software Inc., La Jolla, CA, USA).

Results

A total of 34 patients with ARN (18 females, 16 males) were included in the study (five from NEI, 12 from APEC, and 17 from University of Chile). The mean age at presentation was 44.5 ± 16.8 years, and the duration of symptoms until diagnosis was 17.3 ± 10.9 days (range 2–52). Four patients had bilateral disease within 2 weeks after initial diagnosis despite being on systemic antivirals. Another patient had second eye involvement 2 years after initial evaluation, in spite of acyclovir prophylaxis.

PCR analysis for herpes viruses in the aqueous humor was performed in three of seventeen eyes at University of Chile and in four of five at NIH, and all seven returned positive. *Varicella zoster* virus (VZV) was the most frequent pathogenic agent detected (five eyes, mean patient age: 53.5 ± 8.1). The remaining two tested eyes were found positive for *Herpes simplex* virus (HSV) type 2.

As shown in Table 1, all subjects received oral prednisone with a mean initial dose of 57.7 ± 16.3 mg per day, and most patients were treated initially with intravenous acyclovir. Systemic steroids were added 4.2 ± 3.3 days after baseline evaluation.

At APEC and University of Chile, none of the subjects received intravitreal treatment as first-line therapy. By contrast, 4 out of 5 patients at NEI received intravitreal

Table 1 General features at diagnosis and treatment regimens in patients with acute retinal necrosis ($n=34$ pts—38 eyes)

Mean age ± SD, years, *n* pts	44.5 ± 16.8
Gender, *n* pts (%)	
Male	16 (47.1)
Female	18 (52.9)
Mean follow-up ± SD, months	37.9 ± 35.8
Mean duration of symptoms ± SD, days	17.3 ± 10.9
HIV positive, *n* pts (%)	1 (2.9)
BCVA, *n* eyes (%)	
20/40 or better	8 (21.0)
20/50 to 20/100	9 (23.7)
20/200 or worse	21 (55.2)
Initial antiviral treatment, *n* pts (%)	
Intravenous ACV	26 (76.4)
Intravenous ACV plus intravitreal injection*	1 (2.9)
Oral valacyclovir	4 (11.7)
Oral valacyclovir plus intravitreal injection*	2 (5.9)
Oral valganciclovir plus intravitreal injection*	1 (2.9)
Prednisone, *n* pts (%)	34 (100)
Mean initial dose ± SD, mg	57.7 ± 16.3
Mean treatment length ± SD, months	4.6 ± 3.4
Prophylactic laser retinopexy, *n* pts (%)	16 (47.0)

*Foscarnet 1.2 mg or ganciclovir 2 mg

ACV acyclovir, *SD* standard deviation, *pts* patients, *BCVA* best-corrected visual acuity

ganciclovir and/or foscarnet as first-line therapy in addition to systemic antivirals. During follow-up, six more subjects received intravitreal ganciclovir. Patients were treated as follows: 4 subjects with 1 injection, 1 subject with 2 injections, 1 subject with 8 injections, and 4 subjects with 3 injections. There was a tendency to a higher rate of low vision and legal blindness among patients who did not receive intravitreal drugs, although this did not reach statistical significance. At 3 months, 74.1% and 66.7% of eyes that did not receive intravitreal antivirals had low vision and legal blindness, respectively, versus 63.6% and 45.4% of eyes treated with intravitreal antivirals. At 6 months, low vision and legal blindness were seen in 63.0% and 59.2% of eyes that did not receive intravitreal antivirals versus 45.4% and 36.4% of eyes treated with intravitreal antiviral agents. Three out of eleven eyes (27.2%) in the intravitreal group presented with RD in comparison to 15 out of 27 eyes (55.5%) in the "no intravitreal" group ($p=0.16$, Fisher's exact test).

At 3 months, low vision was found in 27/38 eyes (71.1%) and legal blindness in 23/38 eyes (60.5%). Similarly, at 6 months, low vision was found in 22/34 eyes (64.7%) and legal blindness in 20/34 eyes (58.8%). There were four subjects who did not have the 6-month follow-up visit; thus, functional outcomes were evaluated in 34 eyes at this time point.

The most frequent complication was cataract (28 out of 38 eyes), followed by RD, which presented in 18 eyes (47.8%) during follow-up. The median time to incident RD was 42 days (range 0–217) after baseline evaluation. Other significant complications were glaucoma (seven eyes), ocular hypertension (11 eyes), and epiretinal membrane (seven eyes).

In order to study the possible factors associated with poor functional outcomes, we evaluated the role of these complications in this cohort. In subjects with legal blindness at 3 months, RD was reported in 15 out of 23 eyes (65.2%), versus three out of 15 eyes (20.0%) with no legal blindness at 3 months ($p=0.009$, Fisher's exact test). Similarly, in patients with legal blindness at 6 months, 15 out of 20 eyes (75.0%) had RD in comparison to three out of 14 eyes (21.4%) with no legal blindness at 6 months ($p=0.004$, Fisher's exact test).

In addition, RD was found in 15 out of 27 eyes (55.5%) with low vision versus the "not low-vision" group, who had RD in three out of 11 (27.3%), at the 3-month evaluation. In patients with low vision at 6 months, 15 out of 22 eyes (68.2%) had RD, versus three out of 12 eyes (25.0%) with no low vision ($p=0.03$, Fisher's exact test). There were no significant associations between other complications, such as cataract and ocular hypertension, and vision or treatment type (data not shown).

Prophylactic laser retinopexy was performed in 17 eyes (44.7%), and no impact of this procedure on RD rate was observed. Ten out of 17 (58.8%) laser-treated eyes presented RD and 8/21 (38.1%) in the "no laser" group ($p=0.33$, Fisher's exact test). The median time elapsed to laser treatment from the first visit was 21.0 days (range 0–115). Among laser-treated eyes, there was not a significant difference in laser treatment timing between the RD and no RD groups (data not shown). Furthermore, we compared levels of inflammatory activity (AC cells and vitreous haze) between the prophylactic laser group and no laser group. A median of 2 + AC cells and 2 + vitreous haze was found in both laser and no laser groups ($p=0.99$ and $p=0.83$, respectively).

In order to establish predictive factors for RD, clinical and demographics data were evaluated (Table 2). In this regard, subjects who presented with RD in the follow-up were significantly younger (mean age of 39.2 ± 16.7 years old versus 49.9 ± 15.6 years old, respectively; $p=0.04$, Mann–Whitney test). Additionally, posterior vitreous detachment (PVD) was evaluated in 33 patients (36 eyes), since this information was missing for one patient. No significant differences were observed in the number of eyes with PVD in both groups (9 out of 16 eyes in the RD group and 7 out of 20 eyes in the no RD group, $p=0.31$). Accordingly, a cutoff age of ≤ 50 years for age-related increased risk of RD was defined by performing a ROC curve analysis (area under the curve = 0.70, $p=0.04$) (Fig. 1). In that sense, the risk of RD in ≤ 50 years

Table 2 Acute retinal necrosis: univariate analysis of prognostic factors for retinal detachment

Characteristic	Retinal detachment		*p* value
	Present (17 patients, 18 eyes)	Absent (17 patients, 20 eyes)	
Mean age ± SD, years, *n* pts	39.2 ± 16.7	49.9 ± 15.6	0.04*
Gender—male, *n* pts (%)	8 (47.0)	8 (47.0)	1.0
Mean duration of symptoms ± SD, days	15.8 ± 9.8	19.0 ± 12.0	0.34
AC cells, mean ± SD (*n* eyes)	2.1 ± 1.0 (18)	1.7 ± 1.3 (20)	0.31
Vitreous haze, mean ± SD (*n* eyes)	2.0 ± 0.9 (18)	1.7 ± 1.0 (20)	0.44
Prophylactic laser retinopexy, *n* pts (%)	10 (58.8)	6 (35.3)	0.30
First-line treatment, *n* pts (%)			1.00
ACV IV	14 (82.3)	13 (76.5)	
No ACV IV	3 (17.6)	4 (23.5)	

SD standard deviation, *AC* anterior chamber, *ACV IV* intravenous acyclovir treatment

*$p < 0.05$

old patients was calculated as OR = 14.86 (2.62–84.14, $p = 0.0009$) (Table 3).

Finally, a characterization of this higher risk subset of patients was carried out. In that sense, the cohort was divided into 2 age groups (≤ 50 and > 50 years old subjects), and inflammatory activity was compared between both groups. We observed that younger ARN patients (≤ 50 years old) had significantly more inflammation in both AC and vitreous humor ($p = 0.04$ and $p = 0.03$, respectively, Mann–Whitney test) (Table 4).

Discussion

Despite the availability of a specific therapy, ARN remains a severe disease with poor functional outcomes [3, 4]. Consistent with previous reports, we reported low vision in 71.1% and legal blindness in 60.5% of eyes at 3 months, with similar values reported at 6 months after presentation (low vision: 64.7% and legal blindness: 58.8%).

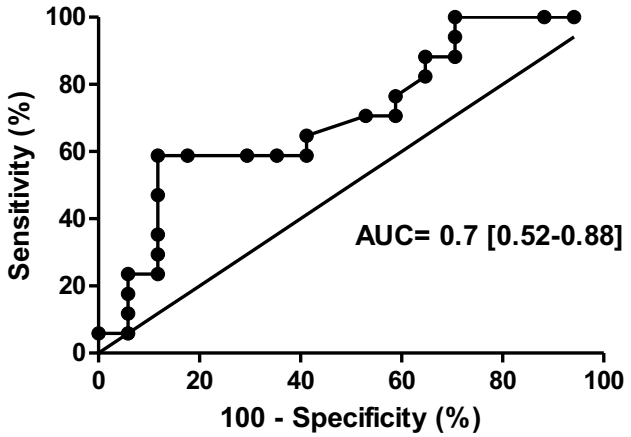

Fig. 1 Utility of age as a predictive factor of retinal detachment in a multicentric case series of patients with acute retinal necrosis. Receiver operating characteristic curve evaluating the performance of age to determine the risk of retinal detachment in acute retinal necrosis. AUC, area under the curve [95% confidence interval]

Several clinical variables have been associated with poor visual outcomes elsewhere. In this regard, the occurrence of RD has become one of the most important determinants of vision loss. Roy et al. reported that RD was the primary cause of unfavorable visual outcomes in patients with ARN [3]. Similarly, Butler et al. [13] found that this complication was the strongest determinant of vision loss, and the extent of retinitis involvement at presentation would increase the risk of RD and poor outcomes [14]. In the present study, we reported a higher incidence of RD in patients with legal blindness or low vision during follow-up (specifically at 3-month and 6-month time points).

Given the correlation of RD with poor visual outcome in patients with ARN, predictive strategies and preventative measures, including therapeutic approaches, are desirable [14]. Our results show a slight trend toward better functional outcomes in patients receiving intravitreal antivirals. Yeh et al. found a significantly lower incidence of RD and a greater rate of visual improvement in patients treated with intravitreal foscarnet (2.4 mg/0.1 ml) [10]. Similarly, Wong et al. described a lower RD rate in intravitreal-treated

Table 3 Accuracy of age at presentation as a predictor of retinal detachment in patients with acute retinal necrosis

		Retinal detachment		
		Present	Absent	
Age	≤ 50 yo	16	7	23
	> 50 yo	2	13	15
	Total	18	20	38

Odds ratio: 14.86 (2.62–84.14); sensitivity: 88.89% (65.29–98.62); specificity: 65% (40.78–84.61)

Table 4 Acute retinal necrosis: clinical features of the higher risk age group (≤50 years old) for retinal detachment

Characteristic	Higher risk age group (≤50 years old)		*p* value
	Yes (22 patients, 23 eyes)	No (12 patients, 15 eyes)	
Gender—male, *n* pts (%)	11 (50.0)	5 (41.7)	0.73
Mean duration of symptoms ± SD, days (*n* pts)	14.4 ± 6.3	23.2 ± 15.5	0.16
AC cells, mean ± SD (*n* eyes)	2.2 ± 1.1	1.4 ± 1.1	0.04*
Vitreous haze, mean ± SD (*n* eyes)	2.2 ± 0.9	1.4 ± 0.9	0.03*
First-line treatment, *n* patients (%)			0.68
ACV IV	18 (81.8)	9 (75.0)	
No ACV IV	4 (18.2)	3 (25.0)	

SD standard deviation, *AC* anterior chamber, *ACV IV* intravenous acyclovir treatment

*$p < 0.05$

patients as well as a highly significant correlation between this complication and final BCVA [7].

In addition, prophylactic laser retinopexy has been advocated as a potential intervention to decrease the occurrence of RD in patients with ARN. However, results have shown no consistency among published case series [8, 9]. In this study, we were not able to demonstrate an advantage of performing laser treatment for prevention of RD. Importantly, a possible explanation for indication of laser could be some variables that impact on the feasibility of the procedure, such as inflammation grade or the presence and severity of media opacity [8]. Here, no differences in levels of AC inflammation and vitreous haze between the prophylactic laser group and no laser group were found.

Yeh et al. reported a higher incidence of RD in patients receiving prednisone [10]. This observation may be considered as likely to be due to selection bias, in the context that increased inflammation could determine greater use of prednisone and, importantly, an increment in the RD rate. In our case series, we did not have steroid therapy as a possible confounding variable due to the fact that all patients received prednisone. In this setting, we found a specific group of patients, comprised of subjects younger than 50 years old, who presented a higher risk of RD. Moreover, after making a clinical characterization, we found that those younger subjects had higher levels of inflammation in both the AC and vitreous humor (Table 4).

Another possible explanation for our findings, regarding the higher risk group, may be virus etiologies. Wong et al. showed a significant greater RD rate in patients with ARN-VZV in comparison to ARN secondary to HSV infection (ARN-HSV) [7]. Van Gelder et al. evaluated the mean age of presentation of ARN related to both VZV and HSV. By combining their data with previous reports, a mean age of 52.4 years and 33.5 years was found for VZV and HSV cases (type 1 or 2), respectively, similar to the ages reported by Wong et al. (51 years and 34 years, respectively) [7, 15]. However, our data suggest younger patients (≤50 years) may be at increased risk of RD. Therefore, younger age, which would be more common with ARN-HSV, as a new predictive factor for RD is likely independent of viral etiology, and possibly related to increased levels of intraocular inflammation.

It has been reported that younger patients undergoing cataract surgery have a significant higher risk of RD after the procedure (hazard ratio = 9.43), probably due to the absence of PVD, a known protective factor for RD [16]. In addition, the mean age of presentation of PVD in patients with uveitis has been calculated as 47.3 years in a large cohort published elsewhere [17]. Also, Labalette et al. (2002) found that the majority of patients with another infectious etiology of uveitis, which was toxoplasmosis, presented a high rate of PVD in those more than 50 years old [18]. Therefore, based on these reports, it may be possible that PVD plays a role in the pathogenesis of RD in patients with ARN. This could be related to the fact that younger individuals have stronger vitreoretinal attachment [19].

Based on our findings, age equal or less than 50 years at disease onset may be an additional risk factor for RD in ARN, possibly related to the absence of PVD, although no association between RD and PVD was found in the present study. In addition, this subset of younger patients may present with higher levels of inflammation and, thus, more aggressive therapy should be considered in these subjects.

In summary, here we find that young age appears to be associated with a higher likelihood of RD. As with all retrospective studies, our study has inherent limitations, for example the small sample size. In this regard, there was a myriad of treatment schemes (i.e., drug type, number of injections) in patients who received other therapies than intravenous acyclovir. Therefore, it was not feasible to evaluate the role of specific treatment in relevant outcomes, such as complications or second eye involvement. Also, in the present case series, majority of cases were not PCR confirmed as PCR testing was not widely available at one of the centers (University of Chile).

In conclusion, we described a multicenter case series of patients with ARN, and we found poor visual outcomes, especially in patients who developed RD. In addition, younger age (50 years old or less) showed to be a risk factor of RD, the major cause of vision loss.

Abbreviations ARN: Acute retinal necrosis; RD: Retinal detachment; VZV: *Varicella zoster* Virus; NEI: National Eye Institute; APEC: Asociacion para Evitar la Ceguera; BCVA: Best-corrected visual acuity; ROC: Receiver operating characteristic curve; HSV: *Herpes simplex* Virus; PVD: Posterior vitreous detachment

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate All patients were seen under an Institutional Review Board–approved protocol at their respective clinics and the Ethics Committee of the University of Chile approved the study (ID: 0062019). The protocol fulfilled the tenets of the Declaration of Helsinki.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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