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RETINAL DISORDERS

Visual outcome and poor prognostic factors in acute retinal necrosis syndrome

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Abstract

Objective To evaluate the impact of selected clinical parameters on the mid-/long-term visual outcome of patients with acute retinal necrosis (ARN)

Design A retrospective cohort study

Methods

Setting Two University Hospitals (Parma, Italy; Lausanne, Switzerland).

Participants Thirty-nine non-HIV patients (39 eyes) with ARN, as confirmed by polymerase chain reaction on intraocular samples. The following potential predictors were tested using linear regression models: age, sex, etiology, best-corrected visual acuity (BCVA) on admission, delay between ARN symptom onset and treatment initiation, and surgery (performed or not).

Main outcome BCVA at the final follow up

Results Thirty-nine of 39 non-HIV patients (22 men and 17 women; mean age, 50 years) diagnosed with ARN were enrolled in the study. Etiologies were: varicella-zoster virus in 25 eyes (64%), herpes simplex viruses in the remaining 14 eyes. The average follow-up duration was 19 ± 13 months. All patients had undergone systemic antivirals; surgery was performed in 16 eyes. The mean delay between onset of visual symptoms and antiviral treatment initiation was 15 ± 31 days (range, 1–180 days). The mean BCVA at baseline was 0.83 ± 0.75 logMAR, while the mean final BCVA was 0.75 ± 0.81 logMAR. Both initial BCVA and treatment delay (TD) were significantly correlated with the final BCVA ($p < 0.05$).

Conclusions Initial BCVA and TD seem to be significant predictors of mid-/long-term visual outcome in non-HIV patients affected by ARN.

Keywords Acute retinal necrosis (ARN) · Visual outcome · Predictors · Treatment

Introduction

Acute retinal necrosis (ARN) is an uncommon but potentially blinding ocular inflammatory syndrome that most commonly affects otherwise healthy, non-HIV adults, with no predilection for gender or race. Whether considered an independent clinical entity, or as part of the spectrum of necrotizing herpetic retinopathies, ARN has clear causative agents and diagnostic criteria, as formerly described by Holland [1], Ganatra et al. [2], and Hillenkamp et al. [3]. ARN is a developing full-thickness retinal necrosis caused by intraocular active replication of herpes viruses (simplex and zoster) or cytomegalovirus (CMV). The latter typically affects highly immunocompromised subjects who may also experience the clinical variant progressive outer retinal necrosis (PORN). In herpetic necrotizing retinopathies, the spectrum of herpes-induced disease is influenced by the immune status of the host, as described by Guex-Crosier et al. [4]. Epstein-Barr virus (EBV) may also be a minor causative agent for ARN.

The clinical presentation of ARN is characterized by peripheral occlusive arteritis and phlebitis of the retinal and choroidal vasculature, confluent necrotizing retinitis, and an inflammatory reaction in the vitreous and anterior chamber. Ocular involvement typically begins in the peripheral retina

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but rapidly extends posteriorly. ARN usually presents unilaterally, but rapid involvement of the fellow eye may occur, mostly in cases receiving improper and/or delayed treatment. Bonfilioli and Eller [5] stated that immunocompromised patients, however, have a higher rate of bilateral involvement (about 90%). Despite such established etiological and clinical features, the therapeutic approach is not so uniform, mostly with regard to intervention timing and surgical management strategies. Medical treatment is based on a viral encephalitis regimen involving an initial intravenous phase targeted against the isolated/suspected agent, followed by several months of oral administration. High dose of only oral regimen and/or adjunctive local therapy may also be considered [6–9]. Rhegmatogenous retinal detachment (RD), often complicated by proliferative vitreoretinopathy, occurs in up to 75% of ARN patients. Wong et al. [10] and Butler et al. [11] showed that RD development is the greatest determinant of adverse visual outcome.

Our study included all cases of confirmed ARN in non-HIV subjects recorded from two tertiary referral centers. Demographics, clinical characteristics upon admission and at the end of each patient's follow-up, the delay between onset of symptoms and antiviral treatment initiation, whether surgery was performed or not, were evaluated with respect to final visual acuity to statistically evaluate the impact of these factors on final best-corrected visual acuity (BCVA).

Patients and methods

This was a two-center retrospective cohort study on non-HIV patients with a diagnosis of ARN who were treated at the University hospitals in Parma (Italy) and Lausanne (Switzerland) between January 2005 and December 2018. We reviewed hospital charts to select ARN cases with positive PCR results on ocular sampling of the affected eye and with at least 3 months follow-up. Exclusion criteria were positive HIV blood test, which was performed in all cases of PORN or in the presence of extensive retinal necrosis; major surgery or antineoplastic treatments within 12 months prior to ARN onset; and history of organ transplantation or ongoing immunosuppressive treatment. In cases of a very long-term follow-up, final data were collected within a maximum of 40 months from diagnosis. The study was approved by each local Ethics Committee (i.e., Parma, Italy ID: 1058/2018; Lausanne, Switzerland ID: 2019-00322).

The following data were collected: demographics, ocular samples PCR result (on aqueous samples in all patients and on vitreous samples when performed), the delay (days) between onset of ARN symptoms and initiation of systemic antiviral treatment, initial and final BCVA, the execution of pars plana vitrectomy (PPV), and onset of complications that may influence visual prognosis (e.g., RD, recurrence, vitreous hemorrhage, concomitant infection). For BCVA assessment Snellen values were converted into the logarithm of the minimum angle of resolution (logMAR). Non-numerical acuities were converted using an arbitrary scale as used in the series by Martinez-Serrano et al. [12]: counting fingers, 1.7 logMAR; hand movements, 2.0 logMAR; light perception, 2.3 logMAR; no light perception, 3.0 logMAR.

Statistics

The mean ± standard deviation and ranges were used for descriptive analysis. In order to preserve data's statistical independence, in the case of bilateral involvement, only one eye (OD/OS) was randomly selected for inclusion. The paired *t* test was used for BCVA comparison, once checked the appropriate numerousness and the normal distribution of the values. The Pearson's Chi-squared test with Yates' continuity correction was used for categorical data (e.g., gender and surgery). To evaluate variables possibly predictive of final BCVA, analyses were conducted by means of linear regression models in the R Cran environment (https://cran.r-project.org/ ver. 3.4.0) [13].

A full regression model was first performed to assess correlations between final BCVA and seven predictor variables: age, sex, causative virus, delay between symptom onset and systemic antiviral therapy, initial BCVA, and RD surgery (yes or no). For each predictor, the corresponding *p* value was calculated: a low *p* value indicated that the considered variable likely provided a substantial addition to the model. Along with the conventional statistical significance (*p* value), other statistical criteria were used to evaluate the model's goodness of fit. These included residual standard error (RSE), R^2, and adjusted R^2. In order to further inspect the most important predictive variables, different reduced models (with a number of variables lowering up to 3) were implemented by a stepwise selection procedure, taking into account the corresponding adjusted R^2 and the residual sum of squares (RSS) values. The reduced model with the highest adjusted R^2 value, but not significantly different from the full model in terms of *p* value (i.e., $p > 0.05$ with ANOVA analysis), was accepted as the best parsimonious (reduced) fit of the data.

Results

Fifty-one eligible patients were identified in our electronic database. Among these, 12 were excluded because they did not fulfill the study criteria. In particular, 5 subjects for unavailable medical record (deceased patients); 4 subjects for positive HIV test; and 3 patients for recent neoplastic surgery and/or treatment. Thirty-nine eyes from 39 patients were included in the study. The cohort consisted of 22 men (56%) and 17 women (44%): mean age, 50 years; and age range, 8–

Table 1 Demographics and major explanatory variables

Eyes	Sex	Age	Trt. delay (days)	AH PCR	iBCVA (logMAR)	fBCVA (logMAR)	PPV	F-U (months)
1	M	78	8	VZV	1.20	0.10	Y	9
2	F	60	7	HSV	1.00	0.10	NP	17
3	F	46	3	HSV	0.40	0.20	NP	31
4	M	31	45	VZV	0.84	0.60	Y	7
5	M	37	21	HSV	0.74	0.90	Y	8
6	M	61	18	VZV	0.70	0.90	Y	15
7	F	61	64	VZV	1.30	1.50	Y	18
8	F	39	7	HSV	0.20	0.00	NP	22
9	F	25	3	VZV	0.50	0.00	NP	12
10	M	57	5	VZV	1.70	1.50	NP	3
11	F	42	5	HSV	0.30	−0.10	NP	7
12	M	40	1	VZV	0.12	0.00	NP	12
13	F	83	1	VZV	3.00	2.30	NP	36
14	F	57	4	VZV	0.12	0.00	NP	12
15	M	71	4	VZV	2.00	0.00	Y	30
16	F	45	23	VZV	0.80	1.00	Y	6
17	F	50	12	VZV	0.00	0.00	Y	24
18	M	44	9	VZV	0.22	0.52	Y	36
19	M	75	7	VZV	0.30	1.00	NP	3
20	M	60	10	VZV	0.22	1.70	Y	34
21	F	42	4	HSV	0.40	0.40	Y	37
22	F	47	7	HSV	0.92	1.00	Y	33
23	F	54	3	VZV	1.00	0.10	NP	3
24	F	80	7	HSV	0.53	0.30	NP	3
25	F	82	2	HSV	0.80	0.40	NP	36
26	M	15	3	VZV	1.00	0.50	NP	18
27	M	8	14	VZV	2.30	2.30	NP	3
28	M	43	180	HSV	2.30	3.00	NP	3
29	M	49	1	VZV	1.70	1.70	Y	36
30	M	64	14	VZV	0.05	0.00	NP	3
31	M	16	60	HSV	0.05	0.26	NP	31
32	M	33	1	HSV	0.00	0.00	NP	35
33	M	71	1	VZV	1.70	0.70	NP	8
34	M	44	10	VZV	0.70	0.40	Y	35
35	F	32	9	VZV	0.70	1.00	NP	36
36	M	39	7	VZV	0.00	0.10	NP	34
37	M	71	5	HSV	0.60	1.70	Y	5
38	M	55	3	VZV	0.15	1.00	NP	36
39	F	42	7	HSV	2.00	2.30	Y	8

M, male; *F*, female; *AH*, *aqueous humor; PCR*, polymerase chain reaction result; *HSV*, herpes simplex virus; *HZV*, herpes zoster virus; *Trt. D*, treatment delay; *iBCVA*, initial best corrected visual acuity; *fBCVA*, final best-corrected visual acuity; *PPV*, pars plana vitrectomy; *Y*, performed; *NP*, not performed; *F-U*, follow-up

83 years. The mean duration of the follow-up was 19 ± 13 months (range, 3–37 months). Demographic information and all other collected data are summarized in Table 1. Based on aqueous PCR results, the etiologies were varicella-zoster virus (VZV) in 25 eyes (64%) and herpes simplex viruses (HSV1 / 2) in the remaining 14 eyes (36%). No statistic difference was found between these two groups in terms of demographics and outcomes. No cases of CMV or EBV were recorded in our series. Vitreous samples PCR was performed in only three of the 16 operated eyes, the samples being

withdrawn at the beginning of the PPV. Viral DNA identification was obtained in one sample (VZV).

With regard to antiviral treatment, all VZV and HSV patients underwent an intravenous acyclovir regimen for 2 weeks (10 mg/kg every 8 h), followed by oral therapy for at least 1 year. No intraocular antiviral injections were performed. Systemic corticosteroids were administered according to the European guidelines on the management of Herpes Zoster (therapy of ARN section) in 11 subjects (28%). Therapy was limited to a short induction period (median time of corticosteroid therapy limited to 15 days; with a median dosage of less than 0.3 mg/kg) after initiation of antiviral therapy [14].The mean delay between the reported onset of visual symptoms and the beginning of antiviral treatment was 15 ± 31 days (range, 1–180 days). Surgery consisting of PPV with lensectomy, extensive endolaser treatment, and silicon oil (polydimethylsiloxane) tamponade was performed in the following scenarios: (A) in the presence of RD and/or (B) in the event of non-visualization of the fundus due to vitreous opacity. Based on these findings, sixteen eyes (41%) underwent surgery (in 7 eyes was present the condition A; in 1 eye the condition B; in 8 eyes both A and B). Only one eye, with very late referral (180 days) and presenting a total funnel-shaped retinal detachment, did not undergo PPV due to the lack of any chance of recovery. A first attempt at silicone oil removal was performed in all operated cases after at least 6 months following the initial surgery. Thirteen eyes needed additional PPV because of recurrent RD or new vitreous hemorrhage. In 4 eyes (25%), the silicon oil was still present at the end of the considered follow up.

Taking the cohort as a whole, no statistical significance was found in the improvement from a mean initial BCVA of 0.83 ± 0.75 logMAR to the final 0.75 ± 0.81 logMAR. Under selective analysis of the eyes presenting at least one RD, however, these with a mean final BCVA of 1.10 ± 0.83 logMAR and the difference between the latter and the non-detached eyes tested significantly ($p = 0.02$). As detailed in the Methods section, all categorical and continuous explanatory variables listed in Table 1 were correlated to the final BCVA (the outcome variable). The full model showed very high statistical significance for the initial BCVA ($p < 0.000$) and borderline significance for the treatment delay (TD, $p = 0.053$). The stepwise reducing procedure is identified as best parsimonious model (in terms of adjusted R^2 and RSS), the one including the following three variables: TD, initial BVCA, and surgery (see Table 2). In this model, TD achieved full statistical significance ($p = 0.016$), while surgery remained under the threshold of significance. The initial BCVA significance was fully confirmed ($p < 0.000$).

Table 2 Significance of the predictors tested in the "best reduced" model

Predictor	Full Model Multiple R^2, 0.570 Adjusted R^2, 0.490 RSE, 0.575 p value[(a)]	Best reduced model Multiple R^2, 0.561, Adjusted R^2, 0.523 RSE, 0.556 p value[(a)]
Gender	0.434	–
Age	0.818	–
T_delay	0.053	0.016*
Agent	0.690	–
iBCVA	2.33e-05**	1.01e-05**
Surgery	0.286	0.248

ANOVA comparison between models has p = 0.864

RSSfull_model = 10.576, RSSred_model = 10.819

[(a)] p value significance codes: * "< 0.05"; ** "< 0.01"

T_delay, treatment delay; *iBCVA*, initial best corrected visual acuity

Discussion

Although ARN syndrome was first described over 40 years ago, the topic is still of interest, as evidenced by the many articles recently published in ophthalmologic and medical science journals [8, 11, 15–18]. The difficulties in entirely understanding this disease are probably due to its rarity (approximately 1 case per 1.6 to 2.0 million population per year), protean clinical pattern, and different options for medical and surgical treatment [9, 19].

The purpose of this study was to explore any possible correlation between visual prognosis, defined as BCVA at the maximum follow-up accepted for the study and potential predictors, such as demographics, causative virus, visual acuity prior to antiviral treatment initiation, and indications for surgery. Given the retrospective nature of the study, we sought to increase its robustness (1) by enrolling a substantial number of cases in consideration of the rarity of the disease and (2) by achieving a high homogeneity in the selection of the cohort. This chiefly refers to the inclusion of cases of non-HIV hosts alone for whom the viral etiology was confirmed on ocular samples. We also emphasize the importance of consistent management in terms of both the clinical (same systemic protocol, no intravitreal antiviral therapies) and surgical (same four surgeons, all following the same surgical protocol) aspects.

Among the predictors tested, initial BCVA showed a strong significant correlation with final BCVA in the full regression model. This evidence, confirmed by Lei and coauthors in a recent article [20], might be quite easily predictable and explainable by a certain level of dependency between two variables. The model may have been affected by a markedly elevated final BCVA starting from a good baseline or a poorer

final BCVA but starting from a lower baseline (i.e., BCVA differential was accounted for).

The treatment delay (TD) was the second variable with notable correlation. Conversely, there were very little correlations between final BCVA and age at disease onset, sex, and viral infection etiology. The best parsimonious model included the following three variables: TD, initial BVCA, and surgery. In this model TD showed a statistically significant correlation ($p = 0.016$). To our knowledge, this is the first evidence of any such clear correlation. The influence of initial BCVA was confirmed, while the requirement of surgery, based on the abovementioned criteria, still tested non-significant.

Other studies such as those by Hillenkamp et al. [3] and Ishida et al. [21] assessed the effect of the execution (yes or no) and timing of the PPV on the visual prognosis, without conclusive results. Our results align with recent observations that development of RD was among the greatest determinants of adverse VA [11, 18]. This can be accounted for by reference to the correlation between a poor visual outcome and delayed systemic treatment, and we can also hypothesize that a longer delay may favor the development of RD. Another important conclusion of Butler and coauthors [11] was that risk of development of RD, this associated with high probability of a poor visual outcome, remains low if the disease is controlled when less than 25% of the retina is involved.

In conclusion, the present study showed that in non-HIV subjects treated according to standard protocols for medical and surgical management of ARN, the BCVA prior to initiation of a specific systemic antiviral treatment and the treatment delay were statistical predictors of mid-/long-term visual outcome in affected eyes. This underscores the importance of implementing diagnostic procedures in each case of suspected ARN, in order to promptly start specific antiviral treatment.

The possibility that other environmental, clinical, or genetic factors play a key role in affecting the final BCVA cannot be excluded. Additionally, if the so-called slow-type or indolent form of ARN is present, a more benign course is expected, not strictly related to treatment delay. Genetic typing in large cohorts of patients may provide crucial information on the risk of developing ARN once the patient is infected or on the severity of the disease.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of each local Ethics Committee (i.e., Parma, Italy, ID: 1058/2018; and Lausanne, Switzerland, ID: 2019-00322) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all available individual participants included in the study.

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