Varicella-zoster virus as a causative agent of acute retinal necrosis in younger patients

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Abstract

Background: Herpes virus is considered to be the pathogen of acute retinal necrosis (ARN) infection. Previous studies have found that patients with ARN caused by the varicella-zoster virus (VZV) are often older, and patients with herpes simplex virus (HSV) induced ARN are considerably younger. However, in our clinical work, we find that VZV is also a pathogen in younger ARN patients. We, therefore, aimed to analyze the common etiology of younger ARN patients.

Methods: A retrospective analysis was made of 20 eyes (18 patients) diagnosed as having ARN in the Department of Ophthalmology of Peking Union Medical College Hospital from 2014 to 2016. All patients were reviewed for demographic data, clinical course, clinical manifestations, time from onset to initial physician visit, duration of follow-up, visual acuity at both presentation and final visit, and treatment strategies. A paired *t* test was used to compare visual acuity between the presenting vision and those of final follow-up. Vitreous or aqueous specimens from 18 eyes of 18 patients were analyzed with multiplex polymerase chain reaction (mPCR)/quantitative PCR (qPCR) and xTAG-liquid chip technology (xTAG-LCT) to determine the causative virus of ARN.

Results: Final best visual acuity (BCVA) improved significantly from 1.36 ± 0.95 (median 20/400) to 0.95 ± 0.82 (median 20/100) ($t = 2.714$, $P = 0.015$) after systemic and intravitreal antiviral treatment combined with or without pars plana vitrectomy. PCR and xTAG-LCT results showed four of the five samples in the younger group (32.2 ± 5.2 years) and 12 of the 13 samples in the senior group (53.6 ± 4.9 years) were positive for VZV, and two of the five samples in the younger group were positive for HSV-1.

Conclusions: This study demonstrates that VZV is also a common causative virus for ARN in younger patients. Considering this finding, a systemic antiviral treatment protocol should be immediately changed to intravenous ganciclovir when the patient does not respond to acyclovir before determining the causative virus, especially in younger patients.

Keywords: Retinal necrosis syndrome; Acute; Varicella zoster virus infection; Simplex virus; Ganciclovir; Acyclovir

Introduction

Acute retinal necrosis (ARN) was first described by Urayama in 1971 in Japan as an acute diffuse necrotizing retinitis with panuveitis progressing to retinal detachment.[1] The standard diagnosis for ARN from the American Uveitis Society clinical criteria in 1994 is primarily based on ocular manifestations.[2] However, when clinical manifestations are atypical, misdiagnosis often occurs, which may lead to delayed or incorrect therapy. Therefore, the Japanese ARN Study Group added etiology into the ARN criteria in 2015.[3] Etiological studies indicated that the leading cause of ARN is varicella-zoster virus (VZV, over 50%) followed by herpes simplex virus (HSV)-2 (5.1%) and HSV-1 (3.5%). Also, ARN may rarely be caused by cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Previous studies demonstrated that patients with ARN due to the VZV are often older, and patients with HSV-induced ARN are considerably younger.[4,5] In this study, we described 18 cases of ARN in the Department of Ophthalmology of Peking Union Medical College Hospital, and VZV was also a common pathogen of ARN in the younger group.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K659). As a retrospective study and data analysis

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were performed anonymously, this study was exempt from the informed consent from patients.

Study population and laboratory assessments

A retrospective analysis was made of 20 eyes (18 patients, nine males and nine females) diagnosed as having ARN in the Department of Ophthalmology of Peking Union Medical College Hospital from 2014 to 2016. Diagnosis of ARN was based on American Uveitis Society clinical criteria.[2] The records of all ARN patients were reviewed for demographic data, clinical course, clinical manifestations, time from onset to initial physician visit, duration of follow-up, visual acuity at both presentation and final visit, and treatment strategies. Specifically, eighteen vitreous or aqueous specimens from 18 eyes of 18 patients were analyzed by multiplex polymerase chain reaction (mPCR)/quantitative PCR (qPCR) and xTAG-liquid chip technology (xTAG-LCT) to determine the causative virus of ARN. All patients provided informed consent before anterior chamber paracentesis, vitreous paracentesis, or pars plana vitrectomy (PPV) for pathogenic detection. xTAG-LCT is a kind of liquid-phase array technology that could be a useful alternative for etiological diagnosis of ARN, which was introduced in our previous study.[6] A visual acuity of "counting fingers (CF)" or "hand motion (HM)" was recorded as 20/2000 and 20/20,000, respectively.[7] Since light perception (LP) and no light perception (NLP) are not actually visual acuity measurements but simply the detection of a stimulus, visual acuities of LP and NLP in this study were excluded for statistical analysis.[8]

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) when normally distributed and as the median when not normally distributed. A Kolmogorov-Smirnov test was used to test the parameter distribution. A paired *t* test was used to compare visual acuity between the presenting state and final follow-up state. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered to be statistically significant for all analyses.

Results

The patients were classified into a younger group (age ≤ 38 years, two males and three females) and a senior group (age > 38 years, seven males and six females). The ages of the two groups were 32.2 ± 5.2 years (range 31–38 years) and 53.6 ± 4.9 years (range 46–62 years), respectively. The left eye was affected in eight of 18 cases, and there were two cases of bilateral ARN. The mean disease duration at presentation and mean duration of follow up were 19.9 ± 9.7 (range 7–45) days and 15.5 ± 8.2 (range 4–41) months, respectively [Table 1].

Three of five patients in the younger group had documented histories, including one with viral meningitis 3 years ago (case 1); one with epilepsy 1 year ago (case 3); and one with a history of several facial plastic surgeries (case 5). There was no specific virus infection or surgery history in the senior group, except for one male patient with a fever 5 days before onset of ocular symptoms (case 9), two cases with a history of diabetes mellitus and good glycemic control (cases 6 and 15) [Table 1].

All patients in this study presented with characteristic manifestations of ARN; that is, acute redness, pain, floaters, and blurred vision. Clinical examination revealed prominent anterior chamber inflammation with mutton-fat or stellate keratic precipitates (KPs), flare (+ to ++), and cells (+ to ++); vitritis and peripheral retinal multifocal or confluent full-thickness necrotizing retinitis with accompanying occlusive retinal arteritis in all cases; optic nerve edema in seven eyes; serous retinal detachment in two eyes (cases 3 and 9); and posterior pole retinal hemorrhage in two eyes (cases 9 and 15). B-scan ultrasound revealed vitreous inflammatory opacity, serous or tractional retinal detachment [Figure 1]. Clinical features of the younger group had no significant differences from those of the senior group [Table 1].

Fifteen vitreous samples and three aqueous samples from all 18 ARN patients were analyzed with xTAG-LCT and mPCR/qPCR. xTAG-LCT revealed positive results in 17 of the 18 samples: ten for VZV alone; five for VZV and EBV; one for HSV-1 and EBV; and one for VZV, HSV-1and EBV. mPCR confirmed the same results as xTAG-LCT for VZV and HSV-1 in all samples, while only two of the seven samples that were positive for EBV on xTAG-LCT were confirmed by qPCR.[6] Four of the five samples in the younger group and 12 of the 13 samples in the senior group were positive for VZV. Two of the five samples in the younger group were positive for HSV-1 [Table 1].

All patients in this study were initially treated with systemic anti-virals; that is, intravenous antiviral treatment (acyclovir 10 mg/kg, 3 times/d or ganciclovir 5 mg/kg, 2 times/d) for 2 to 4 weeks followed by oral antiviral treatment (valacyclovir, 500 mg or 1 g, 3 times/d) with an overall period of no less than 3 months. Seventeen of 20 eyes with extensive necrotizing retinitis were treated with intravitreal injection of ganciclovir (0.4–2.0 mg) for one to four times when systemic antiviral treatment alone was not satisfactory. Seventeen of 20 eyes received three-port PPV in cases with severe vitritis, proliferative vitreoretinopathy, or rhegmatogenous retinal detachment. Silicone oil tamponade was performed in 12 of 17 eyes, and one eye underwent tamponade with 18% C3F8 intraocular gas. In some patients with severe vitritis or serous retinal detachment, oral corticosteroid (0.5–1.0 $mg \cdot kg^{-1} \cdot d^{-1}$ prednisone or equivalent with rapid tapering) was added to the treatment regime after initiation of antiviral therapy [Table 1].

Of the 20 eyes, 13 eyes had improved, whereas three and four eyes had equal or worse final best visual acuity (BCVA), respectively, compared to baseline. Four eyes had BCVA of HM or worse at the last follow-up. The medium presenting BCVA of the 20 eyes was 20/400 (range LP to 20/33, mean 1.36 ± 0.95 logMAR units). The medium final BCVA was 20/100 (range NLP to 20/20, mean 0.95 ± 0.82 logMAR units). The improvement in visual acuity of 0.41 logMAR units was statistically significant ($P = 0.015$). Final BCVA improved significantly from 1.36 ± 0.95

Table 1: Clinical features of acute retinal necrosis in younger and senior patients.

Patient no.	Age (years)	Sex	History	Eye affected	Clinical features	Presenting BCVA	Sample type	Virus			Surgical Therapy	Final BCVA	DFV (days)	DFU (months)
								mPCR	qPCR	xTAG-LCT				
Younger group (age ≤ 38 years)														
1	24	M	Viral meningitis 3 years ago	os	①④	20/500	V	VZV+HSV-1		VZV+HSV-1+EBV	IVG × 2; PPV+SO	20/100	13	18
2	31	F		os	①②③	20/50	AH	VZV		VZV	IVG × 2	20/20	7	20
3	34	M	Epilepsy 1 year ago	od	①②③④⑤⑥	20/400	V	HSV-1		HSV-1+EBV	PPV+IVG+SO	NLP	8	9
4	38	F		os	①②③	20/100	V	VZV		VZV+EBV	PPV+IVG	20/50	29	10
5	34	F		od	①②	20/133	V	VZV		VZV	IVG × 2; PPV+SO	20/80	20	13
Senior group (age > 38 years)														
6	62	M	DM	od	①②③	20/200	V	VZV		VZV+EBV	PPV+SO	LP	15	41
7	49	M		os	Invisible fundus	20/133	V	VZV		VZV	PPV+18%C3F8	20/80	30	24
8	49	F	HBP	od	Invisible fundus	CF	V	VZV		VZV	PPV+IVG; PPV+SO;IVG	CF	29	15
9	57	M	Fever 5 days before	os	①②③④⑤⑥	HM	V	VZV		VZV+EBV	IVG × 2; PPV+IVG+SO	HM	11	17
				od	①③	20/33					IVG	20/20		
10	50	M		os	①②③④	20/400	V	VZV		VZV	PPV+IVG+SO	20/167	45	15
11	58	F		od	①④	HM	V	VZV		VZV	PPV+SO	CF	17	15
12	56	F		os	①②③	20/400	AH	VZV		VZV	IVG × 2; PPV+SO	CF	14	23
13	58	M	HBP	od	①②	20/2000	AH	VZV		VZV	IVG	20/100	30	12
				os	①②	20/1000					PPV+IVG	20/100		
14	56	F		od	①④	HM	V	VZV		VZV	IVG; PPV+IVG	20/200	20	11
15	54	F	HBP; DM	od	①②④⑥	LP	V	VZV		VZV	IVG; PPV+IVG; PPV+SO	LP	22	4
16	55	M		os	①②③④	20/80	V	(−)		(−)	IVG; PPV+IVT+SO	20/80	14	12
17	46	F		os	①②③④	20/67	V	VZV	EBV	VZV+EBV	IVG × 4; PPV	20/33	13	8
18	47	M		od	①②④	20/167	V	VZV	EBV	VZV+EBV	IVG × 2; PPV+IVT+SO	20/100	21	12

The ages of the younger group and the senior group are 32.2 ± 5.2 years and 53.6 ± 4.9 years, respectively. AH: Aqueous humor; BCVA: Best correct visual acuity; CF: Counting fingers; DFU: Duration of follow-up; DFV: Duration at first visit; DM: Diabetes mellitus; EBV: Epstein-Barr virus; F: Female; ①: Retinal necrotizing retinitis; ②: Occlusive retinal arteritis; ③: Optic nerve edema; ④: Retinal hemorrhage; ⑤: Serous retinal detachment; ⑥: Macula involved; HBP: High blood pressure; HM: Hand motion; HSV: Herpes simplex virus; IVG: Intravitreal injection of ganciclovir; IVT: Intravitreal injection of triamcinolone acetonide; LP: Light perception; M: Male; mPCR: Multiplex polymerase chain reaction; NLP: No light perception; od: Right eye; os: Left eye; PPV: Pars plana vitrectomy; qPCR: Quantitative polymerase chain reaction; SO: Silicone oil; V: Vitreous; VZV: Varicella-zoster virus; xTAG-LCT: xTAG-liquid chip technology; –: No data.

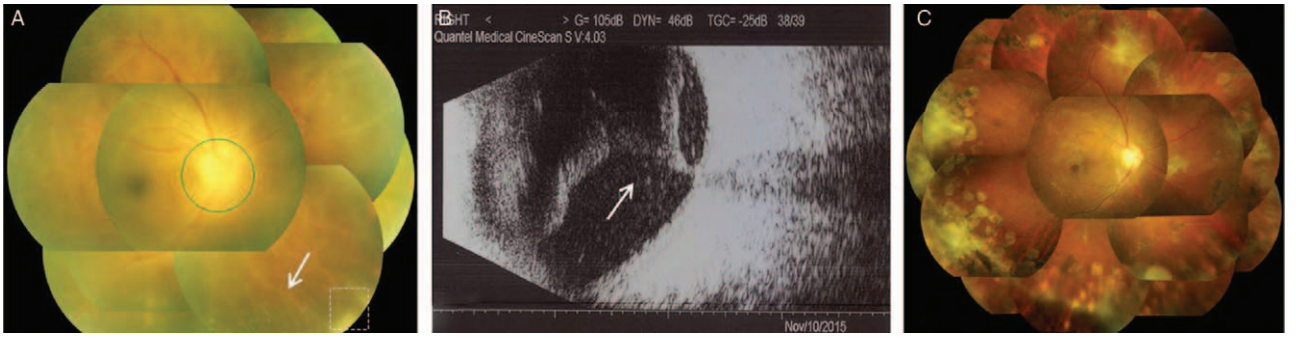

Figure 1: Color fundus photography (A and C) and B-scan ultrasound (B) of patient 18. After treatment with systemic antiviral therapy and two doses of intravitreal ganciclovir (0.4 mg), her fundus (A) still presented with severe vitritis, optic nerve edema (green circle), occlusive retinal arteritis (arrow) and periretinal necrotizing retinitis (rectangle); B-scan ultrasound (B) revealed vitreous inflammatory opacity and tractional retinal detachment (arrow). The patient then received PPV combined with silicone oil tamponade. Her visual acuity at the last visit was 20/100 with retinal reattachment and necrotic lesion regression (C).

(median 20/400) to 0.95±0.82 (median 20/100) (t=2.714, P=0.015) after systemic and intravitreal antiviral treatment combined with or without pars plana vitrectomy.

Discussion

The present study confirms VZV is the most frequent cause of ARN, which is consistent with the existing literature. However, in contrast with the previous opinion that patients with ARN due to the VZV are often older (50.4±13.4 years) and that patients with HSV induced ARN are considerably younger (38.6±13.1 years),[4,5] the present study shows four of five samples in the younger group (32.2±5.2 years) were positive for VZV, which indicates VZV is also a common pathogen of ARN in patients younger than 40 years old. A retrospective study conducted in the United State in 2000 used PCR to determine the viral cause of ARN in vitreous or aqueous samples from 30 eyes (28 patients). VZV DNA was detected in 15 eyes (13 patients) (50%) with a median age of 57 years, among which four patients were younger than 40 years old and the youngest patient with VZV infection was 9 years old.[9] In another prospective surveillance study carried out by the British Ophthalmological Surveillance Unit in 2012, viral DNA was isolated from aqueous, vitreous or cerebrospinal fluid biopsy in 30 ARN patients, and VZV was detected in 18 cases (60%) with a mean age of 57.4 years and a 24-year-old patient to be the youngest VZV infector.[10] All of these results supported the hypothesis that VZV is also a common causative virus for ARN in younger patients.

Due to the rare occurrence and lack of large case series studies, there is no established standard treatment scheme for ARN. The most commonly used and current gold standard initial treatment for ARN is acyclovir, which prevents viral replication by inhibiting viral DNA polymerase.[11] Treatment at a dose of 10 mg/kg every 8 h or 1500 mg/m^2 per day divided into three doses for 14 days followed by an oral anti-viral is the most established treatment regimen.[12] Evidence has supported the therapeutic effectiveness of intravenous or oral acyclovir for the initial treatment of ARN and prevention of fellow eye involvement.[12-14] However, acyclovir is more effective against primarily HSV infections, and less effective against VZV cases, which often tend to be more severe and progress more rapidly than those with HSV-ARN.[4,15] VZV-ARN was associated with a greater degree of visual loss and a 2.5-fold greater chance of retinal detachment compared with HSV-ARN.[16] As an alternative, ganciclovir could be effective for those cases that do not fully respond to acyclovir at a dose of 5 mg/kg every 12 h for 14 days. Therefore, previous studies suggested intravenous acyclovir and ganciclovir as an initial treatment regimen to younger patients (mean 33 years) mainly with HSV infection and senior patients (mean 45 years) mainly with VZV infection, respectively.[17,18] However, since our present study finds VZV is also a common causative agent for the younger group, the initial treatment protocol to these patients should be immediately changed to intravenous ganciclovir when they do not respond to acyclovir therapy for 7 to 10 days, before determining the causative virus by PCR using intraocular fluid. Intravitreal injection of ganciclovir and prophylactic vitreous surgery could be an alternative choice for patients with severe vitritis and progressive retinal lesions, especially when they are close to the posterior pole. In cases with rhegmatogenous retinal detachment, one of the main late-stage complications, pars plana vitrectomy combined with or without silicone oil or 18% C3F8 tamponade should be performed for reattachment and recovery of vision.[15]

A study has indicated that 18% of the ARN patients had herpetic central nervous system involvement,[10] with HSV encephalitis and meningitis more commonly associated with HSV-1 in older patients and HSV-2 in younger patients, respectively. In consistent with the previous study, two cases in our study with HSV-1 infection had viral meningitis 3 years ago and epilepsy 1 year ago, respectively. Several epidemiological studies have suggested a possible involvement of viral infection in the development of epilepsy and supported a role for HSV-1 in the pathogenesis of epilepsy.[19,20] Since patients with a history of herpetic central nervous system disease are at significant risk of ARN within 12 months,[10] prompt medical attention should be sought if they develop visual symptoms.

Thirteen of 20 eyes had an improved final BCVA after optimal treatment with systemic or intravitreal antiviral therapy combined with anti-inflammation treatment. However, patients with serous retinal detachment, posterior pole retinal hemorrhage, or a history of diabetes mellitus had a BCVA of HM or worse at the last follow-up, which suggests that prognosis of ARN may be poor despite optimal treatment, especially in cases where the optic disk or macula is involved. Poor visual outcomes are also associated with extensive retinitis at presentation and inappropriate use of corticosteroids.[1,21] Since the pathogenesis of intraocular inflammation and diabetic retinopathy acts through similar biochemical mediators and pathways,[22] it is feasible that poor glycemic control would accelerate the progression of ARN. Thus, ARN patients with diabetes mellitus should be advised to maintain good glycemic control. Systemic and intravitreal antiviral agents help to prevent bilateral involvement, which can occur in up to one third of patients.[5] In the study, with optimal treatments, only two patients had fellow eye involvement by the last follow-up.

Due to the low incidence of ARN, the limitations of this study include a small number of cases and its retrospective nature. Prospective and multi-center studies are needed to address these limitations.

In summary, we present the clinical manifestations and the causative virus of 18 cases of ARN. The present study confirms that VZV is the most frequent cause of ARN. However, to be inconsistent with the previous opinion that patients with ARN due to VZV are often older and patients with HSV induced ARN are considerably younger, we found that VZV is also a common causative virus for ARN in younger patients. Considering this fact, it is noteworthy that a systemic antiviral treatment protocol should be immediately changed to intravenous ganciclovir when the patient does not respond to acyclovir before the causative virus is determined, especially in younger patients. Optimal treatment with systemic or intravitreal antiviral therapy, anti-inflammation treatment and PPV combined with or without silicone oil or 18% C3F8 tamponade can dramatically improve visual function in ARN patients, however, the prognosis may be poor in cases with optic disk or macula involvement. Patients with a history of herpetic central nervous system diseases, such as encephalitis and meningitis, are at significant risk of ARN, thus prompt medical attention should be sought if they develop visual symptoms. Since poor glycemic control might accelerate the progression of ARN, patients with diabetes mellitus should have their blood glucose well-controlled.

Conflicts of interest

None.

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