Case report

INTRAVITREAL HAEMORRHAGE COMPLICATING ACUTE RETINAL NECROSIS SYNDROME ASSOCIATED WITH HERPETIC VASCULITIS OF THE OTHER EYE: DIAGNOSIS AND TREATMENT MODALITIES

ABSTRACT

The purpose of the study is to present a complicated case who present a very rare retinal viral infection masqued initially By intravitreal hemorrage .

KEY WORDS

Acute retinal necrosis,uveitis,herpes simplex virus,intravitrealhemorrage , anterior chamber ponction

INTRODUCTION

Acute retinal necrosis syndrome was first described in 1971 by Urayama et al [1]. It combines full-thickness, well-defined retinal necrosis, initially in the mid-periphery, with a tendency to spread circumferentially and then towards the posterior pole, occlusive vasculitis predominating in the arterial network, and marked inflammation of the anterior and posterior segments [2]. Viruses of the herpes group, most commonly varicella-zoster virus (VZV) and herpes simplex virus 1 and 2 (HSV-1 and 2) [3-4], and rarely cytomegalovirus (CMV) [5], are implicated in RNA syndrome. These viruses can be detected either by indirect methods such as serology and assessment of local synthesis of specific antibodies, or by direct methods such as viral culture, microscopic detection of viral particles by electron microscopy, detection of viral antigens by immunofluorescence and, more recently, detection of the viral genome using molecular biology techniques [6, 4, 7].

Case presentation

We report the case of a 24-year-old patient with chronic asthma on inhaled beta-2 mimetics and corticosteroids who had been presenting with reduced visual acuity in the right eye with bilateral myodesopsias for 6 months.

Ophthalmological examination revealed visual acuity of 4/10 in the right eye and 9/10 in the left eye. Examination of the adnexa and anterior segment and ocular tone were normal in both eyes.

The fundus of the right eye showed an intravitreous hemorrhage organised in the inferior region with a whitish area of ischaemia in the inferior temporal region with retinal hemorrhages and a poor macular reflection with signs of vasculitis and lower vascular loops and slight papillary hyperhaemia(figure1). in the left eye, a papillary hyperhaemia with vascular envelopment and signs of peripheral vasculitis, with two chorioretinal foci in contact with the inferior temporal arcade of half a papillary diameter.(figure2)

Fluorescein angiography was carried out, which revealed hyperfluorescence in the supra macular region of the right eye in the early stages in relation to a neovascular bundle with several areas of hypofluorescentischaemia at the periphery with the presence of a mask effect inferiorly in relation to the haemorrhage with the presence of neovessels(figure3),and in the left eye a perivascular diffusion

of fuorescein in the temporal region with the presence of a lower chorioretinal focus which takes up fluorescein and papillary retention at late stages.(FIGURE4)

We also realised macular oct int both age which shows a cystoid macular oedema of right eye (figure 5)

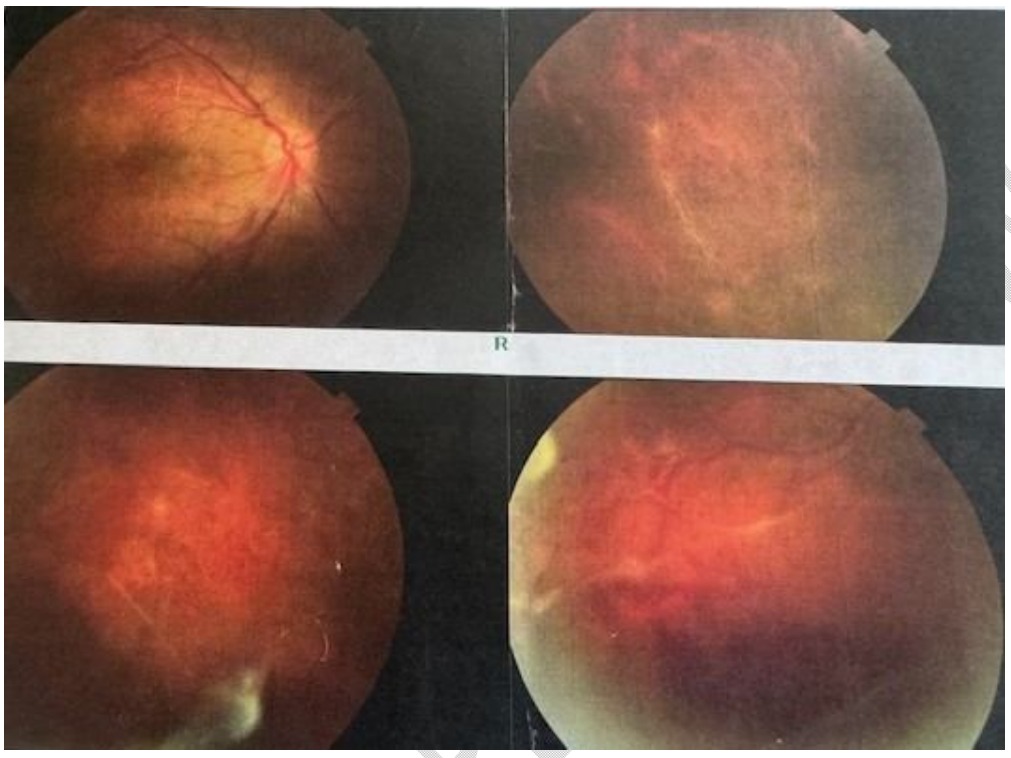

FIGURE 1 :retinophotos of the right eye showing the acute retinitis necrosis

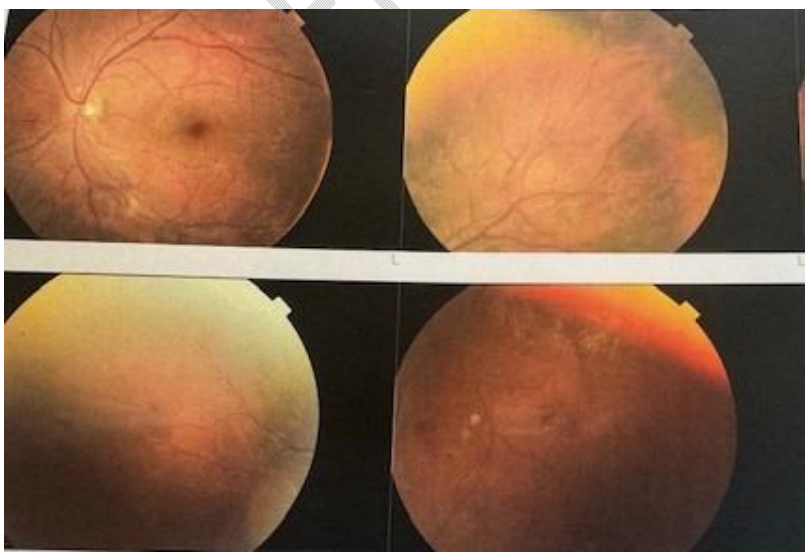

FIGURE 2 :Retinophotos of left eye showing peripheral vasculitis

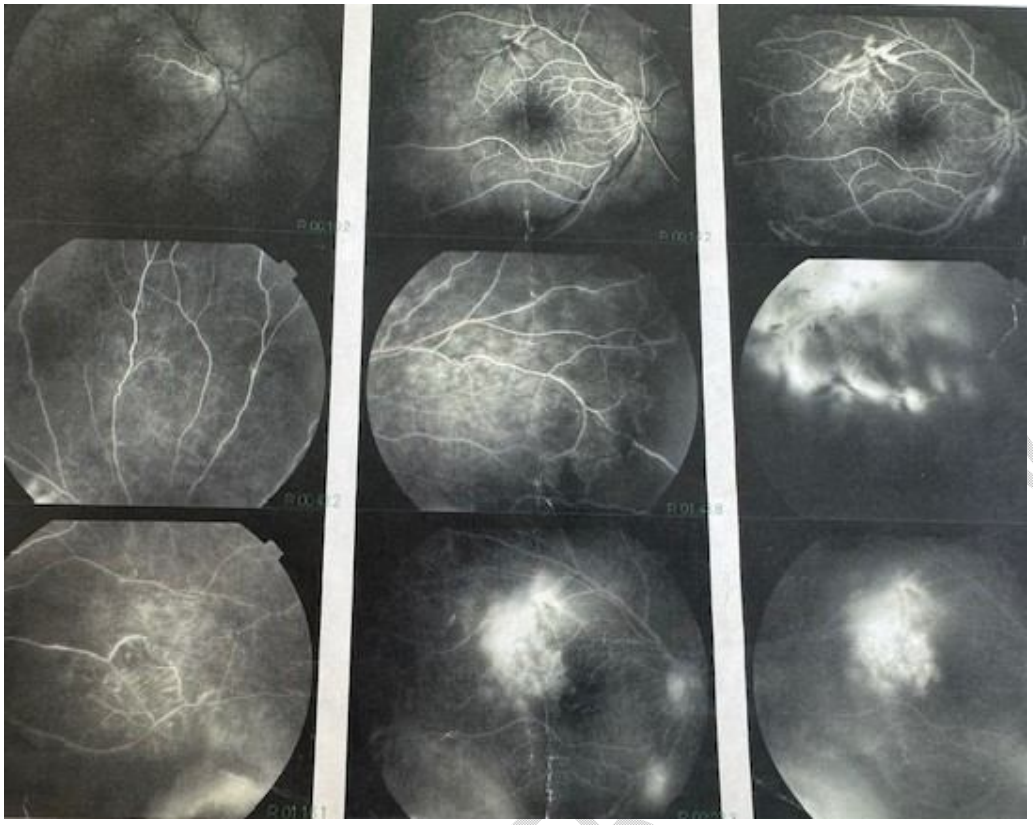

Figure 3 : Fluorescein angiography of the right eye, note the presence of the hemorrages,ischemic zones with neovasclarisation and the inferior necrosis masqued by the intravitroushemorrage

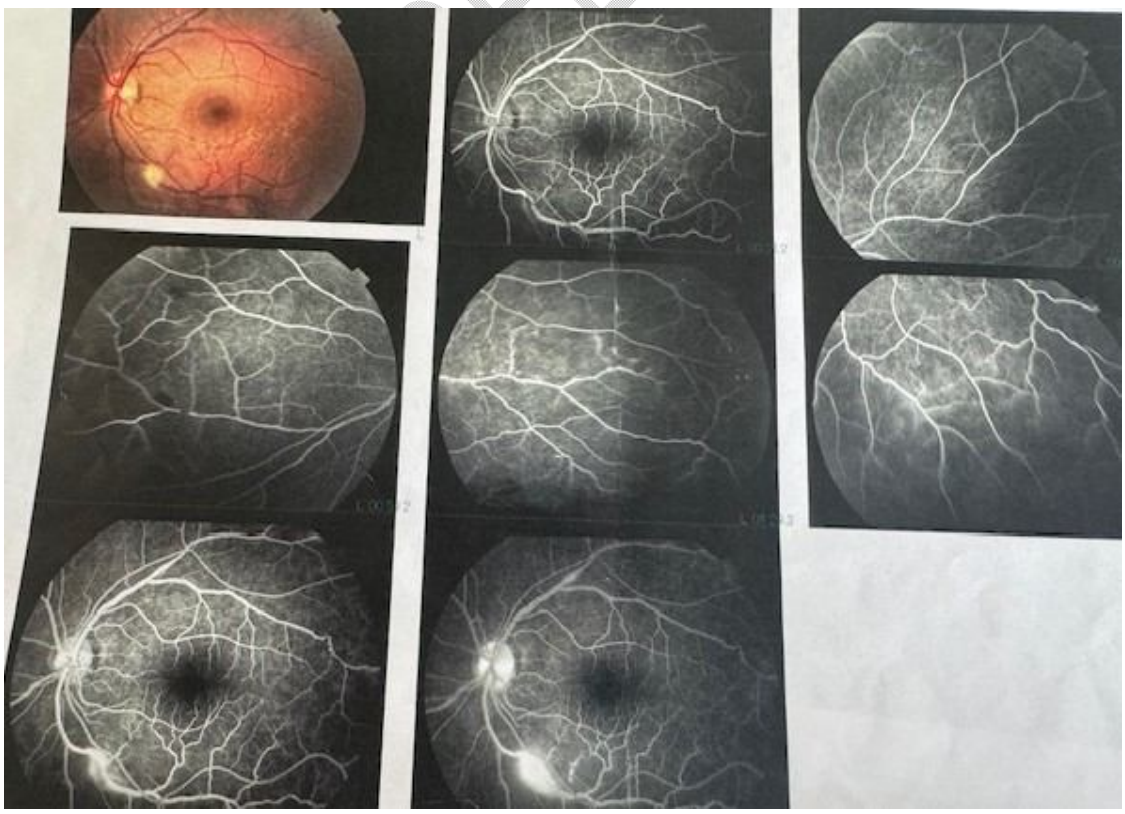

Figure 4 : fluorescein angiography of left eye showing the peripheral vasculitis

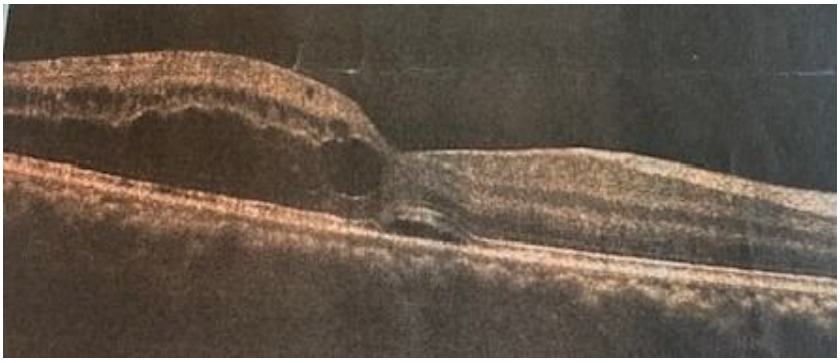

Figure 5 : macular oct of right eye showing cystoid macular oedema and thin detachement of the pigmentary epithélium

we suspected acute retinal necrosis syndrome of the right eye and vasculitis of the left eye and we carried out serologies which came back positive for HSV2. We also carried out a puncture of the anterior chamber for analysis of the PCR polymerase chain which came back positive for HSV2,and the treatment was immediately started with therapeutically, the patient was placed on intravenous (IV) acyclovir (500 mg/m2administered 3 times daily or 10 mg/kgevery 8 hours) for 7 to 10 days,followed by oral acyclovir (800 mg 5 timesper day) for 6-12 weeks after thetreatment initiated,with a good evolution with stagnation then regression of the areas of retinal necrosis and visual acuity passing to 6/10 On D7, we also did an urgent PPR with argon laser of the areas of ischemia (figure 6) and three injections of anti vegf to treat macular edema.

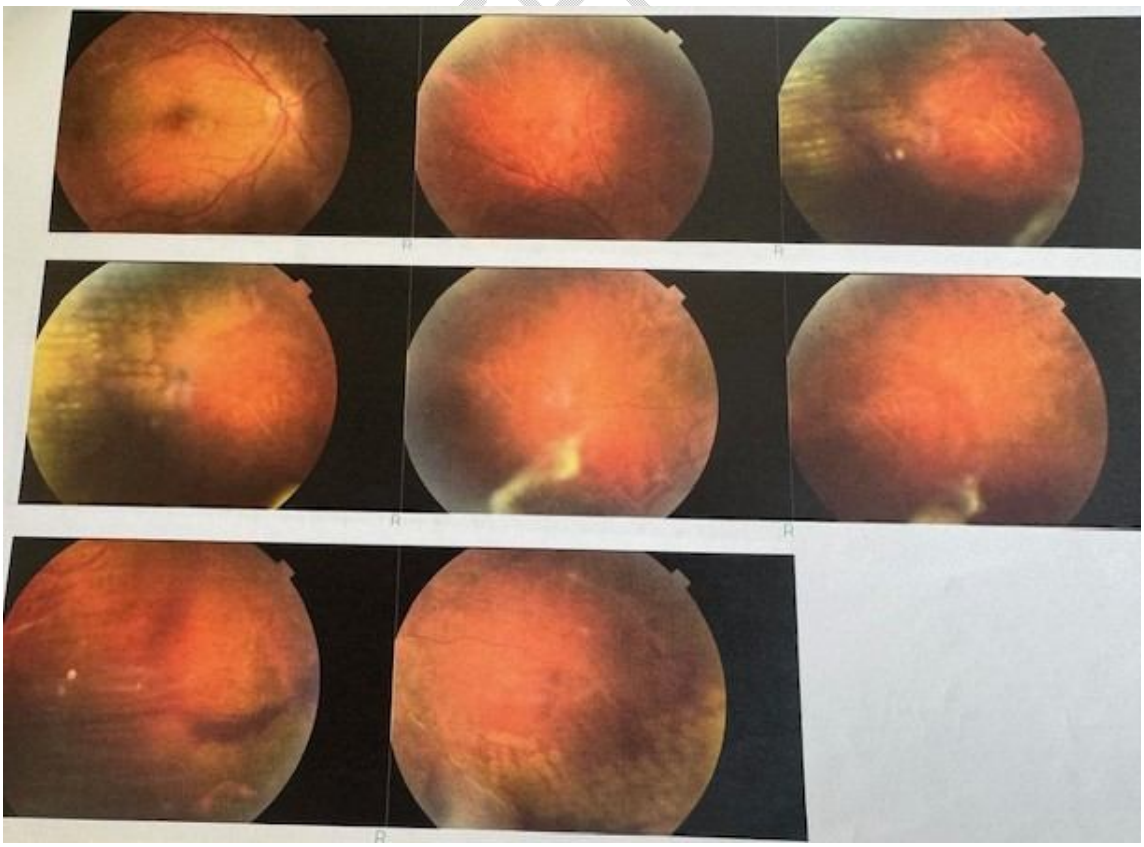

FIGURE 6 :retinophotos of right eye after urgent pan photocoagulation of ischemic zones

DISCUSSION

The diagnosis of acute retinal necrosis (ARN) syndrome is primarily based on clinical presentation. Patients typically report decreased visual acuity, conjunctival redness, and the presence of floaters. Physical examination reveals inflammation of the anterior segment, including conjunctival hyperemia, a Tyndall effect, and fine or granulomatous keratic precipitates. The posterior segment often exhibits a varying degree of vitreous haze, peripheral retinal necrosis that spreads centrally, and vascular inflammation of the retina and choroid.1

ARN syndrome is considered a medical emergency due to its rapid progression and the severity of potential complications, such as involvement of the fellow eye, retinal detachment, optic nerve damage, and cystoid macular edema. Analyzing ocular samples can help identify the causative infectious agent, assess visual prognosis, guide treatment, and confirm the diagnosis.

Two primary methods are used to detect the viruses responsible for ARN syndrome: direct gene amplification by PCR and indirect measurement of the Goldmann-Witmer immune load coefficient. PCR is a highly sensitive technique (80-96%) that requires only a small sample volume and can provide quantitative information, which can be a prognostic indicator. The Goldmann-Witmer coefficient is useful in immunocompetent patients but has a higher rate of false-negative results in immunocompromised individuals.There are two peaks in the frequency of acute retinal necrosis (ARN) syndromes: a first peak around the age of 20-30 years where the herpes simplex virus type 2 (HSV-2) is predominant, and a second peak around the age of 50-60 years where the varicella-zoster virus (VZV) is predominant [8,9 ,4].

The most common viral pathogen involved is VZV according to Lau et al. [10] and Muthiah et al. [11], while it is HSV in the series by Tran et al. [11]. VZV seems to be more aggressive, causing more extensive necrosis, than other viruses [11] and can be a source of resistance to acyclovir [8], while HSV appears to have a higher number of recurrences [8]. Furthermore, there is no correlation between the specific pathogen and the incidence of retinal detachment [10 ,11].

The at-risk population includes patients with a history of viral infections [12 ,13]: varicella (70.6%), herpes zoster (shingles) (29.2%), ophthalmic herpes zoster (20.7%), HSV-like pseudoflu syndrome (25%), and HSV encephalitis (15.4%). Additionally, there may be a genetic predisposition, as Holland et al. [9] found that more than 50% of patients with ARN syndrome were HLA-DQw7 positive versus 19% in the control population, and 16% of ARN patients expressed HLA-Bw62DR4 versus 2.6% in the control group [8].

ARN syndrome is most often unilateral at diagnosis, but its involvement of the fellow eye is frequent and occurs rapidly, within the first few days or weeks. A murine experimental model suggests the existence of two mechanisms of virus propagation : transsynaptic and local in the optic chiasm between infected and uninfected axons (non-transsynaptic).

The goals of treatment are to accelerate the resolution of the infection in the infected eye and to prevent contralateral involvement. Intravenous acyclovir has the following side effects: increased serum creatinine levels, urinary stones, elevated liver enzymes, and central nervous system toxicity (lethargy, delirium, seizures). The standard treatment regimen for ARN was defined by Palay et al. and consists of intravenous (IV) acyclovir (500 mg/m2 administered 3 times a day or 10 mg/kg every 8 hours) for 7 to 10 days, followed by oral acyclovir (800 mg 5 times a day) for 6-12 weeks after the

initial treatment; however, no randomized controlled study of this regimen has been conducted [9, 14].

Our practice is to use this intravenous regimen with oral valacyclovir (1 g 3 times a day) as a relay for 6 weeks after the initial treatment, then at a dose of 500 mg x 3 for 5 months. We use this lifelong treatment for prophylactic purposes in monocular patients. In addition to intravitreal injections of foscarnet (1.2-2.4 mg per 0.1 mL) or ganciclovir, topical and sometimes systemic corticosteroids are used as adjunctive therapy. One study has shown that the use of intravitreal foscarnet results in a lower incidence of retinal detachment [15].

In general practice, we first use the combination with intravitreal foscarnet injections, which we repeat twice in the first week depending on the clinical response. It should be noted that CMV retinitis syndrome does not respond to acyclovir and requires the use of intravenous ganciclovir or foscarnet [16].

Blood concentrations are similar to those obtained with IV administration, as these molecules have pharmacokinetics that allow them to reach therapeutic serum levels when converted to their active form. In this study, no difference in visual acuity was found between the intravenous and oral forms. However, clinicians should be cautious, as although the publications suggest comparable efficacy between oral valacyclovir at a dose of 1 g 3 times a day and intravenous acyclovir, there are no controlled trials comparing these two routes of administration. Guex-Crosier et al. [18] recently suggested that a higher dose of oral valacyclovir (2 g 4 times a day) could be a good alternative to intravenous acyclovir.

It is certain that this modality is attractive, as oral valacyclovir is less expensive than the standard therapy and has delivery advantages. However, severe cases are primarily treated at our center with the standard intravenous regimen combined with intravitreal injections.The goals of treatment are to accelerate the resolution of the infection in the affected eye and to prevent involvement of the contralateral eye. Intravenous acyclovir has the following side effects: increased serum creatinine levels, urinary stones, elevated liver enzymes, and central nervous system toxicity (lethargy, delirium, seizures). The standard treatment regimen for acute retinal necrosis (ARN) was defined by Palay et al. and consists of intravenous (IV) acyclovir (500 mg/m2 administered 3 times a day or 10 mg/kg every 8 hours) for 7 to 10 days, followed by oral acyclovir (800 mg 5 times a day) for 6-12 weeks after the initial treatment; however, no randomized controlled study of this regimen has been conducted. Our practice is to use this intravenous regimen with oral valacyclovir (1 g 3 times a day) as a relay for 6 weeks after the initial treatment, then at a dose of 500 mg 3 times a day for 5 months. We use this lifelong treatment for prophylactic purposes in monocular patients. In addition to intravitreal injections of foscarnet (1.2-2.4 mg per 0.1 mL) or ganciclovir, topical and sometimes systemic corticosteroids are used as adjunctive therapy. One study has shown that the use of intravitreal foscarnet results in a lower incidence of retinal detachment. In general practice, we first use the combination with intravitreal foscarnet injections, which we repeat twice in the first week depending on the clinical response. It should be noted that cytomegalovirus (CMV) retinitis syndrome does not respond to acyclovir and requires the use of intravenous ganciclovir or foscarnet. Recent studies have shown that oral antiviral therapy (valacyclovir, famciclovir, and valganciclovir) and intravitreal therapy without initial intravenous treatment is an effective treatment for ARN.

The main complications of ARN syndrome are cataract (26%), optic atrophy (23.9%), and retinal detachment (17.4%) [9] The frequency of retinal detachment is about 40% [15].Its prophylaxis by laser cerclage would reduce its incidence: thus, Lau et al. [9] report a detachment rate after laser of 35.3% versus 80% without laser [5].Laser cerclage should be performed within the first two weeks of the disease, as retinal detachment most often occurs after the 3rd week and within the first 5 months of the condition [9]. Retinal detachment surgery is intraocular, combining vitrectomy, endolaser, and internal tamponade by gas or silicone oil: intravitreal proliferation is often significant, and tears are often numerous and large, even giant, and located at the junction between healthy and affected retina [17].

CONCLUSION

In conclusion, the functional prognosis of acute retinal necrosis syndromes remains poor. Early management with intravenous antiviral administration followed by prophylactic treatment seems to limit necrosis and improve prognosis. The treatment of cystoid macular edema, refractory to corticosteroids, with interferon alpha-2a appears promising in terms of its efficacy and tolerability.

References:

1. Uryama A, Yamada N, Sasaki T, Nishiyama Y, Watanabe H, Wakusawa S, et al. Unilateral acute uveitis with periarteritis and detachment. Jnp J Ophthalmol, 1971;25:607-19.

2. Holland GN. Standard diagnostic criteria for the acute retinal necrosis syndrome. Am J Ophthalmol, 1994;117:663-7.

3. Danise A, Cinque P, Vergani S, Candino M, Racca S, De Bona A et al. Use of polymerase chain reaction assays of aqueous humor in the differential diagnosis of retinitis in patients infected with human immunodeficiency virus. Clin Infect Dis, 1997;24:1100-6.

4. Ganatra JB, Chandler D, Santos C, Kuppermann B, Margolis TP. Viral causes of the acute retinal necrosis syndrome. Am J Ophthalmol, 2000;129:166-72.

5. Pedroli GL, Garweg JG, Imesch P, Bohnke M. Varicella zoster virus and atypical necrotizing retinopathies in HIV and AIDS patients. Klin Monatsbl Augenheilkd, 1998;212:353-5.

6. Rungger-Brandle E, Roux L, Leuenberger PM. Bilateral acute retinal necrosis (BARN). Identification of the presumed infectious agent. Ophthalmology, 1984;91:1648-58.

7. Dussaix E. Virologiegénérale. In: Offret H. Œil et Virus. Editeur Masson. Paris ; 2000, p. 137-46.

[1] Urayama A, Yamada N, Sasaki T, Nishiyama Y, Watanabe H, Wakusawa S, et al. Unilateral acute uveitis with retinal periarteritis and detachment. RinshoGanka1971;25:607—19.

[8] Tran TH, Bodaghi B, Rozenberg F, Cassoux N, Fardeau C, LeHoang P. Prise en charge diagnostique et thérapeu- 60.e6 C. Izambart et al. tique des rétinites nécrosantes herpétiques. J Fr Ophtalmol2004;27:223—36.

[9] Fardeau C. Rétinites nécrosantes herpétiques. J Fr Ophtalmol2004;27:538—46.

[10] Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. Ophthalmology 2007;114:756—62.

11] Muthiah MN, Michaelides M, Child C, Mitchell SM. Acute Retinal Necrosis : a national population based study to assess the incidence, methods of diagnosis, treatment strategies and outcomes in the United Kingdom. Br J Ophthalmol2007;91:1452—5.

[12] Holland GN, Cornell PJ, Park MS, Barbetti A, Yuge J, Kreiger AE, et al. An association between acute retinal necrosis syndrome and HLA-DQw7 and phenotype Bw62. DR4 Am J Ophthalmol1989;108:370—4.

[13] Aizman A, Johnson MW, Elner SG. Treatment of acute retinal necrosis syndrome with oral antiviral medications. Ophthalmology 2007;114:307—12.

14.Wong R, Pavesio CE, Laidlaw DA et al. Acute retinal necrosis the effects of intravitreal foscarnet and virus type on outcome. Ophthalmology, 2010; 117: 556-560.

15.Wellington K. Valganciclovir: a review of its use in the management of CMV infec- réalitésophtalmologiques # 200_Février 2013 Le dossier Œil et herpès 4 tion and disease immunocompromised patients. Drugs, 2005; 65: 859-878.

16.Aizman A, Johnson MW, Elner SG. Treatment of acute retinal necrosis syndrome with oral antiviral medications. Ophthalmology, 2007; 114: 307-312.

17.Guex-Crosier Y, Meylan PR. High dosage of oral valaciclovir as an alternative treatment of varicella zoster acute retinal necrosis syndrome. Eye, 2006; 20: 247.

[18] Labetoulle M, Frau E. Syndrome de nécrose rétinienne aiguë. In : Œil et virus. Offret H, editor. Masson, Paris; 2000. p. 307—17.