Case Report

Acute Retinal Necrosis in a Patient with HSV-1 Encephalitis

Dimitrios Kalogeropoulos1*, Dimitri Anastasopoulos2, Constantina Gartzonika3, Anastasia K Zikou4, George Kitsos2 and Chris Kalogeropoulos1

1Department of Ophthalmology, Faculty of Medicine, School of Health Science, University of Ioannina, Greece
2Department of Neurology, Faculty of Medicine, School of Health Science, University of Ioannina, Greece
3Laboratory of Microbiology, Faculty of Medicine, School of Health Science, University of Ioannina, Greece
4Department of Radiology, Faculty of Medicine, School of Health Science, University of Ioannina, Greece

Abstract

Reason
This case report highlights the importance of thorough clinical investigation of patients with Herpetic Encephalitis (HE) and Acute Retinal Necrosis (ARN), as it appears that there is a substantial correlation between these two clinical entities.

Methods
In this study we present a case of a 68 year-old female patient who was diagnosed with unilateral ARN associated with Herpes Simplex Virus 1 (HSV-1) herpetic encephalitis. ARN has been associated with past medical history of herpetic encephalitis, but the reverse condition has also been reported, suggesting that the virus can access the retina from the brain through the trans-axonal pathway. The diagnosis of ARN was based on specific clinical features and medical history, but aqueous humor Polymerase Chain Reaction (PCR) assays were also carried out for confirmation.

Results
Unfortunately, our patient had poor compliance and was reluctant to continue with the suggested pharmaceutical treatment and attend regular follow-up appointments, leading to poor visual outcome and universal occlusive vasculitis.

Conclusion
Early diagnosis and long-term antiviral treatment are necessary for a better visual outcome and prevention of complications(e.g. retinal detachment), viral reactivation and bilateral disease. Clinicians need to remember that apart from the haematogenous spread, the trans-axonal transmission of HSV-1 from brain to retina (and vice versa) is also possible.

Key Words: Acute Retinal Necrosis; Herpetic Encephalitis; HSV-1; Trans-Axonal Transmission; Polymerase Chain Reaction; Antiviral Treatment; Patient's Compliance; Follow-Up.

Introduction
Herpetic Encephalitis (HE) is a severe inflammation of the central nervous system that can be complicated with acute retinal necrosis, which constitutes a devastating inflammatory ocular disease. The incidence of Acute Retinal Necrosis (ARN) is 1 case per 1.6-2 million population and most often immunocompetent adults are affected [1]. As for the prevalence of the disease, it is documented to be equal in both sexes, presenting usually in the 5th-7th decade of life [2]. HE should be considered as a risk factor for ARN, but this ocular viral infection can potentially lead to an HE too, if not treated appropriately. This correlation is attributed to the hypothesis of brain to eye transmission through the optic nerve [3,4], but the exact mechanism is still unknown. The particular study adds to the literature with a case of unilateral HSV-1 acute retinal necrosis related to a precedent encephalitis caused by the same virus.

Case Presentation
A 68 year-old lady was admitted to the Department of Neurology of the University Hospital of Ioannina (Greece) with fever (39 °C on admission), headache and confusion over the last 48 hours. Her medical and family history was free and no drug-induced allergies were recorded. However, she had gone through a very stressful period, since her son and also her nephew passed away during the last year. On physical examination she was anxious and irritable, but the deep tendon reflexes were normal. She had no paresis and Kernig’s and Brudzinski’s signs for meningismus were both negative. Full blood count and biochemical blood assay results were within normal limits. C-Reactive Protein test (CRP-test) and Erythrocyte Sedimentation Rate test (ESR-test) were slightly increased. A Magnetic Resonance Imaging (MRI) brain
scan was conducted, but no pathological features were elucidated. However, during her hospitalization, the condition deteriorated as divagation, polyneuropathy and finally generalized tonic-clonic seizures appeared (convulsive status epilepticus) and the patient was referred to the Intensive Care Unit (ICU). She was treated with Valproate Acid and was continued on Diazepam. Consequently, a Cerebrospinal Fluid (CSF) analysis was performed, showing a CSF cell count equal to 9 cells. In the next few days, seizures of similar character re-occurred. In a second CSF analysis a Polymerase Chain Reaction (PCR) assay was also requested and Herpes Simplex Virus 1 (HSV-1) was detected in this examination. It is worth mentioning that the MRI brain scan was repeated showing a high-intensity signal lesion of temporal lobe in T2-weighted image and the same anatomical area as a low-intensity lesion in flair image (Figure 1(a), (b)). A diagnosis of HSV-1 herpetic encephalitis (HSE) was set and the patient was immediately started on the suggested antiviral treatment (intravenous acyclovir: 10mg/kg every 8 hours for 21 days according to the typical protocol for the antiviral treatment of herpes simplex encephalitis) [5]. Fortunately she responded well to the antiviral therapy and the clinical image started to improve gradually until she was discharged with minor neurological defects. To prevent relapse of the HSE the patient was treated, after the initial course of intravenous acyclovir administration, with oral acyclovir for 3 months (800 mg/day; 1 dispersible tablet acyclovir). This supplementary therapy is administered in our Neurology Department as a standard prolonged treatment after the intravenous (IV) one, since more relapses occur within 3 months of completing the initial IV course. At the end of the treatment a PCR assay of CSF after a new lumbar puncture did not revealed the HSV-1 DNA.

However, approximately seven months after her admission, she was referred to the Department of Ophthalmology with blurred vision and eye redness on her left eye. Snellen visual acuity was 10/10 in the right eye, but the patient could only count fingers at 1 meter using the left eye. The ophthalmological examination revealed no pathological findings in the right eye. Regarding the left eye, slit lamp biomicroscopy showed anterior chamber inflammation with keratic precipitates, mild Tyndall effect 1+ and 2+ cells population. Examination of the fundus showed vitritis and yellow-white multifocal areas of peripheral retinopathy spreading towards the posterior pole, accompanied by sheathing, perivascular hemorrhages and occlusive arteritis (Figure 2(a)). The retinitis was also confirmed by a fundus fluorescein angiography (Figure 2(b), (c)). The intraocular pressure in the right and left eye was 13mm Hg and 12mm Hg, respectively. These particular clinical findings are typical of acute retinal necrosis and combined with an aqueous humor PCR assay that detected HSV-1 and the medical history of herpetic encephalitis, a diagnosis of ARN by HSV-1 was made.

Apparently, the MRI scan was performed to rule out an intracranial...
Unfortunately, the long-term oral (per os) use of acyclovir has caused side-effects and particularly increased liver enzymes, so she considered this procedure to be extremely unpleasant for her. She was also reluctant to continue with any kind of medication and did not appear again in her follow-up appointments, despite the suggestions of her physicians. She appeared again after an interval of 3 months; her left eye visual acuity had dropped to light perception and universal occlusive vasculitis had developed at the same eye.

**Discussion**

Acute retinal necrosis (ARN) was initially described in 1971 by a Japanese ophthalmologist, Akira Urayama, who described a unilateral ocular disease defined by panuveitis and arteritis of the retina that gradually led to necrotizing retinitis and retinal detachment [6]. A few years later, the term BARN was introduced by Young and Bird, in order to depict the presence of bilateral ARN [7].

ARN syndrome is a dreadful eye condition that can potentially lead to blindness if not recognized early and treated properly [8]. It is usually expected present in immunocompetent individuals [10]. It is a well-established knowledge that the antiviral treatment often than not, attributed to the reactivation of a prior infection usually expected present in immunocompetent individuals [10]. Especially HSV related cases are, more often than not, attributed to the reactivation of a prior infection usually expected present in immunocompetent individuals [10]. Herpesviruses primarily caused by Herpes Zoster Virus (HZV), Herpes Simplex Viruses (type 1 and 2) (HSV-1 and HSV-2), less frequently by Cytomegalovirus (CMV), but cases associated with Epstein Barr Virus (EBV) have also been reported [8,9]. Particularly HZV and HSV-1 are correlated with ARN in older patients, while HSV-2 is more common in patients aged under 25 years old [10,11]. HSV-2 is regarded as the most common etiologic factor in childhood; patients have been found to suffer from HSV-2 associated ARN up to 30 years after the neonatal infection [12]. According to the literature this disease may occur many years after the primary infection or it can follow a systemic infection caused by herpesviruses (e.g. herpetic dermatitis) [11]. Especially HSV related cases are, more often than not, attributed to the reactivation of a prior infection usually expected present in immunocompetent individuals [10]. However, there is increasing evidence that patients diagnosed with ARN may have particular underlying immune features that

**Figure 3.** Six months after the initiation of the treatment: optic disc atrophy with occlusion of some retinal vessels and absence of active vitritis.
increase the risk of infection. As it is expected the patients with more severe immune deficits are found to have less intraocular inflammation, but the same does not apply for those with a normal immune system [9]. The majority of cases are unilateral, but bilateral occurrence has been reported to climb up to 35% of patients and is presumably related with the early diagnosis and treatment of the eye initially involved [13].

Progressive outer retina necrosis and CMV retinitis may present with similar findings and should be taken into account in the procedure of differential diagnosis. The possibility of chorioretinitis induced by Toxoplasma needs also to be excluded. Apparently we cannot omit to think of masquerade syndromes, such lymphoma, leukemia or syphilis. Finally other diseases that could also imitate the clinical image of ARN include sarcoidosis, Adamantiades-Behcet disease, endophthalmitis and sympathetic ophthalmia in patients with Vogt Koyanagi Harada (VKH) disease.

To our knowledge ARN caused by HSV has been associated with medical history of HSV encephalitis, meningoitis or neurosurgery trauma, verifying the significance of a detailed history that might reveal possible exposure to a herpes virus [12].

In our case patient was administered to the Department of Ophthalmology with unilateral deterioration of vision, after hospitalization in the ICU and the Department of Neurology and the ICU of the same hospital due to a Herpetic Encephalitis (HE) caused by HSV-1. The literature suggests that ARN has been reported in several cases after herpetic encephalitis [14,15]. The first report that highlights an association of HE with ARN was in 1991, when bilateral ARN developed in two healthy adults briefly after severe HE [16]. Insipite of the proposed correlation between these two diseases, more systematic studies need to be carried out. Surprisingly, the interval between these two clinical entities (i.e. HE and ARN) can be up to 20 years. However, the time lapse usually ranges from 1 to 5 months [8]. As it was previously cited, in our patient ARN emerged approximately 7 months after the HE, indicating that this interval is in accordance with the current literature. This is indicative of the fact that ophthalmologists need to be integrally informed about their patients’ medical history, including the exposure to infectious agents, such as viruses. Another interesting feature of our case is that although the brain imaging showed left side neurological abnormalities, it was the left eye of our patient that was complicated with ARN, meeting the results of similar published cases [3,11].

The precise pathogenesis of ARN after HE remains unclear and further investigation needs to be conducted. According to information deriving from electron microscopic analysis of HSV antigens in the optic tract, the virus seems to transmit by retrograde axonal transport via the optic nerve. When the HE precedes the ARN there is a direct invasion of the retinal tissue. Presumably retinal neurons could be considered as reservoir for HSV until a future reactivation occurs [3,4]. The occurrence of HE following after ARN has also been recorded, implying that there might be also a direct viral transmission from the eye to the brain, supporting the bidirectional transport of herpes virus [17].

The diagnosis of ARN is based mainly on clinical findings and in 1994 the American Uveitis Society established the diagnostic criteria for ARN. These features include one more foci of retinal necrosis with well distinguished borders detected in the periphery of the retina, rapid and devastating progression when antiviral therapy is not provided, circumferential spreading, occlusive vasculopathy (mainly arteries), vitritis and anterior segment inflammation. Moreover, episcleritis or scleritis (especially during the onset of the inflammation), periorbital pain and optic neuropathy may coexist, but they are not required to set the final diagnosis [18]. It is important to mention that the aforementioned criteria are not in dependence with the etiologic factor and whether the patient is immunocompetent or not [12]. Apart from these criteria, a group of Japanese scientists published in 2015 a new series of diagnostic characteristics for ARN, targeting to achieve high statistical values [19], but for the time being there are not adequate studies to support their sensitivity and specificity. Despite the importance of clinical diagnosis, in some cases which are thought to be atypical and may cause clinical controversy, Polymerase Chain Reaction (PCR) assays of the aqueous humor should be performed for confirmation [1,11]. Nevertheless, patients should be immediately started on the appropriate medical treatment, without any delays while awaiting for the laboratory results [1]. The acute phase of the inflammation may last from 4 up to 6 weeks. During this interval there is a high likelihood of exudative retinal detachment to occur. Tractional or/ rhegmatogenous retinal detachment can also be observed during the course of the disease.

Regarding the treatment, all patients diagnosed with ARN must be immediately started on antiviral treatment; 10 mg/kg of intravenous acyclovir every 8 hours for 10 days, followed by 1000 mg of oral valacyclovir three times per day for 6 to 14 weeks [20]. Due to the absence of randomized control trials the ideal duration and the relative efficacy of the current recommended treatment is still obscure. It should also be stated that currently there is no single standard therapeutic approach [12]. According to our centre’s experience, it is preferable to maintain a longer duration of intravenous acyclovir up to 6 weeks in severe cases. Additionally, we typically recommend an oral (per os) administration of acyclovir (800mg/day) for an overall period of 12 months. Long-term antiviral treatment is suggested so as to protect the second eye as well. Intravitreal injections of antiviral agents (most usually ganciclovir) to the affected eye are also considered as a useful therapeutic tool, delivering a bolus of antiviral medication directly to the eye. Topical therapy with NSAID and corticosteroid eye drops is also advised. Aspirin is administered to patients with retinal vascular occlusion and extensive arteritis.

Prophylactic laser retinopexy seems to be very substantial as it contributes to decreased incidence of retinal detachment; according to a study conducted in Moorfields Eye Hospital this figure dropped from 80% to 35% in cases that prophylactic laser photocoagulation was performed [21].

The use of systemic steroids remains controversial, due to the consideration that they could provoke viral replication mainly in the acute phase [17], but studies propose that their administration...
in ARN should commence after the first 24 to 48 hours [1].

The final visual outcome in patients with ARN is unfavorable, even in patients that were diagnosed in the very early stages of ARN and received the recommended treatment [1]. The inflammation resolves spontaneously within 2-3 months with or without treatment, but in the second case retinal detachment is significantly more plausible to arise. It is noteworthy that despite the developments in the antiviral, surgical and laser therapy, the percentages of retinal detachment in ARN can climb up to 80%. Apart from the retinal detachment, vision might be affected by other complications, such as optic atrophy, macular lesions, vitreoretinopathy, extensive occlusive vasculitis, glaucoma and cataract [20]. The majority of patients are expected to develop variable levels of optic atrophy, while some may also develop ocular hypotony [8].

Considering the cases where HE preceded the ARN, immediate treatment of HE plays a crucial role in the encountering both of these pathological conditions. Mortality and morbidity rates of HE declined significantly after the introduction of acyclovir treatment. In addition, prompt treatment may conduce to limiting the virus reactivation or its neuronal translocation that would probably result in spreading to other anatomical areas of the central nervous system, including the eye [10].

Conclusions

It appears that acute retinal necrosis is a devastating eye inflammatory condition that has been correlated with the precedence of herpetic encephalitis and vice versa. Our case is a bright example that the thorough medical history of related diseases or viral exposure (i.e. HSV-1 related encephalitis) is of great importance and can lead earlier to the final diagnosis. Therefore, patients with herpetic encephalitis are at risk of developing acute retinal necrosis, even after a long period of time (several years). An ophthalmological monitoring might prove extremely beneficial and we suggest that non-symptomatic patients should attend their ophthalmologist twice a year for the first year after HE and annually considering the developments in the antiviral, surgical and laser therapy, the percentage of bilateral involvement. Finally, the combination of early diagnosis, emphasizing the risks of the disease and the therapeutic choices in treatment and follow-up, an individualized approach is required, be administered without any delay irrespectively of intraocular fluids PCR results. In regard with patient’s compliance considering treatment and follow-up, an individualized approach is required, emphasizing the risks of the disease and the therapeutic choices in a comprehensive way. Finally, the combination of early diagnosis, prompt treatment and compliance of the patient can limit or prevent the complications and lead to a better prognosis, including the prevention of bilateral involvement.

Copyright Statement

Dimitrios Kalogeropoulos, The Corresponding Author, has the right to assign on behalf of all authors and does assign on behalf of all authors, a full assignment of all intellectual property rights for all content within the submitted case report (other than as agreed with the BAOJ Publishing Group) in any media known now or created in the future, and permits this case report (if accepted) to be published on BAOJ Ophthalmology and to be fully exploited within the remit of the assignment as set out in the assignment which has been read.

Ethical Guidelines

This study does not involve experiments on human or animal subjects.

Consent

The authors confirm that a written consent of the patient has been obtained and is available upon request.

References


