Fulminant bilateral acute retinal necrosis complicated with secondary herpes simplex type-1 viral encephalitis

A case report

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Abstract

Rationale: Acute retinal necrosis (ARN), which is characterized by peripheral necrotizing retinitis, severe retinal arteritis, and progressive inflammatory reaction in the vitreous and anterior chambers, has been reported in cases with herpes simplex encephalitis (HSE). It is a relatively rare complication secondary to HSE. However, cases presented with viral encephalitis following ARN were seldom reported.

Patient concerns: A 43-year-old immunocompetent male patient manifested the aforesaid reverse situation. He developed HSE following 3-day systemic steroid therapy for abrupt ocular pain and rapidly decreased visual acuity, which was later diagnosed as ARN. Polymerase chain reaction (PCR) analysis of vitreous specimen verified herpes simplex virus-1 (HSV-1) infection.

Diagnosis: HSE associated with ARN.

Interventions: The patient was treated with intravenous acyclovir (500 mg every 8 h) for 21 days. A pulse of intravenous methylprednisolone, 500 mg/d for 5 days was given as an anti-inflammatory therapy, followed by prednisone taper.

Outcomes: The patient’s neurological symptoms got improved very soon after the therapy, but his vision acuity remained no perception of light in both eyes.

Lessons: The present case indicates that ARN can also be a risk factor for HSE. Once ARN was suspected, corticosteroid should be applied with caution and in combination with antiviral treatment to avoid progressive duplication of virus and its spread to the brain.

Abbreviations: ARN = acute retinal necrosis, CNS = central nervous system, HSE = herpes simplex encephalitis, HSV = herpes simplex virus, PCR = polymerase chain reaction.

Keywords: acute retinal necrosis syndrome, encephalitis, herpes simplex virus, polymericase chain reaction, Steroid

1. Introduction

Herpes simplex encephalitis (HSE) is a severe disease which happens in 2 to 4 cases per million/year.1,2 Herpes simplex virus type-1 (HSV-1) accounts for most adult HSE cases, but HSV-2 is also involved especially in young patient and neonatal herpes.2

As 1 of its uncommon but disastrous complications, acute retinal necrosis (ARN) could occur weeks or years after HSE. HSE has been well recognized as a risk factor for ARN.3 In this article, we report a reverse situation, in which the immunocompetent patient developed encephalitis 1 week following ARN, and polymerase chain reaction (PCR) analysis of the vitreous humor confirmed HSV-1 infection.

2. Case presentation

A 43-year-old immunocompetent man was admitted to our hospital with a generalized tonic-clonic seizure attack and loss of vision in bilateral eyes. Eight days (May 8, 2018) before admission, the patient developed continuous ophthalmodynia and conjunctive redness in his left eye, followed by blurred vision that night. He was treated with levofloxacin on the following day, but without any improvement. On May 10, 2018, the vision of his left eye deteriorated, and his right eye was also affected. He was initially diagnosed as bilateral uveitis and was prescribed intravenous methylprednisolone, 120 mg/day for 3 days. However, no response was observed, on the contrary, the patient began to complain of a complete loss of vision in left eye and only light perception in right eye. Fluorescein fundus angiography (FFA) was conducted on May 14, 2018, which (Fig. 1. a–f)
displayed obstruction of the majority of the retinal arteries, shown as scattering and sparse branches, especially in the left eye. He was then diagnosed with ARN.

On May 15, 2018, the patient developed severe headache, followed by sudden onset of a generalized tonic-clonic seizure for about 3 minutes that morning. He was sent to our emergency room, and lumbar puncture was immediately performed. The pressure was 185 mmH2O. The cerebrospinal fluid testing results showed a moderate pleocytosis (160 × 10^3/μL, normal range 0–8 × 10^3/μL) and increased protein level (51.60 mg/dL, normal range 0–43 mg/dL). Electroencephalogram revealed diffuse slow-wave activity. The brain magnetic resonance imaging (MRI) showed abnormal signals in the right optic-radiation of lateral thalamus, bilateral medial temporal lobes, and the insular lobes (Fig. 2. a–d). On his admission to the neurological department, he had a high fever at 39 degree Celsius. On neurological examination, he was confused and disoriented. His vision acuity was no perception of light in both eyes. Bilateral mydriasis was observed (Pupil diameter = 8 mm) and both light reflex disappeared. He also had neck stiffness and Kernig’s sign, but did not show other focal neurological deficits. Combining clinical manifestation with imaging changes and cerebrospinal fluid testing results, viral encephalitis was suspected and intravenous acyclovir (500 mg every 8 h) therapy was immediately initiated, together with a pulse of intravenous methylprednisolone, 500 mg/d for 5 days, as an anti-inflammatory therapy. The neurological symptoms gradually resolved after 4 days of treatment. He was alert and oriented, with mild short-term memory loss, but his vision was not restored.

On May 22, 2018, 1 week after his admission, the patient received ophthalmological examination again. Fundus photography (Fig. 1, g–h) manifested extensive retinal arterial occlusion and diffuse fundus hemorrhage, which were more severe in the left eye. Ophthalmic ultrasound revealed bilateral vitreous opacity with detachment of retina. HSV-1 DNA was detected in the vitreous humor sample by PCR.
The patient continued to receive a total 21-day intravenous antiviral course and then was discharged with oral valacyclovir as maintenance therapy. However, his vision acuity remained no perception of light in both eyes.

3. Discussion

ARN is an uncommon and rapidly destructive disease that has substantial ocular morbidity. The diagnosis of ARN is based on the following clinical characteristics that proposed by the Executive Committee of the American Uveitis Society:[4];

(1) 1 or more foci of retinal necrosis with incontinuous borders located in the peripheral retina,
(2) rapid progression without antiviral therapy,
(3) circumferential spread,
(4) occlusive vasculopathy with arterial involvement,
(5) a severe inflammatory reaction in the vitreous and anterior chamber.

Traditional laboratory techniques include antibody testing in serum or intraocular fluid, viral culture, retinal biopsy, and immunocytochemistry. But recently, PCR has become a more specific method to identify the viral DNA of ARN.[5] ARN has a similar virus spectrum to viral encephalitis, including varicella-zoster virus (VZV, over 50%), HSV-2 (5.1%), HSV-1 (3.5%),[6] cytomegalovirus (CMV), and Epstein-Barr virus (EBV).[7] HSV-1 is mostly seen in patients over 23-year-old, while HSV-2 is more likely to be detected in children and neonates.[8] Neglect or misdiagnosis of the disease could cause a delay of timely and effective treatment. A retrospective observational cohort study illustrated poor prognosis of ARN, referring to which, retinal detachment disclosed the highest risk of irreversible loss of vision, and the risk increased more prominently if a quarter or even more of the retina was involved.[9]

ARN has been occasionally reported in cases with prior viral encephalitis or meningitis. Another retrospective study published in 2008 evaluated the association between ARN and preceding neurologic illnesses.[10] This study revealed that 7 patients had ARN after herpetic encephalitis, indicating that herpetic encephalitis may be a risk factor for ARN. Brain-to-eye transmission of virus and reactivation of latent virus in the inferior fronto-temporal lobe and optic chiasma has been suggested to be the possible underlying mechanisms.[10,11]

We also reviewed literature published in the past 33 years (from 1985 to 2018) and found 19 cases with both HSE and ARN. Sixteen patients who developed ARN had previous viral encephalitis history (the latency ranges from 6 days to 17 years). One case in Japan presented with a simultaneous occurrence of ARN and HSE.[12] Only 3 cases presented in which ARN preceded the encephalitis.[13–15] The case reported in 1985 was an immunodeficient patient who developed reduced visual acuity of the left eye 24 days before the onset of encephalitis. Treatment was not mentioned and the patient died of cardiac arrest in the end. Postmortem biopsy of his eye and brain confirmed HSV-1 infection.[13] The second case reported in 2011 was an elderly systemic lupus erythematosus (SLE) patient with a HSV infection history years before. She presented encephalitis 5 weeks after ocular findings and died 3 weeks later. The third case reported in 2012 was an elderly and immune-competent patient who developed HSE 2 weeks following ARN, resembling the case we report here. PCR of vitreous specimen confirmed HSV-2. In our case, the patient developed HSE following ARN in 8 days, which is much shorter than that of the 3 above-mentioned cases. Different from the first 2 cases, our patient is an immune-competent and healthy young adult with no history of taking immunosuppressive medication. Surprisingly, the latter 2 together with the case we report here were all administered with corticosteroids without conjunctive antiviral therapy when ocular syndrome occurred. The third case was treated with oral prednisolone, 60 mg/day for 3 days and 120 mg/day for 3 days, followed by intravenous methylprednisolone, 1 g/day for 5 days, before his onset of encephalitis. However, in our patient, he only took intravenous methylprednisolone, 120 mg/day for 3 days and very soon, his ocular symptoms progressively deteriorated and he had a seizure 8 days following the development of the first symptoms of ARN. Granulomatous uveitis, retinal vasculitis,[16] and panuveitis were initially suspected respectively in these 3 cases, resulting in delayed antiviral treatment. It is assumed that single use of steroids without antiviral protection may lead to reactivation and duplication of latent virus, and thus spread to the brain and the contralateral eye.[14] It has been generally accepted that the earlier initiation of acyclovir in suspected HSE patients, the better prognosis of this catastrophic disease might be.[16,17] Therefore, we treated this patient empirically with acyclovir soon after the initial diagnostic evaluation.

The pathophysiology underlying this process is not well established yet. Animal studies have shed lights on the understanding of this clinical phenomenon. HSV has been shown to spread transneuronally to distant connections within the central nervous system (CNS) via retrograde and anterograde axonal transport. One study performed on mice identified that virus could spread from the affected eye to the CNS by parasympathetic fibers of the oculomotor nerve.[18] Another study showed that HSV-1 could be detected in all primary targets of the retina, including thalamus, hypothalamus, and superior colliculus following inoculation of the virus into the mouse vitreous body.[19] The virus was later detected in the primary visual cortex, and also in other connectively related cortical and subcortical areas that receive efferent projections from the cortex.[19] It can be postulated that infectious HSV firstly causes uveitis, then travels to the brain by retrograde axonal transport within the parasympathetic fibers of the oculomotor nerve, and subsequently, via anterograde, transneuronal spread, to other regions of the brain. The virus could also spread from the suprachiasmatic nuclei to the contralateral eye by retrograde axonal transport along the optic nerve. Therefore, it is important to consider viral etiology in cases of atypical uveitis. Given the potential transmission of virus from the eye to the CNS and the immunomodulatory effects of corticosteroid, which may facilitate viral replication, the use of corticosteroid to ease the ocular inflammation should be cautiously initiated after or at least in combination with sufficient antiviral therapy.

In conclusion, HSE can be a risk factor for ARN, and vice versa. To the best of our knowledge, we are the first to report a previously healthy middle-aged immunocompetent man who developed HSE just 1 week following ARN. PCR of the vitreous humor sample verified HSV-1 infection. Once ARN was suspected, corticosteroid should be applied with caution, and active antiviral treatment should be initiated with no hesitation to avoid the spread of virus to the contralateral eye and the brain.

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