

Human herpesvirus 6-associated uveitis with optic neuritis diagnosed by multiplex PCR

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Abstract

Purpose Human herpesvirus 6 (HHV-6), which is usually responsible for exanthem subitum in children, can be reactivated from its latent state. We report a case of unilateral optic disc edema and retinal vasculitis associated with HHV-6 infection.

Case A healthy 63-year-old man noted a decrease in the vision of his left eye. On examination, his left eye had moderate mutton-fat keratic precipitates, vitreous opacities, significant optic disc edema surrounded by yellowish-white swelling in the inner retina, retinal arteritis, and cotton-wool-like exudates. He was started on corticosteroid therapy and aspirin. After 1 month, the disc edema was reduced, the cotton wool-like exudates had decreased, and his visual acuity had improved to 10/20 OS. Multiplex polymerase chain reaction (PCR) of an aqueous humor sample revealed the presence of genomic DNA of HHV-6 but not of the other HHVs.

Conclusions The HHVs are known to infect the ocular tissues, but the differential diagnostic signs of HHV-6 are still not well known. We recommend that multiplex PCR of the aqueous humor be performed to search for the genomic DNA of HHV-6 in suspected cases of herpesviral infection.

Keywords Human herpesvirus 6 (HHV-6) · Human herpesvirus · Uveitis · Disc edema · Multiplex PCR

Introduction

Human herpesvirus 6 (HHV-6), a T-lymphotropic herpesvirus, is a member of the HHV family [1] and has been associated with immunodeficiency disorders and neurological diseases [2]. HHV-6 infects almost all children by the age of 2 years and persists for a lifetime [3]. HHV-6 is the cause of exanthema subitum in children [4]. Prospective studies have shown that HHV-6 is the most common pathogen responsible for febrile illness in infants and is associated with febrile convulsions in some infants [5].

Primary infection with HHV-6 is rare in healthy adults. However, reactivation of latent HHV-6 can occur especially in immunocompromised individuals and can cause serious illnesses [5]. However, the ocular signs and symptoms caused by HHV-6 infection are still not well known.

We describe a healthy adult who manifested unilateral uveitis, optic disc edema, and retinal vasculitis. The HHV-6 genome was detected in his aqueous humor by multiplex polymerase chain reaction (PCR).

Case report

A 63-year-old man who had been healthy noticed a decrease in his vision and visual field defect in the left eye of 2 days' duration. He visited another hospital and was diagnosed as having optic disc edema of the left eye on December 30, 2009. His corrected visual acuity was 25/20 OD and 25/20 OS. The symptoms worsened, and he visited our hospital on January 6, 2010.

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On his first visit, his corrected visual acuity was 25/20 OD and 4/20 OS, and the intraocular pressure (IOP) was 15 mmHg OD and 25 mmHg OS. The right eye was completely normal. Slit-lamp examination of the left eye revealed mild anterior chamber inflammation, moderate mutton-fat keratic precipitates, and vitreous opacities. Ophthalmoscopy of the left eye revealed significant edema of the optic disc, yellowish-white swelling of the surrounding inner retina, retinal arteritis with sheathing, and cotton wool-like exudates (Fig. 1a). The peripheral retina was normal. Fluorescein angiography revealed hyperfluorescence of the optic disc, delay of arterial filling in the early phase, and fine leakage from the arteries in the late phase in his left eye (Fig. 1b). Goldmann perimetry revealed a defect of the peripheral visual field and an enlarged Mariotte blind spot in the left eye.

Laboratory test results including blood cell count, C-reactive protein, and testing for connective tissue

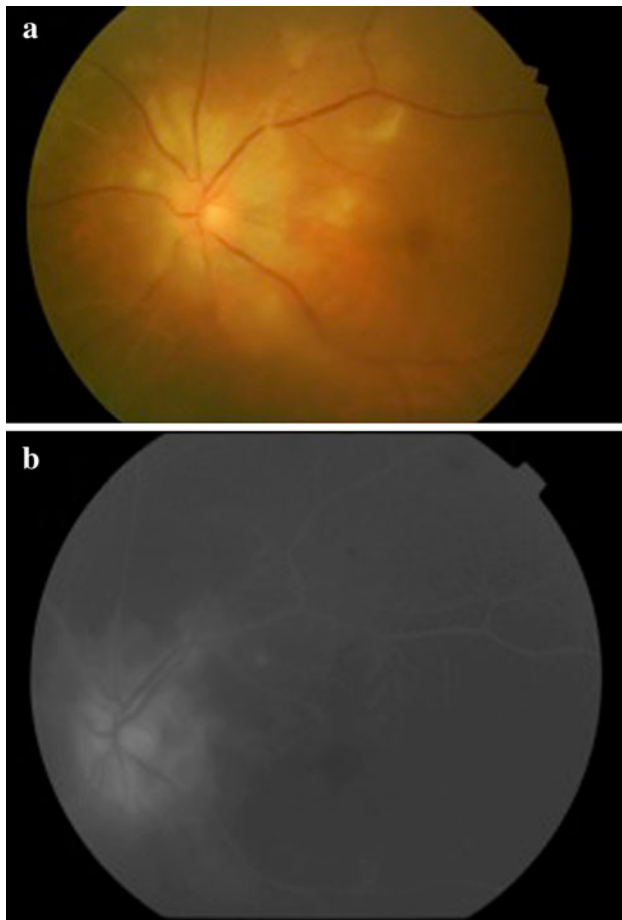


Fig. 1 Fundus photographs and fluorescein angiograms at the first visit. **a** Fundus photograph of the left eye reveals significant swelling of the optic disc surrounded by yellowish-white swelling of the inner retina, retinal arteritis with white sheathing, and cotton wool-like exudates. **b** Fluorescein angiogram of the left eye reveals hyperfluorescence of the optic disc and fine leakage from the arteries (789 s)

diseases were essentially normal. Blood testing for syphilis and human immunodeficiency virus (HIV) was negative. However, the anti-varicella zoster virus (VZV) IgG and anti-cytomegalovirus (CMV) IgG antibodies were, respectively, 8.9 times and 107.9 times higher than normal.

Although the cause of the inflammation was not definitively determined, the slightly increased IOP and retinal arteritis led us to consider the possibility of HHV family infection. He was started on corticosteroid therapy (100 mg prednisolone for 3 days) on the day of his first examination. The dose of corticosteroids was gradually reduced, and aspirin was added. As soon as the treatment was started, the anterior chamber inflammation, vitreous opacities, and disc edema decreased. The yellowish-white swelling around the disc and the cotton wool-like exudates also decreased. Eight days after initiation of the treatment, the visual field had improved.

Fifteen days after initiation of the treatment, his corrected visual acuity was 8/20 OS, and the IOP was 17 mmHg OS. The disc edema was reduced, and the yellowish-white swelling of the inner retina and the cotton wool-like exudates were not observed (Fig. 2).

Multiplex PCR was performed using the aqueous humor collected 3 days after his first visit. DNA extraction and viral PCR were performed by a Japanese company specializing in laboratory testing services (SRL, Tokyo, Japan) according to the manufacturer's procedure. Briefly, DNA was extracted from specimens using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). Six primer sets were used in the multiplex PCR assay [6]. The PCR primers (sense and antisense, respectively) were 5' TGT TGG CCT TCA TGA CCC TTG TGA AA 3' and 5' TAG CTC GAG AGC TTG ATC TTG TCG GTT 3' for herpes

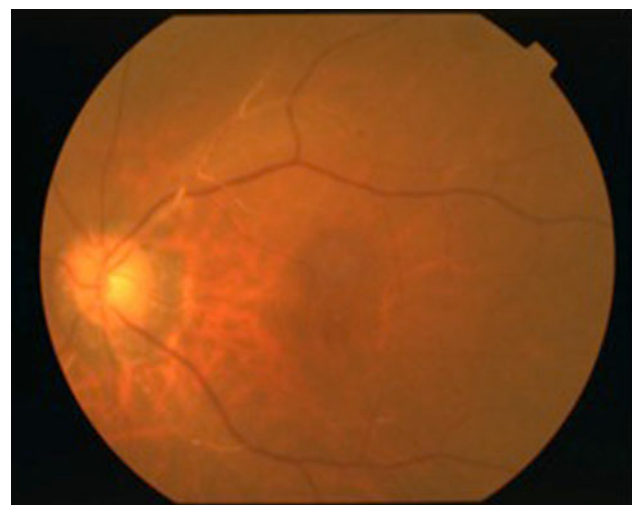


Fig. 2 Fundus photograph of the left eye 15 days after the initiation of treatment. The yellowish-white retinal swelling around the disc is not present, and the cotton wool-like exudates cannot be seen

simplex virus-1 (HSV-1); 5' AGT CCC ACC TCA GCG ATC TCG CCT 3' and 5' TAG CTG GAG AGT TTG ACC TTG TCG GTG 3' for HSV-2; 5' CTT AGA ATG GTG GCC GGG CTG TAA AAT 3' and 5' ATC CAG TAC GTC TTT GTG GAG CCC AAG 3' for Epstein–Barr virus (EBV); 5' ATG CGC CAT CAT AAT GCT CGG ATA CA 3' and 5' CCC TGC ATT CTT ACG GAA GCA AAA CG 3' for HHV-6; 5' TCC GAC ATG CAG TCA ATT TCA ACG TC 3' and 5' GGT CGG GTA GAC GCT ACC ACT CGT TT 3' for VZV; and 5' GCG CGT ACC GTT GAA AGA AAA GCA TAA 3' and 5' TGG GCA CTC GGG TCT TCA TCT CTT YAC 3' for CMV. After preheating at 95°C for 10 min, 2-step amplification of 40 cycles at 95°C for 20 s and at 65°C for 1 min was performed. The amplified products were electrophoresed in 3% agarose gel, stained with ethidium bromide, and photographed under ultraviolet light.

The results of the multiplex PCR showed genomic DNA for HHV-6 but not for HSV types 1 and 2, VZV, EBV, or CMV (Fig. 3). In addition, anti-HHV-6 IgG antibodies were 160 times higher than normal but anti-HHV-6 IgM antibodies were less than 10 times higher than normal in the blood samples collected 1 month after the first visit.

Because the inflammation in his left eye was reduced, the patient did not receive any anti-herpesvirus therapy. After 1 month, his corrected visual acuity was 10/20 OS

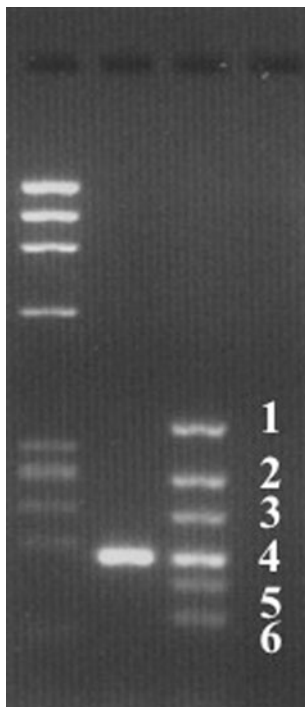


Fig. 3 Results of multiplex PCR on the aqueous humor. The presence of genomic DNA of HHV-6 is detected (line 4). Line 1 herpes simplex virus type-2; line 2 herpes simplex virus type-1; line 3 Epstein–Barr virus; line 4 HHV-6; line 5 varicella zoster virus; line 6 cytomegalovirus

and the IOP, 17 mmHg OS. After that, no evidence of recurrence of the inflammation was observed in his eye.

Discussion

The HHVs can affect the ocular tissues and are known to cause anterior and/or posterior uveitis. The ocular infection associated with HHV-1 and 2, VZV, and CMV has been well described; however, little is known about the ocular signs and symptoms associated with HHV-6.

A number of studies have suggested that the central nervous system is the site of persistent HHV-6 infection [3, 6–9]. However, only 3 cases of ocular inflammation-associated HHV-6 have been reported [10–12]. The first of those reports described a 31-year-old patient with bilateral optic neuropathy, disc edema, and tonic pupil associated with acute HHV-6 infection [10]. Our patient also had optic neuritis and disc edema, although the infection was considered to be latent because the level of anti-HHV-6 IgM antibodies was low. Given the localization of HHV-6 to astrocytes [8] and another report that demonstrated that HHV-6 was isolated in both the aqueous fluid and cerebrospinal fluid [12], we suggest that the optic nerve is one of the sites of HHV-6 infection.

The second report described a 75-year-old patient who manifested severe unilateral panuveitis with ciliary hyperemia, moderate mutton-fat keratic precipitates, severely inflamed anterior chamber containing cells with hypopyon, dense vitreous opacities, optic disc swelling, and large yellowish-white retinal lesions [11]. The third report described an 81-year-old patient who manifested bilateral uveitis and significant disc edema [12]. Taken together, the findings in these earlier reports indicate that HHV-6 is associated with optic disc edema and other signs that are characteristic of HHV infection.

Primary infection with HHV-6 in healthy adults is rare. Reactivation of latent HHV-6 can occur and is especially common in immunocompromised individuals [5]. HHV-6 antigens have been found in the retinas of patients with acquired immunodeficiency syndrome (AIDS) with and without AIDS-associated retinitis [13]. Fillet et al. found HHV-6 in the retinas of patients with AIDS-associated retinitis but not in HIV-seropositive patients with a normal fundus or in HIV-seronegative patients [14]. Our patient was healthy but had a high titer of anti-HHV6 IgG antibodies, which suggested reactivation, although we do not know what the trigger for the reactivation of HHV-6 was. Interestingly, our patient's infection was resolved with systemic corticosteroid alone without any antiviral agent. He was healthy and reactivation of latent HHV-6 would have induced his ocular inflammation; thus, these factors might affect the clinical therapeutic course.

Cell-free herpes virus DNA has been detected in the aqueous humour and vitreous fluids of patients with uveitis [15, 16]. We used multiplex PCR, which has the advantage of combining several different primer pairs in the same amplification reaction with the net result of producing different specific virus-amplicons [17]. Therefore, multiplex PCR can be used to detect the presence of different viruses in the same samples. Sugita et al. [18] used multiplex PCR to detect human herpesvirus genomes in the ocular fluids of patients with uveitis and reported that HHV-6 DNA was detected in only 1 patient [11] and HHV-7 and HHV-8 were not detected in any patient.

In our case, the titers for anti-VZV IgG and anti-CMV IgG antibodies were high in the serum, but multiplex PCR showed that VZV and CMV DNAs were negative in the aqueous fluid and only HHV-6 DNA was detected. Thus, we supposed that HHV-6 was the cause of the ocular inflammation because no other pathogenic agents were found.

In conclusion, the ocular infection caused by HHV-6 is still not well known. However, we should consider HHV-6 infection in patients with mutton-fat keratic precipitates, ocular hypertension, vitreous opacity, optic disc edema, retinal arteritis, and retinitis, which are characteristic of HHV infection of the eye. Multiplex PCR using the aqueous humor is effective in detecting the genomic DNA of HHV-6.

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