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Case Report

Human encephalitis complicated with bilateral acute retinal necrosis associated with pseudorabies virus infection: A case report

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ABSTRACT

We report the case of a patient who presented with viral encephalitis and a pulmonary infection complicated with bilateral acute retinal necrosis after direct contact with diseased swine. Next-generation sequencing of the cerebrospinal fluid and vitreous humor detected pseudorabies virus (PRV) simultaneously. Intravenous acyclovir and dexamethasone treatment improved the symptoms of encephalitis, and vitrectomy surgery with silicone oil tamponade was used to treat the retinal detachment. This case implies that PRV can infect humans; thus, self-protection is imperative when there is contact with animals.

Introduction

Pseudorabies virus (PRV), also known as Suid herpesvirus and Aujeszky's disease virus, primarily infects the members of the Suidae family and can potentially infect different hosts, such as horses, dogs, and cattle (Ehlers et al., 2007). Although the susceptibility of man to PRV has not been confirmed (Wozniakowski and Samorek-Salamonowicz, 2015), previous reports have indicated that the infection can lead to viral encephalitis or endophthalmitis (Ai et al., 2018; Mravak et al., 1987; Yang et al., 2019).

Acute retinal necrosis (ARN) is a rare viral disease of the retina characterized by well-demarcated areas of retinal necrosis in the peripheral retina, occlusive vasculopathy, and vitreous inflammation (Holland, 1994). In most of the reported cases, ARN has been caused by varicella zoster virus (VZV) or herpes simplex virus type 1 (HSV-1); PRV infection in ARN is rare.

This article reports a human case of viral encephalitis combined with bilateral ARN that was suspected to be caused by PRV infection.

Case report

A 44-year-old male was admitted to Qilu Hospital of Shandong University (Jinan, China) with fever lasting 11 days and unconsciousness with convulsions for 3 days. His daily work was to dispose of diseased swine and sell pork. Chest computed tomography (CT) at another hospital had indicated bilateral pulmonary inflammation. Magnetic resonance imaging (MRI) of the brain showed high signal intensity in T2-weighted images (T2WI), hypointensity in T1-weighted images (T1WI), hyperintense foci in T2-FLAIR sequences, and diffusion-weighted imaging (DWI) in the bilateral temporal lobe and hippocampus; the left lesion was more severe than that on the right side (Figure 1A).

PCR using blood tested negative for JC polyomavirus (JCV), Epstein–Barr virus (EBV), human cytomegalovirus (CMV), and HSV-1. A cerebrospinal fluid (CSF) sample of about 5 ml was obtained by lumbar puncture for next-generation sequencing

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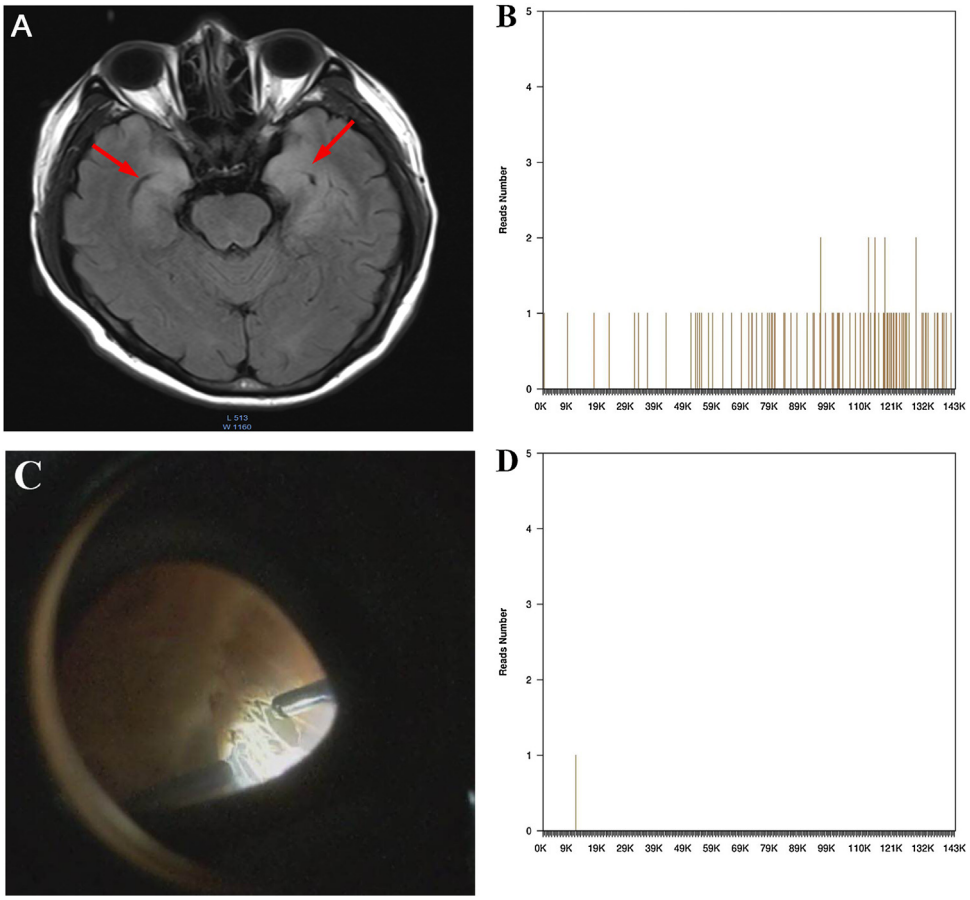

Figure 1. (A) Cranial MRI at the initial visit (before antiviral therapy), showing abnormal T2-FLAIR hyperintensity signals in the bilateral medial temporal lobe and hippocampus. (B) Sequencing of Suid herpesvirus 1 (pseudorabies virus) yielded a total coverage of 3.35% in the cerebrospinal fluid sample. (C) Peripheral retinal necrosis and retinal detachment were observed during vitrectomy of the left eye. (D) Sequencing of Suid herpesvirus 1 (pseudorabies virus) yielded a total coverage of 0.0286% in the vitreous humor sample. The GenBank accession number for the PRV whole genome sequence used as the source for comparison is BK001744.1.

(NGS) analysis (for details of the steps used in the NGS test, see the Supplementary material). The results showed 72 PRV reads, covering 3.35% of the nucleotide sequences (Figure 1B; Table 1). Therefore, the patient was diagnosed with viral encephalitis and a pulmonary infection (for diagnostic details of the pulmonary infection, see the Supplementary material), and was hospitalized in the intensive care unit for treatment of the virus infection using intravenous acyclovir, intravenous mannitol to adjust intracranial pressure, dexamethasone and gamma-globulin for anti-inflammation, and immune support.

Table 1
Pathogens detected using next-generation sequencing of cerebrospinal fluid and vitreous humor.[a]

Pathogen	Coverage,%	Depth	Unique reads
Cerebrospinal fluid NGS			
Virus			
Suid herpesvirus 1	3.35	1	72
Bacteria			
Staphylococcus warneri	0.13	1	22
Staphylococcus cohnii	0.03	1	11
Corynebacterium tuberculostearicum	0.08	1	8
Corynebacterium pseudogenitalium	0.08	1	7
Prevotella intermedia	0.05	1	20
Prevotella corporis	0.04	1	15
Vitreous humor NGS			
Virus			
Suid herpesvirus 1	0.03	1	2
Bacteria			
Staphylococcus pasteuri	0.12	1	14
Gordonia polyisoprenivorans	0.005	1	7
Leptospira noguchii	0.007	1	5
Rhodoferax ferrireducens	0.005	1	3

NGS, next-generation sequencing.
[a] Fungi, parasites, *Mycobacterium tuberculosis* complex, *Mycoplasma*, and *Chlamydia* were all negative, and no viruses other than pseudorabies virus were detected.

After his condition had stabilized, the patient was transferred to the Neurology Department for further treatment. After treatment for 3 months, the size of the lesion was smaller than that observed previously on cranial MRI. During these 3 months, he gradually developed blurred vision in both eyes (OU), but had not focused on the condition due to his weak health.

Due to the progressive visual loss in the left eye, the patient was transferred to the Department of Ophthalmology. The examination revealed that his best-corrected visual acuity was 5/20 in the right eye and hand movement/30 cm in the left eye, and the pupillary direct light reflex was negative in both eyes. The intraocular pressure was 11.2 mmHg in the right eye and 9.7 mmHg in the left. The vitreous opacity of the left eye prevented detailed visualization of the retina, but fundus examination could distinguish funnel-shaped retinal detachment, as well as an atrophied and thinned peripheral retina. The vitreous of the right eye was mildly opaque, and the fundus examination showed pallor of the optic disc with a clear border and loss of the foveal reflex. Retinal detachment in the left eye and the scar stage of ARN in both eyes was diagnosed clinically.

The left eye underwent pars plana vitrectomy with silicone oil tamponade. Vitreous opacity and complete retinal detachment

were observed during surgery, and the peripheral retina was thinned and had a broken, bug bite-like appearance (Figure 1C); some parts of the retinal neuroepithelial layer were almost completely destroyed. All of these symptoms were consistent with retinal necrosis. It was also found that the lesion had progressively spread from the periphery to the posterior pole.

Approximately, 5 ml of the vitreous humor sample was collected for pathogenic examination (for details of the NGS test, see the Supplementary material). NGS of the vitreous humor detected two sequences of PRV type 1, covering 0.0286% of the nucleotide sequences (Figure 1D; Table 1). Taking into consideration the positive results for PRV in both the CSF and vitreous humor, along with the patient's history of contact with diseased swine and his clinical symptoms, it was thought that PRV infection had probably led to the encephalitis complicated with bilateral retinal necrosis.

After the vitrectomy of the left eye, retinal holes of retinal necrosis with discrete borders in the peripheral retina were distinctly visible. Four months after vitrectomy of the left eye, retinal detachment of the right eye and recurrent detachment of the left eye with silicone oil tamponade occurred. Both eyes underwent surgery for retinal reattachment. It was speculated that the retinal detachment in the right eye was also probably because of PRV infection. Therefore, during surgery to the right eye, 5 ml of vitreous cavity fluid was extracted for NGS testing; however, PRV was not found.

The patient was then followed-up for 6 months. His visual acuity decreased to 2/20 in the right eye owing to a complicated cataract.

Discussion

Previously, PRV was thought to be transmitted only in swine. However, in 2017, Li et al. reported a case of endophthalmitis caused by PRV, which was highly homologous to three highly pathogenic PRV variants in China. Moreover, they discovered that PRV could interact with both human and swine cellular receptor nectin-1 via the envelope glycoprotein D (gD) on the viral surface (Li et al., 2017). This discovery might explain the possibility of zoonosis caused by PRV variants and stresses the necessity for researchers and workers in the breeding industry to increase awareness of self-protection.

A brief review of the literature identified seven cases of PRV infection in humans, including suspected and confirmed cases, reported up until June 2019 (Ai et al., 2018; Mravak et al., 1987; Yang et al., 2019). PRV leading to endophthalmitis was reported in only one of these cases; NGS detected PRV only in the vitreous humor and not in the CSF (Ai et al., 2018).

This article reports the first case of intraocular infection, in which the PRV sequence was detected in both the CSF and vitreous humor by NGS. In addition, the intraocular inflammation in this patient continued to progress even after a series of drug treatments and surgery. Although NGS testing was negative for PRV in the vitreous humor of the right eye, the patient's vision in the right eye gradually and continuously became impaired, owing to retinal detachment and a complicated cataract; meanwhile, retinal detachment recurred in the left eye after vitrectomy. Hafidi et al. found that numerous and prolonged intravitreal antiviral injections, used as adjunctive therapy, could improve the prognosis of ARN patients by decreasing the risk of retinal detachment and improving visual acuity (Hafidi et al., 2019). This discovery provides a new idea for the treatment of our patients in the future.

Although the pathogenicity of the detected PRV in our patient could not be determined, we consider that there is a strong correlation between PRV infection and our patient's diseases. First of all, PRV was the only virus detected in both the CSF and vitreous cavity fluid by NGS, although the sequence reads were low at 72 and 2, respectively. The use of antiviral treatment before detection might be the main reason for the limited number of virus sequences. Second, antiviral therapy was effective in controlling the nervous system and respiratory system infections. Furthermore, viral encephalitis may be a risk factor for retinal necrosis. The mechanism of ARN has yet to be elucidated; however, it has been indicated that the virus may be transmitted via the brain–optic nerve axon–retina pathway (Gaynor et al., 2001; Liang et al., 2015). Also, it has been shown that after PRV infects the rat retina, the virus can invade the central nervous system via anterograde trans-synaptic spread through axons in the optic nerve and also perhaps via retrograde transport through the oculomotor nucleus that innervates the extraocular muscles of the eye (Rassnick et al., 1998).

The detection of virus DNA sequences allows early antiviral treatment, which can reduce the risk of complications and limit disease progression. NGS is based on high-throughput sequencing technology. Microbial nucleic acid sequences in samples are analyzed and compared to those of existing microorganisms in the database, so as to identify microorganisms. Therefore, NGS not only offers the possibility of pathogen detection without prior knowledge of the target, but also provides a rapid and accurate diagnosis. In 2015, Guan et al. highlighted the feasibility of using NGS of the CSF as a tool to diagnose viral central nervous system infections (Guan et al., 2015). Moreover, in a recent study, NGS of CSF obtained from patients with meningitis or encephalitis improved the diagnosis of neurological infections (Wilson et al., 2019). However, if we had confirmed the PRV detection by PCR or Sanger sequencing as well, this would have given further support to our patient's infection with PRV.

In conclusion, PRV infection is a possible cause of encephalitis and ARN in the human, with serious consequences, including ocular inflammation that is difficult to control. Hence, protective measures for those in contact with animals are much needed. In addition, sensitive and accurate techniques of virus detection are of great significance for early diagnosis and treatment of PRV infection.

Author contributions

Wenjuan Wang, Xin Wang, and Ziwei Li collected the patient data and images. Yuwei Wang wrote the original manuscript with support from Hong Nian. Yan Cui was responsible for revising the draft. All authors contributed to the final manuscript and agreed to submit.

Ethical approval

Approval was given by the patient for the reporting of his case details.

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Conflict of interest

All authors declare no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.09.019.

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