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Characteristics of human encephalitis caused by pseudorabies virus: A case series study

Xue Yang[a], Hongzhi Guan[b], Chen Li[c], Ying Li[d], Shengjun Wang[a], Xiuhe Zhao[a], Yuying Zhao[a,*], Yiming Liu[a,*]

[a] Department of Neurology, Qilu Hospital of Shandong University, Jinan, China
[b] Department of Neurology, Peking Union Medical College Hospital, Beijing, China
[c] Department of Intensive Care Unit, Qilu Hospital of Shandong University, Jinan, China
[d] Department of Geriatric Medicine, Qilu Hospital of Shandong University, Jinan, China

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ABSTRACT

Background: Pseudorabies virus (PRV) has been thought to cause diseases only in animals. However, recent studies have shown that PRV can also cause illnesses in humans.
Methods: This was a case series study. The cases of five patients with clinical symptoms of acute encephalitis, which were confirmed to be caused by PRV infections, were reviewed.
Case presentation: The five patients all had jobs involving the handling of pigs. They had acute onset and rapid progression of clinical presentations, which were consistent with central nervous system infections. Four of them had respiratory failure, which required ventilator support. Brain magnetic resonance imaging showed abnormal signals in the bilateral temporal lobes and insular cortex in all five patients, bilateral frontal lobes in one patient, and caudate nucleus in one patient. Cerebrospinal fluid analysis results were consistent with a viral infection. Next-generation sequencing of the cerebrospinal fluid confirmed the presence of PRV. All patients received human immunoglobulin, glucocorticoids, antiviral agents, and symptomatic supportive treatments. All patients survived until discharge, but suffered from various sequelae. Pneumonia was the most common complication during the disease course.
Conclusions: PRV encephalitis should be included in the differential diagnosis of patients with a clinical presentation of central nervous system infection, especially for those who have had recent contact with pigs.

Introduction

Pseudorabies virus (PRV) is a double-stranded DNA herpes virus and a member of the α-herpesviridae subfamily (Pomeranz et al., 2005). PRV primarily infects swine, with only sporadic cases in developed countries, but with possible endemic outbreaks in developing countries (Muller et al., 2011; Yu et al., 2014). Similar to other herpes viruses, PRV is highly neurotropic and can infect the nervous system by trans-synaptic passage and retrograde axonal transportation (Pomeranz et al., 2005). Humans are not the natural hosts for PRV and have generally been thought to be refractory to PRV infections (Tischer and Osterrieder, 2010; Wozniakowski and Samorek-Salamonowicz, 2015). However, there have been recent case reports indicating that PRV can cause human endophthalmitis and encephalitis (Ai et al., 2018; Zhao et al., 2018). This suggests that more studies should be performed to investigate human PRV infections.

In the current study, the cases of five patients with clinical symptoms of acute encephalitis that were confirmed to be caused by PRV infection are reported. Their clinical characteristics and management approaches are discussed.

Methods

A case series study was performed in which the cases of five patients (four male and one female) with acute PRV encephalitis were reviewed. These cases of PRV encephalitis were confirmed by next-generation sequencing of cerebrospinal fluid (CSF) (Zhao et al., 2018). The patients presented to our hospital between February and April, 2018, and were treated with human immunoglobulin 0.4 g/kg/day for 5 days, glucocorticoids, antiviral agents, and symptomatic supportive

* Corresponding authors at: Department of Neurology, Qilu Hospital of Shandong University, No. 107 West Wenhua Road, Jinan 250012, China.
E-mail address: amyliu831@163.com (Y. Liu).

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care. All patients survived until hospital discharge. Informed consent was obtained from the healthcare proxies.

Case presentations

Case 1

A 50-year-old man who worked as a pig slaughterer presented to the hospital on February 18, 2018. On the day he attended the hospital, he had a fever (highest temperature 39.0 °C), which was accompanied by headache and visual disturbance. On the day before he presented, the patient had started to have episodic altered mental status, facial and extremity convulsions, and urinary and stool incontinence. These events happened more than 10 times a day, with each episode lasting for 10 s. The patient had no previous medical history, except an injury to the fourth finger on the right hand, which had been sustained when he was kicked by a pig 5 days ago (Figure 1A). Physical examination revealed a comatose man with nuchal rigidity. Both Kernig's and Brudzinski's signs were positive. A lumbar puncture was performed and CSF analysis showed a white blood cell (WBC) count of 4×10^6/l (which increased to 14×10^6/l with 48% small lymphocytes and 52% monocytes on day 9 after hospitalization), glucose of 4.7 mmol/l, and protein of 0.4 g/l. The tryptophan test, India ink staining, and bacterial smear were all negative. Next-generation sequencing of the CSF detected PRV with 37 unique sequence reads and 3.9% coverage (Figure 1B). Brain magnetic resonance imaging (MRI) showed intense T1 and T2 signal changes in the bilateral frontal temporal lobes and insular cortex (Figure 1C, D). On day 27, when he was discharged from the hospital, he had slow mental responses with occasional seizures. His modified Rankin Scale (mRS) score was 3.

Case 2

A 50-year-old woman who worked as a pork cutter presented to the hospital on March 3, 2018. Six days ago, she had started to have a fever (highest temperature 38.6 °C) and experience memory loss. Two days ago, she had gradually fallen into a coma, with episodic extremity convulsions, and had then developed respiratory failure. She was immediately intubated and admitted to the medical intensive care unit. The patient had a history of a hand injury at work 7 days ago (Figure 2A). Physical examination showed a medically sedated woman with a Glasgow Coma Scale (GCS) score of 3. She had nuchal rigidity but negative Kernig's and Brudzinski's signs. CSF analysis on day 4 after hospitalization showed a WBC count of 26×10^6/l (66% small lymphocytes and 18% monocytes), lactate of 2.8 mmol/l, glucose of 3.9 mmol/l, and protein of 0.9 g/l. The tryptophan test and India ink staining were negative. Next-generation sequencing of the CSF detected PRV with 20 unique sequence reads and 1.9% coverage (Figure 2B). Brain MRI showed abnormal signals in the bilateral temporal lobes and insular cortex (Figure 2C, D). After hospitalization for 27 days, the patient was discharged to a local hospital under ventilator support through a metal tracheostomy tube.

Case 3

A 43-year-old man who worked as a sick pig handler presented to the hospital on March 27, 2018. He had experienced a persistent fever

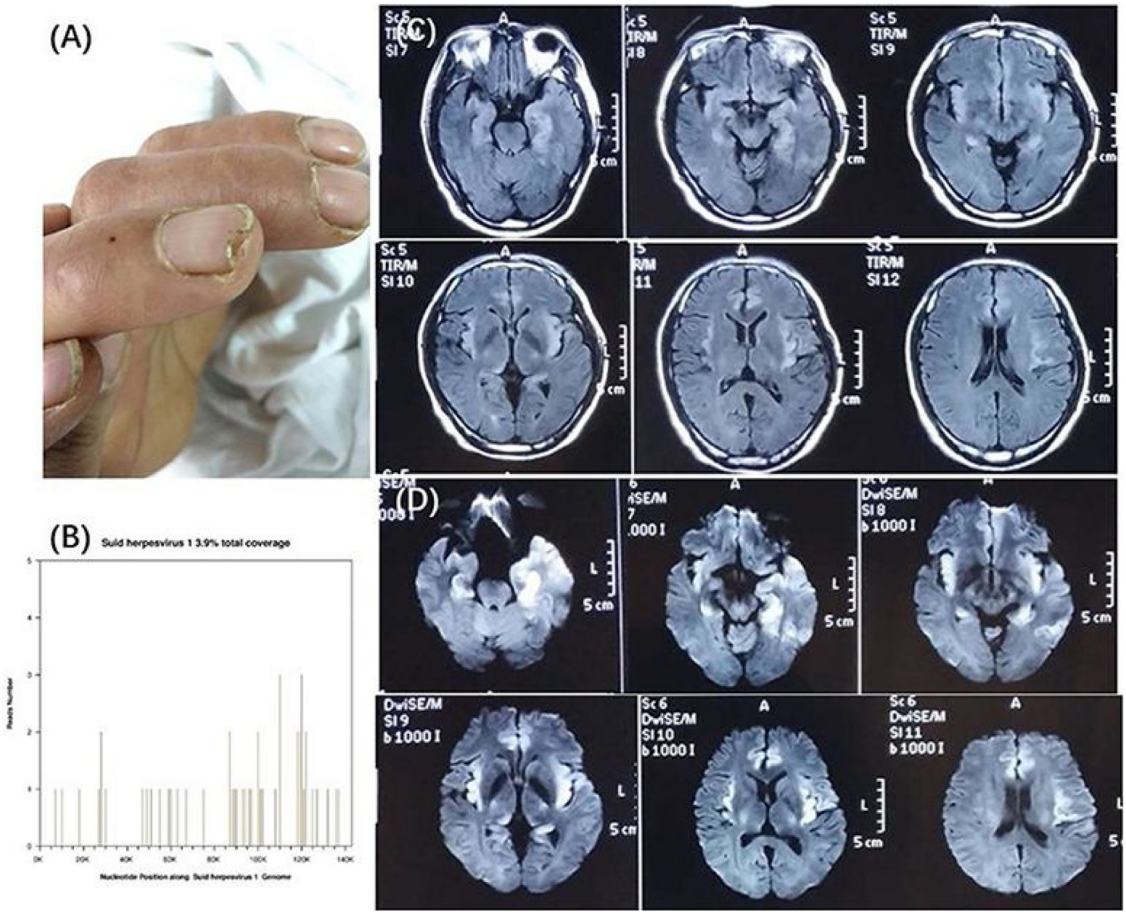

Figure 1. Case 1. (A) Injury to the fourth finger on the right hand. (B) Next-generation sequencing of the cerebrospinal fluid detected pseudorabies virus with 37 unique sequence reads and 3.9% coverage. (C) and (D) Brain MRI showed intense T1 and T2 signal changes in the bilateral frontal temporal lobes and insular cortex.

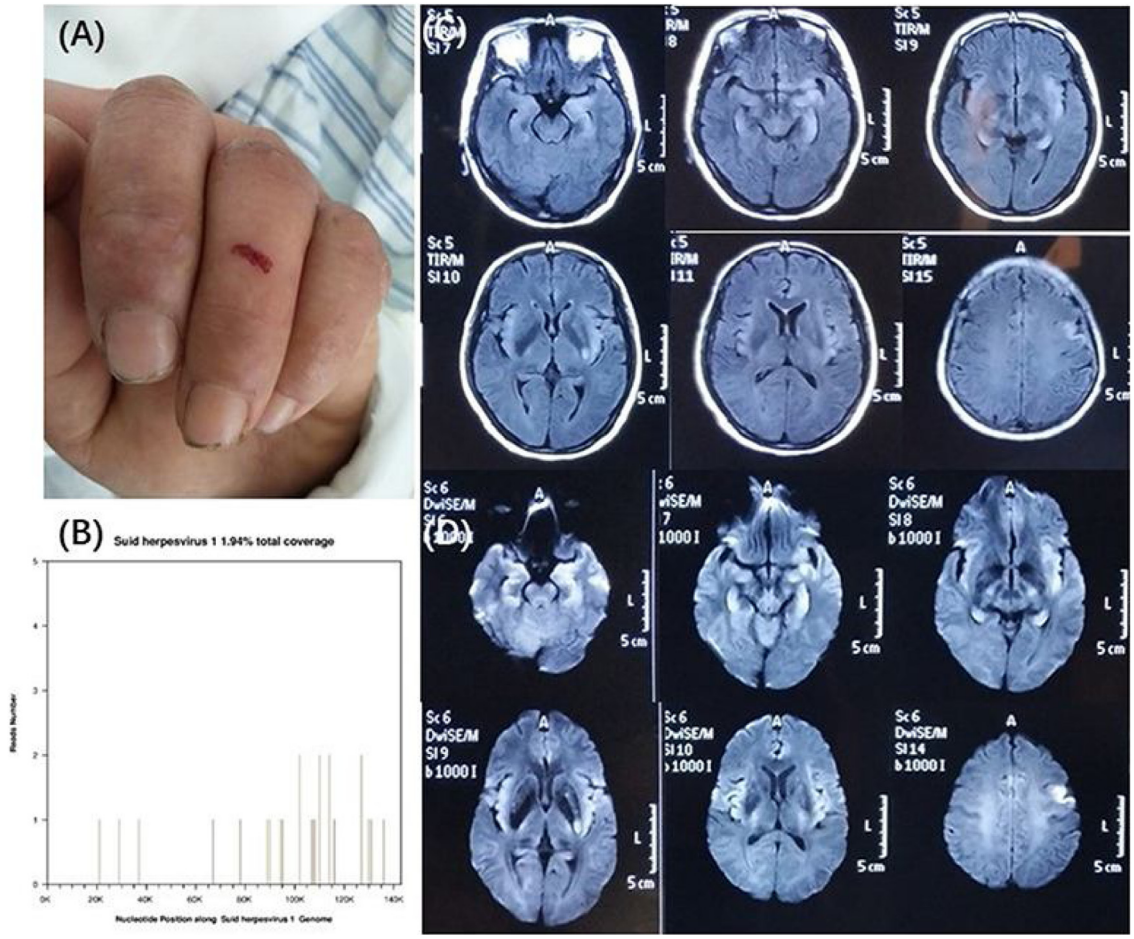

Figure 2. Case 2. (A) Injury to the fourth finger on the left hand. (B) Next-generation sequencing of the cerebrospinal fluid detected pseudorabies virus with 20 unique sequence reads and 1.9% coverage. (C) and (D) Brain MRI showed abnormal signals in the bilateral temporal lobes and insular cortex.

and altered mental status with extremity tremors during the prior 11 days. He had sustained a hand injury at work 18 days ago (Figure 3A). The patient rapidly developed respiratory failure and was intubated. Physical examination showed a comatose man with a GCS score of 3, nuchal rigidity, and positive Kernig's and Brudzinski's signs. CSF analysis showed a WBC count of 24×10^6/l with 20% monocytes (which decreased to 4×10^6/l on day 14 after hospitalization), glucose of 4.1 mmol/l, and protein of 0.5 g/l. The tryptophan test and India ink staining were both negative. Next-generation sequencing of the CSF detected PRV with 72 unique sequence reads and 3.4% coverage (Figure 3B). Brain MRI showed abnormal signals in the bilateral temporal lobes and insular cortex, with more significant signals on the left side (Figure 3C, D). On day 29 after hospitalization, the patient could identify relatives and follow simple instructions to raise his hands. The patient was transferred to the rehabilitation department. At the clinical follow-up 1 month later, funduscopic examination revealed retinal arterial stiffness with exudation and optic nerve atrophy (Figure 3E, F). Four months after disease onset, the patient was hospitalized in the ophthalmology department due to progressive vision loss. Next-generation sequencing of the vitreous humor detected the unique sequence number 2 of PRV.

Case 4

A 59-year-old man who worked as a porker cutter presented to the hospital on April 23, 2018. Seven days ago, the patient had started to have a high temperature of between 39.0 °C and 40.5 °C. He had also experienced episodic extremity convulsions starting 5 days ago and gradually went into respiratory failure. The patient had a history of a hand injury at work. The patient was immediately intubated and admitted to the hospital. Physical examination showed a medically sedated man with a GCS score of 4, positive nuchal rigidity, and negative Kernig's and Brudzinski's signs. CSF analysis showed a WBC count of 23×10^6/l with 87% monocytes (which decreased to 4×10^6/l on day 14 after hospitalization), glucose of 6.0 mmol/l, and protein of 0.4 g/l. The tryptophan test and India ink staining were both negative. Next-generation sequencing of the CSF detected PRV with 16 unique sequence reads and 0.4% coverage (Figure 4A). Brain MRI showed abnormal signals in the left temporal lobes and bilateral insular cortex, with more significant signals on the left side (Figure 4B, C). After hospitalization for 27 days, the patient was discharged to a local hospital under ventilator support through a metal tracheostomy tube.

Case 5

A 50-year-old man who worked as a pork cutter presented to the hospital on April 26, 2018. Two weeks ago, he had started to have a fever (highest temperature 41 °C). Ten days ago, he had started to experience extremity convulsions and altered mental status, and gradually developed respiratory failure. He had no significant history of recent injury. He was immediately intubated and admitted to the hospital. A tracheostomy was performed later on, due to a prolonged course of intubation. Physical examination showed a medically sedated man with a GCS score of 3, mild nuchal rigidity, and negative Kernig's and Brudzinski's signs. CSF analysis

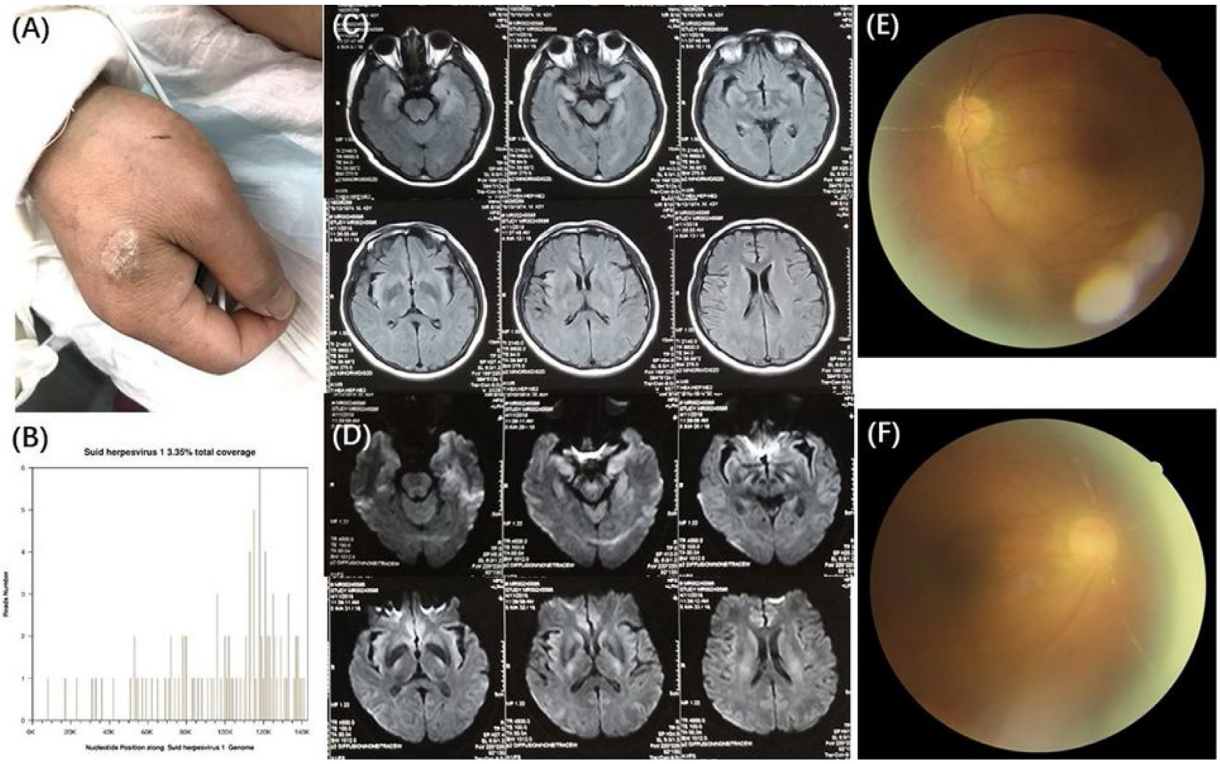

Figure 3. Case 3. (A) Injury to the right hand. (B) Next-generation sequencing of the cerebrospinal fluid detected pseudorabies virus with 72 unique sequence reads and 3.4% coverage. (C) and (D) Brain MRI showed abnormal signals in the bilateral temporal lobes and insular cortex., with more significant signals on the left side. (E) and (F) Funduscopic examination revealed retinal arterial stiffness with exudation and optic nerve atrophy.

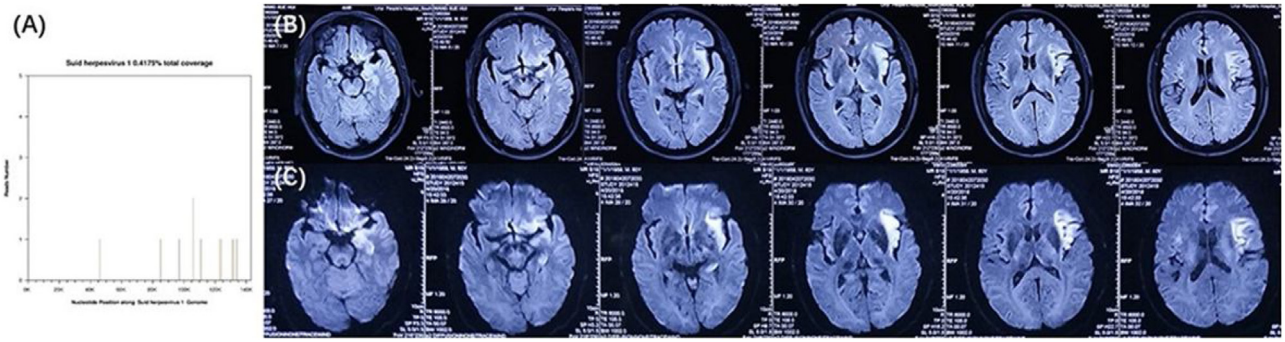

Figure 4. Case 4. (A) Next-generation sequencing of the cerebrospinal fluid detected pseudorabies virus with 16 unique sequence reads and 0.4% coverage. (B) and (C) Brain MRI showed abnormal signals in the left temporal lobes and bilateral insular cortex, with more significant signals on the left side.

showed a WBC count of 12×10^6/l with 98% monocytes (which increased to 32×10^6/l with 70% lymphocytes and 30% monocytes 3 days later), glucose of 4.8 mmol/l, and protein of 0.3 g/l. The tryptophan test and India ink staining were both negative. Next-generation sequencing of the CSF detected PRV with two unique sequence reads and 0.1% coverage (Figure 5A). Brain MRI showed abnormal signals in the bilateral temporal lobes, insular cortex, and caudate nucleus (Figure 5B, C). After endotracheal intubation, mechanical ventilation, and intravenous immunoglobulin, antiviral, anti-epileptic, and glucocorticoid treatments, his temperature gradually subsided to the normal range and the frequency of seizures decreased. One month after disease onset, his visual acuity started to decrease gradually. Ultrasound examination showed vitreous opacity, fundus optic atrophy, bilateral retinal edema, and left retinal detachment. During the clinic follow-up visit 1 month after hospital discharge, a funduscopic examination showed lens and vitreous opacity, as well as optic nerve atrophy (Figure 5D). Ultrasound showed left eye ametropia and posterior scleral staphyloma, as well as vitreous opacity and traction. Forty days after disease onset, the patient developed fever again. A repeat lumbar puncture showed an increased intracranial pressure of 220 cm H_2O, with a cell count of 22×10^6/l and protein level of 1.1 g/l. CSF autoimmune brain antibody was negative. Repeat brain MRI showed that the lesions in the bilateral frontal temporal lobes, insular lobe, cingulate gyrus, left thalamus, and bilateral basal ganglia were enlarged (Figure 5E, F).

Results

All of these patients received intravenous human immunoglobulin 0.4 g/kg/day for 5 days, glucocorticoids, antiviral agents, and symptomatic supportive treatments. Their clinical characteristics, examination results, treatments, complications, and outcomes are summarized in Tables 1–3.

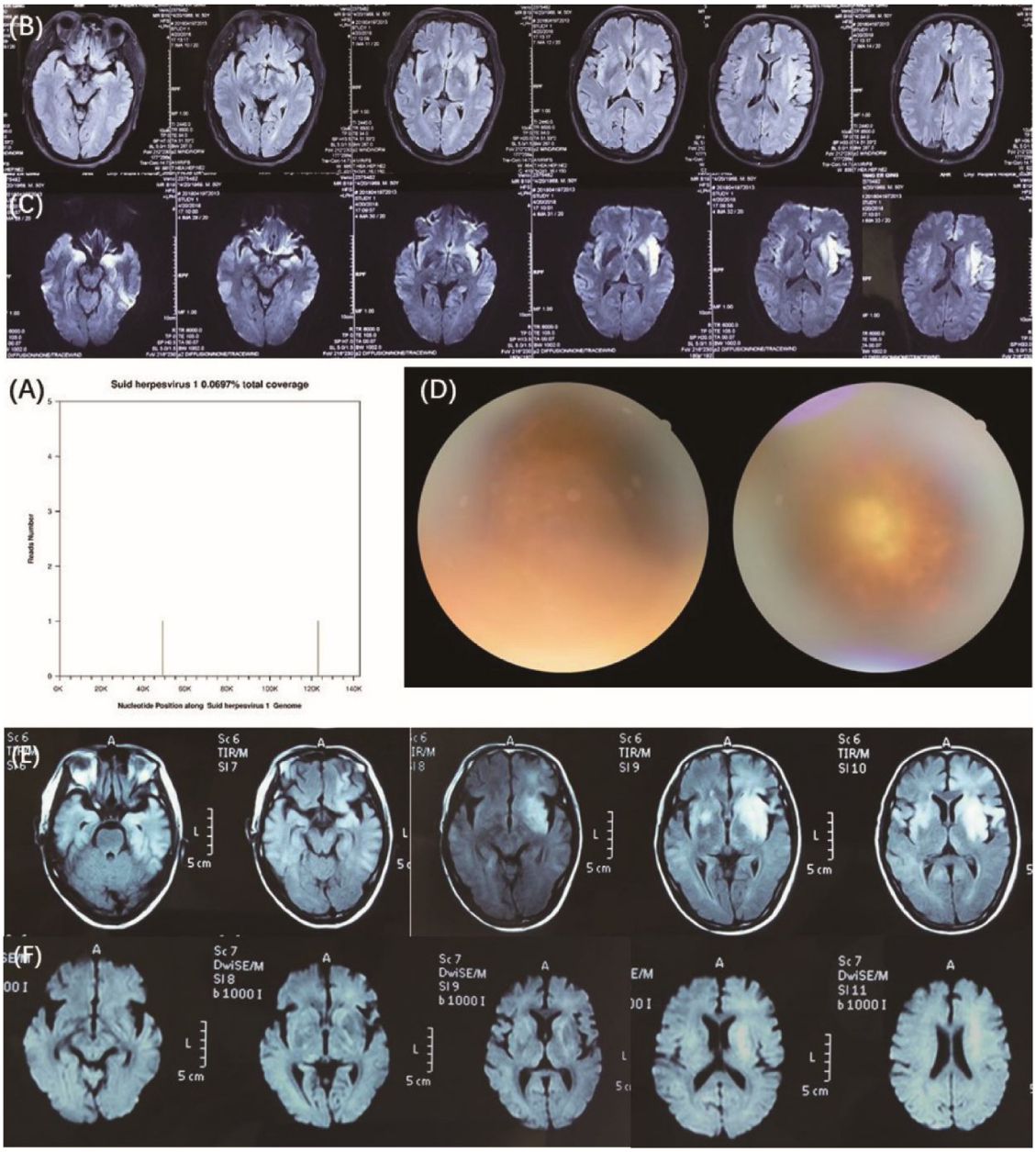

Figure 5. Case 5. (A) Next-generation sequencing of the cerebrospinal fluid detected pseudorabies virus with two unique sequence reads and 0.1% coverage. (B) and (C) Brain MRI showed abnormal signals in the bilateral temporal lobes, insular cortex, and caudate nucleus. (D) Funduscopic examination showed lens and vitreous opacity, as well as optic nerve atrophy. (E) and (F) Repeat brain MRI showed that the lesions in the bilateral frontal temporal lobes, insular lobe, cingulate gyrus, left thalamus, and bilateral basal ganglia were enlarged.

Discussion

PRV is primarily hosted in swine, but other mammals, such as dogs, cats, raccoons, rodents, and rabbits, can also catch PRV infections. Humans were thought to have resistance to PRV infections (Tischer and Osterrieder, 2010; Wozniakowski and Samorek-Salamonowicz, 2015). However, recent case reports have suggested that PRV can cause human infections (Ai et al., 2018; Zhao et al., 2018). In the current case series report, we also show that five patients with clinical symptoms of encephalitis were confirmed to have PRV in their CSF. Although none of them died during their hospital stay, all five of these patients suffered from various degrees of morbidity. The results of this study should remind physicians to rule out PRV infection in patients with clinical symptoms of encephalitis, especially in those working with pigs. The high incidence of human PRV infections identified here might be related to the high prevalence of PRV in swine in China (Gu et al., 2018; Liu et al., 2018).

In mammals, PRV usually causes respiratory or central nervous system (CNS) infections. There are three pathways for PRV to spread: (1) tonsils and pharyngeal epithelium cells → olfactory nerve and glossopharyngeal nerve → spinal cord → cerebral cortex pathway; (2) tonsils and nasopharyngeal epithelium cells → lymphatic vessels → lymph nodes → olfactory nerves, glossopharyngeal nerve, and distal trigeminal nerve → trigeminal nerve → pons and spinal cord → cerebellum and cerebral cortex pathway; (3) local uptake or attachment to leukocytes → viremia → whole body tissue pathway. No study has yet been performed to investigate the

Table 1
Clinical characteristics and examination results of five patients with encephalitis caused by pseudorabies virus.

Characteristics	Patient number				
	1	2	3	4	5
Age, years	50	50	43	59	50
Sex	Male	Female	Male	Male	Male
Occupation	Pig slaughterer	Pork cutter	Sick pig handler	Pork cutter	Pork cutter
Injury at work	Yes	Yes	Yes	Yes	No
Interval after injury	5 days	7 days	7 days	10 days	Denied injury
Symptoms	Fever, headache, seizure, coma	Fever, headache, seizure, coma	Fever, seizure, coma	Fever, seizure	Fever, seizure, coma
Signs					
Nuchal rigidity	Yes	Yes	Yes	Yes	Yes
Kernig's and Brudzinski's signs	Yes	No	Yes	No	No
Respiratory failure	No	Yes	Yes	Yes	Yes
Hepatic dysfunction	Yes	Yes	No	No	Yes
Brain MRI	Abnormal frontal temporal lobes and insular cortex	Abnormal temporal lobes and insular cortex	Abnormal temporal lobes and insular cortex	Abnormal left temporal lobes and insular cortex	Abnormal temporal lobes, insular cortex, caudate nucleus

MRI, magnetic resonance imaging.

Table 2
Cerebrospinal analysis of five patients with encephalitis caused by pseudorabies virus.

Characteristics	Patient number								
	1		2	3		4		5	
Interval after injury	Day 5	Day 14	Day 9	Day 10	Day 14	Day 5	Day 11	Day 12	Day 15
Opening pressure	180	102	130	–	290	–	165	–	165
WBC, $\times 10^6$/l	4	14 L 48%, M 52%	26 L 66%, M 18%	24 M 20%	4	23 M 87%	4	12 M 98%	32 L 70%, M 30%
Glucose, mmol/l	4.7	3.9	3.9	4.1	3.5	6.0	6.9	4.8	3.7
Protein, g/l	0.4	0.3	0.9	0.5	0.6	0.4	0.5	0.3	0.5
Chloride, mmol/l	119	128	125	108	123	126	142	–	120
Lactate, mmol/l	–	2.3	2.8	–	2.3	–	2.5	–	2.9
PRV sequencing	37 copies (day 10)		20 copies (day 27)	72 copies (day 13)		16 copies (day 11)		2 copies (day 15)	

WBC, white cell count; L, lymphocyte; M, monocyte; PRV, pseudorabies virus.

Table 3
Treatments, complications, and outcomes of five patients with encephalitis caused by pseudorabies virus.

Characteristics	Patient number				
	1	2	3	4	5
Treatments	IVIG, GC, antiepileptic, antiviral, antibiotics	IVIG, GC, antiepileptic, antiviral, antibiotics	IVIG, GC, antiepileptic, antiviral, antibiotics	IVIG, GC, antiepileptic, antiviral, antibiotics	IVIG, GC, antiepileptic, antiviral, antibiotics, antacids
Intubation	No	Yes	Yes	Yes	Yes
Complications	Pneumonia	Pneumonia	Pneumonia	Pneumonia, hypernatremia	Pneumonia, peptic ulcer
Outcome	Slow responses, occasional seizures, mRS 4	Ventilator-dependent	Follow simple instructions, mRS 3	Ventilator-dependent	Slow responses, mRS 3
Eye involvement	No	No	Yes; blurry vision	No	Yes; blindness

IVIG, intravenous human immunoglobulin; GC, glucocorticoids; mRS, modified Rankin Scale.

infectious pathway in humans. However, from animal studies, it is possible that PRV affects not only the brain but also other organ systems in the human body, causing serious outcomes. It is important to consider PRV infection in the differential diagnosis and to select appropriate tests in order to make an early diagnosis and provide appropriate treatment.

The five patients in this case series had the following common characteristics: (1) a job involving the handling of pigs. All of the patients worked with pigs and most of them reported a hand injury at work prior to their clinical symptoms. This suggests that viral transmission from pig to human is possible, although the exact mechanism needs to be clarified. (2) Acute onset with rapid progression. Within 1–2 weeks of disease onset, all five patients had developed severe clinical symptoms and a life-threatening illness. (3) Clinical characteristics mainly of a CNS infection, but also possibly involving other systems, including the pulmonary and hepatic systems. The patients started with a high fever and headache, with rapid progression to signs of a CNS infection, including altered mental status, seizures, and coma, with nuchal rigidity and positive Kernig's and Brudzinski's signs. Four of the five

patients had respiratory failure and required endotracheal intubation and ventilator support. Three of five patients had hepatic dysfunction according to laboratory test results. (4) Optic involvement. Two of the five patients had optic involvement identified during their hospital admission or at a clinical follow-up visit. Treatment had improved their CNS and respiratory symptoms, but seemed not to stop the progression of the optic involvement. Examinations revealed lens and vitreous opacities, optic nerve atrophy, and retinal edema and exfoliation. A previous study has shown that herpes simplex virus (HSV) can replicate in epithelial cells and enter the sensory neurons through the sensory nerve terminals (Aranda and Epstein, 2015). In addition, HSV can also cause a latent infection in the CNS and replicate in the neurons (Sloutskin et al., 2014). Maertzdorf et al. identified the same virus strain in the CSF and vitreous humor in two patients with HSV encephalitis and acute retinal necrosis syndrome. They concluded that HSV could remain latent in the frontal lobe and optic chiasm after acute brain infection. When the virus becomes reactivated, it can be transmitted to the retina through the optic nerve (Maertzdorf et al., 2001). (5) All five of the patients received intravenous human immunoglobulin, glucocorticoids, antiepileptic, antiviral, and antibiotic treatments, and all survived until hospital discharge. Pneumonia was a frequent complication during the disease course.

The underlying pathological pathway for PRV in humans is unknown. Animal and in vitro studies have shown that PRV infection can activate the pulmonary mTOR signal pathway and induce cell apoptosis, which might be responsible for the rapid onset of respiratory failure (Yuan et al., 2009). Another study showed that wild-strain PRV can infect retinal ganglion cells and then migrate in a retrograde manner along the optic nerve to affect secondary neurons in the optic chiasm (Ambagala et al., 2003). Another study found that PRV was a retrograde cross-synaptic marker in the CNS, due to its capability of self-replication and its trans-synaptic and neurotropic transmission properties (Enquist et al., 1994). These might explain the optic involvement during PRV infection.

A lumbar puncture should be performed early for patients with clinical signs of a CNS infection. In PRV encephalitis, CSF analysis showed results similar to those of other viral encephalitis, with a mildly or moderately elevated WBC count, lymphocyte or monocyte reactions, mildly elevated protein level, and normal glucose level. If there are no improvements in the clinical symptoms, repeated lumbar punctures should be considered to rule out other possibilities and monitor disease progression.

In the current study, brain MRI showed abnormal signals in the bilateral temporal lobes and insular cortex. One patient had bilateral frontal lobe abnormal signals and another patient had bilateral lenticular nucleus abnormal signals. A previous study also showed that PRV infection could involve the limbic system (amygdala, island leaf, and cingulate gyrus), basal ganglia, and brainstem, as well as the lenticular nucleus, caudate nucleus, and thalamus (Zhao et al., 2018). This might explain the clinical symptoms of altered mental status and frequent seizures. The brain MRI images of patients with PRV infections differ from those of patients with human HSV encephalitis. The abnormal signals in the latter infection are usually limited to the limbic system and almost never pass claustrum to involve the basal ganglia and thalamus. These characteristic brain MRI findings might be helpful in the differential diagnosis of PRV encephalitis.

In summary, this study showed that PRV infection could be one of the causes of human encephalitis. In patients with acute onset and rapid progression of clinical signs of CNS infection, especially those with recent contact with pigs, the differential diagnosis should include PRV encephalitis. Brain MRI and next-generation sequencing of CSF should be performed. Once the diagnosis has been made, prompt management including eye funduscopic examination, human immunoglobulin, glucocorticoids, antiviral, and symptomatic supportive treatments should be started. In addition, education on skin protection to minimize viral remission should be given to persons with close contact with pigs. When visual disturbance occur in patients with PRV encephalitis, early diagnosis and timely treatment with antiviral and corticosteroid therapy might prevent severe visual impairment, since acute retinal necrosis syndrome as a complication of the encephalitis could cause vision loss.

Authors' contributions

YZ and YL contributed to the study design; all authors collected the data and performed the data analysis; all authors prepared the manuscript.

Ethics approval and consent to participate

Ethical approval was given by the Ethics Committee of Qilu Hospital of Shandong University, China. All patients gave their written information consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Conflict of interest

All authors declare that they have no conflict of interest.

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