

CASE REPORT

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The underlying mechanism of Guillain-Barré syndrome in a young patient suffered from Japanese encephalitis virus infection: a case report

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Abstract

Background: The presentation of Guillain–Barré syndrome (GBS) caused by Japanese encephalitis virus (JEV) is uncommon, although clusters of GBS cases were observed in China in 2018. The underlying mechanism is unclear, particularly in individuals vaccinated against Japanese encephalitis in childhood.

Case presentation: We report a patient with acute flaccid paralysis involving four extremities and respiratory muscles, while magnetic resonance imaging of the brain and spine were standard. Electrophysiological examination displayed slowed motor nerve conduction speed and reduced evoked velocity amplitude. GBS was finally considered which was related to JEV infection verified by positive anti-JEV immunoglobulin M antibody and positive immunoglobulin G antibody in the serum. Unfortunately, the patient refused intravenous immunoglobulin and declined the use of mechanical ventilation again. He voluntarily withdrew from the hospital and died on the 36th day after the onset of illness. We also performed a review of previously reported related cases and discussed the underlying mechanism.

Conclusion: JEV infection-associated GBS is unusual. We should pay attention to the atypical manifestations of JEV infection and explore possible pathogenesis in particular individuals.

Keywords: Guillain-Barré syndrome, Japanese encephalitis virus, Vaccination, Pathogenesis

Background

The incidence rate of Japanese encephalitis (JE) is 30,000–50,000 cases yearly [1]. JE is a mosquito-borne zoonotic disease mainly occurring in eastern and southern Asia, caused by the Japanese encephalitis virus (JEV). The prevalence of JE has decreased in China due

to vaccination programs. JEV genotype 1 is currently circulating in China. The typical clinical manifestation includes fever, headache, vomiting, neurological symptoms, coma, convulsions, and respiratory failure [2]. Most cases with JEV-associated acute flaccid paralysis (AFP) met the case definition of Guillain–Barré syndrome (GBS), while a small number of cases were thought to have myelitis [3, 4]. Herein we report a young man with JEV infection who developed GBS after several days of fever. The underlying mechanism warrants further study.

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Case presentation

A young man aged 18 years first developed muscle weakness of the bilateral lower limbs, followed by fever, dizziness and muscle weakness of the neck and bilateral upper limbs. He had no gastrointestinal or respiratory symptoms. On the 5th day after illness onset (on October 3, 2018), he felt dyspnea without convulsions or impaired consciousness and was referred to the emergency room of our hospital. He was intubated and invasive mechanical ventilation was employed due to dyspnea progression. The brain's magnetic resonance imaging (MRI) was normal (Fig. 1C). Blood tests revealed elevated white blood cell counts ($11.79 \times 10^9/L$) and neutrophil count ($9.56 \times 10^9/L$). Anti-JEV immunoglobulin (Ig) M antibody (EEB-IgM, Enzyme immunoassay test kit, Shanghai B&C Biological Technology Company) was positive in his serum. Unexpectedly, a high level anti-JEV IgG antibody (JE detectTMIgG, ELISA, InBios) was also detected in his serum. Polymerase chain reaction (PCR) of serum was negative for JEV RNA. PCR was also negative for other viruses such as Zika, Dengue, West Nile, Forest encephalitis, Coxsackie, poliovirus, Echovirus, Enterovirus, and herpesviruses. The cerebrospinal fluid (CSF) showed

elevated leukocyte counts ($49 \times 10^6/L$, lymphocytic pleocytosis) and protein level (814 mg/L, normal range: 100–600 mg/L). Indian ink staining, acid-fast staining and bacterial and fungal culture of the CSF sample were all negative. Unfortunately, no CSF sample was available for anti-JEV IgM and JEV RNA testing. The patient was from a rural area in the Liaoning province of China, where a JEV outbreak occurred in the summer of 2018. He was vaccinated against JE in childhood at eight months and two years of age. He was medicated with methylprednisolone (500 mg per day) followed by tapering.

Ten days later, his condition partly improved. He refused to continue invasive ventilation though he still had respiratory disturbance with an elevated PaCO₂ of 58.0 mmHg and decreased PaO₂ of 72.0 mmHg (on intranasal oxygen therapy of 10 L/min). Despite lucidity, proper cognition, and functional bladder and bowel, he had marked disturbances in coughing, articulation, and swallowing with absence of pharyngeal reflex and disabled soft palate movement, indicating injured cranial nerves (bulbar paralysis). He performed pectoral type breathing without any thoracic breathing, suggesting respiratory myoparalysis. Examination revealed weakened

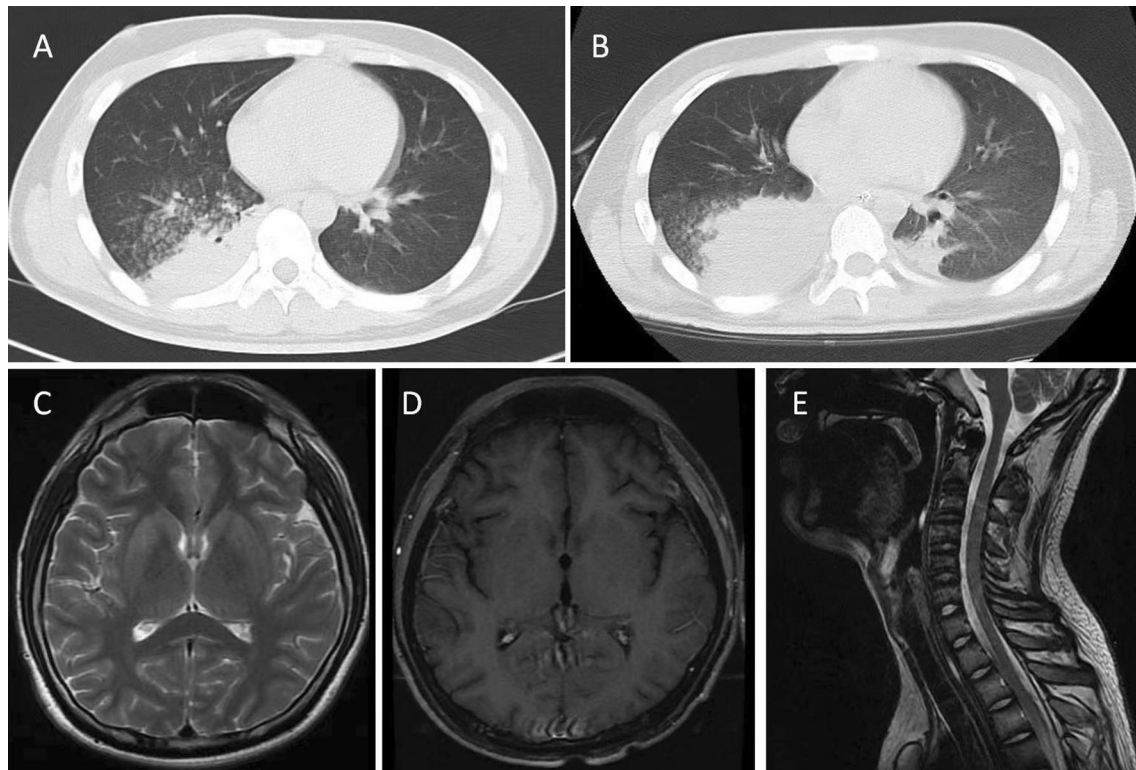


Fig. 1 The radiographs in this case. **A** At 19th day of illness onset, lung CT indicated consolidation in the right lung. **B** At 24th day of illness onset, lung CT indicated aggravated consolidation in the lower lobe of bilateral lung adjacent to the pleura, mainly in the right lung. **C** At 5th day of illness onset, brain MRI (T2 weighted image) was normal. **D** At 24th day of illness onset, enhanced brain MRI was normal. **E** At 24th day of illness onset, spine MRI (T2 weighted image) was normal

Table 1 Clinical features in patients with acute flaccid paralysis caused by Japanese encephalitis virus

Case numbers	Reference number/year of publication	Age (year)	Gender (M/F)	Area of report	Clinical presentations	Encephalitis	Brain MRI	JEV detection in serum/CSF	JE vaccination	Treatment	Outcome D/S/N
1	[3]/2007	22	1/0	Taiwan	AFP	No	Normal	JEV-IgM+/+	Yes	GC + MV	S
21	[5]/1994	6–58	18/3	India	GBS	No	NM	JEV-IgM+/+	NM	GC or MV	4/15/2
1	[6]/2014	23	1/0	China	GBS	No	Normal	JEV-IgM+/+	No	IG + GC	S
47	[11]/2020	*59 (24–63)	26/21	China	GBS	39	NM	JEV-IgM+/+	Yes(2)	IG(28) + GC(47) + MV(44)	S
12	[14]/1998	3–15	9/3	Vietnam	AFP including GBS(1)	Yes (4)	NM	JEV-IgM+/+	NM	No MV	S
1	[15]/2015	14	1/0	India	GBS	Yes	Abnormal	JEV-IgM+/+	NM	IG + MV	S
1	[16]/2021	43	0/1	China	GBS	Yes	Abnormal	JEV-IgM+/+	NM	IG + GC + MV + PAIA	S
1	PR	18	1/0	China	GBS	No	Normal	JEV-IgM+/ND	Yes	GC + MV	D

GBS Guillain-Barre syndrome; AFP acute flaccid paralysis; NM not mentioned; PR present report; D died; S survived; N no follow up; ND not done; IG immunoglobulins; GC glucocorticoid; MV mechanical ventilator; PAIA protein A immunoadsorption

*Median age (IQR)

muscle power in the left upper limb (grade 4/5), right upper limb (grade 2/5), and bilateral lower limbs (grade 2/5), which were improved compared to day after illness onset. The muscle tone of his four extremities was decreased. Deep tendon reflexes were decreased without pathological reflex and sensation disturbance.

Auscultation revealed a purring sound in bilateral lungs. Lung computed tomography (CT) indicated consolidation in the lower lobe of the right lung (Fig. 1A). The blood test was negative for the antibodies of Epstein–Barr virus, herpes simplex virus, varicella-zoster virus, cytomegalovirus and human immunodeficiency virus. On the 24th day after illness onset, repeated MRI of the brain and spine appeared normal (Fig. 1D, E). The patient refused a second lumbar puncture. The assay for anti-gangliosides antibodies was unavailable at our hospital. On the 27th day after illness onset, electrophysiology examination revealed abnormal findings including prolonged latency of H reflex in bilateral tibial nerves, reduced amplitude of evoked velocity in the right median nerve, and slowed motor conduction in the right tibial nerve, while the conduction of the sensory nerves was normal. JEV infection-associated GBS was considered, which agreed with Brighton criteria level 1. The patient declined intravenous Ig and mechanical ventilation. Despite applying of broad-spectrum antibiotics and sputum clearance with bronchoscopy, he developed progressive dyspnea, increased carbon dioxide retention, and respiratory acidosis (PaCO₂, 120 mmHg; PH, 7.185). Lung CT indicated aggravated consolidation in the lower lobe of bilateral lung, mainly in the right lung (Fig. 1B). He still refused mechanical ventilation and tracheotomy. He voluntarily withdrew from the hospital and died on the 36th day after illness onset.

We prepared a literature review of a total of 85 cases of JEV-associated AFP reported previously (Table 1), 73 cases were considered as GBS. There were 4 cases with a reported history of previous JE vaccination.

Discussion and conclusion

GBS is generally regarded as a post-infection immune-mediated disease. JEV infection is an important etiology of GBS in endemic regions [5]. Most patients with JEV-associated GBS did not receive the JE vaccination previously [6]. Our patient is similar to the case reported by Chung, et al [3] of a patient who had also received JE vaccination in childhood. The high ratio of IgG to IgM is a distinction between rapid seroconversion of IgM and IgG due to acute infections and IgG antibodies derived from previous vaccine viruses. All available vaccines belong to the JEV genotype 3 strain. A partial cross-protection between JEV genotype 1 and genotype 3 strain [1, 7] and the inferior protective efficacy due to inadequate

neutralizing antibody levels probably explain why JE vaccination could not provide complete protection.

Liaoning province is located in northeast of China, where neither Zika nor Dengue virus [8, 9] are endemic. Although Liaoning province had a low prevalence of JE [10], there was an outbreak of 69 cases with a 30.4% fatality rate in the summer of 2018, which was very similar to the prevalence of JEV infection in the north of Ningxia in 2018 [11]. JEV genotype 1 was the pathogen in that outbreak, and no cases were reported in children, indicating that the JEV vaccine was still effective. The chance of JEV detection by PCR in the blood and CSF is extremely low [4, 8]. Our patient was confirmed with JEV infection by positive anti-JEV IgM antibody in serum, a sensitive, specific, and early indicator of JEV infection. His characteristic clinical manifestation included weakness of the four extremities and respiratory myoparalysis accompanied by the involvement of several cranial nerves. Electrophysiology examination suggested decreased evoked potential amplitude and slowed conduction speed of motor nerves. Acute disseminated encephalomyelitis and acute transverse myelitis were excluded based on normal brain and spinal MRI images [4, 12]. Glucocorticoid-induced myopathy was also ruled out as his muscle paralysis preceded glucocorticoid application [13]. We must also differentiate between anterior horn cell myelitis [3, 14] and GBS [5, 15, 16]. Viral myelitis tends to present with a fever and a moderate pleocytosis in the CSF, while GBS typically presents a prodromal infection 1–2 weeks prior and an albumin cytologic dissociation in the CSF. However, anterior horn cell myelitis was not supported by the normal MRI of the spinal cord and slowed motor nerves conduction speed. Therefore, GBS was finally considered. The mortality of GBS is 2–10% [17]. GBS was involved in the pathogenesis of humoral and cellular immunity [16]. The underlying mechanism for the clusters of GBS cases in 2018 was unclear [11]. Molecular mimicry, anti-glycolipid autoantibody, and immune complexes were implicated in the pathogenesis of GBS, which caused a kind of demyelinating neuropathy or axonal neuropathy [18, 19]. Although this patient received two doses of JEV vaccine in childhood, another booster vaccine should be provided by reason of the reduced protective antibody levels over time or primary “low-responders” [20]. Moreover, the presence of high levels of anti-JEV IgG in early serum provided the possibility that antibody-dependent enhancement (ADE) between pre-existing antibody targeting genotype 3-derived JE vaccine and subsequent genotype 1 virus infection may play a role in the development of GBS [21].

In summary, JE combined with GBS shows an increasing trend in recent years. Rapid diagnosis and early application of intravenous Ig or plasma exchange will be

beneficial for GBS while glucocorticoids are not recommended [17, 21, 22]. JEV genotype 1 is currently circulating in China [23]. The longevity and titers of protective antibody responses induced by the JE vaccine depend on the type of vaccine, number of doses, and the immune status of hosts. Up to now, there is no standardized protocol for a neutralization test. A commercial kit for neutralizing antibody detection is unavailable. Therefore, another booster dose should be recommended approximately a decade after the first booster immunization. The protective role of genotype 3-derived JE vaccine in preventing genotype 1 virus infection needs additional attention.

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Author contributions

WY and YJ made the conception and design of the work. LS helped to collect the data of the case. LS, W-JY and WY wrote the manuscript. All authors carried out final approval of the version to be published.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

We had got the permission for publication from ethical board.

Consent for publication

Informed written consents for all treatment regimens were obtained from the patient. Informed written consent for being written and publication was obtained from the patient's father and mother.

Competing interests

The authors declare that they have no competing interests.

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References

- Zhang JS, Zhao QM, Guo XF, et al. Isolation and genetic characteristics of human genotype 1 Japanese encephalitis virus, China, 2009. *PLoS ONE*. 2011;6(1):e16418.
- Solomon T, Vaughn DW. Pathogenesis and clinical features of Japanese encephalitis and West Nile virus infections. *Curr Top Microbiol Immunol*. 2002;267:171–94.
- Chung CC, Lee SS, Chen YS, et al. Acute flaccid paralysis as an unusual presenting symptom of Japanese encephalitis: a case report and review of the literature. *Infection*. 2007;35(1):30–2.
- Verma R, Praharaj HN, Patil TB, Giri P. Acute transverse myelitis following Japanese encephalitis viral infection: an uncommon complication of a common disease. *BMJ Case Rep*;2012.
- Ravi V, Taly AB, Shankar SK, et al. Association of Japanese encephalitis virus infection with Guillain-Barre syndrome in endemic areas of south India. *Acta Neurol Scand*. 1994;90(1):67–72.
- Xiang JY, Zhang YH, Tan ZR, Huang J, Zhao YW. Guillain-Barre syndrome associated with Japanese encephalitis virus infection in China. *Viral Immunol*. 2014;27(8):418–20.
- Wei J, Wang X, Zhang J, et al. Partial cross-protection between Japanese encephalitis virus genotype I and III in mice. *PLoS Negl Trop Dis*. 2019;13(8):e0007601.
- Zhou CM, Liu JW, Qi R, et al. Emergence of Zika virus infection in China. *PLoS Negl Trop Dis*. 2020;14(5):e0008300.
- Wu T, Wu Z, Li YP. Dengue fever and dengue virus in the People's Republic of China. *Rev Med Virol*. 2022;32(1):e2245.
- Zhang H, Wang Y, Li K, Mehmood K, Gui R, Li J. Epidemiology of Japanese encephalitis in China (2004–2015). *Travel Med Infect Dis*. 2019;28:109–10.
- Wang G, Li H, Yang X, et al. Guillain-Barre Syndrome Associated with JEV Infection. *N Engl J Med*. 2020;383(12):1188–90.
- Chen WL, Liao MF, Chiang HL, Lin SK. A possible case of acute disseminated encephalomyelitis after Japanese encephalitis. *Acta Neurol Taiwan*. 2013;22(4):169–73.
- Pereira RM, Freire de Carvalho J. Glucocorticoid-induced myopathy. *Jt Bone Spine*. 2011;78(1):41–4.
- Solomon T, Kneen R, Dung NM, et al. Poliomyelitis-like illness due to Japanese encephalitis virus. *Lancet*. 1998;351(9109):1094–7.
- Bandyopadhyay D, Ganesan V, Choudhury C, et al. Two uncommon causes of Guillain-Barre syndrome: hepatitis E and Japanese encephalitis. *Case Rep Neurol Med*. 2015;2015:759495.
- Zang Q, Wang Y, Guo J, et al. Treatment of severe Japanese encephalitis complicated With Hashimoto's thyroiditis and Guillain-Barre syndrome With protein A immunoabsorption: a case report. *Front Immunol*. 2021;12:807937.
- Verboon C, van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry*. 2017;88(4):346–52.
- Cook SD, Dowling PC. the role of autoantibody and immune complexes in the pathogenesis of Guillain-Barre syndrome. *Ann Neurol*. 1981;9(Suppl):70–9.
- Hughes RA, Cornblath DR. Guillain-Barre syndrome. *Lancet*. 2005;366(9497):1653–66.
- Paulke-Korinek M, Kollaritsch H, Kundi M, Zwazl I, Seidl-Friedrich C, Jelinek T. Persistence of antibodies six years after booster vaccination with inactivated vaccine against Japanese encephalitis. *Vaccine*. 2015;33(30):3600–4.
- Raboni SM, Bonfim C, Almeida BM, et al. Flavivirus cross-reactivity in serological tests and Guillain-Barre syndrome in a hematopoietic stem cell transplant patient: a case report. *Transpl Infect Dis*. 2017;19(4):e12700.
- van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. *Lancet*. 2004;363(9404):192–6.
- Pan XL, Liu H, Wang HY, et al. Emergence of genotype I of Japanese encephalitis virus as the dominant genotype in Asia. *J Virol*. 2011;85(19):9847–53.

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