pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2024;20(1):106-108 / https://doi.org/10.3988/jcn.2023.0151

Chikungunya Encephalitis Presenting as Rhombencephalitis

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Dear Editor,

Chikungunya virus (CHIKV), a member of the *Alphavirus* genus, is primarily transmitted to humans by *Aedes aegypti* mosquitoes as a ribonucleic acid virus. This tropical disease was described during the 1950s in East/Central Africa but re-emerged in Indian Ocean islands and Africa during 2005 and 2006.[1] Although it is usually a nonfatal, self-limiting disease, CHIKV infection can manifest as various neurological complications.[2] Here we report the first case of a male infected with CHIKV who presented with rhombencephalitis in South Korea.

A 40-year-old male with an unremarkable medical history presented at the emergency room having experienced drowsiness, confusion, headache, and disequilibrium for 3 days. He had recently stayed in Cambodia for 5 months and returned to South Korea the day before this presentation. The patient was febrile (38.1°C) with otherwise normal vital signs and had no other systemic manifestations such as skin rash or arthralgia. Cerebrospinal fluid (CSF) analysis showed pleocytosis (white blood cells, 59/μL; 85% lymphocytes) and protein elevation (109 mg/dL) with a normal opening pressure (162 mmH_2O) and glucose levels (CSF glucose, 122 mg/dL; serum glucose, 197 mg/dL). Routine viral, bacterial, fungal, and mycobacterial polymerase chain reaction results were negative. The complete blood count revealed mild thrombocytopenia (hemoglobin, 17.4 g/dL; white blood cells, 6,460/μL; and platelets, 120,000/μL). Brain magnetic resonance imaging (MRI) revealed high-intensity lesions in diffusion-weighted imaging (DWI) in the splenium of the corpus callosum, right superior cerebellum, mid-ventral pons, bilateral ventral medulla, and mid-dorsal medulla, with no signal changes on the apparent-diffusion-coefficient map (Fig. 1A-C). Because we could not rule out the possibility of autoimmune encephalitis, we initiated intravenous high-dose methylprednisolone infusion (1 g/day) empirically for 5 days, which resulted in the fever gradually subsiding during the first week of admission. However, the patient persistently showed confusion, ataxia, and vertigo, along with newly developed intractable hiccups and horizontal diplopia. The 1-week follow-up MRI revealed newly appearing subtle enhancements along multiple cranial nerves (Fig. 1D-F). Autoimmune, paraneoplastic, and anti-GQ1b antibody test results were negative.

Considering the recent travel history of the patient, we conducted serological screening for rare infectious diseases, including those caused by Zika virus, dengue fever virus, and CHIKV, and severe fever with thrombocytopenia syndrome. An elevated IgM antibody titer (1.3; cutoff=1.0) against CHIKV was detected using an enzyme-linked immunosorbent assay. Intravenous immunoglobulin (400 mg/kg/day) was promptly administered for 5 days. The patient's mental status slowly began to improve, and the horizontal diplopia and hiccups completely resolved. However, tongue deviation to the left and erectile dysfunction developed. The 1-month follow-up MRI showed resolution of the high-intensity lesions in DWI and enhanced lesions along the cranial nerves, and revealed malacic changes (Fig. 1G-L).

Neurological complications of CHIKV infection are rare, reportedly accounting for 0.1%–9% of all infections. However, the incidence rate appears to have increased in recent

Received April 28, 2023
Revised July 11, 2023
Accepted July 31, 2023

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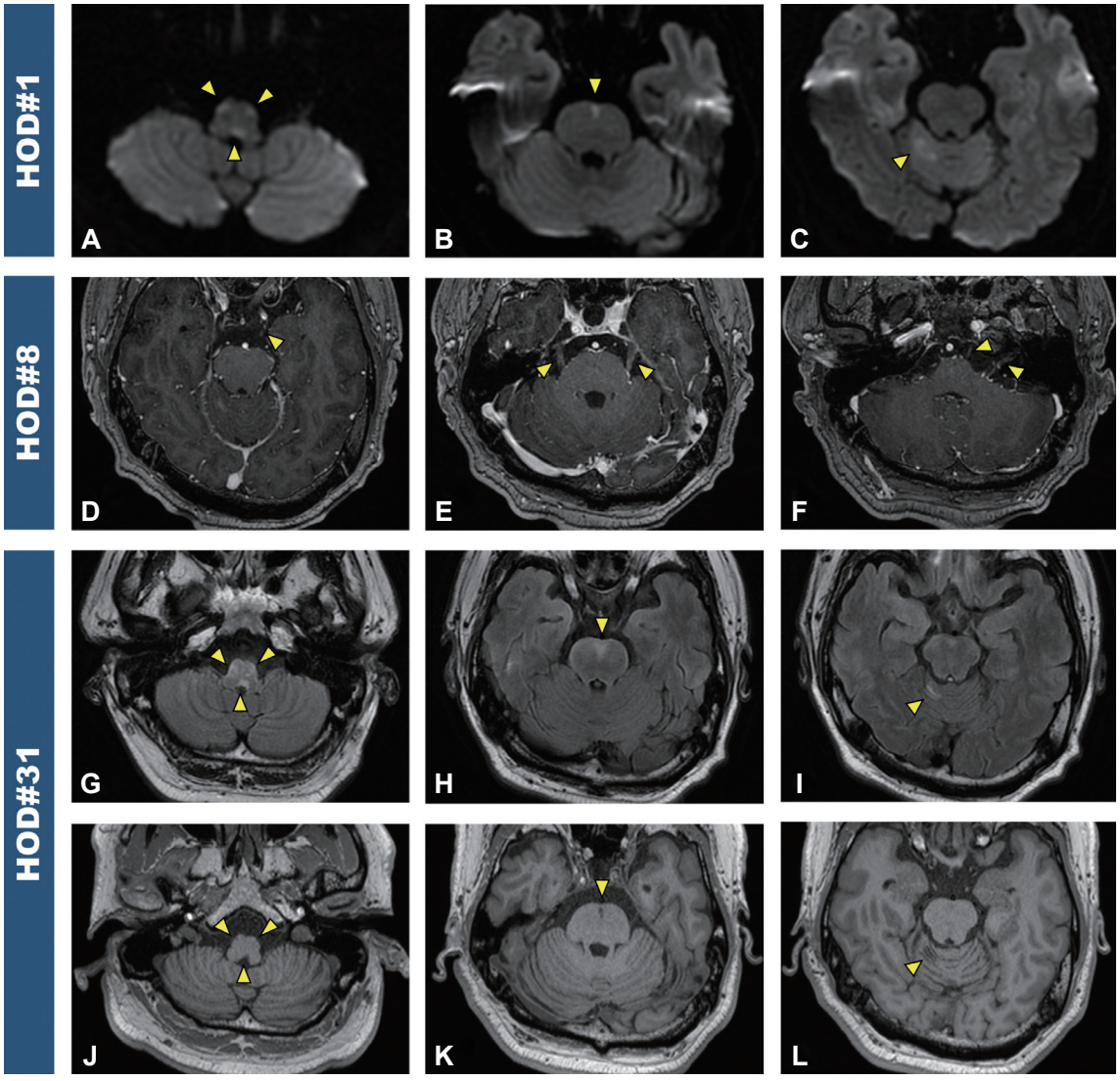

Fig. 1. Serial brain magnetic resonance imaging of the patients. A-C: Diffusion-weighted images obtained 1 day after admission show high-intensity lesions in the bilateral ventral medulla and mid-dorsal medulla areas (A, arrowheads), mid-ventral pons (B, arrowhead), and right superior cerebellum (C, arrowhead). D-F: T1-weighted images with gadolinium enhancement obtained 8 days after admission show subtle enhancement along multiple cranial nerves: III (D, arrowhead), V (E, arrowheads), VI, and the VII/VIII complex (F, arrowheads). G-L: Fluid-attenuated inversion-recovery and T1-weighted images obtained 31 days after admission show malacic changes in the medulla (G and J, arrowheads), pons (H and K, arrowheads), and right cerebellum (I and L, arrowheads). HOD, hospital day.

decades, particularly among those with severe disease.[3] It can manifest as various symptoms from encephalitis to Guillain–Barre syndrome (GBS) and acute disseminated encephalomyelitis, with a fatality rate of 16.6%. As in our case, all other patients were confirmed to have visited areas endemic for Chikungunya fever 2 weeks prior to the onset of symptoms. Up to 10 positive cases of CHIKV have been reported each year in South Korea since the first case was reported in July 2013.[4] However, neurological manifestations of CHIKV infection have not been reported previously. If patients with acute neurological symptoms have a history of visiting a CHIKV-endemic area, CHIKV infection should be suspected.

Being aged >60 years, being an infant, and comorbidities such as respiratory or cardiac diseases are known to be associated with severe complications, including neurological diseases.[5,6] However, a case series of CHIKV-associated GBS found that only 33.3% of patients had comorbidities.[7] Our patient was a 40-year-old male with no comorbidities. The pathophysiology and major risk factors for the neurological manifestation of CHIKV infection are still to be identified.

It is challenging to differentiate CHIKV infection from infection with Zika virus or dengue fever virus (which produces another arboviral disease with similar epidemiology) based only on clinical signs and symptoms. Silent and prolonged

polyarthralgia, often accompanied by rash, is typically more indicative of CHIKV infection, while hemorrhagic manifestation and myalgia are more commonly observed in dengue-fever-virus infection.[1] However, a case report of neurological disorders found no signs or symptoms indicative of either dengue fever or chikungunya encephalitis.[6] Our patient had no specific systemic or neurological signs or symptoms suggestive of CHIKV infection. Therefore, screening should be performed for all arboviral infections, including with CHIKV, if patients with acute neurological symptoms have a history of visiting an endemic area.

Brainstem encephalitis is a very rare complication of CHIKV infection, and a systematic review in 2018 found that only 3 of 856 cases of CHIKV infection had neurological disease.[8,9] Similar to our case, one of those patients presented with vertigo, dysarthria, ataxia, and symptoms suggestive of multiple cranial neuropathies, along with lesions in the bilateral middle cerebellar peduncles, medulla oblongata, and cervical spinal cord in MRI. That patient was administered high-dose methylprednisolone and showed almost complete resolution.[8] The other two patients manifested as Bickerstaff brainstem encephalitis: one did not respond to intravenous immunoglobulin treatment and died,[9] and the other had concurrent Miller–Fisher syndrome and GBS, experienced deterioration of the medical condition, and regained a normal mental status and cranial nerve function 1.5 years after the onset.[10] These results suggest that CHIKV infection can manifest as rhombencephalitis and that, unlike CHIKV infection with Bickerstaff brainstem encephalitis (which has a poor prognosis), simple rhombencephalitis with multiple cranial neuropathies can have a good prognosis.

To the best of our knowledge, this is the first report of CHIKV encephalitis (and specifically of rhombencephalitis) in South Korea. CHIKV infection could be easily underestimated or misdiagnosed in an area where it is unfamiliar and unexpected. Clinicians in areas of low prevalence should therefore consider the possibility of CHIKV infection if patients with rhombencephalitis have a recent history of visiting CHIKV-endemic areas.

Ethics Statement

Written informed consent was obtained from the patient.

Availability of Data and Material

The data sets generated or analyzed during the study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

Acknowledgements

The authors thank the patient and his family.

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