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Title:

Serologic evidence of Tick-borne encephalitis virus infection in a patient with suspected Lyme disease in Japan

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Running title: TBEV infection in Lyme-suspected patient in Japan

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ABSTRACT:

Tick-borne encephalitis (TBE) is widely prevalent on the Eurasian continent, including Japan, but four cases of TBE have been reported in Japan. To inspect unconfirmed TBE cases in Japan, we conducted a retrospective sero-epidemiological study of a total of 158 samples from 81 meningoencephalitis patients suspected as Lyme disease. Two serum samples from one patient showed neutralizing antibodies against tick-borne encephalitis virus. The patient with severe and progressive encephalitis had a history of tick bite in Hokkaido in 2012. These results demonstrated that TBEV case was actually unconfirmed in Japan. Further sero-epidemiological surveys are required to identify unconfirmed TBEV infections to consider the pros and cons of introducing specific countermeasures including vaccination in Japan.

TEXT:

Tick-borne encephalitis (TBE) virus (TBEV) belongs to the Flaviviridae family and Flavivirus genus, and may causes fatal encephalitis in humans. In nature, TBEV is transmitted between ticks and wild vertebrate hosts, especially rodents.¹ TBE is widely prevalent on the Eurasian continent, including Japan. In Japan, the first confirmed case of TBE was reported in 1993 in Hokkaido, the northernmost prefecture.² Since that time, three other cases of TBE have been reported in Japan in 2016 and 2017^{3,4}, although endemic foci of TBEV have been detected in various parts of Japan, especially in Hokkaido.⁵ Therefore, the possibility exists that TBE patients are being unconfirmed in Japan.

TBEV is transmitted by *Ixodes* ticks, which are also the primary vector for Lyme disease-causing bacteria, *Borreliae*.⁶ In Japan, almost 5- 20 cases of Lyme disease patients are reported annually. Through the dissemination of the bacteria, Lyme disease often presents with neurological symptoms, similar to those of TBE. In a previous study,

confirmed infection of Powassan virus, one of TBE-serocomplex virus, was detected in patients with suspected Lyme disease in a Lyme disease-endemic area, indicating that Powassan virus infection had been unconfirmed in northern Wisconsin.⁷ In Japan, many meningitis or meningoencephalitis cases associated with tick bites are subjected to the diagnosis of Lyme disease, but not to that of TBE. This is due to the low awareness of TBE and the difficulty in performing laboratory examinations for the diagnosis of TBEV infection. In this study, we conducted a retrospective sero-epidemiological study of meningoencephalitis patients suspected as Lyme disease to inspect unconfirmed TBE cases in Japan.

We selected 158 serum or spinal fluid samples from 81 meningoencephalitis patients with suspected Lyme disease collected by National Institute of Infectious Disease (NIID) between 2010 and 2017. The samples were from patients in their first to eighth decade of life living throughout Japan, including Hokkaido. A neutralizing antibody test was conducted using the TBEV isolate from Hokkaido in 1993.² To differentiate TBEV infections from Japanese encephalitis virus (JEV) infection, which is seen in southwestern Japan, a neutralization test for JEV was conducted on all TBEV-positive samples. A sample was determined positive if a plaque reduction of 50% or greater compared with the virus control was observed. A neutralizing titer was defined as the reciprocal of the highest dilution. Approval for this study was obtained from the Medical Ethics Committee of the Faculty of Veterinary Medicine, Hokkaido University and the NIID.

Of 158 total samples, 2 serum samples from one patient showed neutralizing antibodies against TBEV but were both negative for JEV (antibody titers <20). Significant increases in the neutralizing antibody titers against TBEV (100 to 800) were detected in the paired serum samples. The patient was a male in his 80s who was reported ill in Hokkaido in 2012. His symptoms included fever, nausea, and vomiting 21 days after a tick bite. After

hospitalization, his condition deteriorated over several days. He experienced progressive and severe paralysis as well as difficulty breathing. A physician initially diagnosed the patient with neuroborreliosis, because he had a history of tick-bite in endemic area of Lyme disease and he had a fever (ranging from 37.6 to 39.7 degrees) with elevation of C-reactive protein level (4.4–7.5 mg/dl). PCR and serological tests for Lyme disease were negative.

In this study, infection with TBEV in a Lyme disease-suspected patient was diagnosed serologically, demonstrating that TBEV cases are actually unconfirmed in Japan. Although TBEV or TBEV-infected animals have been detected, four severe human encephalitis cases have been reported in humans in Japan; two of these patients died, and the other two recovered but severe sequelae such as paralysis remained. Furthermore, two patients infected with a virus within the TBE-serocomplex developed encephalitis during an epidemic of Japanese encephalitis in 1948 in the Tokyo area. The isolated virus was retrospectively identified as a member of the louping ill virus through antigenic and phylogenetic analyses conducted decades later.^{8, 9} It is likely that other human TBEV infections existed during these years, including not only subclinical and mild cases but also unconfirmed severe cases, as shown in this study. For example, we recently reported unrecognized subclinical infections with TBEV in Japan Self Defense Force members from Northern Army.¹⁰ Further sero-epidemiological surveys with larger sample sizes and a broader scope of subjects are required to identify unconfirmed TBEV infections to consider the pros and cons of introducing specific countermeasures including vaccination. Such a survey is also desirable to measure the virulence of TBEV of the so-called Far-Eastern subtype, because the detection of subclinical or mild cases may lead to an overall decrease in its alleged high risk of fatality.¹¹

Conflict of interest:

We declare that we have no conflict of interest.

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References:

1. Mansfield KL, Johnson N, Phipps LP, Stephenson JR, Fooks AR, Solomon T, 2009. Tick-borne encephalitis virus - a review of an emerging zoonosis. *J Gen Virol* 90: 1781-1794.
2. Takashima I et al., 1997. A case of tick-borne encephalitis in Japan and isolation of the virus. *J Clin Microbiol* 35: 1943-1947.
3. Yoshii K, Tajima Y, Bando K, Moriuchi R, 2016. A confirmed case of tick-borne encephalitis in Hokkaido in 2016. *Infectious Agents Surveillance Report* 38: 126.
4. Yamaguchi H, Komagome R, Miyoshi M, Ishida S, Nagano H, Okano M, Shimada K, Fukami M, Tanaka K, Takauchi N, Yoshii K, Kobayashi S, Kariwa H, 2018. Confirmed cases of tick-borne encephalitis in Hokkaido in 2017. *Infectious Agents Surveillance Report* 39: 46-47.
5. Yoshii K et al., 2011. Epizootiological study of tick-borne encephalitis virus infection in Japan. *J Vet Med Sci* 73: 409-412.
6. Miyamoto K, Nakao M, Uchikawa K, Fujita H, 1992. Prevalence of Lyme borreliosis spirochetes in ixodid ticks of Japan, with special reference to a new potential vector, *Ixodes ovatus* (Acari: Ixodidae). *J Med Entomol* 29: 216-220.

- 127 7. Frost HM et al., 2017. Serologic Evidence of Powassan Virus Infection in Patients with
128 Suspected Lyme Disease. *Emerg Infect Dis* 23: 1384-1388.
- 129 8. Venugopal K, Buckley A, Reid HW, Gould EA, 1992. Nucleotide sequence of the
130 envelope glycoprotein of Negishi virus shows very close homology to louping ill virus.
131 *Virology* 190: 515-521.
- 132 9. Okuno T, Oya A, Ito T, 1961. The identification of Negishi virus, a presumably new
133 member of Russian spring-summer encephalitis virus family isolated in Japan. *Jpn J*
134 *Med Sci Biol* 14: 51-59.
- 135 10. Yoshii K, Kojima R, Nishiura H, 2017. Unrecognized Subclinical Infection with
136 Tickborne Encephalitis Virus, Japan. *Emerg Infect Dis* 23: 1753-1754.
- 137 11. Leonova GN, Pavlenko EV, 2009. Characterization of neutralizing antibodies to Far
138 Eastern of tick-borne encephalitis virus subtype and the antibody avidity for four
139 tick-borne encephalitis vaccines in human. *Vaccine* 11: 2899-2904.