HOKKAIDO UNIVERSITY

Title	Serologic Evidence of Tick-Borne Encephalitis Virus Infection in a Patient with Suspected Lyme Disease in Japan
Author(s)	Yoshii, Kentaro; Sato, Kozue; Ishizuka, Mariko et al.
Citation	American journal of tropical medicine and hygiene, 99(1), 180-181 https://doi.org/10.4269/ajtmh.18-0207
Issue Date	2018-07-01
Doc URL	https://hdl.handle.net/2115/74863
Type	journal article
File Information	American journal of tropical medicine and hygiene99(1)180-181.pdf



Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Title:

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

Authors:

Kentaro Yoshii[1*], Kozue Sato[2], Mariko Ishizuka[1], Shintaro Kobayashi[1], Hiroaki Kariwa[1], Hiroki Kawabata[2]

1. Laboratory of Public Health, Faculty of Veterinary Medicine, Hokkaido University, Kita 18 Jo Nishi 9 Chome, Kita-ku, Sapporo 060-0818 Japan
2. Department of Bacteriology-I, National Institute of Infectious Diseases, Tokyo 162-8640, Japan

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

*Correspondence

Kentaro Yoshii

Laboratory of Public Health, Faculty of Veterinary Medicine, Hokkaido University, Kita 18 Jo Nishi 9 Chome, Kita-ku, Sapporo 060-0818 Japan

Tel: +81 11 706 5212, Fax: +81 11 706 5213; E-mail: kyoshii@vetmed.hokudai.ac.jp

Keywords: Tick-borne encephalitis, Lyme disease, tick-borne disease

Word counts for the abstract: 115

Word counts for the text: 762

No figure and table.

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,

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

61 We selected 158 serum or spinal fluid samples from 81 meningoencephalitis patients
62 with suspected Lyme disease collected by National Institute of Infectious Disease (NIID)
63 between 2010 and 2017. The samples were from patients in their first to eighth decade of life
64 living throughout Japan, including Hokkaido. A neutralizing antibody test was conducted
65 using the TBEV isolate from Hokkaido in 1993.[2] To differentiate TBEV infections from
66 Japanese encephalitis virus (JEV) infection, which is seen in southwestern Japan, a
67 neutralization test for JEV was conducted on all TBEV-positive samples. A sample was
68 determined positive if a plaque reduction of 50% or greater compared with the virus control
69 was observed. A neutralizing titer was defined as the reciprocal of the highest dilution.
70 Approval for this study was obtained from the Medical Ethics Committee of the Faculty of
71 Veterinary Medicine, Hokkaido University and the NIID.

72 Of 158 total samples, 2 serum samples from one patient showed neutralizing antibodies
73 against TBEV but were both negative for JEV (antibody titers <20). Significant increases in
74 the neutralizing antibody titers against TBEV (100 to 800) were detected in the paired serum
75 samples. The patient was a male in his 80s who was reported ill in Hokkaido in 2012. His
76 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.

Acknowledgement:

This work is supported by JSPS KAKENHI Grant Numbers 16K1503206 and 17H03910, the Research Program on Emerging and Re-emerging Infectious Diseases from Japan Agency for Medical Research and Development (AMED), the research grand provided by The Akiyama Life Science Foundation.

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 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.

7. Frost HM et al., 2017. Serologic Evidence of Powassan Virus Infection in Patients with Suspected Lyme Disease. *Emerg Infect Dis 23:* 1384-1388.

8. Venugopal K, Buckley A, Reid HW, Gould EA, 1992. Nucleotide sequence of the envelope glycoprotein of Negishi virus shows very close homology to louping ill virus. *Virology 190:* 515-521.

9. Okuno T, Oya A, Ito T, 1961. The identification of Negishi virus, a presumably new member of Russian spring-summer encephalitis virus family isolated in Japan. *Jpn J Med Sci Biol 14:* 51-59.

10. Yoshii K, Kojima R, Nishiura H, 2017. Unrecognized Subclinical Infection with Tickborne Encephalitis Virus, Japan. *Emerg Infect Dis 23:* 1753-1754.

11. Leonova GN, Pavlenko EV, 2009. Characterization of neutralizing antibodies to Far Eastern of tick-borne encephalitis virus subtype and the antibody avidity for four tick-borne encephalitis vaccines in human. *Vaccine 11:* 2899-2904.