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Tick-Borne Encephalitis Virus within and outside Japan: a Cause for Concern?

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The tick-borne encephalitis (TBE) virus is an etiologic agent of serious illnesses including neuroinfections and is endemic in Europe and Asia. The TBE virus which belongs to the family of *Flaviviridae* is transmitted by ticks. Based on serological analyses, the TBE virus can be subdivided into the European and the Far Eastern subtypes. Human infection is characterised by two clinical stages: after an incubation period of 7-14 days, the disease manifests itself as an influenza-like syndrome with fever, headache, and vomiting. After a symptom-free interval of 1-3 weeks, 6-20% of patients develop meningitis, and 10% of the originally infected patients go on to develop encephalitis and myelitis, with sequelae occurring in 3-11% of cases; the mortality rate is 1-2%. A specific therapy is not available (for a review, see reference 1).

In 1993, a case of TBE was reported in the southern part of Hokkaido. To determine the seroprevalence of the TBE virus, a seroepidemiological survey was performed among humans and animals known to be susceptible for the virus. Sera from goats, dogs, and cattle were found to be antibody positive. Two of 24 residents in the case study area were TBE antibody positive, one of whom had suffered from severe encephalitis 35 years ago. Moreover, the TBE virus was isolated from unconfined dogs (2) and from small rodents (3) from this region. Genomic sequence and phylogenetic analyses of one canine virus isolate revealed a close relationship with the Far Eastern subtype of the TBE virus (4). The TBE virus was also isolated from various tick species (5). While in Europe the main host of the TBE virus is the tick *Ixodes ricinus*, the principal vector in Far Eastern Russia is *I. persulcatus*. The main host on Hokkaido was identified as *I. ovatus* (6). It may thus be concluded that the TBE virus is endemic in Japan, at least on the island of Hokkaido.

The TBE virus is widely distributed throughout Europe and Asia. TBE cases are reported from Northern Europe (coastal areas of Southern Scandinavia) to south of the Alps (some regions in Northern Italy). The most westerly location where the TBE virus is endemic is the Alsace region (France) and in an easterly direction the endemic region extends across the Asian continental shelf as far as Siberia. Some highly endemic regions are Austria, Slovenia, the Czech Republic, the Baltic countries, and Russia. Infection with the TBE virus can be controlled by vaccination, which is recommended in all endemic countries. In the pre-vaccination era, more than 700 cases annually were reported in Austria, whereas now only 50 to 70 patients annually are hospitalized following

implementation of the vaccination recommendations (7). Seroepidemiological studies have shown that more than 90% of the young adults were found to have protecting antibody levels and about 80% follow the official TBE vaccination recommendations (8). In contrast to the success of vaccination in Austria, there has been an increase in TBE cases over the last 20 years in Czechoslovakia (now the Czech Republic and Slovak Republic) from around 100 to about 700 cases yearly. This neighbouring region is comparable to Austria in population density and TBE epidemiology, but TBE vaccination coverage is much lower.

About 2.3 million Japanese tourists travel to Europe every year (Keizai Koho Center, personal communication). Many of them favour attractive towns and locations where the TBE virus is endemic, e.g., Southern Germany (Heidelberg) or the Alpine region in Switzerland and Austria (more than 400,000 Japanese visit Germany and Austria). In 2001, a Japanese tourist became infected in Salzburg (Austria), where he was visiting his daughter, a music student in "the city of Mozart". He fell severely ill in June 2001 with the typical biphasic course and died in September 2001 (9).

In Denmark, the TBE virus is found only on the island of Bornholm in the Baltic sea. Until 1999, no cases of TBE had been reported for a period of 40 years. In 1998, a resident of Bornholm developed meningo-encephalitis, but the cause remained unidentified until his general practitioner, who happened to learn about TBE during a refresher course, re-examined the patient for TBE antibodies. Since then, three TBE cases were reported in 1999 and one case each in 2000 and 2001 (10, and K. Kristiansen, personal communication).

Seroepidemiological studies carried out by hemagglutination and neutralization tests among forest workers from Bornholm showed that 30% were TBE virus positive (12/40) and three had experienced symptoms of TBE. Of 508 adult residents of Bornholm examined for TBE antibodies, 1.4% were positive. In the 1960s, sera from deer were found to be TBE positive in 83% and new studies indicate that about 2% of the ticks are infected by the TBE virus (10).

TBE had been virtually forgotten on Bornholm for the last 40 years. It is thus not surprising that TBE has not been diagnosed for many years among its 45,000 residents, since causes can only be identified if suitable surveys are performed.

It was conclusively demonstrated that the TBE virus is endemic in Japan. Considering the level of underreporting on Bornholm, it may be justified to assume that the number of TBE cases may also be underreported on Hokkaido and possibly in other regions of Japan. Physicians should take TBE more seriously as a possible cause of viral encephalitis

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and possibly distinguish it from Japanese encephalitis.

Travellers to TBE-endemic regions in Europe (often the most popular tourist areas, e.g., the wine-growing region around Heidelberg in Germany, Salzburg in Austria, etc.) should be vaccinated against TBE. "Last minute" protection is possible thanks to newly developed TBE vaccines for children and adults offering a clinically proven and licensed vaccination schedule on days 0, 7, and 21 (11,12). Furthermore, the viral strains used to produce the vaccines approved in Europe also induce antibodies that confer neutralizing activity against isolates of the Far Eastern and Japanese subtypes of the TBE virus and could therefore be used for residents of or visitors to TBE endemic areas in Eastern Asia (Hokkaido, Siberia).

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