Tick-borne encephalitis and its global importance

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Tick-borne encephalitis (TBE) is the most important tick-transmitted human viral disease in Europe and Asia with up to 10 000 human cases annually. The etiologic agents of TBE are the three subtypes of tick-borne encephalitis virus (TBEV), a member of the genus Flavivirus in the family *Flaviviridae*. The Far-Eastern subtype and the Siberian subtype are both mainly transmitted by *Ixodes persulcatus*; the European subtype is mainly transmitted by *Ixodes ricinus*. Besides tick bite, TBEV can be transmitted by unpasteurised milk from goat, sheep and cattle during the viremic phase of infection by the oral route of infection (alimentary form of TBE). There is no treatment for TBE available, but there are effective and well tolerated vaccines against TBE, which are recommended for people living or travelling to endemic countries with a risk of infection.

Tick-borne encephalitis is the most important tick-borne viral disease in Europe and Asia, but regarding numbers of patients it is the most important tick-borne viral disease in the world[1]. The disease is endemic exclusively in Europe and Asia. It is caused by a group of viruses of the genus *Flavivirus* in the family *Flaviviridae*. Three subtypes, the European, the Siberian and the Far-Eastern subtype can be distinguished by molecular methods and they are transmitted by different vectors and cause a different clinical picture of disease[2] (Figure 1). An additional two other subtypes, the Baikalian (TBEV-Bkl) and the Himalayan subtype (TBEV-Him) have been described recently[3,4].

The five subtypes of TBEV have a different, but partially overlapping geographical distribution and biological transmission cycles involving different tick species and rodents[5]. The European subtype (TBEV-EU) is geographically distributed mainly in Europe[6]. However, some TBEV-EU strains have been isolated and characterised in Siberia (Lake Baikal region) and also in South Korea. In Europe the most important vector of TBEV is *I. ricinus*. Goats, sheep and cattle shed TBEV into the milk during the viremic phase of infection without showing signs of disease. Infection with TBEV by the alimentary route from drinking unpasteurised virus containing milk or dairy products is a common way of infection in some European countries and occasionally also occurs in countries with a highly industrialised agriculture, as recently reported in Germany and Austria[7,8].

The Siberian subtype is geographically distributed mainly in Russia east of the Ural Mountains, but it is also found in the Baltic countries and in localised places in Finland[9]. *I. persulcatus*, the Taiga tick, mainly transmits this subtype. The Far-Eastern subtype of TBEV is geographically distributed mainly in the far-eastern part of Russia and the northern parts of China. TBEV-FE is also found on the northern Japanese island of Hokkaido, where *I. ovatus* was identified as its vector[10]. The Baikalian subtype was detected at the Lake Baikal region in different *Myodes* spp. and in *I. persulcatus*[3]. The Himalayan subtype was identified two times from respiratory fluid of *Marmota himalayana* from the Qinghai-Tibet Plateau in China[4].

Earlier serological data suggest that only about 30% of the TBEV infections present with clinical symptoms, ranging from febrile ('flu-like') disease to meningitis, encephalitis and encephalomyelitis[1]. In milk-borne and diary product-borne infections the manifestation index seems to be much higher ranging in many outbreaks to up to 100% of exposed individuals[8].

The incubation period of TBE ranges from 5 to 14 days. In many of the human cases caused by the TBEV-EU a biphasic course is reported. In the first phase of the disease, symptoms of a general infection ('flu-like') are seen. Many patients report elevated temperatures, headache, muscle ache, fatigue and also gastrointestinal symptoms or symptoms of the respiratory tract. During this phase of disease, the TBE virus can be detected and isolated from the blood of the patients. The symptoms reflect the virus replication in the different organs of the body. The first phase lasts from four to seven days[11].

After a symptomless phase of 4–7 days, symptoms of general infection of the central nervous system (CNS) may follow in

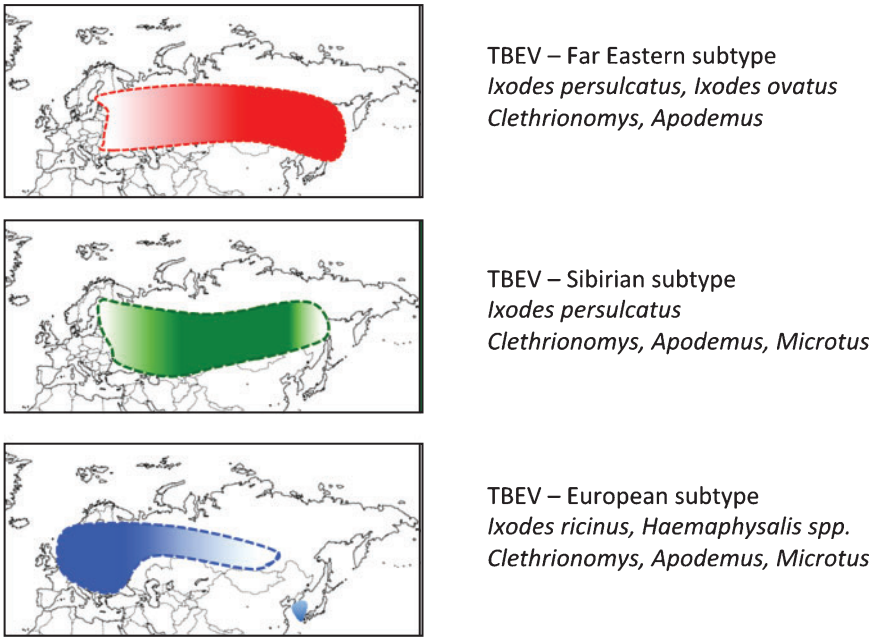

Figure 1. Geographical distribution of the three main TBE virus subtypes including main vectors and main vertebrate hosts.

~30% of patients. The CNS symptoms may range from headache and mild meningitis to severe encephalomyelitis with a fatal outcome. Generally three clinical forms of the CNS disease of TBE infection can be distinguished[11]:

- Meningitis: fever, headache, nuchal rigidity
- Encephalitis: change of consciousness, stupor, coma, epileptic attacks, disorientation, dysarthria
- Myelitis: flaccid paralysis of different muscles; mainly muscles of the upper musculo-skeletal system

The Siberian and the Far-Eastern forms of TBE infections follow a more severe clinical course. These infections mostly show a monophasic form with more severe encephalitic and myelitic features. The fatality rates range from 3% to 20%. In patients with the Siberian subtype virus infection a chronic form of TBE has been described. However, it is unclear, whether these more severe clinical courses in the Russian forms of TBE are due to differences in case-reporting, due to differences in medical interpretation or to genuine different pathogenicity of this TBE virus subtype[12].

Despite the manifestation of central nervous system disease, the isolation or detection of TBE virus in the cerebrospinal fluid (CSF) of the patient is difficult and only rarely successful. Within the brain the virus seems to spread from one cell to the next without being shed into the CSF. Therefore the diagnostic method of choice is the detection of specific antibodies. The detection of IgM and IgG antibodies against TBE virus together with typical clinical CNS symptoms and tick exposure is strong evidence for a diagnosis of acute TBE infection[11]. However, there are many serological cross-reactions with other flaviviruses. The detection of antibodies in a single serum, without further serological follow up and diagnostic information, may make the diagnosis difficult. Also IgM might be very low or even missing in the case of pre-existing antibodies against other flaviviruses (e.g. dengue virus, Zika virus) or after vaccination against other flaviviruses (yellow fever virus, Japanese encephalitis virus)[13]. Therefore, the diagnosis of TBE should be made after excluding other flavivirus antibodies, e.g. against yellow fever virus, dengue fever viruses, or Japanese encephalitis virus.

So far, there is no effective treatment for TBE[11]. Treatment may include symptomatic therapy to lower temperature, to relieve pain and especially in case of encephalitis to avoid complications from inflammatory brain damage. In severe clinical forms patients are put into an artificial coma. Rehabilitation medicine plays an important part in the post-acute treatment to control the neurological and psychiatric sequelae. The fatality rate of the European form of TBE ranges from 0.5% to 2%[10].

There are six inactivated and adjuvanted vaccines available against TBEV infection[14,15]. Two vaccines, Encepur (GSK) and FSME-Immun (Pfizer) are produced in Europe and contain European type TBEV. Three vaccines, TBE vaccine Moscow and EnceVir and Tick-E-Vac/Klesh-E-Vac are produced in Russia and contain Far Eastern TBEV strains. The name of the Chinese TBE vaccine is Sen Tai Bao; however, no further information on this vaccine is available. The two European vaccines need three doses for a basic immunisation. Two are given 1–3 months apart. Two weeks after the second dose a vaccine efficacy of more than 95% can be assumed. For both vaccines a third dose is recommended after

6–12 months after the start of immunisation. A fourth vaccine dose is recommended after three years. Depending on the patient's age, subsequent boosters are recommended after 3 or 5 years. For both vaccines, rapid immunisations schemes are available, which might induce immunity as early as three weeks. Both European vaccines can be used in special formulations in children >12 months of age. The Russian Tick-E-Vac/Klesh-E-Vac can also be used for children >12 months of age. Data indicate that the European vaccines also provide protection against infections with the Siberian and the Far Eastern subtype of TBEV. Due to the close genetic relatedness a similar assumption may be made also for the three Russian vaccines in relation to the European subtypes.

The two Russian TBE vaccines, TBE vaccine Moscow and EnceVir, are not licensed for children <3 years of age. They are administered in two doses 1–2 and 1–7 months apart. A third dose is recommended after 12 months. Further booster doses should be given after 3 years. TBE-E-Vac/Klesh-E-Vac is given in two doses 1–7 months apart. A third dose is recommended one year after the second dose.

In the northern hemisphere tick-borne encephalitis is the most important tick-borne virus infection. An estimated 10 000 human cases occur every year in Europe and Asia[16]. Incidence rates of TBE infection in endemic areas of Europe range from 0.1 to 20/100 000 inhabitants. The European countries with the highest incidence rates are the Baltic countries and Slovenia, followed by the Czech Republic, Slovakia, Poland and Austria (non-vaccinated population)[17]. However, the incidence rates may vary on a local district level. For example, in some German districts incidence rates of >10/100 000 per annum are recorded, while in the whole country the incidence rate is below 0.5/100 000 per annum (G. Dobler, personal observation).

Besides the imminent risk of infection in residents of endemic areas, TBE is becoming an important travel-related disease. According to estimates, the risk of exposure for acquiring a TBE infection was calculated at 1 case per 77 000 to 200 000 visitors[18]. Travel-related cases have been reported from Israel, The Netherlands, Australia, United States and England[19–22]. The Australian patient travelled by car from Moscow to Novosibirsk with ample contact in nature although it was unclear whether he was infected by a tick bite or by the alimentary route. He developed a generalised infection with drowsiness, fatigue and lower limb myalgia. After acute symptoms subsided the patient noticed a severe depressiveness and changes in his handwriting, which was explained as a cerebellar dysfunction of the right upper limb. However, the clinical course was complete recovery after one month[22].

Conflicts of interest

The author declares no conflicts of interest.

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Biography

Gerhard Dobler is a medical doctor and specialist in medical microbiology. He is head of the Department of Virology and Rickettsiology at the Bundeswehr Institute of Microbiology in Munich and associate professor at the Unit of Parasitology of the Institute of Zoology at the University of Hohenheim. He is head of the German reference laboratory for tick-borne encephalitis (TBE). His main areas of research are the molecular phylogeny, the eco-pathogenesis of TBE virus and the eco-epidemiology of TBE and other tick-borne diseases.

Ticks in Australia: endemics; exotics; which ticks bite humans?

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At least 71 species of ticks occur in Australia; a further 33 or so species are endemic to its neighbours, New Guinea and New Zealand. The ticks of Australia and other parts of Australasia are phylogenetically distinct. Indeed, there are at least two lineages of ticks that are unique to Australasia: the genus *Bothriocroton* Klompen, Dobson & Barker, 2002; and the new genus *Archaeocroton* Barker & Burger, 2018. Two species of ticks that are endemic to Australia are notorious for feeding on humans: (i) *Ixodes holocyclus*, the eastern paralysis tick, in eastern Australia; and (ii) *Amblyomma triguttatum triguttatum*, the ornate kangaroo tick, in Western Australia, at one place in South Australia, and in parts of Queensland. Three of the other endemic species of ticks that feed on humans in Australia are also noteworthy: (i) *Bothriocroton hydrosauri*, the southern reptile tick, which is a vector of *Rickettsia honei* (Flinders Island spotted fever); (ii) *Haemaphysalis novaeguineae*, the New Guinea haemaphysalid; and (iii) *Ornithodoros capensis*, the seabird soft tick. Here, we present images of female *Ixodes holocyclus*, *Amblyomma t. triguttatum*, *Bothriocroton hydrosauri* and *Haemaphysalis novaeguineae* and our latest maps of the geographic distributions of *Ixodes holocyclus*, *Amblyomma t. triguttatum* and *Bothriocroton hydrosauri*. None of the five exotic species of ticks in Australia typically feed on humans.

The Australian tick fauna

At least 71 species of ticks are known in Australia: 57 hard ticks (family Ixodidae) and 14 soft ticks (family Argasidae)[1,2]. Five of these 71 species of ticks were brought to Australia by humans and thus might be called exotic: (i) *Argas persicus*, the poultry tick; (ii) *Otobius megnini*, the spinose ear tick, a recent introduction, probably in the ears of horses; (iii) *Haemaphysalis longicornis*, the bush tick, which occurs in much of east Asia; (iv) *Rhipicephalus sanguineus*, the brown dog tick, a worldwide species; and (v) *Rhipicephalus* (*Boophilus*) *australis*, the Australian cattle tick. Barker and Walker[3] has detailed species accounts for these five ticks.

Australia has a special place in the history of hard ticks (Ixodidae). Indeed, the hard ticks[4–6], soft ticks and nutalliellid ticks[1] may have first lived in Australia, or more accurately, that part of the super continent Gondwana that became Australia, as early as the Devonian era (362–409 million years ago). Accordingly, six of the eight subfamilies of ticks (Ixodida) are endemic to Australia: Argasinae,