



Tick-Borne Encephalitis (TBE) During a “Grand-Tour” of Europe Clinically Manifesting in a TBE-Free Region

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We report the case of an unvaccinated tourist who was exposed to multiple tick bites during a bike tour crossing several European countries with ongoing tick-borne encephalitis (TBE) transmission and who presented a typical TBE clinical course with favorable outcome.

Tick-borne encephalitis (TBE) is the most important flavivirus infection of the central nervous system (CNS) in Europe and Russia. TBE is distributed in an endemic pattern of so-called natural foci over a wide geographical area focussed on central Europe, the Baltic states, and Russia,¹ but also extending eastward up to China and Korea. There are different and geographically specific strains causing various degrees of disease severity. The distribution of TBE is determined by the occurrence of the respective tick vectors in certain regions. Nevertheless, the virus prevalence in ticks as well as the prevalence of infected ticks within the risk areas can vary.¹ There are countries with few or several, and limited or wide high-risk areas. In particular, TBE is considered a significant health issue for unvaccinated residents and tourists in Russia, Latvia, Lithuania, Estonia, Japan, Mongolia, China, Korea, Kazakhstan, Germany, the Czech Republic, Poland, Switzerland, Sweden, Finland, Slovakia, Hungary, Austria, and Slovenia.^{1–3} The total annual number of cases is estimated to be up to 10,000 in Russia and about 3,000 in European countries.¹ In particular, infections caused by European strains typically take a biphasic course^{1,3–5}: after a short incubation period (usually 7–14 days, with extremes of 4–28 days), the first (viraemic) phase presents as an uncharacteristic flu-like illness lasting 2–4 days (range 1–8 days) with fever, malaise, headache, myalgia, gastrointestinal symptoms, leukocytopenia,

thrombocytopenia, and elevated liver enzymes, often followed by a symptom-free interval of about 1 week (range 1–33 days). The second phase of TBE occurs in up to 20 to 30% of infected patients and is marked by four clinical features of different severity (meningitis, meningoencephalitis, meningoencephalomyelitis, or meningoencephalo-radiculitis) and the appearance of specific antibodies in the serum and cerebrospinal fluid (CSF). This is usually the time when patients with high fever (>38°C) and severe headache seek medical advice. Neurological signs and symptoms may include: meningeal signs, ataxia, (cognitive dysfunction with impaired concentration and memory) dysphasia, altered consciousness, confusion, irritability, cranial nerve paralysis, and tremor. The European strain infection has a case-fatality rate up to 3.9%.³

Case Report

A 56-year-old retired English man started with his 53-year-old wife a bicycle tour of Europe (Fig. 1). They carefully planned by themselves their itinerary logistically (accommodation, meals, visas) and also from a health point of view. In fact, they had a full insurance package for health care and for anticipated return to home country in case of health problems. They carried a first-aid kit and some over-the-counter drugs. They did not receive any additional recommendation regarding health risks and preventive measures—in particular regarding TBE—from their family doctor or from the insurance company. Notwithstanding extensive consultation of several websites providing suggestions for bicycle tours in the different crossed countries,

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Figure 1 Full line indicates the itinerary of the bike tour; arrows indicate countries where tick bites occurred; stars indicate departure (Hamburg) and arrival (Genoa) of the bike tour.

they did not come across recommendations for TBE vaccination strong enough to push them to ask for it.

Their travel started on June 12, 2008 from Hamburg on two pedal bicycles with one small ridge tent. They were wearing shorts and T-shirts because of the heat. Their typical accommodation for the night was camping, mostly in wooded areas and the like.

During their bike tour, they transited in countries with wide high-risk areas for TBE transmission (Russia, Estonia, Lithuania) and countries where TBE can be relevant in limited high-risk areas (Sweden, Finland, Poland, the Czech Republic, Germany, Austria, and Slovenia).

The patient detected and, almost always, promptly removed ticks (a total of about 20) on various occasions (Fig. 1) and he and his wife did not change their habits nor their behavior in terms of tick-bite prevention. The patient received tick bites for the first time in the woods of Southern Sweden (20–23 June), then in

Finland (25–29 June), Russia (30 June–5 July), Estonia (5–10 July), Lithuania (11–12 July), Russia again in the Kaliningrad exclave (13–15 July), Poland (16–24 July), Germany (15–20 August), Austria (21–23 August), and finally in Slovenia (23–26 August).

Nevertheless, the patient and his wife were healthy until crossing the border between Slovenia and Italy (26 August). On that same day, the patient presented fever and headache.

During the following days, the patient reported recovery alternating with fever and headache until 15 days later when they arrived in Genoa; he always self-administered paracetamol only. Here, on September 15th, his wife accompanied him to the Emergency Room of our Hospital because of fever, extreme fatigue, headache, and bilateral ear pain. Then, he was hospitalized at the Infectious Diseases Department.

Objectively, at entry, he presented fever (maximum 39.1°C), no alteration of consciousness or confusion, and the patient was oriented in time, space, and person; full neurological examination was negative with the exception of intense weakness at legs.

Routine blood tests were all normal, including complete blood count, liver enzymes, creatinine, C-reactive protein, fibrinogen. Serological routine tests showed previous hepatitis A (IgG positive; IgM negative), negativity of screening tests for Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus, syphilis, borreliosis, mycoplasma. Microbiological tests, including blood and urine cultures, were negative. CT scan of the brain with contrast, chest X-ray, and abdominal sonography did not show any alteration.

For the persistent headache and fever, and for the anamnestic report of tick bites in the woods of areas with high risk of TBE transmission, electroencephalography was performed on the third day of hospitalisation. It detected a mild—but significant—slowing of electric activity in the posterior sectors and occasional modest slowing in the left temporal area.

During hospitalization, he received symptomatic treatment only. He progressively improved: fever disappeared after 5 days and electroencephalography was completely normal 1 week after the first one. The patient left the hospital after 12 days still suffering from fatigue.

The reported tick bites occurred in countries with high risk for TBE transmission, therefore blood samples were sent to the Italian National Reference Laboratory at the National Institute for Health (ISS-Istituto Nazionale di Sanità). At this laboratory, an indirect hemagglutination inhibition (IHA) test against ir 968 TBE antigen and neutralization test (PRNT) were performed. The hemagglutination inhibition test showed high positivity for TBE (>1:1,280) and to West-Nile virus (WNV) (>1:1,280), which was expected due to the high level of immunological cross-reactivity between these two members of the Flaviviridae family. Nevertheless, the neutralization test showed positivity for TBE only.

Discussion

The described clinical case presented a typical clinical course with favorable outcome of TBE as a result of the European strain. Nevertheless, there are some aspects of this case that are worth discussing.

Firstly, clinical manifestations and diagnosis occurred in a TBE-free region. Such a clinical onset in regions where TBE is frequent or at least occasionally occurring would rapidly raise the suspicion; conversely, in TBE-free regions it may not be an immediately suspected diagnosis. This case is a reminder that examination and careful medical history (or anamnesis) are extremely useful. Our report reinforces the critical importance—in the medical history of patients—of travels abroad or in specific areas with all the details such as areas visited, time of the day for visits, accommodation, means of transport, food (kind, how cooked, where bought, etc.), sexual behavior, etc. In particular, the patient and his wife did not report use of unpasteurized milk products (another known way of TBE transmission).^{2,3}

The second aspect to be discussed is the travelers' underestimation of usefulness of preventive measures, including the non-vaccination against TBE before the bike tour. Among the visited countries, Austria, Estonia, Finland, Germany, Lithuania, Poland, and Slovenia reported to an ECDC survey that they had more or less official recommendations regarding TBE prevention for people traveling to endemic areas.¹

In general, travelers at risk of TBE are usually considered those who walk and camp in infested areas during the tick season (used to be spring to early autumn, but tick seasons are broadening during recent years)^{3,7} and vaccination is in fact recommended for them.^{1,6} In addition, some degree of protection is afforded by clothing that covers as much skin as possible and by applying insect repellent.³ The vaccine should be, however, offered to high-risk travelers. Unfortunately, outside endemic countries, the vaccines may not be licensed and will have to be obtained by special request, but vaccine against TBE is available in the United Kingdom at Travel Clinics. What was really surprising was that the patient and his wife had not been fully informed about the risks of TBE and were not recommended vaccination. In addition, they did not present any known contraindication for TBE vaccination.⁶ They had planned most of their trip surfing various websites (although they did not provide us a complete list), but they probably missed the key one that would have prevented them from suffering such a bad experience. In fact, their own National Health Service (NHS of the United Kingdom) reported specific recommendations for TBE prevention

for travelers to endemic areas with last update well before their travel.⁸

TBE infection is now becoming a more important issue of travel medicine because of the increasing international travel streams of tourists from non-endemic countries to TBE risk areas. The risk depends on both the traveling season and the degree of unprotected outdoor exposure to infested areas (eg, bicycling, camping, hiking, or collecting flowers, berries or mushrooms, etc.).^{2,3} Tourists probably underestimate their risk for this preventable disease and have little awareness of the actual risk potential, especially when traveling to a knowingly "safe" Europe. In addition, as reported by a recent survey, information for travelers about TBE is not uniform across Europe in content and recommendations.¹

Vaccination against TBE may be important for some tourists, depending on travel destination and behavior, but it should be planned well in advance and tourists should be always reminded that no last-minute vaccination is possible against TBE.

Declaration of Interests

The authors state they have no conflicts of interest to declare.

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