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REVIEW

Tick-borne encephalitis: A review of epidemiology, clinical characteristics, and management

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Abstract

Tick-borne encephalitis is an infection of central nervous system caused by tick-borne encephalitis virus transmitted to humans predominantly by tick bites. During the last few decades the incidence of the disease has been increasing and poses a growing health problem in almost all endemic European and Asian countries. Most cases occur during the highest period of tick activity, in Central Europe mainly from April to November. Tick-borne encephalitis is more common in adults than in children. Clinical spectrum of the disease ranges from mild meningitis to severe meningoencephalitis with or without paralysis. Rare clinical manifestations are an abortive form of the disease and a chronic progressive form. A post-encephalitic syndrome, causing long-lasting morbidity that often affects the quality of life develops in up to 50% of patients after acute tick-borne encephalitis. Clinical course and outcome vary by subtype of tick-borne encephalitis virus (the disease caused by the European subtype has milder course and better outcome than the disease caused by Siberian and Far-Easter subtypes), age of patients (increasing age is associated with less favorable outcome), and host genetic factors. Since clinical features and laboratory results of blood and cerebrospinal fluid are nonspecific, the diagnosis must be confirmed by microbiologic findings. The routine laboratory confirmation of the tick-borne encephalitis virus infection is based mainly on the detection of specific IgM and IgG antibodies in serum (and cerebrospinal fluid), usually by enzyme-linked immunosorbent assay. There is no specific antiviral treatment for tick-borne encephalitis. Vaccination can effectively prevent the disease and is indicated for persons living in or visiting tick-borne encephalitis endemic areas.

Key words: Tick-borne encephalitis; Diagnosis; Epidemiology; Clinical manifestations; Treatment; Prevention/vaccination

Core tip: Tick-borne encephalitis (TBE) is the most common tick-borne central nervous system infection in Europe and Asia. It is caused by three subtypes of TBE virus: European, Siberian and Far-Eastern. Because of relatively severe clinical course, the absence of etiologic treatment, considerable proportion of patients with incomplete recovery after acute illness, as well as due to increasing incidence it represents a growing public health problem that could be substantially reduced with vaccination.

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INTRODUCTION

Tick-borne encephalitis (TBE) is an important viral infection of the central nervous system in Europe and in several regions in Asia. It is caused by the Far-Eastern, Siberian and European subtype of tick-borne encephalitis virus (TBEV). Although the disease is preventable by vaccination, the incidence has been increasing during the last few decades and consequently represents a growing health problem in almost all endemic European and Asian countries. With the increase of tourism TBE is becoming a problem also outside endemic regions[1].

Most cases occur during the highest period of tick activity, in Central Europe mainly from April to November[2-4]. TBE caused by the European virus subtype usually presents as meningitis or meningoencephalitis and has a biphasic course in approximately two-thirds of patients. Up to 50% of patients have long-term sequelae[4]. An occasional clinical manifestation is an abortive form of the disease[5]. Treatment is based on the symptomatic measures. However, TBE can be successfully prevented by safe and highly effective vaccine[4].

ETIOLOGY

The neurotropic TBEV was first described as the cause of TBE by Zilber more than 75 years ago[6]. It is a spherical lipid-enveloped RNA virus, a member of genus Flavivirus within the Flaviviridae family. The mature virion is composed of 3 structural proteins-capsid (C), membrane (M), and envelope (E). Protein E is a major antigen which induces production of neutralizing antibodies. It can be inactivated by pasteurization[4].

The genetic analysis shows the existence of three TBEV subtypes named as European, Siberian, and Far-Eastern subtype[2]. They are genetically very closely related; variation in amino acids sequences between subtypes is 5%-6%[7]. In spite of the pronounced genetic similarity of the subtypes the illness caused by individual subtype is not completely equivalent to those due to the other subtypes.

EPIDEMIOLOGY

TBE is endemic in Europe, Siberia, far-eastern Russia, northern China and Japan. During the past few decades endemic regions have expanded, and within many endemic areas the number of reported cases increased. The increase in the reported incidence rates is thought to be a result of complex interplay of social and ecological factors as well as due to increased medical awareness and advanced diagnostics[8,9].

The European TBEV subtype is predominantly found in Europe, but has also been identified in west Urals, and in Siberia, whereas the Siberian TBEV subtype is found in Siberia, the Baltics, and northern Finland. The Far-Eastern TBE virus subtype is endemic in far-eastern Asia and Japan, and has been identified also in central and eastern Siberia[1,2,10,11].

In Europe and Asia between 10000 and 15000 TBE cases are reported annually[12]. The number is very likely underestimated because in many countries notification of the disease is not mandatory and only in a subset of the countries TBE case definition is in place. TBE is endemic in 27 European countries, and is a reportable disease in only 16 countries[1,12,13]. European countries with the highest incidence of the disease in the period 2005-2009 were Slovenia (14.1 cases per 100000 inhabitants per year), Estonia (11.1), Lithuania (10.6), and Latvia (8.8)[1]. Pronounced yearly variations of registered TBE cases occurred. According to the latest available epidemiological data for Slovenia the incidence of the disease in 2013 was 15.0 cases per 100000 inhabitants[14].

The primary reservoirs and hosts of TBEV in nature are small rodents; humans do not play any role in the maintenance of TBEV in nature and they are only accidental hosts. TBEV is transmitted to humans mainly by hard tick bites; in Europe the principal vector is *Ixodes ricinus* (*I. ricinus*), in parts of Eastern Europe, Russia and in far-east Asia the vector is *Ixodes persulcatus* (*I. persulcatus*) whereas in Japan Far-Eastern TBEV subtype has been demonstrated in *Ixodes ovatus* ticks. In endemic areas in Central Europe approximately 0.1% to 5.0% of ticks harbor the virus (depending on the time of the year and geographical location); in Siberia infection rates of up to 40% are reported for *I. persulcatus*[4,15]. In Slovenia, the prevalence of ticks infected with TBEV was found to be 0.47%; 0.54% in 2005 and 0.43% in 2006[16]. Approximately 1% of all TBEV infections in humans are probably acquired by consuming infected unpasteurized milk or milk products from infected livestock, particularly goats[2]. This means of transmission has to be considered particularly in cases of local epidemics. Outbreaks due to oral virus transmission are more common in Eastern Europe and the Baltic states than in Central Europe[17,18]. A few cases of laboratory-acquired TBEV infections have been documented in the literature[19].

TBE cases usually happen in the warm months between April and November, which is also the period of the highest tick activity[20]. In Central Europe, where the dominant tick species is *I. ricinus,* a two-peak distribution of TBE cases can be seen (first in June and July, second in September and October), whereas in the Ural region, Siberia and the Far East, where *I. persulcatus* is widespread, cases as a rule occur in May and June[21]. In all age groups men are affected more frequently than women[14,22-24]. On average, 10%-20%

of all reported cases of TBE occur in children[25]. It should be pointed out that due to its unspecific clinical presentation TBE in children is often missed and is diagnosed as aseptic meningitis of unknown etiology[26].

With increasing of tourism, TBE has become a more global problem. Therefore, it should be included in the differential diagnosis of the central nervous system infections not only for those living within an endemic region but-in case of an appropriate epidemiological history-also in patients living outside endemic areas. The risk of travel-associated TBE depends on the season of travel, degree of unprotected outdoor exposure as well as on consuming unpasteurized dairy products. TBE surveillance data available in Austria shows that an overall risk of acquiring TBE for a non-vaccinated tourist, staying in a highly endemic region for 4 wk during the TBEV transmission season, has been estimated at approximately 1 case per 10000 person-months of exposure, which is approximately equivalent to the risk of contracting typhoid fever or malaria while traveling in India[27,28].

PATHOGENESIS AND PATHOLOGY

After an infected tick bite TBEV replication occurs locally. Dendritic skin cells (Langerhans cells) are assumed to be the first cells for viral replication and to transport the virus to local lymph nodes. From this initial site the TBEV than disseminate to extraneural tissues, especially spleen, liver and bone marrow, where further multiplication maintains viremia for several days. During the viremic phase (which clinically corresponds to the initial phase of TBE) the virus probably reaches the brain[29,30]. The exact mechanism by which TBEV breach the blood-brain barrier is not known; four possible routes have been postulated: (1) peripheral nerves; (2) highly susceptible olfactory neurons; (3) transcytosis through vascular endothelial cells of brain capillaries; and (4) diffusion of the virus between capillary endothelial cells. The primary targets of TBEV infection in central nervous system are neurons[31].

According to rather limited information the neuropathological findings are nonspecific. Cerebral and spinal meninges usually show diffuse infiltration with lymphocytes and sometimes neutrophils. The most extensive meningeal inflammation is in the vicinity of the cerebellum. Pathological lesions which consist of lymphocytic perivascular infiltrations, accumulation of glial cells, nerve cells necrosis, and neuronophagia are localized in the grey matter and are most often present in the medulla oblongata, pons, cerebellum, brainstem, basal ganglia, thalamus, and spinal cord. Rarely, oligodendrocytes are infected. In the motor area of the cerebral cortex degeneration and necrosis of the pyramidal cells, lymphocytic accumulation, and glial proliferation are present[29,32].

MANIFESTATIONS OF TBEV INFECTION

The large majority of infections with TBEV are asymptomatic; published data suggest that the ratio of asymptomatic infections is between 70% and 98%[4,33]. However, the proportion of asymptomatic cases is hard to ascertain because patients with mild clinical signs and symptoms may remain undiagnosed.

The incubation period of TBE ranges from 2 to 28 d and is usually 7-14 d. After alimentary TBEV transmission the incubation period is as a rule shorter, usually 3 to 4 d[20]. Investigation of a recent small outbreak of TBE after drinking raw goat milk infected with TBEV in Slovenia revealed infection with the virus in four out of four exposed individuals. Of them, three developed symptomatic infection 2 to 3 d after the milk consumption, while the one who had been vaccinated against TBE remained healthy[18].

In about 75% of patients with TBE due to the European TBEV subtype the disease has a typical biphasic course. The majority of patients with monophasic course of the disease has central nervous system involvement (meningitis, meningoencephalitis), while a small fraction has a febrile illness with headache but no meningitis (*i.e.,* the initial phase of TBE not followed by the second, meningoencephalitic phase of the disease), named abortive form of TBE or "febrile headache"[4,5,20,34].

The initial phase correlate with viremia and usually presents with non-specific symptoms such as moderate fever, headache, body pain (myalgia and arthralgia), fatigue, general malaise, anorexia, nausea, and others[3]. This phase lasts for 2 to 7 d and is followed by amelioration or even an asymptomatic interval that usually lasts for about 1 wk (1-21 d). Than the second phase appears: in approximately 50% of adult patients it presents as meningitis, in about 40% as meningoencephalitis, and in around 10% as meningoencephalomyelitis[4,34].

Meningitis, encephalitis, myelitis

Meningitis and encephalitis are the most frequent clinical forms of TBE. Meningitis typically manifests with high fever, headache, nausea and vomiting; many patients have photophobia, and some vertigo. Meningeal signs are present in most of patients. Encephalitis can be manifested by impaired consciousness ranging from somnolence to stupor and, in rare cases, coma. Other manifestations comprise personality changes, behavioral disorders, concentration and cognitive function disturbances, tongue fasciculations and tremor of extremities; very rarely focal or generalized seizures, delirium and psychosis develop. Flaccid pareses, that are a typical characteristic of meningoencephalomyelitis, usually arise during the febrile phase of the disease, and are occasionally preceded by severe pain in the affected muscle groups. The upper extremities are more often affected than the lower extremities and the proximal segments more frequently than the distal ones. Patients with pareses of respiratory muscles rather commonly require artificial ventilatory support. Involvement of the central portions of the brainstem and medulla oblongata are associated with poor prognosis. Myelitis usually occur with encephalitis, and only very rarely as the only manifestation of TBE[4,20,35,36].

In patients with TBE the involvement of cranial nerves has been reported. Published data suggests that cranial nerve involvement is rare and mainly asymmetrical, that its occurrence varies with the severity of clinical presentation of TBE, and that in most cases it has a favorable outcome[24,37,38]. Cranial neuritis most commonly affects ocular, facial, pharyngeal and vestibular nerves[4,20]. Of 1218 adult patients with TBE, who were hospitalized at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia from 2003 to 2009, 11 (0.9%) developed peripheral facial palsy during the course of the disease (nine had unilateral and two had bilateral facial nerve involvement; no one had a central facial palsy) and in three of them TBE was associated with borrelia infection[39]. In regions where TBE and Lyme borreliosis are endemic, concomitant infection with TBEV and *Borrelia burgdorferi* sensu lato should be considered.

Occasionally, patients with TBE have pronounced variability in heart rate or other signs of autonomic nervous system dysfunction[40].

Abortive form of TBE

Data on this manifestation of TBE are limited. It manifests with moderate fever, headache, fatigue, and other symptoms of initial phase of the disease that are not followed by nervous system involvement. The fever typically endures for several days, and the outcome of the disease is excellent[41,42]. In Central Europe the majority of patients with the initial phase of TBE develop the second, central nervous system phase of the disease. In 2002, Lotric-Furlan *et al*[5] published a prospective clinical study on the etiology of febrile illnesses after a tick bite. Among 56 patients with confirmed TBE, only one (2%) had an isolated initial phase, whereas all the others (55, 98%) diagnosed at the time of the initial phase developed the second phase of the disease with pleocytosis.

In Russia this clinical manifestation is named "fever form," and is reported to represent up to 50% of all clinical presentations of TBE[43].

TBE with normal cerebrospinal fluid cell counts

A patient with encephalitis and serologically confirmed TBEV infection but without CSF pleocytosis has been reported[44]. In larger studies of serologically proven TBE, CSF pleocytosis was found in all patients[3,4,24,33]. This finding however, might be due to selection bias because in these studies CSF pleocytosis was one of the inclusion criteria for the diagnosis of TBE.

Chronic progressive form of TBE

There is no agreement on the existence of chronic TBE. Cases of a chronic progressive form of TBE have been identified in Siberia and the Russian Far East. This form of TBE is believed to be caused by the Siberian TBEV subtype. Both mutation in the *TBEV NS1* gene as well as an inappropriate T-cell immune response have been implicated to be associated with chronic progressive disease[3]. According to information from Western Siberia 1.7% of patients with acute TBE develop a chronic progressive form of the disease[45]. Clinical presentations include Kozshevnikov's epilepsy, lateral sclerosis, progressive neuritis, progressive muscle atrophy, and a Parkinson-like disease. Pronounced dissimilarities in the incubation period, in time to the onset of individual neurological signs/symptoms, and in the survival time after the onset of the disease have been reported[2]. Nevertheless, progressive form of TBE is most probably not present or is extremely unusual in disease caused by European TBEV subtype. In the study carried out in Lithuania, where both, European and Siberian TBEV subtypes are present, progressive course was noted in two out of 133 consecutive patients with acute TBE[24].

Post-encephalitic syndrome

TBE may cause long-lasting morbidity which often has an impact on patients' quality of life and, sometimes, necessitates an alteration of lifestyle. Many nonspecific neurological/neuropsychiatric symptoms and residual neurological dysfunctions have been reported in some prospective and several retrospective studies, but findings are hard to compare due to diverse study designs, distinct definitions, and variable follow-up times. Most studies also failed to comprise a control group; as a result findings are difficult to interpret because of unclear distinctions between post-encephalitic syndrome, other sequelae of TBE, and symptoms present in general population. Published data suggest that 40% to 50% of patients after acute TBE develop a post-encephalitic syndrome[46]. The most frequently reported symptoms have been cognitive disorders, neuropsychiatric complaints (such as apathy, irritability, memory and concentration disorders, altered sleep pattern), headache, hearing loss and/or tinnitus, disturbances of vision, balance and coordination disorders, and flaccid paresis or paralysis[24,37,38,47-49].

Lithuanian prospective clinical follow-up study showed that 46% of patients with TBE had sequelae 1 year after the onset of acute illness[24]. In a review by Haglund and Günther four retrospective and four prospective studies on the long-term morbidity from TBE were included. Up to 46% patients suffered permanent sequelae at long-term follow-up[47]. In 2009, Misić Majerus *et al*[48] published a prospective study on TBE post-encephalitic syndrome. Of 124 patients aged 16-76 years, who were followed for at least 3 years, 49 (40%) developed moderate or severe post-encephalitic syndrome lasting for up to 18 mo. Permanent sequelae were seen in 14 (11.3%) patients: spinal nerve paresis in 5, hearing impairment in 6, dysarthria in 2, and severe mental disorder in 1 patient.

CLINICAL COURSE OF ACUTE DISEASE AND LONG TERM OUTCOME

Course of acute TBE and its long-term outcome depend upon the subtype of TBEV infection. The disease caused

by the European TBEV subtype usually has a biphasic course, with a severe neurologic deficit in approximately 10% of patients, and a case-fatality rate of less than 2%[4,20]. The abortive form of TBE is rare-the initial phase most of the time move on to the second phase of the disease[5]. Long-lasting sequelae are identified in up to 50% of adult patients[46]. Infections with Far Eastern TBEV subtype often cause an illness with a gradual onset, more severe course, higher rates of severe neurologic sequelae, and a fatality rate of 20%-40%. Little information with a respect to the clinical course of the disease is available for Siberian TBEV subtype. The case-fatality rate is 2%-3% and some reports from Russia suggest an association with a chronic progressive form of TBE[2,21].

Published data suggest the relationship between age of patients and severity of TBE. The disease caused by European TBEV generally has milder course and better outcome in children than in adults. Nevertheless, TBE cases with severe clinical course, permanent sequelae and even death have been described not only in adults but also in children[23,50]. The predominant form of TBE in children and adolescents is meningitis. A summary of 8 studies on 1169 children with TBE, published from 1963 to 2005, showed that meningitis was present in 802 (69%), meningoencephalitis in 356 (30%), and meningoencephalomyelitis in 11 (1%) patients. Twenty out of 945 patients (2.1%) had long-term neurologic sequelae[25]. Limited information is available on the relationship between age and severity of TBE in adults. Mickiene *et al*[24] reported about this correlation but no precise data were given. Comparison of patients over an under 60 years revealed several differences in the course and outcome of TBE and corroborated previous postulation that TBE is a more severe disease in the elderly[22].

Some clinical studies have shown that TBE with monophasic presentation is associated with a more severe course of the acute disease[3,51-55].

The comparison of clinical course of TBE in unvaccinated and vaccinated patients did not reveal significant differences in disease severity[56].

The outcome of TBE is associated with clinical presentation. The risk of incomplete recovery is higher for patients who have more severe clinical illness during acute phase of TBE[24].

In recent years, genetic factors with potential impact on the course and outcome of TBE have been of scientific interest, resulting in several investigations. For example, the assessment of the role of chemokine receptor CCR5 indicated that *CCR5*Δ23 allele may predispose for TBE[57]. Barkash *et al*[58,59] reported on the association between *CD209* gene promoter region polymorphism and predisposition to severe forms of TBE, and on possible association between 5 OAS single nucleotide polymorphisms and the outcome of TBEV infection in a Russian population. Interesting new findings on the role of host genetic factors in TBEV infections may appear in future.

DIAGNOSIS

A case of TBE is delineated by the presence of: (1) symptoms/signs indicating meningitis or meningoencephalitis; (2) an elevated cerebrospinal fluid cell count (> 5×10^6 cells/L); and (3) microbiologic evidence of TBEV infection (the presence of specific IgM and IgG antibodies)[60].

Blood and cerebrospinal fluid analysis

In patients with TBE blood and cerebrospinal fluid findings are nonspecific. In the first (viremic) phase of TBE leukopenia and/or thrombocytopenia is established in approximately 70% of patients, rarely abnormal liver function test results are seen[61]. In the second phase of the disease mildly elevated leukocyte count may be present in peripheral blood (rarely > 15×10^9/L); erythrocyte sedimentation rate and concentration of C-reactive protein are normal in the majority of patients but may be elevated, particularly in some long-lasting severe cases. Cerebrospinal fluid examination typically reveals elevated leukocyte counts (usually lower than 500 cells/mm^3), a normal glucose concentration, and a normal to slightly elevated protein concentration. Early in the course of the disease neutrophils may predominate, while later cerebrospinal fluid profile is characterized by a predominance of lymphocytes. Elevated lymphocyte counts may last for several weeks after clinical improvement[20,62].

Microbiological investigations

At the time when neurological symptoms/signs occur TBEV has already been cleared from the blood (TBEV is present in blood in the initial but not in the meningoencephalitic phase of the disease) and is only very exceptionally present in cerebrospinal fluid. Consequently, isolation of TBEV from blood and detection of viral RNA by reverse transcriptase PCR in blood and cerebrospinal fluid of patients with TBE have a limited diagnostic yield and are as a rule not used in clinical practice[63]. Reverse transcriptase PCR assays is mainly limited to the initial phase of the disease and could be a useful method in a diagnostic procedure of febrile illness occurring after a tick bite in areas where several tick-borne diseases are present[64].

The routine laboratory confirmation of the TBEV infection is based mainly on the demonstration of specific antibodies in serum (and cerebrospinal fluid), usually by highly sensitive and specific enzyme-linked immunosorbent assay[63,65]. In the majority of patients specific serum IgM and IgG antibodies are present at the beginning of the meningoencephalitic phase of the disease; rarely only IgM antibodies to TBEV are found in the first serum sample. In such cases a second serum sample has to be tested 1-2 wk later, because the demonstration of IgM antibodies alone does not suffice for the diagnosis. TBEV IgM antibodies can be detected in the serum for several months (up to 10 mo or even longer) after acute infection, whereas TBEV

IgG antibodies persist for a whole life, and mediate an immunity that prevents symptomatic reinfection[63,66]. In cerebrospinal fluid specific IgM and IgG antibodies are detectable several days later than in serum, and in almost all cases by day 10[63,67].

However, some limitations are necessary to take into account when using and interpreting serological testing. Specific TBE IgM antibodies may be detectable for several months after acute TBEV infection (as well as in some persons after the first two doses of primary immunization) and may lead to erroneous interpretation in case of another central nervous system disease/infection within this time period[63,66]. Because of the close antigenic relationship between TBEV and other flaviviruses cross-reactive antibodies are induced by infections or vaccinations. This may pose a diagnostic challenge in people vaccinated against yellow fever or Japanese encephalitis and in travelers having acquired dengue, West Nile or other flavivirus infections[68]. Such potential problems in TBE serodiagnosis can be resolved by the quantification of IgM antibodies in a single serum sample taken at the time of hospitalization. High IgM values (> 500 Arbitrary Units) are indicative of a recent infection with TBEV. Lower IgM values, however, may require the analysis of a follow-up sample and/or a specific neutralization assay to exclude the possibilities of long persisting IgM antibodies after infection or those induced by vaccination as well as cross reactive IgM antibodies[69]. Carefulness in the interpretation of TBE serology is also needed in patients with meningoencephalitis or meningitis who had been vaccinated against TBE. In the majority of patients with vaccination breakthroughs serological response is distinct from those found in unvaccinated persons with TBE and consequently vaccination breakthrough cases may be overlooked. These cases are characterized by a delayed development of specific IgM response (during the initial week of the meningoencephalitic phase of TBE specific IgM antibodies are usually not detectable) associated with a rapid increase of specific serum IgG antibodies[70-72]. For a reliable diagnosis of TBE in persons previously vaccinated against TBE, demonstration of intrathecal production of TBEV antibodies is required[34].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TBE is extensive and includes a wide variety of central nervous system infections due to other infectious agents as well as noninfectious diseases.

In the initial, viremic phase of TBE, when a patient present with fever, headache, arthralgia, myalgia, and malaise the differential diagnosis may include various viral syndromes; if nausea, vomiting, diarrhea, and anorexia are present, gastroenteritis is a possible explanation. When signs and symptoms of central nervous system involvement develop, TBE needs to be differentiated from encephalitis or aseptic meningitis due to many other viruses. Differential diagnosis comprises also other tick-borne diseases such as Lyme borreliosis, babesiosis, human granulocytic anaplasmosis, tick-transmitted rickettsioses, and tularemia[20].

In many endemic regions TBEV geographically overlaps with bacterial tick-borne pathogens such as *Anaplasma phagocytophilum* and *B. burgdorferi* s.l. Both diseases caused by the two agents, human granulocytic anaplasmosis and Lyme borreliosis, are treatable with antibiotics, and caution must be taken to distinguish them from TBE[20]. Concomitant TBEV and *B. burgdorferi* s.l. infections, as well as concomitant TBEV and *A. phagocytophilum* infections have been described[60,73-76].

The initial, viremic phase of TBE and human granulocytic anaplasmosis have a similar clinical and laboratory presentation. Both diseases are characterized by fever and headache, and both are typically associated with thrombocytopenia and leukopenia; in certain patients also mild abnormalities in liver tests are present. Nevertheless, a clinical report on chills, myalgia and arthralgia, and laboratory findings of elevated concentration of C-reactive protein and lactate dehydrogenase values point to the diagnosis of human granulocytic anaplasmosis and not in favor of the initial phase of TBE[77].

TREATMENT

There is no specific antiviral treatment for TBE. Patients as a rule need hospitalization and supportive care based on the severity of signs/symptoms, and usually encompasses administration of antipyretics, analgesics, antiemetics, maintenance of water and electrolyte balance, and if necessary administration of anticonvulsive agents. In patients with neuromuscular paralysis leading to respiratory failure, intubation and ventilatory support are necessary. In a large prospective German study, 12% of patients were treated in intensive care unit and in 5% assisted ventilation was required[38]. Among Slovenian patients with TBE, hospitalized at the Department of Infectious Diseases, University Medical Centre Ljubljana, in years 2000 to 2004, 6.9% were hospitalized in intensive care unit and 22.5% of them needed mechanical ventilation[22].

Cerebral edema is a potential complication of acute viral encephalitis that aggravates the clinical picture and portends poor neurologic outcome. Patients who have significantly raised intracranial pressure are often treated with intravenous mannitol and/or steroids[78]. Mannitol produces a shift of fluid from the edematous brain back into the intravascular space and subsequently increases circulation volume and improves cerebral perfusion pressure, and lowers intracranial pressure through cerebral autoregulation. It also acts on erythrocyte membrane fluidity and through reducing blood viscosity improves blood flow and oxygen delivery. A rebound phenomenon in intracranial hypertension occurs in about 5% of patients. To avoid complications,

it is frequently recommended that mannitol no longer be administered when the serum osmolality exceeds 320 mOsm/L[78,79]. Despite a rather common clinical practice to treat patients who have significantly raised intracranial pressure with intravenous mannitol, there are no reliable (comparative) studies substantiating the usage of mannitol in patients with TBE.

It has been demonstrated that the use of dexamethasone results in a reduction of brain edema in acute viral encephalitis[80]. In the Baltics and some Eastern European countries patients with TBE are quite common given corticosteroids. The use of steroids is based on the impression that they produce a good and rapid clinical response in patients with TBE, but the validation of the impression in controlled studies has been limited. In a Lithuanian study corticosteroids were used in 81 out of the 133 patients with TBE. Among patients with mild, moderate, and severe disease, 39.7%, 70.7%, and 100% received corticosteroids, respectively. Hospitalization was significantly prolonged among these patients, compared with patients who received only symptomatic treatment. Because all patients with severe disease received corticosteroids it was hard to assess their role in the outcome of TBE[24]. In the group of Polish patients with TBE dexamethasone was used in 54.8% of patients with meningitis, in 69.6% of patients with meningoencephalitis and in 78.3% of patients with meningoencephalomyelitis. In this study the duration of hospitalization was significantly longer only in patients who received dexamethasone longer than 10 d[49]. Perhaps corticosteroid treatment is effective in certain cases, but until the results of the randomized studies are available they cannot be recommend as a standard treatment approach[24,49].

A case report on a patient with severe TBE who substantially improved after application of high dose intravenous immunoglobulins late in the disease course[81], and reports on the successful treatment of encephalitis due to other arboviruses with high doses of intravenous immunoglobulins, prompted Růžek *et al*[82] to propose the implementation of randomized controlled treatment study on the efficacy of high dose intravenous immunoglobulins in patients with severe TBE. Such a proposal should not be interpreted as an indication for treatment of TBE with immunoglobulins.

NONSPECIFIC PREVENTIVE MEASURES

Nonspecific preventive measures comprise pasteurization of milk, reduction of tick population, and personal protective procedures.

Since milk from endemic regions may contain TBEV, pasteurization, and avoiding consumption of unpasteurized milk and dairy products, prevent infection of humans[3,18].

Population of ticks can be reduced by impacts on the environment (*e.g.,* by regular cutting grass around the house, by usage of acaricides, and/or by control of deer population).

Nonspecific personal preventive measures include avoidance of ticks (which means avoidance of contact with vegetation, especially in deciduous and mixed forests with a rich understory and a layer of decaying vegetation on the ground that provides sufficient humidity for the development and survival of ticks), wearing light-colored clothing (light colors enable that ticks are better noticeable) with long sleeves and slacks stuck in socks or footwear (to diminish tick access to the skin), use of repellents, careful examination of the whole body for the presence of ticks, and removal of the attached ticks as soon as possible[83]. However, TBEV is present in salivary glands of the infected tick and may be transmitted from the saliva of an infected tick within a few minutes after attachment[3]. Although the recommended personal measures appear to be self-evident for the prevention of tick-borne diseases including TBE, the effectiveness of certain measures is limited, questionable or has not been properly assessed. Additional problem is that only a small proportion of exposed persons follow the recommended procedures in everyday life[84,85].

VACCINATION

Historically, immunoglobulins containing gamma globulin against TBEV were used as a prophylaxis against TBE within 96 h after a tick bite in the TBE endemic regions (post-exposure prophylaxis). However, due to reports indicating a more severe disease course in children who had received the immunoglobulin[86-88] and because protection was rather unreliable[88], the usage of the immunoglobulins (passive immunization) in European Union has been abandoned[89]. Nevertheless, according to recent studies in Russia, timely single administration of a specific immunoglobulin preparation in a dose of 0.05 mL/kg body weight was protective in approximately 80% of the cases[90]. Further analysis of these findings is needed.

Active immunization is the most effective way to prevent TBE[3,4]. Given that TBE is a zoonosis, that the source of infection is an infected animal, and that TBEV is transmitted by a tick bite and does not spread from human to human, vaccination enables only individual protection. Consequently, high immunization rate of a population in a given environment does not protect persons who are not vaccinated.

Recommendations for TBE vaccination

Because TBE incidence varies within and between different endemic areas recommendations for public vaccination strategies should be based on risk assessments conducted for individual region.

World Health Organization (WHO) recommends vaccination to people of all age groups, including children, in highly endemic areas (≥ 5 cases/100000 per year). In regions where the pre-vaccination incidence of TBE is low to moderate (5 year incidence < 5 cases/100000 per year) immunization should target

persons in the most vulnerable groups. The WHO also recommends TBE vaccination for people travelling from nonendemic areas to rural endemic areas up to altitudes of 1400 m[91].

Central European Vaccination Awareness Group strongly recommends the introduction of universal TBE vaccination for persons > 1 year old for all countries at very high risk of TBE infections. For countries with a very low risk of TBE, recommendations for TBE vaccination should only apply to persons travelling to endemic regions[92].

Vaccines

Two vaccines against TBE, FSME-IMMUN® and Encepur®, are registered in Europe. They contain inactivated European subtype of TBEV-FSME-IMMUN is based on strain Neudorf 1, Encepur on strain K23. Both vaccines prevent not only the disease caused by the European but also those caused by the Siberian and Far-Eastern subtype of TBEV. Procedures used in the preparation of the two vaccines are similar (viruses are grown in chick embryo fibroblast cells, are inactivated by formaldehyde and are purified), and in both vaccines the adjuvant is aluminum hydroxide[89]. Both vaccines are registered for adults and children aged 1 year and older (vaccines for children are called FSME-IMMUN 0.25 mL Junior, and Encepur Kinder, respectively).

In addition to European vaccines, two vaccines based on Far-Eastern subtype of TBEV are registered in Russia (TBE-Moscow and EnceVir); also in these vaccines viruses are grown in chick embryo cells and are inactivated with formalin. Another vaccine, which is produced and used in China, is also based on the Far-Eastern subtype of TBEV[89].

Vaccination schedule

Several vaccination schedules exist; all of them consist of primary (basic) vaccination followed by booster doses. For a complete primary (basic) vaccination three doses, usually with an interval of 1-3 and 5-12 mo between first and second, and second and third dose, respectively, is required. Immunity is maintained with booster doses: the first booster dose is administered 3 years after completion of the primary vaccination, later on one dose is needed every 5 years. Due to the deterioration of the immune response in persons aged > 60 years (FSME IMMUN) or > 50 years (Encepur) boosters are recommended at 3 years intervals in this age group[89].

Vaccination can begin at any time, but immunization with the first two doses is preferably carried out in the winter months to achieve protection before tick activity. Reports on individual cases of severe forms of TBE in subjects who had received only one dose of vaccine against TBE, had historically been an additional reason to start vaccination (receipt the first two doses) in winter. Subsequent information showed that incomplete vaccination does not pose an increased risk for severe disease as compared to unvaccinated persons of the comparable age.

When it is desired to achieve protection in a short time, "fast schedule" can be used in accordance with the manufacturers' instructions[3,4,85]. In contrast to classic approach, in "rapid vaccination" the second dose is usually administered 14 d instead of 1 to 3 mo after the first dose. Protection efficacy is comparable to that seen after classical schedule; however, scientific data on "quick schedule" is less comprehensive than for the conventional approach.

In a person who had not received the recommended doses according to the schedule but with longer intervals, vaccination does not need to be started again from the very beginning but continue with missing doses[93]. Example: if someone had received only two doses of TBE vaccine 5 years ago and afterwards forgot to get the third dose, the vaccination should proceed with the third dose of basic vaccination and then with booster doses according to schedule. Or: a person who had received complete basic vaccination but for 15 years had not obtained any booster dose, does not need to repeat basic vaccination but just get the first booster dose and then continue immunization with booster doses according to the recommended schedule. Longer intervals between doses generally do not reduce antibody concentrations after completion of TBE vaccination, but protection in the period before the delayed dose is less reliable[93].

Persons who had acquired TBE are esteemed to be protected against the disease and do not need vaccination.

Mode of application, dosages

TBE vaccine is administered intramuscularly into the deltoid muscle; in young children it can be given in the anterolateral thigh. The vaccine may be administered simultaneously with other vaccines (live or inactivated) but not on the same place[89].

Doses depend upon the age of the recipient; the age limits for vaccines available in Europe slightly differ. In subjects younger than 16 years, the dose of the FSME-IMMUN vaccine is 0.25 mL, while for persons who have 16 years or are older 0.5 mL is recommended; in subjects younger than 12 years, the dose of the Encepur vaccine is 0.25 mL, while in older the dosage is 0.5 mL.

Efficacy and safety

Both European vaccines are safe and effective; particularly voluminous data exist for FSME-IMMUN vaccine of which more than 100 million doses were used.

Fourteen days after the second dose of basic vaccination protective antibodies develop in about 85% of the subjects, while after three doses more than 98% of persons with normal immunity are protected[89].

In Austria, where the vast majority of the population is vaccinated, the incidence of TBE declined dramatically. The estimated protection after vaccination (field

effectiveness) is more than 98% for persons vaccinated according to the recommended program and more than 90% for those who received basic vaccination, but were later not vaccinated according to the planned schedule[94].

Side effects are mild and relatively rare. They are more frequent after the first dose of vaccine than with later doses. Most commonly local pain and tenderness on pressure at the injection site take place; redness and swelling occur less often. Short-term fever after vaccination is rare in adults but relatively common in young children. Neurological complications are very rare[89].

Storage

The vaccine must be stored in a refrigerator at a temperature between 2 ℃ and 8 ℃. Storage at higher temperatures and freezing are not suitable[89].

Limitations and contraindications

Vaccination is not carried out in subjects with acute febrile illness.

Vaccination is contraindicated in the case of: (1) A severe allergic reaction after previous dose of TBE vaccine; (2) Information on severe allergic reactions to vaccine components (in addition to the active ingredients, TBE vaccine also contains remnants of formaldehyde, neomycin, gentamicin and protamine sulfate); and (3) Anaphylactic hypersensitivity to eggs (TBE viruses are grown in chick embryo fibroblast cells).

Controlled clinical trials to assess the safety of TBE vaccine during pregnancy are not available; thus, pregnant women are vaccinated only after a careful individual assessment of the potential risks and benefits. There is also no sufficient data on the safety of vaccination during lactation. It is not known whether the vaccine components are excreted in human milk or not, however, mother's antibodies produced after vaccination against TBE are probably present in the milk and consequently breast-feeding baby may come in contact with them. Given that TBE vaccines are based on inactivated virus, the damage of fetus or breast-feeding child is highly unlikely.

Although there is no evidence that vaccination may trigger autoimmunity or worsen the course of autoimmune diseases, caution is needed in subjects with an autoimmune disease since information to ensure the safety of vaccination in this group of patients is limited[89].

The manufacturer of the vaccine and some recommendations suggest that in immunocompromised persons the efficacy of vaccination is verified by serological testing approximately four weeks after the second dose, and that-in case of an inadequate antibody response-the second dose is repeated and followed by the third dose in accordance with the normal vaccination schedule. According to some suggestions similar approach may apply also to all subsequent doses. Although the approach appears logical, there is no convincing clinical data to substantiate its use. As a rule the effectiveness of protection after vaccination against TBE is not verified by the detection of antibodies against TBEV in serum.

CONCLUSION

TBE is an important tick-borne central nervous system infection in Europe and Asia. Due to relatively severe clinical course combined with the absence of etiologic treatment, considerable proportion of patients with incomplete recovery after acute illness and increasing incidence, it represents a growing (public) health problem that could be substantially reduced with vaccination.

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