Chapter 3

Tick-Borne Encephalitis

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Additional information is available at the end of the chapter

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Abstract

Tick-borne encephalitis (TBE) is an important central nervous system infection in Europe and Asia. It is caused by three subtypes of TBE virus (TBEV): European, Siberian and Far-Eastern, belonging to the genus *Flavivirus*. TBE is delineated by three criteria: the presence of clinical signs of meningitis, meningoencephalitis or meningoencephalomyelitis; cerebrospinal fluid pleocytosis (>5 × 10^6 cells/L); and demonstration of a recent infection with TBEV by the presence of specific serum IgM and IgG antibodies or IgG seroconversion. Imaging of the brain and spinal cord has a low sensitivity and specificity, but it is useful for the differential diagnosis. Clinical course and outcome of TBE depend on the subtype of TBEV (the disease caused by the European subtype has a milder acute course and a more favorable long-term outcome than the disease caused by the other two virus subtypes), age of patients (increasing age is associated with more severe acute course and poorer outcome) and probably on some host genetic factors. 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, TBE represents a growing (public) health problem that could be substantially reduced with vaccination.

Keywords: tick-borne encephalitis, tick-borne encephalitis virus, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, vaccination

1. Introduction

Tick-borne encephalitis (TBE) is an important human viral infection of central nervous system (CNS) endemic in a large part of Europe and Asia. The causative agents are three different TBE virus (TBEV) subtypes named European, Siberian and Far-Eastern [1]. In spite of the pronounced genetic similarity of these flaviviruses, the illness caused by individual subtype is not entirely comparable to those caused by the other subtypes.

The clinical course of acute illness is highly variable. Due to the relatively high proportion of severe cases and a considerable proportion of patients with long-lasting sequelae which may have a significant impact on quality of life, the disease represents high costs for healthcare system and society.

Herein we present an overview of TBE, including a short historical outline, basic information on TBEV, and of the epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment of TBE, as well as on the course and outcome of the disease and its prevention.

2. History

Historically the first mention of the TBE existence dates back to the eighteenth century in Scandinavian church records from Åland Islands. However, the first medical description of disease was given and published in 1931 by the Austrian physician H. Schneider [2]. Six years later, an expedition headed by Zilber in the Russian Far East isolated for the first time the causative agent (TBEV) from humans, mice, and *Ixodes persulcatus* ticks; they determined the etiology of TBE and its vector [3]. In 1939, Pavlovsky confirmed the preliminary hypothesis on the transmission of the TBEV in nature (between ticks and mammals) and proposed the theory of natural foci [4]. In Europe, TBEV was first isolated, from humans and *Ixodes ricinus* ticks, in Czechoslovakia in 1948 by Gallia and colleagues [5]. In the following years, the disease and/or the virus has been identified in many other European countries and, later, also in the north of China and northern Japan [6].

3. Etiology

TBE is caused by TBEV, a small, neurotropic, lipid-enveloped spherical RNA virus, the member of genus *Flavivirus*, family *Flaviviridae*. The viral RNA contains records for three structural (E (envelope), prM/M (precursor of membrane or membrane, respectively), and C (capsid)), and seven nonstructural viral proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). Glycoprotein E is a major viral antigen and is associated with the production of neutralizing antibodies and the induction of protective immunity. It also plays a key role in the viral life cycle mediating the binding of virions to cell receptors and subsequent intraendosomal fusion [7].

TBEV occurs in three subtypes named as European, Siberian, and Far-Eastern subtype [1]. They are very closely related, both genetically and antigenically; variation in amino acids sequences between subtypes is 5–6% [8]. 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.

An important characteristic of the TBEV, which allows them alimentary route of infection, is their ability to maintain at least residual infectivity at acidic pH (above pH 1.42) [9]. TBEV maintains infectivity at very low environment temperatures (even below −70°C). On the contrary, it is heat labile; total inactivation of the virus occurs within 30 minutes at 56°C [10, 11]. It can be inactivated by pasteurization [12].

4. Epidemiology

TBE arises in an endemic pattern of so-called natural foci over a large geographical area extending from Central Europe and Scandinavia through the Eurasian continent to North-Eastern China and Northern Japan. Over the past few decades, a trend toward both an expansion of the endemic areas and an increase of reported cases have been observed [13, 14]. The increase in the incidence is the result of a complex interrelation of socioeconomic and ecological factors; a part of an increase may also be explained with an increased medical awareness, advanced diagnostics, and improvements in epidemiological surveillance [15, 16].

In Europe and Asia between 10,000 and 15,000 TBE cases are reported per year with pronounced annual fluctuations [17]. The number is very likely underreported mainly due to lack of standardized TBE case definition, the varying diagnostics procedures, and the wide differences in the quality of national surveillance systems.

In 2012, TBE became a notifiable disease at the European Union level. Currently the disease is endemic in 27 European countries; the reporting is mandatory in 18 of them. Two-thirds of the countries where TBE is a notifiable disease use the European Centre for Disease Prevention and Control case definition [13, 18, 19]. A total of 2560 TBE cases were reported in Europe in 2012 with the overall notification rate of 0.52 cases per 100,000 inhabitants. Countries with the highest reported incidence (>5 cases per 100,000 inhabitants per year) were Estonia (13.35), Lithuania (11.69), Slovenia (7.98), and Czech Republic (5.46) [20].

The main hosts and reservoirs of TBEV in nature are wild vertebrate, in particular small rodents. Ticks act as both virus vectors and reservoir and carry the virus throughout their life. Humans are only accidental hosts and do not play any role in the maintenance of TBEV in nature [21, 22].

Most human infections occur through an infected hard tick bites. At least 11 tick species are capable of transmitting TBEV, but only 2 species are of clinical importance. *I. ricinus* is the principal vector throughout Europe and, therefore, the most important transmitter of the European TBEV subtype, while *I. persulcatus* occurs in regions of Eastern Europe, in Russia, and in far-eastern Asia and is the main vector of the Siberian and Far-Eastern TBEV subtype [21, 23]. The Siberian TBEV subtype is found in Siberia, the Baltics, and northern Finland, whereas the Far-Eastern TBEV subtype is endemic in far-eastern Asia and Japan, and also in central and eastern Siberia [13, 22]. In the Baltic States and Finland, where *I. ricinus* overlaps with *I. persulcatus*, all three TBEV subtypes co-circulate [24–26]. The Far-Eastern TBEV was found in *Ixodes ovatus* in Japan in south-western China, while the European TBEV subtype was detected in *Ixodes nipponensis* ticks in Korea [1, 27].

In Europe, the TBEV prevalence in unfed *I. ricinus* ticks ranges from 0.1 to 5.0% (depending on the geographical location and time of the year) and increases with development stage, whereas in Siberia, the reported proportion of infected adult *I. persulcatus* ticks is up to 40% [13, 21]. In Slovenia, the prevalence of TBEV-infected ticks was found to be 0.47%; 0.54% in 2005 and 0.43% in 2006 [28]. About 1% of all human TBEV infections are alimentary-transmitted by consuming contaminated unpasteurized dairy products, especially goat milk [1]. This route of infection has to be considered in cases of local epidemics. The majority of outbreaks

due to oral virus transmission are reported from Eastern Europe and Baltic states [29, 30]. A few cases of laboratory-acquired TBEV infections have been documented [31]. Vertical transmission, person-to-person transmission including breast-feeding, and transmission through blood transfusion have not been reliably described in humans.

TBE is a seasonal disease; most cases occur in the warm period of the year (usually between April and November) which correlates with the period of the highest tick activity and with increased exposure during this time period [32]. In Central Europe, a two-peak distribution of TBE cases can be seen, first in June and July, and second in September and October, whereas in the regions where *I. persulcatus* is widespread, cases as a rule occur in May and June [11]. In all age groups men are affected more frequently than women. The highest notification rate is in the 45–64 year-old age group, followed by the over 65-year olds [20, 33]. On an average, 10–20% of all reported cases of TBE occur in children, with the lowest incidence in those less than 3 years of age [34, 35]. 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 [36, 37].

TBE represents a potential risk for nonvaccinated travelers traveling to countries with high endemic foci and therefore should be included in the differential diagnosis of the CNS infections in case of an appropriate epidemiological history also in patients living outside endemic areas. The risk depends on the season of travel, duration of stay as well as on travel style (degree of unprotected outdoor exposure). In the different endemic areas, the risk for infection after a single tick bite varies from 1:200 to 1:1000 [21].

5. Pathogenesis and pathology

After the bite of an infected tick TBEV replication occurs locally. Dendritic cells (Langerhans cells) are considered to be the most important cells for local viral replication and to transport the virus to the regional lymph nodes where further replication takes place. After release into the bloodstream the virus disseminate to other organs, in particular to the reticulo-endothelial system (mainly bone marrow, spleen, and liver) where the virus continue to multiply and maintain viremia for few days. During the viremic phase (which clinically matches to the initial phase of TBE) the virus probably reaches the brain [38, 39]. The precise mechanism of viral passage through the blood-brain barrier is unclear, but depends on the presence of viremia. Four possible routes have been postulated: (i) peripheral nerves, (ii) highly susceptible olfactory neurons (especially relevant in laboratory infections by aerosols), (iii) transcytosis through vascular endothelial cells of brain capillaries, and (iv) diffusion of the virus between capillary endothelial cells. The primary targets of TBEV infection in central nervous system are neurons. Rarely, oligodendrocytes are infected [38].

TBEV in CNS induces inflammation with inflammatory cell infiltration, activation of microglia, and neuronal degeneration. The exact mechanism of tissue destruction is unclear, but Ružek and coworkers demonstrated that inflammatory reaction mediated by CD8+ T cells significantly contributes to neuronal damage [40]. Limited data are available on the role of cytokines and chemokines.

Pathological lesions are widespread all over the CNS and involve leptomeninges and gray matter, with the brain stem, cerebellum, basal ganglia, thalamus, and spinal cord being most frequently affected. Histological findings are nonspecific; lesions consist of perivascular and parenchymal accumulation of lymphocytes, consisted of T and B cells, and macrophages (microglia), associated with nerve cells necrosis and neuronophagia in regions of viral replication. Residual lesions are characterized by loss of neurons and microglial scarring. Cerebral and spinal meninges usually show diffuse infiltration with lymphocytes and sometimes neutrophils. The most extensive meningeal inflammation is around the cerebellum [38, 41].

6. Clinical manifestations of TBEV infection

Seroepidemiological studies have demonstrated that TBEV infection is often asymptomatic. The exact proportion of such cases is not known, because those with mild clinical presentation may not be diagnosed, but data suggest rates between 70 and 98% [42–44].

Time interval from a tick bite to the beginning of the illness is usually 7–14 days, but it may be as short as 2 days and as long as 4 weeks. After alimentary route of infection, there is regularly a shorter incubation period of 3–4 days [30, 32, 45].

In at least three-quarters of patients who develop CNS involvement, the disease caused by the European virus subtype has a biphasic course [46–48]. The initial phase corresponds to the viremia and usually presents with nonspecific systemic signs and symptoms; the most common are moderate fever (99%), fatigue (63%), general malaise (62%), headache and body pain (arthralgia and myalgia) (54%) [47]. In this phase, which lasts 2–7 days, there are no signs or symptoms of CNS involvement; cerebrospinal fluid (CSF) examination reveals normal findings. After an improvement or even an asymptomatic interval of about 1 week duration (range 1–21 days) the second phase presents as meningitis, meningoencephalitis, or meningoencephalomyelitis in 54, 37, and 9% of adult patients [49]. The far most frequent clinical manifestation of TBE in children is meningitis [34]. Fever in the second phase is typically 1–2°C higher than the peek temperature in the first phase and is of longer duration [12, 50].

In some patients the disease course is monophasic: they may either have CNS involvement or a febrile illness with headache with symptoms subsiding without developing into the second phase (i.e., the initial phase of TBE without subsequent CNS involvement), named abortive form of TBE or "febrile headache" [12, 32, 50, 51].

6.1. Abortive form of TBE

Data on the frequency of this clinical manifestation of the disease caused by European TBEV subtype are conflicting. According to some reports it represents more than a half of all clinically manifested TBEV infections [32, 52]. However, this is not confirmed by the results of a prospective clinical trial on the etiology of acute febrile illness after a tick bite carried out by Lotric-Furlan and coworkers: of the 56 patients diagnosed with TBEV infection during the initial phase of illness, in 55 (98.2%), CNS involvement with pleocytosis later appeared,

whereas only one (1.8%) had an isolated initial phase of the disease [51, 53]. In the Russian publications, this clinical manifestation is named "fever form" and is reported to represent up to 50% of all clinical presentations of TBE [54]. Abortive form of TBE most frequently presents itself by a moderate fever, headache, fatigue, and other nonspecific symptoms of the initial phase of the disease. The fever usually subsides in a few days and the disease does not have long-term consequences [55, 56].

6.2. Meningitis, encephalitis, and myelitis

Meningitis is characterized by fever, headache, nausea, vomiting, and meningeal signs. These symptoms and signs are present in the majority but not in all the patients. In a study encompassing 448 adult patients with TBE from Slovenia, almost all reported headache and had fever, more than 50% suffered from nausea and/or vomiting, and 70% had clearly expressed meningeal signs [33]. Encephalitis may manifest by a variety of neurological symptoms and signs, most often with tremor (especially of the fingers of the upper extremities and tongue), sometimes with nystagmus, speech disorder, ataxia and movement disorders, occasionally with seizures, and very rarely with brain stem symptoms and/or cranial nerve abnormalities. Impaired consciousness, ranging from mild to severe, insomnia, and concentration and cognitive function disturbances are rather frequent. Mental disorders including amnesia, behavioral changes, psychosis, and delirium may also occur. Patients may have sensory impairment. Myelitis is virtually always associated with meningoencephalitis, and as a rule manifests with flaccid paralyses that are occasionally preceded by severe pain in the affected muscle groups. The involvement is usually asymmetrical. Most often extremities are affected, more frequently the upper than the lower limbs, and more often the proximal segments of the extremities than the distal ones. Patients with pareses of respiratory muscles usually require artificial ventilatory support [12, 32, 57].

6.3. Other manifestations in the acute phase of illness

6.3.1. Involvement of cranial nerves

According to rather limited data, involvement of cranial nerves is rare, mostly asymmetrical, typically associated with severe acute illness, and usually has a favorable outcome [46, 47, 58]. Ocular, facial, and pharyngeal muscles are most often affected, but hearing and vestibular defects are also encountered [42].

In a series of 1218 adult patients diagnosed with TBE at a single center, 11 (0.9%) developed peripheral facial palsy (2 bilateral, 9 unilateral); however, 3 out of 11 patients had associated borrelial infection. The latter finding suggests that in patients who develop peripheral facial palsy in the course of TBE, and who had been exposed to ticks in the region where both TBE and Lyme borreliosis are endemic, coexistent infection with Lyme borreliae have to be taken into account [59].

6.3.2. Autonomic disorders

Occasionally, autonomic nervous system disorders are present in patients with TBE [60].

6.3.3. Encephalitis with normal CSF cell counts

Literature review revealed some reports on a serologically confirmed TBEV infection in patient with encephalitis but without CSF pleocytosis [61, 62]. This disagrees with the large series of serologically proven TBE patients, in which CSF pleocytosis was found in all the cases [12, 42, 43, 47]. However, the latter finding might be the result of a selection bias because in the studies CSF pleocytosis was one of the essential inclusion criteria for the diagnosis of TBE.

6.4. TBE in patients who had been vaccinated against the disease

It seems that breakthrough TBE after vaccination is rare: 7 cases were reported in Slovenia, 25 in Austria, and 27 in Sweden in the periods 2000–2006, 2000–2008, and 2002–2008, respectively. The majority (70%) of patients were over 50 years old, but also a pediatric case has been described [63–67]. According to Kunz, disease severity in unvaccinated and vaccinated patients with TBE does not differ substantially; however, the information is limited [68].

6.5. Chronic progressive TBE

A chronic progressive form of TBE, believed to be associated with the Siberian subtype of TBEV, has been described in Siberia and Far East. It may manifest with *epilepsia partialis continua* [69–72].

6.6. Postencephalitic syndrome

According to published data postencephalitic syndrome occurs in up to 58% of patients after acute TBE caused by European subtype of TBEV, and may include various nonspecific neurological/neuropsychiatric symptoms and residual neurological dysfunctions [73]. It often affects the patient's quality of life (sometimes requires a change in lifestyle) and also represents a high cost for the health care system and society.

The most commonly reported symptoms/signs have been cognitive or neuropsychiatric complaints (i.e., apathy, irritability, memory and concentration disorders, altered sleep pattern), headache, hearing defects, disturbances of vision, ataxia, and pareses or flaccid paralyses [46, 47, 58, 73, 74]. At this point it should be noted that most of the studies failed to include a control group; therefore, the findings are difficult to interpret due to unclear differences between postencephalitis syndrome, other consequences of TBE and symptoms present in the general population.

Lithuanian prospective clinical follow-up study showed that 46% of patients with TBE had sequelae 1 year post infection [47]. In 2009, Misić-Majerus et al. published a prospective study on TBE postencephalitic syndrome. One hundred and twenty-four patients, aged 16–76 years, participated in the study with follow-up period for at least 3 years. Forty-nine patients (39.5%) developed moderate or severe sequelae lasting for 3 to 18 months; in 11 patients permanent sequelae were seen—spinal nerve paresis in five, hearing impairment in six, dysarthria in two, and severe mental disorder in one patient [74]. In 2011, Kaiser reported 10-year follow-up

results in patients with encephalomyelitic manifestation of TBE; 11 (19%) out of 57 included patients fully recovered, 29 (51%) patients had long-lasting sequelae (paresis or other impairments), and 17 (30%) died 1–10 years after the acute disease. The most substantial improvements were seen in the first year after acute disease [75]. Recently published case-control study on the long-term sequelae after TBE from Sweden has showed that the neurocognitive and motor symptoms in patients significantly differ from those in the age- and gender-matched control group [76].

7. Diagnosis

For a diagnosis of TBE, three criteria should be fulfilled:

(a) symptoms/signs indicating meningitis or meningoencephalitis,

(b) elevated CSF cell count (>5 × 10^6 leukocytes/L), and

(c) microbiologic evidence of TBEV infection (i.e., the presence of specific IgM and IgG antibodies) [77].

7.1. Blood and cerebrospinal fluid analysis

In the initial (viremic) phase of TBE leukopenia and/or thrombocytopenia are ascertained in around 70% of patients, and abnormal liver test results are seen in about 20% [78]. In the second (meningoencphalitic) phase, platelet count is normal, whereas peripheral blood leukocyte count is normal or mildly elevated (rarely >15 × 10^9/L). Concentration of C-reactive protein and erythrocyte sedimentation rate is usually in normal range throughout the entire course of TBE. In the initial phase of TBE, CSF findings are in the normal range, whereas in the second (meningoencephalitic) phase, elevated CSF leukocyte counts (usually <500 × 10^6/L, extremely rarely ≥1000 × 10^6/L), a normal to moderately elevated protein concentration, and a normal glucose concentration are present. A typical finding is lymphocytic pleocytosis; however, in the first few days of the meningoencephalitic phase of TBE, neutrophils may predominate in CSF. Elevated lymphocyte counts may persist for several weeks after clinical recovery [32, 79].

7.2. Magnetic resonance imaging (MRI) abnormalities

MRI abnormalities of brain and spinal cord are present only in about 20% of patients with TBE. According to a study performed by Kaiser [46], they are found more often in patients with meningoencephalomyelitis (7/25, 29%) than in patients with meningoencephalitis (11/64, 17%), and are not seen in those with meningitis (0/13). Increased signal intensity is most often seen in the thalamus, but can (also) be present in basal ganglia, internal capsule, splenium, cerebellum, peduncles and brain stem [46, 80–92]; in patients with myelitis, the abnormalities are seen predominantly in the anterior horns of the spinal cord [84, 85, 89, 93–97]. Studies of specificity are lacking but the specificity is probably low [89].

7.3. Microbiological investigations

7.3.1. Detection of TBEV

Due to limited diagnostic yield, direct approaches to demonstrate TBEV, such as detection of viral RNA by reverse transcriptase PCR and isolation of the virus, are as a rule not used in clinical practice. TBEV is present in blood in the initial (viremic) phase of TBE but not in the meningoencephalitic phase of the disease and is only very exceptionally present in CSF [98].

7.3.2. Serology

In the routine clinical practice, demonstration of antibodies to TBEV in serum (and in some cases also in CSF) by enzyme-linked immunosorbent assay (ELISA) is a standard microbiologic diagnostic approach with a high sensitivity and specificity [98, 99]. At the beginning of the meningoencephalitic phase, when patients are usually seen by their physicians and admitted to hospital, the large majority had specific serum IgM and IgG antibodies. In rare cases when only IgM antibodies to TBEV are found in the first serum sample, second sampling 1–2 weeks later reveals IgG seroconversion and enables a reliable diagnosis of (recent) TBEV infection. In CSF, IgM and IgG antibodies to TBEV appear several days later than in serum, but are detectable in almost all cases by day 10 [98, 100].

Although the interpretation of the results of serological testing is usually straightforward, there may be some obstacles which should be taken into account. TBEV IgM antibodies may be present in serum for several months (up to 10 months or even longer) after acute infection, whereas TBEV IgG antibodies persist for a whole life and mediate an immunity that prevents symptomatic reinfection [98, 101].

Thus, serum IgG antibodies to TBEV without the presence of specific IgM antibodies do not indicate a recent but previous (symptomatic or asymptomatic) TBEV infection or vaccination against TBE. On the other hand, specific TBE serum IgM antibodies, an indicator of a recent infection with TBEV, may be detectable for several months after acute TBEV infection (and also in some persons after the first two doses of primary immunization); their demonstration may result in incorrect interpretation if another CNS infection/disease developed within this time period [98, 101].

A further challenge is a close antigenic relationship between TBEV and other flaviviruses with cross-reactive antibodies induced by infections or vaccinations, and a consequent diagnostic difficulties in persons vaccinated against Japanese encephalitis or yellow fever and in travelers having acquired dengue, West Nile or other flavivirus infections [7]. Such problems in TBE serodiagnosis can be sorted out by the quantification of IgM antibodies. High IgM values (>500 arbitrary units) are indicative of a recent infection with TBEV, whereas lower IgM levels may require the analysis of a follow-up sample (that enables the assessment of antibody dynamics), and/or a specific neutralization assay, to rule out cross-reactive IgM antibodies and prolonged persistence of IgM antibodies after infection or vaccination [102].

Knowledge in the understanding of TBE serology is required also in patients with meningitis or meningoencephalitis or who had been previously vaccinated against TBE. Serological response in patients with TBE vaccination breakthroughs is as a rule distinct from the response in patients who had not been vaccinated; unawareness of the pattern may result in fail to notice vaccination breakthrough cases. Serologic response in these patients is characterized by a delayed development of specific IgM response (during the initial days of the meningoencephalitic phase of TBE, specific IgM antibodies may not be detectable) associated with a high and rapidly increasing levels of specific serum IgG antibodies [63, 64, 67]. For a reliable diagnosis of TBE in persons previously vaccinated against TBE, demonstration of intrathecal production of TBEV antibodies is needed [45].

8. Factors influencing clinical course of acute disease and/or long-term outcome

8.1. Subtype of TBEV

Subtype of TBEV influences the course of acute TBE as well as its long-term outcome. The disease caused by the European TBEV subtype usually has a biphasic course, around 10% of adult patients have a severe neurologic deficit, case-fatality rate is <2% [12, 32]. According to a prospective study the abortive form of TBE is rare—the initial phase most of the time move on to the second phase of the disease [51]. Long-lasting sequelae are identified in up to 50% of adult patients [103]. The disease is less severe and has a better outcome in children than in adults [34, 50, 104, 105].

Symptomatic 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%; the severity and outcome in adults and children are similar. Limited information about the clinical course of the disease is available for Siberian TBEV subtype. The case-fatality rate is 2–3%; some reports from Russia suggest an association with a chronic progressive form of TBE [1, 11].

8.2. Age of patients

Published data suggest the relationship between age of patients and the severity of TBE and its outcome — the severity of acute illness and the proportion of patients with unfavorable outcome increase with age [33, 47, 50, 106].

The disease caused by European subtype of TBEV generally has a milder course and better outcome in children than in adults. The predominant form of TBE in children and adolescents is meningitis. A summary of 8 studies on 1169 children with TBE showed that meningitis was present in 802 (69%), meningoencephalitis in 356 (30%), and meningoencephalomyelitis in 11 (1%) patients. A total of 20 out of 945 patients (2.1%) had long-term neurologic sequelae [34]. In contrary to children, in adults, and especially in elderly patients with TBE caused by European subtype of TBEV, the most frequent presentation is meningoencephalitis [33, 47].

Furthermore, fatality rate, the ratio of patients who develop pareses, and the frequency of postencephalic syndrome is also parallel with the increasing age [33, 47, 106].

8.3. Other factors associated with severe acute disease

Some clinical studies have shown that TBE with monophasic presentation is associated with a more severe course of the acute disease [42, 107–111].

Concomitant TBE and Lyme neuroborreliosis may occur with a more severe clinical course [59, 112, 113].

8.4. Severity of acute illness and other risk factors for unfavorable outcome

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 [45, 47].

Other identified risk factors found to be associated with unfavorable outcome are CSF cell count > 300 cells/μL, impaired blood-brain barrier (total protein >600 mg/L) and abnormal findings on MRI [46].

8.5. Genetic factors

Host-related factors, particularly genetically determined variability of the inflammatory/immune response, very likely have an important impact on the course and long-term outcome of TBE. In 2008, Kindberg and coworkers published the results of the study carried out on the Lithuanians, showing that a mutation in a chemokine receptor 5 (CCR5) gene increases the risk for the development of TBE after TBEV infection, but not for more severe disease [114]. Three years later the same group reported on an association between the wild-type Toll-like receptor 3 (TLR3) rs3775291 allele and increased risk of TBE and suggested that a functional TLR3 may be associated with disease severity [115]. Similar findings were also reported by Mickiene et al. [116]. Furthermore, Barkhash and coworkers found an association between polymorphism in the promoter region of CD209 gene and predisposition to severe illness, and a possible association between 5 OAS single nucleotide polymorphisms and the TBEV infection outcome in Russians [117, 118].

In the future we expect new interesting discoveries on the role of host genetic factors in TBEV infections.

9. Differential diagnosis

In addition to a variety of viral infections, differential diagnosis of the initial (viremic) phase of TBE includes also several diseases caused by bacteria. There is a striking similarity in clinical and laboratory presentation of the initial phase of TBE and human granulocytic anaplasmosis. For both diseases fever, headache, leukopenia, and thrombocytopenia are typical. However, the presence of clinical symptoms such as chills, myalgia and arthralgia, and laboratory findings

of elevated concentration of C-reactive protein and lactate dehydrogenase values direct toward the diagnosis of human granulocytic anaplasmosis and against the initial phase of TBE [119].

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. Since these diseases are treatable with antibiotics, caution must be taken to distinguish them from TBE [32].

Concomitant TBEV and *Borrelia burgdorferi* sensu lato infections, as well as concomitant TBEV and *Anaplasma phagocytophilum* infections have been described [77, 113, 120–122].

10. Treatment

There is no specific antiviral treatment for TBE. Patients as a rule need hospitalization, supportive care, symptomatic treatment based on the presence and severity of signs/symptoms and therapy of neurologic and systemic complications. The symptomatic treatment usually includes antipyretics, analgesics, antiemetics, maintenance of fluid and electrolyte balance, and if necessary administration of anticonvulsive agents and treatment of cerebral edema [50, 123–125].

In some countries corticosteroids are often used in patients with TBE. However, until reliable studies prove the benefits of corticosteroids, their usage for the treatment of TBE is not recommended [47, 126].

Several patients need intensive care management; in those with neuromuscular paralysis leading to respiratory failure, intubation and ventilatory support are required. In a large prospective study, encompassing 635 patients diagnosed with TBE in the period from 1994 to 1998 in Germany, 12% of patients were treated in intensive care unit and 5% of patients required assisted ventilation [46]. Among patients with TBE, treated at a single medical center in Slovenia in the period from 2000 to 2004, 6.9% were hospitalized in the intensive care unit and 22.5% of them needed mechanical ventilation [33].

11. Prevention

11.1. Nonspecific preventive measures

TBEV is transmitted to humans by a tick bite or consumption of infected milk. Therefore, nonspecific preventive measures consist of reduction of tick population, personal protective procedures, and—as milk from endemic regions may contain TBEV—pasteurization of milk, and avoiding consumption of unpasteurized milk and dairy products [30, 42].

Tick population can be diminished by taking environmental measures, such as control of deer population, treatment with acaricides, and/or regular cutting of grass around the residence.

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Nonspecific personal preventive measures include avoidance of ticks (i.e. avoidance of contact with vegetation, especially in deciduous and mixed forests with a rich understory), 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. However, TBEV is present in salivary glands of the infected tick and may be transmitted from the saliva within a few minutes after attachment [42]. Although the recommended personal measures for the prevention of tick-borne diseases such as TBE and Lyme borreliosis appear to be obvious, the efficiency of some of these procedures is inadequate, uncertain or has not been properly evaluated. Furthermore, in everyday life only a small proportion of exposed persons follow the recommended procedures [127, 128].

11.2. Prevention with immunoglobulins (passive immunization)

In the TBE endemic regions, immunoglobulins containing gamma globulin against TBEV had been used as postexposure prophylaxis within 96 hours after a tick bite. Because protection was rather unreliable [129], and because several reports pointed toward a more severe disease course in children who had received the immunoglobulin [81, 129, 130], passive immunization (the usage of the immunoglobulins) in the European Union has been abandoned [131]. However, the specific immunoglobulins are still used in Russia; the reported protection rate is about 80% [132].

11.3. Vaccination

Active immunization is the most effective and reliable way to prevent TBE [12, 42].

11.3.1. Recommendations for TBE vaccination

Given that TBE occurrence varies within and between individual endemic areas, vaccination strategies need to incorporate risk assessments for a particular region. According to WHO recommendations [133], in highly endemic TBE regions (≥5 cases/100,000/year) vaccination should be offered to whole population, including children, whereas in regions with a moderate or low TBE incidence (<5 cases/100,000/year), immunization has to target individuals at risk, i.e., those having outdoor activities or working under high-risk conditions. Travelers from non-endemic to endemic areas should be vaccinated if extensive outdoor activities are expected [133–136].

Similarly, Central European Vaccination Awareness Group (CEVAG) strongly recommends the introduction of universal TBE vaccination for persons >1-year old for all countries at high risk of TBE [135]. Persons who had acquired TBE do not need vaccination as they are appreciated to be protected against the disease.

11.3.2. Vaccines

In Europe two vaccines against TBE are registered: FSME-IMMUN® and Encepur® (in some countries named TicoVac). Both contain inactivated European subtype of TBEV (strain Neudorf

1 and strain K23, respectively), are prepared in a similar way (viruses are grown in chick embryo fibroblast cells, are inactivated by formaldehyde and are purified, adjuvant is aluminum hydroxide), 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), and effectively prevent TBE caused by the European as well as Far-Eastern and Siberian subtype of TBEV [131].

In addition to the European vaccines, three vaccines based on Far-Eastern subtype of TBEV are registered: two are produced in Russia (TBE-Moscow and EnceVir) and one in China [131].

11.3.3. Vaccination schedule

All of several vaccination schedules consist of primary (basic) vaccination followed by booster doses. Complete primary (basic) vaccination comprises three doses, usually given with an interval of 1–3 months between first and second dose, and 5–12 months between the second and third dose. When protection is wanted to be achieved in a short time, "fast schedule" (second dose is administered earlier, usually 14 days instead of 1–3 months after the first dose) can be used in accordance with the manufacturers' instructions [12, 42]. The first booster dose is administered 3 years after completion of the primary vaccination; after that, one dose is required every 5 years except for persons aged >60 years (FSME IMMUN) or >50 years (Encepur) for whom boosters are recommended at 3 years intervals [131]. Immunization with the first two doses is preferably accomplished during the winter months to achieve protection before tick activity; however, vaccination can start at any time. A person who had not received the recommended doses according to the schedule but with longer intervals does not need to start vaccination again from the very beginning but just to continue with missing doses. 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 consistent [137].

11.3.4. Mode of application and dosages

TBE vaccine is administered intramuscularly into the deltoid muscle; in young children, it can be given in the muscles of anterolateral thigh. It may be administered simultaneously with other vaccines (live or inactivated) but not on the same place [131]. Doses (0.25 or 0.5 ml) depend upon the age of the recipient. The age limits for vaccines available in Europe differ. In persons <16 years old, the dose of the FSME-IMMUN vaccine is 0.25 ml, whereas for persons ≥16 years, 0.5 ml is advised; the corresponding age limits for Encepur vaccine are <12 and ≥12 years, respectively.

11.3.5. Efficacy and safety

Both European vaccines are safe and effective. Fourteen days after the second dose of basic vaccination protective antibodies develop in about 85% of the subjects, whereas after three doses, more than 98% of persons with normal immunity are protected [131]. As a rule the effectiveness of protection after vaccination against TBE is not verified by the detection of antibodies against TBEV in serum. However, the manufacturers of the vaccines and some authors recommend that in persons with immunodeficiency, the response to vaccination is assessed by serological testing approximately 4 weeks after the second dose, and that — if

antibody response was not adequate — the second dose is repeated and followed by the third dose in accordance with the regular TBE vaccination timetable. Along with some proposals similar procedure may possibly refer also to the following doses. While such practice may appear reasonable, no convincing clinical data corroborate its usage.

TBE vaccine field effectiveness is estimated to be >98% in persons vaccinated in line with the advocated schedule, and >90% for those who received basic vaccination, but were later not vaccinated according to the planned timetable [138].

Side effects are mild and relatively rare. They are more frequent after the initial than with later doses of TBE vaccine. The most common side effects are local pain and tenderness on pressure at the injection site; redness and swelling occur less often. Short-term fever after vaccination is relatively common in young children but rare in adults. Neurological complications are very infrequent [131].

11.3.6. Contraindications and limitations

11.3.6.1. Contraindications

The main contraindications are as follows:

a. Severe allergic reaction following preceding dose of TBE vaccine;

b. Information on severe allergic reactions to vaccine constituents (in addition to the active ingredients, TBE vaccine also contains remains of formaldehyde, protamine sulfate, gentamicin and neomycin); and

c. History on anaphylactic hypersensitivity to eggs (TBE viruses are grown in fibroblast cells of chick embryo).

d. Vaccination is not performed in persons with acute febrile illness.

11.3.6.2. Limitations

Pregnancy, breast-feeding: Because information on the safety of TBE vaccine during pregnancy and lactation is inadequate, pregnant and lactating women should receive the vaccine 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. However, since TBE vaccines are based on inactivated virus, the harm of breast-feeding child or fetus is unlikely.

Autoimmune diseases: While there is no indication that vaccination may deteriorate the course of autoimmune diseases or trigger autoimmunity, caution is required in persons with an autoimmune disease because data on the safety of vaccination in this group are limited [131].

11.3.7. Storage

The vaccine must be stored in a refrigerator at a temperature between 2 and 8°C. Storage at higher temperatures and freezing are not suitable [131].

12. Conclusion

TBE is an important central nervous system infection endemic in European and Asian countries. Due to relatively high proportion of cases with severe clinical course and a considerable proportion of patients with permanent sequelae after acute illness, as well as due to high incidence, it represents a growing (public) health problem that could be substantially reduced with vaccination.

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