Open Access Article

Ann. Acad. Med. Siles. (online) 2024; 78: 234–247
eISSN 1734-025X
DOI: 10.18794/aams/183663
www.annales.sum.edu.pl

PRACA POGLĄDOWA
REVIEW

Tick-borne encephalitis and differential diagnosis

Kleszczowe zapalenie mózgu i diagnostyka różnicowa

Patrycja Ochman-Pasierbek[1], Przemysław Olczyk[1], Magdalena Matlakiewicz[1], Justyna Paprocka[2], Adrianna Kalinowska-Doman[2]

[1]Studenckie Koło Naukowe przy Oddziale Pediatrii i Neurologii Wieku Rozwojowego, Górnośląskie Centrum Zdrowia Dziecka im. św. Jana Pawła II, Samodzielny Publiczny Szpital Kliniczny Nr 6 Śląskiego Uniwersytetu Medycznego w Katowicach, Polska / Students' Scientific Club, Department of Pediatrics and Developmental Neurology, Upper Silesian Child Health Center named after John Paul II, Independent Public Clinical Hospital No. 6 of the Medical University of Silesia, Katowice, Poland

[2]Oddział Pediatrii i Neurologii Wieku Rozwojowego, Górnośląskie Centrum Zdrowia Dziecka im. św. Jana Pawła II, Samodzielny Publiczny Szpital Kliniczny Nr 6 Śląskiego Uniwersytetu Medycznego w Katowicach, Polska / Department of Pediatrics and Developmental Neurology, Upper Silesian Child Health Center named after John Paul II, Independent Public Clinical Hospital No. 6 of the Medical University of Silesia, Katowice, Poland

ABSTRACT

INTRODUCTION: Tick-borne encephalitis (TBE) is an infection caused by the tick-borne encephalitis virus transmitted to humans by tick bites. The prevalence of TBE is between 10,000 and 15,000 cases annually and is comparable in Europe and Asia. About 10–20% of all infected persons are children. The vast majority of TBE cases, even up to 70––98% of them, are asymptomatic or undiagnosed. The main clinical symptoms are meningitis (present in 69%), meningoencephalitis (30%), and meningoencephalomyelitis (1%). About 2.1% of patients develop long-term neurological sequelae.

METHODS: The articles for our work were selected from three open-access databases. The databases were searched using keywords such as: "infection/epidemiology" + "tick bites/tick-borne encephalitis" + "clinical manifestation/pathogenesis/treatment" and "aseptic/viral/bacterial" + "encephalitis/meningitis". Ultimately, 71 scientific articles and 8 websites, published between 1995 to 2023 were used.

STATE OF KNOWLEDGE: TBE can be differentiated from diseases such as babesiosis, Lyme disease, southern tick--associated rash illness (STARI), chlamydiosis, ehrlichiosis, Colorado tick fever (CTF), Heartland virus (HRTV), Powassan virus (POWV), granulocytic anaplasmosis, tick-borne relapsing fever (TBRF), toxoplasmosis, tularemia, rickettsioses; or similar symptomatology: stroke, brucellosis, infectious mononucleosis (IM), yellow fever (YF), Japanese encephalitis (JE), other viral meningitis, encephalitis, spinal cord inflammation and aseptic meningitis.

CONCLUSIONS: The differential diagnosis of TBE is extensive and should include a wide range of central nervous system infections caused by both other infectious agents and non-infectious diseases.

KEYWORDS

infection, epidemiology, differential diagnosis, tick bites, tick-borne encephalitis

Received: 29.09.2023 **Revised:** 20.01.2024 **Accepted:** 04.02.2024 **Published online:** 09.10.2024

Address for correspondence: Patrycja Ochman-Pasierbek, Oddział Pediatrii i Neurologii Wieku Rozwojowego, Górnośląskie Centrum Zdrowia Dziecka im. św. Jana Pawła II, Samodzielny Publiczny Szpital Kliniczny Nr 6 Śląskiego Uniwersytetu Medycznego w Katowicach, ul. Medyków 16, 40-752 Katowice, +48 664 195 878, e-mail: patrycja.ochman09@gmail.com

Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

WPROWADZENIE: Kleszczowe zapalenie mózgu (*tick-borne encephalitis* – TBE) jest chorobą wywoływaną przez wirusa kleszczowego zapalenia mózgu, który jest przenoszony przez ukąszenia kleszczy. Rozpowszechnienie TBE ocenia się na 10,000–15,000 przypadków rocznie i jest porównywalne dla krajów europejskich i azjatyckich. Około 10–20% wszystkich zainfekowanych osób jest w wieku dziecięcym. Znaczna większość, bo aż 70–98% z nich, przechodzi tę chorobę bezobjawowo lub jest niezdiagnozowana. Do głównych objawów klinicznych zalicza się zapalenie opon mózgowo-rdzeniowych (obecne w 69% przypadków) i mózgu (30%) oraz rdzenia kręgowego (1%). U około 2,1% pacjentów rozwijają się długotrwałe następstwa neurologiczne.

METODYKA: Artykuły do pracy zostały wybrane z trzech ogólnodostępnych baz danych. Wykorzystano w tym celu następujące hasła: „infection/epidemiology" + „tick bites/tick-borne encephalitis" + „clinical manifestation/pathogenesis/treatment" oraz „aseptic/viral/bacterial" + „encephalitis/meningitis". Ostatecznie wybrano 71 prac naukowych i 8 witryn internetowych opublikowanych w latach 1995–2023.

STAN WIEDZY: TBE, ze względu na wektor kleszczowy, może być różnicowane z takimi jednostkami chorobowymi jak: babeszjoza, borelioza, południowa wysypka związana z kleszczami (*southern tick-associated rash illness* – STARI), chlamydioza, erlichioza, gorączka kleszczowa Kolorado (*Colorado tick fever* – CTF), wirus Heartland (HRTV), wirus Powassan (POWV), anaplazmoza granulocytarna, dur powrotny (*tick-borne relapsing fever* – TBRF), toksoplazmoza, tularemia, riketsjozy; lub z jednostkami o podobnej symptomatologii, takimi jak: udar mózgu, bruceloza, mononukleoza zakaźna (*infectious mononucleosis* – IM), żółta febra (*yellow fever* – YF), japońskie zapalenie mózgu (*Japanese encephalitis* – JE), inne wirusowe zapalenie opon mózgowo-rdzeniowych, mózgu, rdzenia kręgowego oraz aseptyczne zapalenie opon mózgowo-rdzeniowych.

WNIOSKI: Diagnostyka różnicowa TBE jest obszerna i powinna obejmować szeroki zakres zakażeń ośrodkowego układu nerwowego wywołanych zarówno przez inne czynniki zakaźne, jak i choroby niezakaźne.

SŁOWA KLUCZOWE

zakażenia, epidemiologia, diagnostyka różnicowa, ukąszenia przez kleszcze, kleszczowe zapalenie mózgu

INTRODUCTION

Tick-borne encephalitis (TBE) is an infection caused by the tick-borne encephalitis virus (TBEV) transmitted to humans by tick bites. In Europe and Asia, the incidence of TBE is comparable, ranging from 10,000 to 15,000 cases annually [1]. It is worth noting that about 10–20% of all infected persons are children. This number, though, might be even higher (up to 35–45%) due to the unspecific clinical presentation of TBE in this age group, which means that many correct diagnoses have been missed [1,2]. People who work in forests are at the highest risk of tick-borne infection. The risk is also high among the people who rest in meadows [3]. The vast majority of TBE cases, even up to 70–98% of them, especially in Europe, are asymptomatic or undiagnosed [1]. A small number of patients has TBE with symptoms of meningitis or encephalitis. The form of the disease can be severe or mild [1,3]. Most studies indicate that TBE in Europe is more severe among the elderly (more severe among people who are over 60 years old than among those who are younger than 60), although a severe clinical course, permanent sequelae, and even death have also been reported to occur among children. The main clinical manifestation is meningitis (present in 69%), meningoencephalitis (30%), and meningoencephalomyelitis (1%). About 2.1% of patients develop long-term neurological sequelae. Contrasting statistics have been recorded in Far-Eastern Asia where underage people have a more difficult time with this disease [1]. This review is a summary of the most important clinical findings in the differential diagnosis of TBE.

METHODS

The articles for our work were selected using open-access electronic sources like Pubmed, Google Scholar, and cdc.gov. Pubmed is a search engine that uses the largest and the most important American database for medicine called Medline. This database contains an abundance of trustworthy scientific articles adhering to the principles of evidence-based medicine, which makes them an important source of clinical knowledge. Google Scholar on the other hand, is the most popular and known search engine; its search scope is one of the widest among other search engines, which includes science articles, books and resources from repositories of scientific organizations from many fields automatically sorted in terms of author rank, source, publication content and the number of citations. Cdc.gov is a website maintained by the American Department of Health and Human Services and its mission is to protect the public's health, among others, by providing information about diseases. All these sources allow us to preserve a proper balance between reliability and keeping a broad view on our topic, although limitations for this method were difficult in reviewing them systematically, which could cause a lack of some information.

In order to select appropriate articles, we used keywords such as "tick-borne encephalitis" (+ "epidemiology/clinical manifestation/pathogenesis/ treatment"). The articles about the diseases with neurological symptoms were selected using words such as "infection/epidemiology/differential diagnosis /tick bites/tick-borne encephalitis", "encephalitis/ meningitis" and "aseptic/viral/bacterial". The searches were complemented by a manual search of any additional suitable articles that were cited in the reference lists. The inclusion criteria were the publication type (review, systematic review, case report, observational studies) and published in English. The exclusion criterion was the article type (personal communication).

Ultimately, we used 71 scientific articles published between 1995 to 2023 from a variety of sources, which were searched using the keywords, and 8 websites.

The final content of our review was repeatedly read, verified and corrected by all the authors so that questionable fragments were discussed and corrected together.

STATE OF KNOWLEDGE

Clinical subtypes

As mentioned, TBE is a disease caused by TBEV, which, according to the most recent taxonomic scheme, belongs to the tick-borne flavivirus group, family *Flaviviridae*, genus *Flavivirus*. The natural reservoirs and hosts of TBEV are small wild rodents, whereas humans are only accidental hosts. TBEV is transmitted to humans mainly by hard tick bites. There are three main subtypes of this virus, the European, the Siberian, and the Far-Eastern subtype [2]. Figure 1 illustrates the course of typical TBE infections.

The clinical symptoms vary greatly and mainly depend on the subtype of the virus that the patient has been infected with. Furthermore, the subtypes of TBEV are typical of specific regions of the world causing the diagnosis, treatment and prognosis to depend heavily on the geographical location of the acquired infection. Table I provides a summary of the neurological symptoms and a comparison of the disease course among the individual subtypes.

The European TBEV subtype

The European TBEV subtype is mainly found, as the name suggests, in Europe, although it has also been identified in the West Urals and Siberia. The highest numbers of TBE were noted in Slovenia (14.1/100,000 inhabitants per year), Estonia (11.1/100,000), Lithuania (10.6/100,000), and Latvia (8.8/100,000), according to data from 2005–2009 [1]. However, infections also occur in many other countries of Western and Central Europe and Scandinavia, especially in Austria, Croatia, Czech Republic, Estonia, Finland, Germany, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia, Sweden, and Switzerland [2]. The main vector in the region mentioned above is *Ixodes ricinus* (*I. ricinus*), which is mostly active twice a year, the first time in June and July, the second time in September and October, which is reflected in the disease peaks in these months [1,2].

The subtype typically induces a biphasic disease with a severe neurologic deficit in approximately 10% of patients and a case-fatality rate of less than 2% (In Austria 1% fatality before common vaccinations) [1,2].

The initial phase occurs as a moderate fever, body pain (myalgia, arthralgia), fatigue (1–2 days), malaise, anorexia, nausea, pain in the neck, shoulders, and lower back, and sometimes headache. That phase is related to the viremia of TBEV, which occurs during the incubation time that is 7–14 days after the infection (3–4 days for alimentary transmission) and lasts between 2–7 days [1,2]. The second phase is preceded by 1–21 days (usually a week) of a stable condition or even an asymptomatic interval. That phase takes the form of meningitis (50% of adult patients), meningoencephalitis (40% of adult patients), or meningoencephalomyelitis (around 10%) [1].

Some sources explain that viruses of this subtype attack only the lymphoid tissue at first, and the glial cells are infected only during the second inflammation, which contributes to the two-phase manifestation of the disease [2].

Zajkowska et al. [4] report an important reason that led to the misdiagnosis of TBE infections in Poland during the past years. Due to the fact that testing for TBE requires additional costs while the treatment is only symptomatic, some cases are assigned in the 10th revision of the International Classification of Diseases (ICD-10) as different nosologic units. Only about half of TBE cases were reported to the surveillance system as A84 (ICD-10 code for tick-borne viral encephalitis).

The number of TBE cases reported in Poland proves to be higher when considering the samples from patients that were reported with an irrelevant ICD-10 code, especially in the area of the Silesian, Lubusz and Subcarpathian Voivodeships [4].

The Siberian TBEV subtype

The discussed subtype is endemic in Siberia, the Baltic states, and northern Finland. The main tick vector there is *Ixodes persulcatus* (*I. persulcatus*), which also occurs in other parts of Russia, Eastern Europe, and Far-Eastern Asia. The peaks in activity occur in May and June [1].

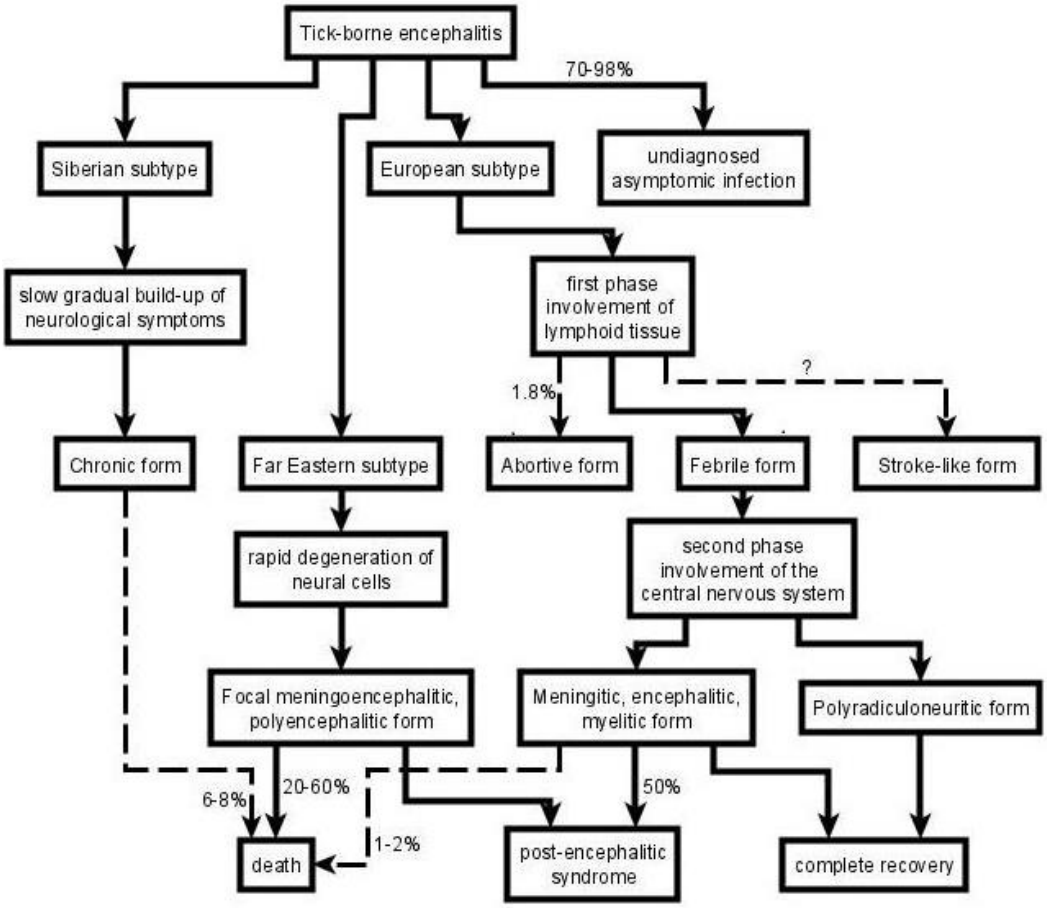

Fig. 1. Diagram of course of typical tick-borne encephalitis (TBE) infections.

In Russia, TBE manifests as an abortive form which is also called the "fever form" and is reported to represent up to 50% of all clinical presentations in Siberia, whereas 80% of cases occur as fever without neurological sequelae, 7–8% as the paralytic form, 4––5% as Kozhevnikov epilepsy, and 7% of infected people die as a consequence of acute encephalitis [2]. According to the case report written by Stragapede et al. [5], a patient with IgG and IgM antibodies for TBE, detected in the serum, was treated with intravenous acyclovir and ceftriaxone. Two weeks later, the patient was admitted to the local Neurology Unit, diagnosed with aura continua as a manifestation of epilepsia partialis continua (EPC) owing to TBE and treated with intravenous Levetiracetam (1000 mg bid). An EEG was repeated the next day and showed a reduction in epileptiform activity. Eggers et al. [6], on the other hand, describe EPC as frequently drug-resistant, where polytherapy with various combinations of intravenously administered antiepileptic drugs is necessary. In the European survey, the relatively best results for continuous treatment were obtained with topiramate and levetiracetam. It is also suggested that EPC has the tendency to be a drug-resistant condition [7,8]. The case-fatality rate is 2–3% (rarely exceeding 6–8%), and some reports from Russia suggest an association with chronic progressive TBE [1,2].

The Far-Eastern TBEV subtype

The same subtype is characteristic of Far-Eastern Asia and Japan, but it has also been identified in central and eastern Siberia. *Ixodes persulcatus*, as mentioned above, occurs in Asia, and the natural vector in Japan is *Ixodes ovatus* (*I. ovatus*) [1]. It often causes an illness with a gradual onset with a more severe course, higher rates of severe neurological sequelae, and a fatality rate of 20–40% (60% in Far-Eastern Russia) [1,2]. Severe neurological sequelae are caused by major damage to different parts of the brain and spinal cord, which result in the development of focal meningoencephalitis or polioencephalitis, loss of consciousness, and prolonged convalescence with a feeling of persistent fatigue [2]. Studies performed on animals support the high neurovirulence of TBEV-FE [9]; therefore, this subtype may take the form of a chronic progressive disease. Both mutation in the *TBEV NS1* gene as well as an inappropriate T-cell immune response are associated with the severe course of infection with the Far-Eastern subtype [1]. The neurological disease severity is linked to several defined differences in the viral strain's genome. Changes in the host's immune responses are linked to the neurological disease [10]. Some studies show that this has to do with the viral tropism of this subtype for the neurons of the brain and spinal cord, leading to its

Table I. Comparison of disease course among individual subtypes (based on [1,2,63,78,79])

Form & subtype	Frequency	Duration	Neurological symptoms	Complications and prognosis
Febrile (Abortive) European subtype	33% of all symptomatic cases	from few hours to 7 days	no neurological symptoms	no damage to CNS and full recovery
Meningeal European subtype	50% of all symptomatic cases	lasting 7–14 days	meningeal signs, vertigo, photophobia	gradual recovery
Encephalitic (Meningoencephalitic) European subtype	40% of all symptomatic cases	hemiplegia is irreversible	hallucinations, fibrillar constrictions, tongue fasciculations, tremor of extremities, hemiparesis, hemiplegia, epileptic fits, personality changes, behavioral disorder, cognitive disturbances	damage to CNS, 30% of cases are fatal, very slow convalescence with nervous exhaustion, rarely focal or generalized seizures, delirium, psychosis
Myelitic (Poliomyelitic, Meningoencephalomyelitic) European subtype	10% of all symptomatic cases (almost always with encephalitis)	up to 2 weeks or occasionally several months	flaccid paresis, wrist drop, "hung head", periodic muscle contractions, muscles atrophy	poor prognosis when medulla oblongata and central portions of brainstem are involved, quite rarely paresis or paralysis of lower limbs
Focal meningo/poly-encephalitis Far-Eastern subtype	40% of all symptomatic cases	damage to CNS is irreversible	major damage to different parts of brain and spinal cord with more severe form of symptoms of encephalitic form	high rates of severe neurological sequelae, fatality rate of 20–60%
Polyradiculoneurittis European subtype	0.9% for cranial nerve	usually subsides after 3–6 weeks	damaged peripheral nerves, pain in peripheral nerves, meningeal and focal neurological symptoms, cranial nerve involvement	normally complete recovery; often occurs with Lyme disease
Post-encephalitic syndrome Far-Eastern subtype and European subtype	40% to 50% of patients after acute TBE	lasting up to 18 months and 11.3% are permanent	spinal nerve paresis, hearing impairment, dysarthria, severe mental and cognitive disorders, dysarthria, apathy, irritability, memory and concentration disorders, tinnitus disturbance of vision, balance and coordination disorder, flaccid paresis or paralysis	long-term impact on patient's quality of life, forced lifestyle change, and sometimes constant complications
Chronic Siberian subtype	1.7% of all symptomatic cases	long-term delayed sequelae	perivascular infiltration in brain and spinal cord, Kozhevnikov epilepsy, progressive neuritis of shoulder plexus, lateral sclerosis, dispersed sclerosis, Parkinson-like disease, progressive muscle atrophy, physical deterioration, mental deterioration, dementia	pronounced dissimilarities in incubation, onset of symptoms and survival time, fatal cases
Stroke-like European subtype	single cases described	acute phase for 26 days, some symptoms remain	monoparesis of lower extremity, slightly paretic leg, hyperreflexia of patella, sided mild hearing loss, dysmetria, hyperreflexia of biceps and quadriceps, allodynia of upper arm, lower distal power, dysarthria	permanent weakness in arms and legs, recurrence of dysarthria and hearing problems

CNS – central nervous system; TBE – tick-borne encephalitis.

degeneration due to the direct replication of the virus in these cells [1].

Pathophysiology

When an infected tick bites a person, replication occurs in local subcutaneous tissues. Probably the first cells where replication of the virus takes place are the Langerhans cells. These cells are also responsible for transporting the virus to the regional lymph nodes. From this site, the TBE virus gradually disseminates throughout the organism causing viremia. The viremic phase is clinically the initial phase of TBE when the virus crosses the blood-brain barrier [1,11]. A few possible routes of how the TBEV breach the barriers have been postulated. The diffusion of the virus between the capillary endothelial cells in the brain seems to be the most probable route. The other possible routes are peripheral nerves or the highly susceptible olfactory neurons. Neurons are the main targets of TBEV infections [1].
Pathological changes are localized in the gray matter and are present in the medulla oblongata, cerebellum, pons, brainstem, spinal cord, basal ganglia, thalamus, and the motor area of the cerebral cortex. The most extensive meningitis occurs in the region of the cerebellum. In most cases, we can observe lymphocytic perivascular infiltrations, neuron necrosis, and the accumulation of glial cells. We can usually observe infiltration with lymphocytes and neutrophils in the cerebral and spinal meninges [1,11,12].

Diagnosis

The diagnosis of TBE should be suspected in patients living in endemic areas with symptoms indicating meningitis or meningoencephalitis. In the summer and fall seasons, the risk of infection is higher. Furthermore, a case of TBE can be defined by cerebrospinal fluid (CSF) pleocytosis ($> 5 \times 10^6$ cells/L) and the presence of specific IgM and IgG antibodies. Virus-specific IgM is present in the acute phase, while virus-specific IgG can be detected in a sample at least 2 weeks later. Potential cross--reactivity in serological tests may manifest among individuals afflicted with infections caused by Dengue or Zika viruses [13,14,15].
In the diagnosis of TBE, it is possible to isolate the TBE virus from blood serum and CSF. The genome of the virus can be detected by RT-PCR (a reverse transcriptase-polymerase chain reaction) both in the blood serum and in the CSF in the acute phase of the disease. Nevertheless, these methods are not helpful in clinical diagnosis because patients usually see their doctors in the second phase of their disease (due to clinical symptoms), when the virus is no longer present there [11,16].

Treatment and prophylaxis

Patients diagnosed with TBE are treated symptomatically. Depending on the severity of symptoms, hospitalization may be necessary [17,18]. According to the surveillance and outbreak report, *Tick-borne encephalitis in Europe, 2012 to 2016*, written by Beauté et al. [19], 8,081 cases were reported with hospitalization status, 7,672 (94.9%) were admitted to hospital. A huge prospective study of 656 patients conducted in Germany revealed that 12% of patients were treated in the intensive care unit, and assisted ventilation was required in 5% of these cases (especially when neuromuscular paralysis occurs, which leads to respiratory failure). Cerebral edema should be taken into consideration as a potential complication of TBE. In order to lower the intracranial pressure, a 20% mannitol solution along with hypertonic fluids of 3% sodium chloride are administered intravenously (they must be used carefully owing to the risk of severe dehydration, especially in older patients). In individual severe cases, the procedure of decompressive craniotomy or treatment with therapeutic hypothermia may be necessary [13,20]. Case reports of corticosteroid usage have been published, although they are not supported by any controlled trial; therefore, corticosteroid treatment cannot be recommended as a standard treatment approach. The emergence of epileptic seizures requires the immediate administration of anticonvulsive agents. Routine anti-epileptic therapy includes the intravenous administration of benzodiazepines, fosphenytoin, valproic acid, and/or levetiracetam. There is ongoing research on specific substances displaying antiviral activity against TBEV. The nucleoside analog 7-deaza-2'-C-methyladenosine (7-deaza-2'-CMA), which has shown good antiviral activity and low cytotoxicity in porcine kidney cells and human neuroblastoma cells, is a promising candidate for further investigation [1,21]. Unfortunately, no medication intended for the causal treatment of TBE has been registered yet. Symptomatic treatment includes the administration of antipyretics, analgesics, antiemetics, and maintenance of water and electrolyte balance aimed to alleviate the illness. Due to the absence of elective treatment, we are obligated to rely on efficient prophylaxis to prevent disease-related morbidity and mortality. For over thirty years, European vaccines have been instrumental in significantly mitigating the incidences of TBE infections, which proves their high effectiveness. Currently, in Europe and Russia, there are a few types of licensed vaccines, including FSME-Immun® (Baxter, Austria), Encepur® (Novartis Vaccines, Germany), EnceVir® (Scientific Production Association Microgen, Russia), and TBE vaccine Moscow® (Federal State Enterprise of

Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences, Russia). FSME-Immun® and Encepur® are available in the European Union and have been authorized by the European Medicines Agency (EMA) [1,21]. The process of immunization is closely connected with virions, and more specifically, with envelope protein E, which is responsible for significant functions such as virion assembly, membrane fusion, and binding to receptors. An excellent example of the efficacy of the aforementioned boosters is the Austrian population, where mass vaccinations using FSME-Immun® injections resulted in a substantial decrease in the number of cases – from 600 in 1981, down to approximately 50–60 in the following years [15,17,19]. Nonetheless, according to the newest ECDC tick-borne encephalitis surveillance report, the number of new cases is constantly increasing. Comparing with the 2019 data, the number of confirmed TBE cases has substantially risen, from 96 in 2016 to 250 in 2020 [12,22].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TBE should include a wide range of central nervous system (CNS) infections caused by both other infectious agents and non-infectious diseases. There is also the potential for concurrent exposure to multiple infectious factors, particularly in the context of travel. In the first phase of TBE, when the symptoms are nonspecific, gastroenteritis should be considered [1]. However, in the next phase when symptoms related to the CNS develop, the differential diagnosis is extensive and should include the following diseases.

Tick-borne diseases (in order of occurrence in America)

Chlamydia

Ticks are known to transmit many pathogenic microbes. The presence of organisms like Chlamydia has been noted in *I. ricinus* ticks. There are a few chlamydial species such as *Chlamydia pneumoniae*, *Chlamydia trachomatis* and *Chlamydia psittaci*, which are the primary human pathogenic species. *Chlamydia pneumoniae* is a pathogen that causes respiratory infections. This microorganism also causes other disorders, including disorders of the CNS; therefore, it should be included in the differential diagnosis of TBE [23,24].

Toxoplasmosis

Toxoplasmosis is a worldwide disease spread by the intracellular protozoan parasite *Toxoplasma gondii* (*T. gondii*) [25]. Humans usually become infected after the ingestion of food or water that contains oocysts excreted in the feces of infected felines. The consumption of either undercooked or raw meat with tissue cysts is another possibility of acquiring the infection [25,26]. The primary infection with *T. gondii* can usually go unnoticed due to an asymptomatic course; however, in immunodeficient patients, the disease may start more severely. The most common clinical manifestation is isolated lymphadenopathy, either cervical or occipital with lymph nodes that are not tender, do not suppurate, and become discrete and non-supportive [27,28]. The accompanying symptoms often include fever, sore throat, malaise, abdominal pain, myalgia, hepatosplenomegaly, maculopapular rash, and night sweats. A concerning sign in laboratory tests may be a small number of atypical lymphocytes (less than 10%). Another manifestation of *T. gondii* infection is known as ocular toxoplasmosis and usually comprises recurrent episodes of necrotizing retinal inflammation with subsequent scarring. The lesion destroys the architecture of the neural retina and can even affect the choroid (retinochoroiditis). The well-known “headlight in the fog” appearance is relevant to the presence of active retinal lesions along with a severe inflammatory reaction [29].

Another condition known as *Toxoplasma* encephalitis (TE) occurs mostly in patients suffering from AIDS or other diseases which impair the immune system. A huge variety of nonspecific symptoms such as seizures, ataxia, or weakness, impede the diagnosis. The presence of numerous brain abscesses is also very specific in TE.

Multiple analyses carried out on cadavers revealed that the most frequent sites of *T. gondii* brain infection are the basal ganglia and the corticomedullary junction [30]. Studies have also shown that *T. gondii* may also be a strong risk factor for the development of schizophrenia or other behavioral disorders in humans [31].

Lyme disease

One of the most important tick-borne infections of the temperate northern hemisphere is Lyme disease. It manifests itself in two ways. Specific ways include a unique skin lesion, called erythema migrans, enabling immediate diagnosis in highly endemic areas of Lyme disease. Nevertheless, sometimes this disease manifests itself in a nonspecific way with a headache, arthralgia, a low-grade fever, or it may even be asymptomatic.

In the differential diagnosis of TBE, Lyme neuroborreliosis should first be taken into account. The neurological symptoms of the early stage of the disease include cranial and peripheral neuropathy and meningitis, rarely meningoencephalitis. The most

frequently affected cranial nerve is the facial nerve, but there is also the possibility of involvement extending to the eighth nerve, resulting in hearing loss, and the oculomotor nerves, leading to diplopia. In the rare, late stage of neuroborreliosis, patients may experience chronic fatigue, memory problems and cognitive impairment, which are associated with inflammation of the brain. The diagnosis relies on distinct clinical symptoms, serological tests, in addition to the analysis of CSF, and the treatment is mainly with ceftriaxone or doxycycline.
The commonly neglected disease symptoms of the cardiac or neurological systems include myocarditis, and an atrioventricular block of intensity between the first-degree (Wenckebach) to complete heart block. In this case and in areas with a rare occurrence of Lyme disease, laboratory testing should be performed by a two-step algorithm including an initial ELISA test, followed by a western blot test, which allows a sensitive and specific diagnosis. As a treatment for the early stage of Lyme disease, doxycycline or amoxicillin are mostly used to shorten disease duration as well as to prevent the development of the late stage. In addition, anti-inflammatory medications may be helpful for joint symptoms, while hospitalization and monitoring of the patient for some time may be advisable for cardiac complications [32].

Rickettsioses

Rickettsiae are intracellular gram-negative bacteria that are usually classified into two main groups: the spotted fever group (SFG) and the typhus group (TG). The first group of bacteria induces diseases associated with infections throughout the world, like spotted fevers (e.g. Rocky Mountain spotted fever), while the second group of bacteria is responsible for causing endemic and epidemic typhus [33,34]. Most species are endemic as a result of climate differences, where the vector and the natural host cannot meet. Nonetheless, two of them, *Rickettsia felis* (from SFG) and *Rickettsia typhi* (from TG) are globally distributed [33,34]. The course of the disease depends on the pathogen involved, and currently, the highest mortality is caused by *Rickettsia rickettsii* associated with Rocky Mountain spotted fever. The symptoms include high fever, headache, muscle pain, nausea, vomiting, anorexia, abdominal pain, and diarrhea [34]. Infection may be limited to local skin lesions, such as eschar or red macules, with local inflammation and rash or it can be disseminated, which is often associated with a more severe course involving severe vasculitis with endothelial damage, cutaneous necrosis, or gangrene, pneumonitis, meningoencephalitis, up to multiple organ failure [33]. Serological tests are utilized to diagnose these diseases by detecting antibodies with indirect immunofluorescence and sole titer above 1:1024 [34]. The laboratory tests indicate thrombocytopenia, hyponatremia, leukopenia, and an elevation of transaminase. [33,34]. In the treatment, doxycycline remains the standard drug of choice. Alternatively tetracycline, oxytetracycline, and chloramphenicol have proven efficiency [34].

Human granulocytic anaplasmosis

Human granulocytic anaplasmosis (HGA) is a tick--borne acute zoonosis caused by *Anaplasma phagocytophilum* – a bacterium that infects neutrophils intracellularly [35]. Ungulates, such as roe deer, as well as rodents, are the major reservoir of this pathogen [36]. The greatest diagnostic concern is the absence of specific symptoms and the coexistence with other tick-borne diseases, particularly Lyme borreliosis [37]. Clinical presentation usually consists of pyrexia exceeding 38.5ºC, gastrointestinal issues (nausea, diarrhea, vomiting), respiratory (shortness of breath, cough) or neurological (headache, confusion, malaise) signs, excessive sweating, myalgia, and arthralgia [38]. Patients may also experience a non--pruritic rash with erythema and elevated liver tests [37]. Severe manifestations of HGA are rare, but they might occur in elderly people who are burdened with autoimmune diseases and an overall weakened immune system. Renal failure is a possible, life--threatening condition [39,40].

Babesiosis

Babesiosis (piroplasmosis) is a malaria-like parasitic disease caused by protozoa of the genus *Babesia*, which are transmitted by ticks. Microscopic parasites infect red blood cells. Babesiosis is asymptomatic in most people, but the course of the disease may be severe or even life-threatening to people with immune deficiencies or the elderly. The clinical symptoms resemble malaria. They include high fever, chills, headaches, muscle aches, and gastrointestinal problems. The symptoms also include hemolytic anemia, hepato- and splenomegaly, and sometimes renal failure as well as pulmonary edema. In order to diagnose babesiosis, the microscopic examination of blood smears is necessary (Giemsa Stain or Wright Stain) [3,41].

Tularemia

Tularemia is a rare zoonotic infection caused by the gram-negative bacterium, *Francisella tularensis* (*F. tularensis*) [42,43]. The main vectors of transmission are arthropods such as ticks, and deerflies, whereas small animals like rabbits, hares, or beavers serve as amplifying hosts. The etiological agent can be transmitted to humans by direct contact

with the infected animals, contaminated food or water, and the aforementioned hematophagous vectors [42]. The clinical presentation depends on the bacterial subspecies, the route of transmission, and the patient's condition. It ranges from mild to life-threatening. At first, patients usually develop fever and enlargement of the lymph nodes. A complicated course of the disease may include suppuration, pneumonia and meningitis [42]. A skin ulcer appears in the area of bacteria entry along with lymphadenopathy of regional lymph glands (often the armpit or groin). Another typhoidal form can manifest as a combination of some general symptoms, the most severe of which is the pneumonic variation with symptoms such as cough, chest pain, and shortness of breath. It may occur due to breathing dust and aerosols containing *F. tularensis* or when the bacteria spread through the bloodstream to the lungs [42,43].

Ehrlichiosis

Ehrlichiosis is a bacterial infection spread to people mostly through the bite of infected ticks and is mainly found in regions where the lone star tick (*Amblyomma americanum*) is present. Symptoms usually begin 1––2 weeks after an infected tick bite. In the early phase, patients with ehrlichiosis typically present with nonspecific symptoms such as fever, muscle aches, and chills. Gastrointestinal problems and rash may also be symptoms of the early stage of the disease. A rash occurs mainly in children. Sometimes, untreated ehrlichiosis can develop into a serious illness. CNS disorders like meningitis and meningoencephalitis occur in up to 20% of patients. In certain cases, patients may develop acute respiratory distress syndrome (ARDS), coagulopathy, cardiovascular failure, or sepsis-like symptoms. It is worth paying attention to leukopenia, thrombocytopenia, and slightly elevated transaminase levels in laboratory tests during diagnostics [44,45].

Heartland virus

The Heartland virus (HRTV) is transmitted by the lone star tick (*Amblyomma americanum*) bite, while animals such as raccoons or deer may serve as a reservoir [46]. Clinically, the symptoms are nonspecific, and they include an acute onset of fever, fatigue, anorexia, diarrhea, myalgia, leukopenia, and thrombocytopenia [47]. The aforementioned clinical signs have a close resemblance to ehrlichiosis; nevertheless, administering appropriate antibiotics results in clinical improvement within 48–72 hours in the case of ehrlichiosis, whereas no significant improvement is achieved in the case of HRTV. The virus is said to be genetically closely related to the severe fever with thrombocytopenia syndrome (SFTS) virus, a tick-borne phlebovirus with a similar clinical manifestation in China, Korea, and Japan [48]. In order to examine the virus' genetic material (ssRNA) in blood, an RT-PCR test can be performed [46]. Illness caused by HRTV infection often requires hospitalization and there are several cases reported that resulted in death [49,50]. In the fatal cases, all of those infections progressed to develop acute renal injury and failure, respiratory failure, and hypotension consistent with sepsis [48].

Tick-borne relapsing fever

Tick-borne relapsing fever (TBRF) is a bacterial infection caused by *Borrelia* (*B.*) spirochetes, which might be transmitted to humans by exposure to an infected soft-shelled Ornithodoros tick. The *Borrelia* species implicated in the etiology of TBRF encompass *B. hermsii*, *B. parkeri*, *B. turicatae*, *B. hispanica*, *B. crocidurae*, *B. duttoni*, and *B. miyamotoi* [51,52, 53]. The incubation period of TBRF lasts around 4––18 days, while the early stage of this disease is characterized by recurring febrile episodes (up to 106.7°F or 41.5°C), accompanied by a variety of non--specific symptoms, such as headache, myalgia, arthralgia, nausea, and chills. Patients may even become tachycardic, tachypneic and delirious or agitated [51,53]. The bouts of fever last around three days and are separated by afebrile periods of approximately 7 days in duration. This sequence is induced by the unique ability of TBRF spirochetes, which can alter their outer-membrane lipoprotein (vmp) causing repetitive stimulation of the infected host's immune system [51,52]. Neurological complications that may occur include meningitis, encephalitis, hemiplegia, facial palsy, radiculopathy, or even subarachnoid hemorrhage in some cases. Observations of cases of meningoencephalitis linked to *B. miyamotoi* in immunocompromised patients indicate that these pathogens in such a population may act as opportunistic pathogens. Furthermore, the course of febrile episodes in an infection with this pathogen differs from the classic course of TBRF [51]. A greater number of febrile episodes increases the possibility of the aforementioned disorders. The diagnosis is usually made after the microscopic identification of spirochetes in peripheral blood samples along with the noticeable thrombocytopenia. However, the blood should be collected during the febrile episode as those pathogens are not visible once the temperature decreases [53,54]. The treatment consists of beta-lactams, tetracyclines, or macrolides. TBRF is commonly linked with residing in rodent--infested houses in the mountains or potholers who occupy themselves with exploring caves [52,53]. A clinically similar febrile illness that requires distinction from TBRF is louse-borne relapsing fever (LBRF), caused by *B. recurrentis*. The distinction

between these entities can be achieved using molecular techniques [51].

Powassan virus

The Powassan virus (POWV) is a flavivirus that is spread through the bite of an infected black-legged "deer" tick (*Ixodes scapularis*) [1,3]. Since the late 1990s, a recent increase in exposure to infected ticks may result in a larger number of Powassan cases [55]. Powassan virus disease should be considered in any patient who presents with a febrile or acute neurological illness and who has recently had a likely exposure to ticks. The clinical symptoms reported most frequently in the studies included fever, headache, confusion, generalized weakness and fatigue, encephalopathy, neurological symptoms, focal deficit, and vomiting. The incubation period for the POWV ranges from 1 to 4 weeks. The disease might progress to encephalitis, meningoencephalitis, or aseptic meningitis [1,3,55].

Colorado tick fever

Colorado tick fever (CTF) is a rare disease caused by the Rocky Mountain wood tick (*Dermacentor andersoni*), which is found in the United States and Canada. The first clinical symptoms that appear about a week after the tick bite are similar to those of influenza. Fever and muscle aches are typical, and vomiting may also occur. About 50% of patients develop "biphasic fever". After a few days, the fever goes down and then a short period of fever reappears. Sometimes, patients have abdominal pain and a sore throat as well. In certain cases, patients may experience a more severe disease with symptoms such as bewilderment and a stiff neck. These symptoms mean that the CNS has been attacked. Blood smears are very important for diagnosis, which are stained by immunofluorescence for the presence of the virus. There are no vaccines or medications to treat CTF. Patients are treated symptomatically [56,57].

Tick paralysis

Some ticks in North America and Australia, like *Dermacentor andersoni* and *Ixodes holocyclus*, have been known to cause ataxic-type gate symptoms called tick paralysis. The clinical presentation imitates the Guillain-Barré syndrome, leading to the misdiagnosis of these diseases. Nevertheless, tick paralysis develops much faster, typically in 2–6 days, without raising the protein concentration in CSF and disappears similarly as quick in a few hours or days after successfully tick removal [58].

Southern tick-associated rash illness

Southern tick-associated rash illness (STARI) is a zoonotic disease described to occur in humans following bites of *Amblyomma americanum.* The characteristic skin manifestation of STARI is an annular rash with central clearing that resembles the erythema migrans observed in Lyme disease. In addition, patients can manifest influenza-like symptoms, such as fever, chills, body aches and malaise [41,59]. The diagnosis should be based on the clinical manifestation and geographic location since there is no established diagnostic method for identifying STARI at this time. Patients with suspected STARI tend to show a favorable response to doxycycline [41].

Severe fever with thrombocytopenia syndrome

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne viral infection caused by the severe fever with thrombocytopenia syndrome virus (SFTSV). The first case was identified in China. It is characterized by an acute onset of fever, thrombocytopenia, leukocytopenia, diarrhea, vomiting, and multi-organ dysfunction. SFTS can lead to severe illness with a high fatality rate [60].

Neoehrlichiosis

Neoehrlichiosis is an infectious disease attributed to the gram-negative bacterium *Candidatus* Neoehrlichia mikurensis, transmitted by *I. ricinus* ticks. Infection typically presents with symptoms such as headache, fever, arthralgia, nausea, may lead to thrombotic or hemorrhagic complications and aneurysms. The infection may exhibit either an acute or chronic course. A case resembling recurrent fever with thrombotic complications has been delineated [61].

TBE may also be confused with other diseases because of the common symptoms of the nervous system

Stroke

Increasingly more research indicates that TBEV infection influences brain perfusion. The symptoms of TBE can also simulate a stroke of this organ [62]. Common signs for both of these disease entities are headache, vertigo, nausea, vomiting, consciousness disorders and meningeal symptoms. For focal strokes, pyramidal symptoms, sensory disorders and cranial or peripheral nerve pathology appear more frequently, nontheless, they can also be present for 8.3–33.3%

TBE patients. On the other hand, additional infection symptoms like fever, blood leukocytosis and pleocytosis in CSF and a raised level of C-reactive protein are more characteristic for TBE [62,63]. Besides that, a serology test to detect specific antibodies and a lack of acute focal ischemia changes in tomography or magnetic resonance can be very helpful [62]. Its pathomechanism has not been fully determined, although some speculations indicate the role of inflammation atrophy of the deep gray matter, especially the thalamus and microangiopathy [62,63].

Human brucellosis

Brucellosis is the most common worldwide zoonosis. Infection of this gram-negative bacteria occurs by the consumption of unpasteurized dairy products and by direct contact with infected animals [64,65]. In Poland, individual cases are reported every year (the last two date from 2017) [66]. The common symptoms of brucellosis are nonspecific as fever, chills, headache, sweating, weakness myalgia and arthralgia. Other symptoms depend on the involved systems and include arthritis, spondylitis, epididymo--orchitis, acute renal failure, endocarditis, splenic abscess, abortion, and neurobrucellosis. Neurobrucellosis appears in 2–7% of child cases as meningitis, encephalitis, and myelitis. Some other neurological symptoms that may appear are impaired consciousness, seizures, sensory deficit, motor deficit, increased deep tendon reflexes and even hemiparesis [64]. Diagnosis should be based mainly on the isolation of brucella bacteria from the blood or body tissues supported by a compatible clinical picture and nucleic acid amplification detection methods. In the treatment of neurobrucellosis, aminoglycosides in combination with doxycycline, trimethoprim--sulfamethoxazole or a fluoroquinolone and rifampicin are used [65].

Infectious mononucleosis

Infectious mononucleosis (IM) is a lymph node disease manifested as fever, sore throat, lymph node enlargement, fatigue, rushes and pharyngeal inflammation, characteristic of the human population, among people between the age of 15 and 24. Generally, it affects the posterior cervical, axillary or inguinal nodes causing them to enlarge [67]. However, some studies show that sometimes, especially for children less than 4 years old, this disease can be complicated with neurological problems such as convulsions or cranial nerve involvement. Furthermore, meningoencephalitis, aseptic meningitis, transverse myelitis or peripheral neuritis can occur, but that clinical presentation of IM has not yet been well described due to the lack of cases [67,68]. In that case, differentiation from TBE may be required. In order to exclude IM, a blood test with a white blood cell count that detects the presence of atypical lymphocytosis must be performed [67].

Yellow fever

Yellow fever (YF) is an acute viral hemorrhagic disease in tropical Africa and Latin America that is transmitted by infected mosquitoes (*Haemagogus*, *Sabethes* and *Aedes* species) [69,70]. Patients may report symptoms such as fatigue, yellowing of the skin or eyes, headache and muscle pain, often with severe pain in the back. Then, after a period of provisional remission that usually lasts from 24 to 48 hours, symptoms may recur and be frequently accompanied by liver and kidney disease. Dark urine, vomiting, jaundice and hemorrhagic diathesis are among the presenting symptoms in patients. Edema and hemorrhage of the CNS may also occur. Yellow fever is diagnosed by detecting the antigen using a monoclonal immunoassay of the enzyme in serum samples. The detection of viral genome sequences by PCR and ELISA tests are also used. Since there is currently no reliable treatment or vaccine available, the most important approach is to focus on prevention [69,71].

Japanese encephalitis

The Japanese encephalitis (JE) virus is related to the TBEV, both of which are neurotropic flaviviruses; therefore, differential diagnosis seems necessary. Initially, the virus was endemic to the areas of Indonesia-Malaysia and Southeast Asia, but for the past 70 years, this area has been gradually expanding. Humans, as dead-end hosts, become accidentally infected as a result of a bite by an infected mosquito. The disease mainly affects children and travelers from regions where JE is absent, and it is associated with the development of strong immunity after the first infection. The symptoms are usually absent or flu-like. 0.1% to 4% of cases (depending on the region) develop nonspecific febrile illness, aseptic meningitis, or even severe encephalitis with a clinical manifestation that is very similar to TBE. In the diagnostic ELISA test, there is moderate pleocytosis and a slight protein rise in CSF, while the characteristic computed tomography (abnormal in 56% patients with JE) or magnetic resonance imaging (abnormal in all patients with JE) shows abnormal lesions mainly in the thalamus and basal ganglia [72].

Other viral meningitis and encephalitis

Viral infection of the CNS is classified as aseptic inflammation according to some sources because of the fact that viral infections are more difficult to detect

than bacterial infections, as well as owing to the similarity of symptoms to a truly aseptic form. Inflammation can affect both the meninges and the brain because of the anatomic continuum between these biological structures. Changes in the mental status and the focal or diffuse neurological signs indicate encephalitis, while fever, gastrointestinal symptoms, and meningeal symptoms point to meningitis, and a mix of these symptoms is typical for meningoencephalitis. The diagnosis is based on finding pleocytosis of the cerebrospinal fluid and no growth on routine bacterial culture. Nucleic acid sequence-based amplification tests (NAAT), especially PCR, have become the revolutionary golden standard for the detection of specific viruses. The common etiological factors in this case are non--polio human enteroviruses (NPEV, 23–61% of all detected viral meningitis), mumps virus (7.5–15.8%), lymphocytic choriomeningitis virus (LCMV, 1.9––9.7%), Herpes simplex virus (HSV, 0.5–18%) [73].

Aseptic meningitis and encephalitis

There are three other causes of CNS inflammation besides infection: certain systemic diseases, drugs or neoplastic change. Regardless of that, up to two-thirds of aseptic meningitis cases are labeled as idiopathic. The systemic diseases, in the course of which CNS inflammation may develop, include neurosarcoidosis, Behçet's disease, Sjögren's syndrome, systemic lupus erythematosus, or granulomatosis with polyangiitis (formerly Wegener's granulomatosis). In order to differentiate between these diseases, it is crucial to conduct a detailed interview and physical examination with attention to non-neurological signs characteristic of this disease. Additional tests, such as immunological tests, imaging studies, or ophthalmological consultation, are also often helpful. Drug-induced encephalitis or meningitis is difficult to recognize due to the absence of specific symptoms and a diagnostic method capable of its detection. Nevertheless, the lack of evidence of other pathologies may be a clue to checking the medications taken by the patient. For example, limited biochemical abnormalities in laboratory tests or correct results of brain imaging can help rule out many other causes. The ultimate proof is attaining full recovery after discontinuation of the suspected medication. The most common related drugs are non-steroidal anti--inflammatory drugs (NSAIDs), some antibiotics, intravenous immunoglobulin, or monoclonal antibodies. Finally, there are neoplastic meningitis and encephalitis. Solid cancer in 4–15% of cases and hematological malignancy in 5–15% of cases are mainly responsible for this type of meningitis. Breast cancers, lung cancers, and melanoma among solid cancers and leukemia and lymphoma among hematological malignancies are the ones that stand out as the most common causes. Performing several analyses of 10 ml of fresh CSF by well-trained cytologists is a useful practice in the diagnosis [73].

West Nile fever

West Nile fever is caused by the West Nile virus (WNV). In most cases, it is transmitted to humans through the bite of an infected mosquito, but infection is also possible through the blood (e.g. blood transfusion). The clinical symptoms of West Nile fever are similar to TBE, and they occur in two phases. Initially, nonspecific symptoms such as fever and muscle pain occur. In the second phase, the development of encephalitis, which can be potentially fatal, can be observed [74,75]. Cross-reactive antibodies develop during the infection of the West Nile fever, which can be a challenge during differential diagnosis [1]. Symptomatic treatment is given to patients with mild symptoms, whereas those with neurological symptoms require treatment in an intensive care unit [74].

Autoimmune encephalitis

Autoimmune encephalitis (AE) is an inflammatory disease marked by a subacute decline in short-term memory, accompanied by psychiatric symptoms, seizures, as well as numerous other disorders affecting the CNS. Autoimmune encephalitis manifests in two types: classic AE, with onconeural antibodies causing brain damage, responds modestly to immunosuppression, and AE with neuronal surface antibodies (nsAb) directly affecting the brain often shows a better response to immunotherapy [76,77].

CONCLUSIONS

This review summarizes the most important clinical findings in the differential diagnosis of TBE. The similarity of the symptoms of TBE to the diseases presented above makes the diagnosis difficult and requires a detailed comparison not only of the clinical symptoms but also of the results of additional tests. It is also pertinent to accentuate the specific significance of immunization in the prevention of TBE infections.

Author's contribution

Study design – J. Paprocka, P. Ochman-Pasierbek, P. Olczyk, M. Matlakiewicz
Data collection – P. Ochman-Pasierbek, P. Olczyk, M. Matlakiewicz, J. Paprocka
Manuscript preparation – P. Ochman-Pasierbek, P. Olczyk, M. Matlakiewicz, A. Kalinowska-Doman
Literature research – P. Ochman-Pasierbek, P. Olczyk, M. Matlakiewicz
Final approval of the version to be published – J. Paprocka, A. Kalinowska-Doman

REFERENCES

1. Bogovic P., Strle F. Tick-borne encephalitis: A review of epidemiology, clinical characteristics, and management. World J. Clin. Cases 2015; 3(5): 430–441, doi: 10.12998/wjcc.v3.i5.430.
2. Gritsun T.S., Lashkevich V.A., Gould E.A. Tick-borne encephalitis. Antiviral Res. 2003; 57(1–2): 129–146, doi: 10.1016/S0166-3542(02)00206-1.
3. Kmieciak W., Ciszewski M., Szewczyk E.M. Tick-borne diseases in Poland: Prevalence and difficulties in diagnostics. [Article in Polish]. Med. Pr. 2016; 67(1): 73–87, doi: 10.13075/mp.5893.00264.
4. Zajkowska J., Waluk E., Dunaj J., Świerzbińska R., Hordowicz M., Zajkowska O. et al. Assessment of the potential effect of the implementation of serological testing tick-borne encephalitis on the detection of this disease on areas considered as non-endemic in Poland – preliminary report. Przegl. Epidemiol. 2021; 75(4): 515–523, doi: 10.32394/pe.75.48.
5. Stragapede L., Dinoto A., Cheli M., Manganotti P. Epilepsia partialis continua following a Western variant tick-borne encephalitis. J. Neurovirol. 2018; 24(6): 773–775, doi: 10.1007/s13365-018-0671-z.
6. Eggers C., Burghaus L., Fink G.R., Dohmen C. Epilepsia partialis continua responsive to intravenous levetiracetam. Seizure 2009; 18(10): 716––718, doi: 10.1016/j.seizure.2009.09.005.
7. Mameniškienė R., Wolf P. Epilepsia partialis continua: A review. Seizure 2017; 44: 74–80, doi: 10.1016/j.seizure.2016.10.010.
8. Motika P.V., Bergen D.C. Epilepsia Partialis Continua. In: Encyclopedia of Movement Disorders. K. Kompoliti, L.V. Metman [ed.]. Academic Press, 2010, p. 450–452, doi: 10.1016/B978-0-12-374105-9.00028-9.
9. Gritsun T.S., Nuttall P.A., Gould E.A. Tick-borne flaviviruses. Adv. Virus Res. 2003; 61: 317–371, doi: 10.1016/s0065-3527(03)61008-0.
10. Beltz L.A. Zika and Other Neglected and Emerging Flaviviruses: The Continuing Threat to Human Health. Elsevier 2021.
11. Růžek D., Dobler G., Mantke O.D. Tick-borne encephalitis: pathogenesis and clinical implications. Travel Med. Infect. Dis. 2010; 8(4): 223–232, doi: 10.1016/j.tmaid.2010.06.004.
12. Eyer L., Seley-Radtke K., Ruzek D. New directions in the experimental therapy of tick-borne encephalitis. Antiviral Res. 2023; 210: 105504, doi: 10.1016/j.antiviral.2022.105504.
13. Rostasy K. Tick-borne encephalitis in children. Wien. Med. Wochenschr. 2012; 162(11–12): 244–247, doi: 10.1007/s10354-012-0101-4.
14. Pancewicz S.A., Hermanowska-Szpakowicz T., Kondrusik M., Zajkowska J.M., Grygorczuk S., Świerzbińska R. Aspekty epidemiologiczno-kliniczne
i profilaktyka kleszczowego zapalenia mózgu. Pol. Przegl. Neurol. 2006; 2(1): 7–12.
15. Ruzek D., Avšič Županc T., Borde J., Chrdle A., Eyer L., Karganova G. et al. Tick-borne encephalitis in Europe and Russia: Review of pathogenesis, clinical features, therapy, and vaccines. Antiviral Res. 2019; 164: 23–51, doi: 10.1016/j.antiviral.2019.01.014.
16. Lindquist L., Vapalahti O. Tick-borne encephalitis. Lancet 2008; 371(9627): 1861–1871, doi: 10.1016/S0140-6736(08)60800-4.
17. Riccardi N., Antonello R.M., Luzzati R., Zajkowska J., Di Bella S., Giacobbe D.R. Tick-borne encephalitis in Europe: a brief update on epidemiology, diagnosis, prevention, and treatment. Eur. J. Intern. Med. 2019; 62: 1–6, doi: 10.1016/j.ejim.2019.01.004.
18. Pulkkinen L.I.A., Butcher S.J., Anastasina M. Tick-borne encephalitis virus: A structural view. Viruses 2018; 10(7): 350, doi: 10.3390/v10070350.
19. Beauté J., Spiteri G., Warns-Petit E., Zeller H. Tick-borne encephalitis in Europe, 2012 to 2016. Euro Surveill. 2018; 23(45): 1800201, doi: 10.2807/1560-7917.ES.2018.23.45.1800201.
20. Amicizia D., Domnich A., Panatto D., Lai P.L., Cristina M.L., Avio U. et al. Epidemiology of tick-borne encephalitis (TBE) in Europe and its prevention by available vaccines. Hum. Vaccin. Immunother. 2013; 9(5): 1163–1171, doi: 10.4161/hv.23802.
21. Kuchar E., Zajkowska J., Flisiak R., Mastalerz-Migas A., Rosińska M., Szenborn L. et al. Epidemiology, diagnosis, and prevention of tick-borne encephalitis in Poland and selected European countries – a position statement of the Polish group of experts. [Article in Polish]. Med. Pr. 2021; 72(2): 193––210, doi: 10.13075/mp.5893.01063.
22. European Centre for Disease Prevention and Control. Tick-borne encephalitis. In: ECDC. Annual epidemiological report for 2020. Stockholm: ECDC; 2022.
23. Sapi E., Gupta K., Wawrzeniak K., Gaur G., Torres J., Filush K. et al. *Borrelia* and *Chlamydia* can form mixed biofilms in infected human skin tissues. Eur. J. Microbiol. Immunol. (Bp) 2019; 9(2): 46–55, doi: 10.1556/1886.2019.00003.
24. Davar K., Wilson M.R., Miller S., Chiu C.Y., Vijayan T. A rare bird: Diagnosis of psittacosis meningitis by clinical metagenomic next-generation sequencing. Open Forum Infect. Dis. 2021; 8(12): ofab555; doi: 10.1093/ofid/ofab555.
25. Dard C., Fricker-Hidalgo H., Brenier-Pinchart M.P., Pelloux H. Relevance of and new developments in serology for toxoplasmosis. Trends Parasitol. 2016; 32(6): 492–506, doi: 10.1016/j.pt.2016.04.001.
26. Ben-Harari R.R. Tick transmission of toxoplasmosis. Expert Rev. Anti Infect. Ther. 2019; 17(11): 911–917, doi: 10.1080/14787210.2019.1682550.
27. Rawlings J.A. An overview of tick-borne relapsing fever with emphasis on outbreaks in Texas. Tex. Med. 1995; 91(5): 56–59.
28. Furtado J.M., Smith J.R., Belfort R. Jr, Gattey D., Winthrop K.L. Toxoplasmosis: a global threat. J. Glob. Infect. Dis. 2011; 3(3): 281–284, doi: 10.4103/0974-777X.83536.
29. Weiss L.M., Dubey J.P. Toxoplasmosis: A history of clinical observations. Int. J. Parasitol. 2009; 39(8): 895–901, doi: 10.1016/j.ijpara.2009.02.004.
30. Elsheikha H.M., Marra C.M., Zhu X.Q. Epidemiology, pathophysiology, diagnosis, and management of cerebral toxoplasmosis. Clin. Microbiol. Rev. 2020; 34(1): e00115–00119, doi: 10.1128/CMR.00115-19.
31. Fuglewicz A.J., Piotrowski P., Stodolak A. Relationship between toxoplasmosis and schizophrenia: A review. Adv. Clin. Exp. Med. 2017; 26(6): 1031–1036, doi: 10.17219/acem/61435.
32. Schoen R.T. Lyme disease: diagnosis and treatment. Curr. Opin. Rheumatol. 2020; 32(3): 247–254, doi: 10.1097/BOR.0000000000000698.
33. Abdad M.Y., Abou Abdallah R., Fournier P.E., Stenos J., Vasoo S. A concise review of the epidemiology and diagnostics of rickettsioses: *Rickettsia* and *Orientia* spp. J. Clin. Microbiol. 2018; 56(8): e01728-17, doi: 10.1128/JCM.01728-17.
34. Jorge Miranda R., Salim Mattar V., Marco Gonzalez T. Rickettsiosis. Rev. MVZ Cordoba 2017; 22(Supl): 6118–6133, doi: 10.21897/rmvz.1080.
35. Corrin T., Greig J., Harding S., Young I., Mascarenhas M., Waddell L.A. Powassan virus, a scoping review of the global evidence. Zoonoses Public Health 2018; 65(6): 595–624, doi: 10.1111/zph.12485.
36. Bakken J.S., Dumler J.S. Human granulocytic anaplasmosis. Infect. Dis. Clin. North Am. 2015; 29(2): 341–355, doi: 10.1016/j.idc.2015.02.007
37. Factsheet on Human granulocytic anaplasmosis. European Centre for Disease Prevention and Control [online] https://web.archive.org/web/20220601153625/https://www.ecdc.europa.eu/en/all-topics-z/human-granulocytic-anaplasmosis/factsheet-human-granulocytic-anaplasmosis [accessed on 6 June 2022].
38. Cho J.M., Chang J., Kim D.M., Kwak Y.G., Cho C.R., Song J.E. Human granulocytic anaplasmosis combined with rhabdomyolysis: a case report. BMC Infect. Dis. 2021; 21(1): 1184, doi: 10.1186/s12879-021-06869-z.
39. Kandhi S., Ghazanfar H., Qureshi Z.A., Kalangi H., Jyala A., Arguello Perez E.S. An atypical presentation of a severe case of anaplasma phagocytophilum. Cureus 2022; 14(3): e23224, doi: 10.7759/cureus.23224.
40. de Jesus M., Lopez A., Yabut J., Vu S., Manne M., Ibrahim L., Mutneja R. Anaplasmosis-induced hemophagocytic lymphohistiocytosis. Proc. (Bayl. Univ. Med. Cent.) 2022; 35(3): 379–381, doi: 10.1080/08998280.2022.2039046.
41. Abdelmaseih R., Ashraf B., Abdelmasih R., Dunn S., Nasser H. Southern tick-associated rash illness: Florida's Lyme disease variant. Cureus 2021; 13(5): e15306, doi: 10.7759/cureus.15306.
42. Nualnoi T., Kirosingh A., Basallo K., Hau D., Gates-Hollingsworth M.A., Thorkildson P. et al. Immunoglobulin G subclass switching impacts sensitivity of an immunoassay targeting *Francisella tularensis* lipopolysaccharide. PLoS One 2018; 13(4): e0195308, doi: 10.1371/journal.pone.0195308.

43. Faber M., Heuner K., Jacob D., Grunow R. Tularemia in Germany – A re-emerging zoonosis. Front. Cell. Infect. Microbiol. 2018; 8: 40, doi: 10.3389/fcimb.2018.00040.
44. Rochlin I., Toledo A. Emerging tick-borne pathogens of public health importance: a mini-review. J. Med. Microbiol. 2020; 69(6): 781–791, doi: 10.1099/jmm.0.001206.
45. Biggs H.M., Behravesh C.B., Bradley K.K., Dahlgren F.S., Drexler N.A., Dumler J.S, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis – United States. MMWR Recomm. Rep. 2016; 65(2): 1–44, doi: 10.15585/mmwr.rr6502a1.
46. Heartland Virus. Columbia University Irving Medical Center [online] https://www.columbia-lyme.org/heartland-virus [accessed on 6 June 2022].
47. Staples J.E., Pastula D.M., Panella A.J., Rabe I.B., Kosoy O.I., Walker W.L. et al. Investigation of Heartland virus disease throughout the United States, 2013–2017. Open Forum Infect. Dis. 2020; 7(5): ofaa125, doi: 10.1093/ofid/ofaa125.
48. Brault A.C., Savage H.M., Duggal N.K., Eisen R.J., Staples J.E. Heartland virus epidemiology, vector association, and disease potential. Viruses 2018; 10(9): 498, doi: 10.3390/v10090498.
49. Tuten H.C., Burkhalter K.L., Noel K.R., Hernandez E.J., Yates S., Wojnowski K. et al. Heartland virus in humans and ticks, Illinois, USA, 2018–2019. Emerg. Infect. Dis. 2020; 26(7): 1548–1552, doi: 10.3201/eid2607.200110.
50. Pastula D.M., Turabelidze G., Yates K.F., Jones T.F., Lambert A.J., Panella A.J. et al. Notes from the field: Heartland virus disease – United States, 2012–2013. MMWR Morb. Mortal. Wkly Rep. 2014; 63(12): 270––271.
51. Jakab Á., Kahlig P., Kuenzli E., Neumayr A. Tick borne relapsing fever – a systematic review and analysis of the literature. PLoS Negl. Trop. Dis. 2022; 16(2): e0010212, doi: 10.1371/journal.pntd.0010212.
52. Domínguez M.C., Vergara S., Gómez M.C., Roldán M.E. Epidemiology of tick-borne relapsing fever in endemic area, Spain. Emerg. Infect. Dis. 2020; 26(5): 849–856, doi: 10.3201/eid2605.190745.
53. Tick and Louse-borne Relapsing Fevers. CDC [online] https://www.cdc.gov/relapsing-fever/index.html [accessed on 6 June 2022].
54. Toxoplasmosis. CDC, 2019 [online] https://www.cdc.gov/parasites/toxoplasmosis/index.html [accessed on 6 June 2022].
55. Ebel G.D. Update on Powassan virus: emergence of a North American tick-borne flavivirus. Annu. Rev. Entomol. 2010; 55: 95–110, doi: 10.1146/annurev-ento-112408-085446.
56. Williamson B.N., Fischer R.J., Lopez J.E., Ebihara H., Schwan T.G. Prevalence and strains of Colorado tick fever virus in Rocky Mountain wood ticks in the Bitterroot Valley, Montana. Vector Borne Zoonotic Dis. 2019; 19(9): 694–702, doi: 10.1089/vbz.2018.2407.
57. Padgett K.A., Kjemtrup A., Novak M., Velez J.O., Panella N. Colorado tick fever virus in the Far West: forgotten, but not gone. Vector Borne Zoonotic Dis. 2022; 22(8): 443–448, doi: 10.1089/vbz.2022.0018.
58. Pecina C.A. Tick paralysis. Semin. Neurol. 2012; 32(5): 531–532, doi: 10.1055/s-0033-1334474.
59. Molins C.R., Ashton L.V., Wormser G.P., Andre B.G., Hess A.M., Delorey M.J. et al. Metabolic differentiation of early Lyme disease from southern tick-associated rash illness (STARI). Sci. Transl. Med. 2017; 9(403): eaal2717, doi: 10.1126/scitranslmed.aal2717.
60. Seo J.W., Kim D., Yun N., Kim D.M. Clinical update of severe fever with thrombocytopenia syndrome. Viruses 2021; 13(7): 1213, doi: 10.3390/v13071213.
61. Moniuszko A., Dunaj J., Czupryna P., Zajkowska J., Pancewicz S. Neoehrlichiosis – a new tick-borne disease – is there a threat in Poland? Przegl. Epidemiol. 2015; 69(1): 23–26, 131–133.
62. Tyrakowska-Dadełło Z., Tarasów E., Janusek D., Moniuszko--Malinowska A., Zajkowska J., Pancewicz S. Brain perfusion alterations in tick-borne encephalitis-preliminary report. Int. J. Infect. Dis. 2018; 68: 26–30, doi: 10.1016/j.ijid.2018.01.002.
63. Eleftheriou A., Lundin F., Petropoulos E.A. Tick-borne encephalitis: stroke-like presentation. J. Stroke Cerebrovasc. Dis. 2019; 28(8): e119–e122, doi: 10.1016/j.jstrokecerebrovasdis.2019.05.028.
64. Tarfarosh S.F., Manzoor M. Neurological manifestations of Brucellosis in an Indian population. Cureus 2016; 8(7): e684, doi: 10.7759/cureus.684.
65. Bukhari E.E. Pediatric brucellosis: An update review for the new millennium. Saudi Med. J. 2018; 39(4): 336–341, doi: 10.15537/smj.2018.4.21896.
66. Choroby zakaźne i zatrucia w Polsce rok 2017 (Tabele). Narodowy Instytut Zdrowia Publicznego – Państwowy Instytut Badawczy [online] https://epibaza.pzh.gov.pl/choroby-zaka%C5%BAne-i-zatrucia-w-polsce-rok-2017-tabele [accessed on 24 January 2024].
67. Cai X., Ebell M.H., Haines L. Accuracy of signs, symptoms, and hematologic parameters for the diagnosis of infectious mononucleosis: A systematic review and meta-analysis. J. Am. Board Fam. Med. 2021; 34(6): 1141–1156, doi: 10.3122/jabfm.2021.06.210217.
68. Arslan F., Karagöz E., Beköz H.S., Ceylan B., Mert A. Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis presenting with acute sensorineural hearing loss: a case report and review of the literature. Infez. Med. 2017; 25(3): 277–280.
69. Simon L.V., Hashmi M.F., Torp K.D. Yellow fever. 2023 Feb 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan, https://www.ncbi.nlm.nih.gov/books/NBK470425/ [accessed on 6 June 6 2022].
70. Douam F., Ploss A. Yellow fever virus: knowledge gaps impeding the fight against an old foe. Trends Microbiol. 2018; 26(11): 913–928, doi: 10.1016/j.tim.2018.05.012.
71. Yellow fever. World Health Organization, 31 May 2023 [online] https://www.who.int/news-room/fact-sheets/detail/yellow-fever [accessed on 6 June 2022].
72. Tattevin P., Tchamgoué S., Belem A., Bénézit F., Pronier C., Revest M. Aseptic meningitis. Rev. Neurol. (Paris) 2019; 175(7–8): 475–480, doi: 10.1016/j.neurol.2019.07.005.
73. Wright W.F., Pinto C.N., Palisoc K., Baghli S. Viral (aseptic) meningitis: A review. J. Neurol. Sci. 2019; 398: 176–183, doi: 10.1016/j.jns.2019.01.050.
74. Clark M.B., Schaefer T.J. West Nile virus. 2022 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan, https://www.ncbi.nlm.nih.gov/books/NBK544246/ [accessed on 6 June 2022].
75. Shin A., Tukhanova N., Ndenkeh J. Jr, Shapiyeva Z., Yegemberdiyeva R., Yeraliyeva L. et al. Tick-borne encephalitis virus and West-Nile fever virus as causes of serous meningitis of unknown origin in Kazakhstan. Zoonoses Public Health 2022; 69(5): 514–525, doi: 10.1111/zph.12941.
76. Schwarz L., Akbari N., Prüss H., Meisel A., Scheibe F. Clinical characteristics, treatments, outcome, and prognostic factors of severe autoimmune encephalitis in the intensive care unit: Standard treatment and the value of additional plasma cell-depleting escalation therapies for treatment-refractory patients. Eur. J. Neurol. 2023; 30(2): 474–489, doi: 10.1111/ene.15585.
77. Machado S., Pinto A.N., Irani S.R. What should you know about limbic encephalitis? Arq. Neuropsiquiatr. 2012; 70(10): 817–822, doi: 10.1590/S0004-282x2012001000012.
78. Lotric-Furlan S., Avsic-Zupanc T., Strle F. An abortive form of tick--borne encephalitis (TBE): a rare clinical manifestation of infection with TBE virus. Wien. Klin. Wochenschr. 2002; 114(13–14): 627–629.
79. Logina I., Krumina A., Karelis G., Elsone L., Viksna L., Rozentale B. et al. Clinical features of double infection with tick-borne encephalitis and Lyme borreliosis transmitted by tick bite. J. Neurol. Neurosurg. Psychiatry 2006; 77(12): 1350–1353, doi: 10.1136/jnnp.2004.060731.