Chapter 9

Tick-borne encephalitis in adults

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Key points:

- Tick-borne encephalitis (TBE) is a viral infectious disease that involves the nervous system.
- Frequently, there is a febrile illness phase 1-21 days before the onset of neurological symptoms.
- The most common neurological manifestations include meningitis, encephalitis, myelitis, radiculitis, or a combination thereof.
- Long-term sequelae are present in almost every second person with nervous system involvement in this vaccine-preventable disease.

Introduction

Tick-borne encephalitis (TBE) encompasses various diseases caused by infection with the TBE virus (TBEV). TBEV is a positive-strand RNA virus in the genus Flaviviridae, which is primarily transmitted by infected ticks (primarily genus Ixodes) and occasionally by consuming unpasteurized dairy products from infected ruminants.[1] Among the several viral subtypes of TBEV, the European subtype (TBEV-Eur) is predominantly found in Europe. Siberian (**TBEV**-Sib) and Far Eastern (**TBEV**-FE) are additional prominent subtypes.

An overall increase in TBE cases in the European Union (EU)/European Economic Area (EEA) was observed between 2012 and 2020, according to the European Centre for Disease Control (ECDC).[2] In 2021, there was a slight decrease of cases compared to 2020. The drivers of the rising incidence remain unclear.[3] For 2021, 22 EU/EEA countries reported 2.949 confirmed cases, with Czechia (n=589), Sweden (n=533), and Germany (n=417) as the front runners. The notification rate was highest in Lithuania (13.1 cases per 100,000 population), followed by Latvia (11.7) and Estonia (6.2). Among the confirmed cases in which information for vaccination was available, 93.2% were not vaccinated against TBE. There is a seasonal pattern for occurrence. In 2021, 90% of confirmed cases occurred between June and November in the EU/EEA, with July being the month with the highest number of reported cases.[2]

The clinical manifestation of TBE depends on the virulence of the pathogen and the immune status of the host. The majority of the infected people remain asymptomatic or suffer from a self-limiting febrile illness. Some patients develop neurological and neuropsychiatric disturbances caused by meningitis, encephalitis, myelitis, radiculitis, or combinations thereof.[4] Cases of nervous system manifestation are more frequently reported among men (male-to-female ratio 1.5:1) and in the age group 45–64 years.[2] Mortality of TBE caused by TBEV-Eu is in the range of 0.5-2%. Involvement of the nervous system is associated with long-term sequelae in almost every second survivor.

Clinical course and long-term outcome vary by TBE virus subtype, although some of the reported differences could be related to access to medical care or testing or methodologic biases.[6] Preventive strategies include vaccination and avoiding tick bites; no antiviral medication has been approved.

Risk factors

Ecological variables

TBEV transmission is affected by place, time, and tick population density. However, infection rates in TBE virus–endemic areas are inconsistent, which impedes risk assessments.[6] People with outdoor occupations, e.g., farmers, forestry workers, and training in forested areas, are at increased risk for contracting TBE. The risk for TBEV infection for an individual traveler is greatly affected by their itinerary and activities. Among the ECDC cases of 2021, only 1.6% were associated with travel.[2] Most infections result from tick bites acquired in forested areas while bicycling, birdwatching, camping, fishing, hiking, or collecting berries, flowers, or mushrooms.[6] In contrast, the risk is negligible for people who remain in urban or unforested areas and do not consume unpasteurized dairy products.

Epidemiological data from different European countries demonstrate that the incidence of TBE is higher in older adults than in younger age groups. More than half of the patients are ≥50 years of age.[7-9] Both a decline in adaptive and innate immunity and changed lifestyle habits may contribute to this observation.[10] This age distribution is also present among TBE cases in vaccinated people.[11]

Risk factors for severe or protracted course

The most endangered groups for severe clinical manifestation are older adults.[12-15] Immunosuppression is another risk factor for unfavorable outcomes. The case fatality rate for TBE is higher in these patient groups.[16] A report on a cluster of TBE in organ transplant recipients underscores the association between host immune suppression and fatal outcomes.[17] Whether vaccination breakthrough TBE is associated with more severe disease is a matter of investigation.[18] A recent study reported that a severe disease course was associated with a low serum TBEV-specific IgG antibody response at the time of onset of the neurologic phase of the disease.[19] Another factor that may result in a more severe clinical picture of TBE is the relatively rare occurrence of co-infection with other tick-borne pathogens like *Borrelia burgdorferi*, *Anaplasma phagocytopilum*, *Rickettsia* spp. or *Listeria monocytogenes*.[20,21]

Host genetic risk factors

Clinical and epidemiological data indicate that human susceptibility to clinical TBEV infection greatly varies according to age and gender. Mouse models of TBE corroborate that genetic control influences the clinical course of TBE. In this regard, sufficient neutralizing antibody response might be crucial for preventing host fatality. In addition, high expression of various cytokines/chemokines during TBE can mediate immunopathology and be associated with a more severe course of infection and increased fatality.[22] Genetic polymorphisms and immune signatures that may predispose to TBEV infection and its severity are covered in the following sections.

The CCR5 plays a crucial role in leukocyte migration and attraction. In human immunodeficiency virus (HIV) infections, the CCR5Δ32 mutation is crucial for invading CD4 cells by HIV particles with a CCR5 tropism.[23] In mouse models for flaviviral infections, homozygote CCR5-deficient (-/-) mice died in almost 100% of all infections with West Nile virus (WNV), whereas CCR5 (-/+) heterozygote mice, and homozygote mice with a wildtype CCR5 receptor, had a significantly lower mortality rate.[22] These observations from animal studies could be corroborated during a WNV outbreak by identifying the CCR5Δ32 mutation as a strong predictor for a severe clinical disease course in humans. Following the epidemiological results from WNV research, a potential effect of the CCR5Δ32 mutation on TBE was investigated. A clinical study from Lithuania analyzed the incidence of the CCR5Δ32 mutation in different patient populations and found individuals homozygous for CCR5Δ32 only among patients with TBE.[24] Moreover, the CCR5Δ32 allele prevalence also increased with the clinical severity of the disease. In another study by this author group, the prevalence of CCR5Δ32 homozygotes was higher in children (2.5%), in adults with severe TBE (1.9%), and in the combined cohort of TBE patients (2.3%) than in controls (0%).[25] In a Polish study, the blood expression of CCR5 neither differed between the groups nor did it change in the course of TBE.[26] The cerebrospinal fluid (CSF) concentration of the CCR ligand CCL5 was increased in TBE, the highest in the most severe presentation and correlated with pleocytosis. In another Polish study, there were 17.6% CCR5Δ32 heterozygotes and 1.5% homozygotes in the TBE cohort, with no statistically significant difference compared to the controls.[27]

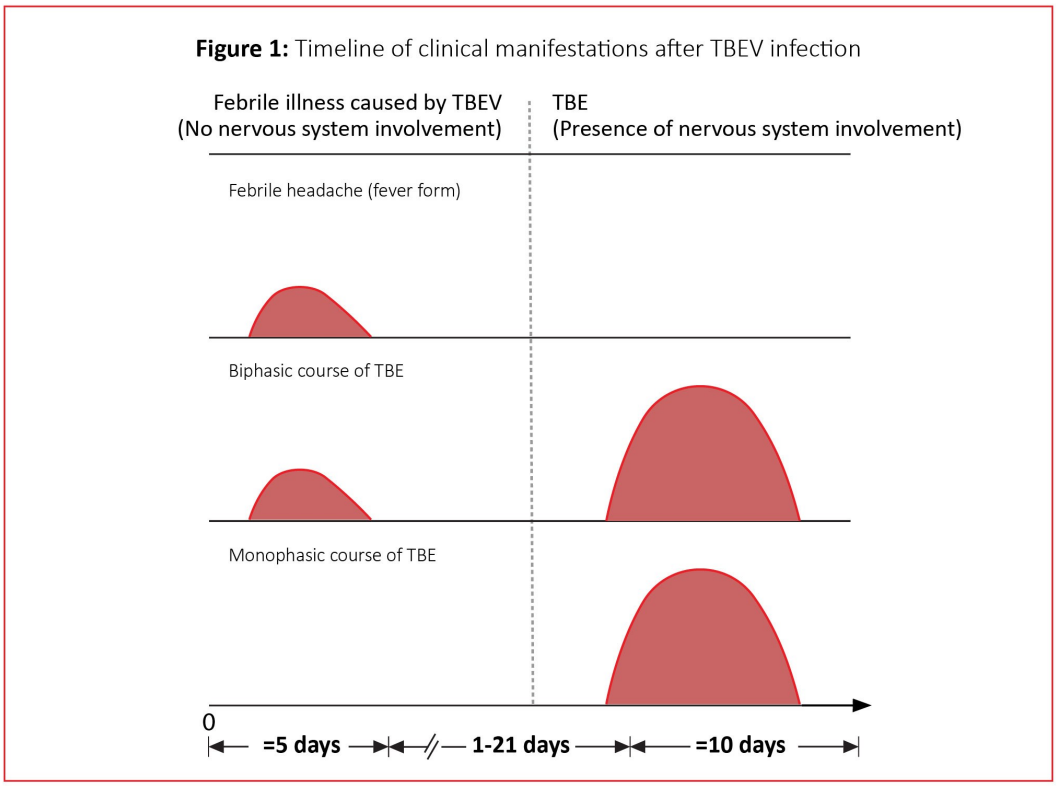
2'-5'-oligoadenylate synthetases (OAS) are a family of interferon-induced enzymes that play an essential role in mammal antiviral defense. Several polymorphisms in the OAS genes correlated with susceptibility and severe forms of Russian TBE.[28,29] The authors of these studies also analyzed OAS polymorphisms in different ethnic populations of the Russian Federation.[30] The studies revealed that the frequency of these SNPs correlated with the probability of disease after exposure to TBEV. Very low SNP frequencies were detected in Altaians, Khakasses, Tuvinians, and Shorians, groups with a high exposure risk for TBEV in their native habitats. These findings implicate that TBE risk SNPs may have served as selection factors.

A Czech study evaluated whether innate immunity genes predispose to TBE in humans.[31] The analysis showed an association of IFIT1 rs304478 SNP and DDX58 rs3739674 and rs17217280 SNPs and TBE in the Czech population.

The IL-28B polymorphism (rs12979860) is associated with an improved sustained virological response upon treatment with antivirals against Hepatitis C virus (HCV).[32] Given the close genetic relationship of flaviviral pathogens like HCV and TBEV, the role of the IL-28B and IL-10 polymorphism was investigated in TBEV infections.[33] In a study from the Novosibirsk region of Russia, the IL-28B polymorphism (rs8103142, rs12980275) and the IL-10 polymorphism (rs1800872) were associated with higher risk for severe TBE.

Dendritic cell (DC)-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) is a C-type lectin, expressed by DCs and a subpopulation of macrophages, involved in the detection of pathogen-associated molecular patterns (PAMPs), cell migration, and interaction with T lymphocytes, potentially contributing to an early response to TBEV at the site of tick feeding and initiation of a specific immune response.[34] Findings in the context of dengue virus and HCV infections pointed to an increased risk of dengue hemorrhagic fever and advanced hepatic injury in hepatitis C when there is an underlying SNP (rs4804803) located in the promotor region of the CD209 gene.[30] DCs in the skin and gut may play an important role as antigen-presenting cells and virus spread early in TBEV infection.[35] A study from Russia of presumably TBEV-Sib cases showed a correlation between the presence of 2 SNPs (rs4804803, rs2287886) in

Figure 1: Timelines of clinical manifestations of illness caused by TBEV



the promotor region of the CD209 gene and the severity of the TBE disease course.[30]

MMP-9 directly degrades extracellular matrix proteins and activates cytokines and chemokines to regulate tissue remodeling. In a study of Russian TBE cases, the frequency of the rs17576 G allele of MMP-9 was significantly higher in TBE cases with severe CNS diseases.[36]

Taken together, several studies disclosed a potential role for various gene polymorphisms in the susceptibility and severity of TBE. These findings need to be corroborated in independent cohorts with appropriate controls, using uniform criteria for disease severity and characterization of the virus strain, as there are also trials that could not confirm these observations.[37]

Clinical course

Definitions of the clinical presentations and time frames

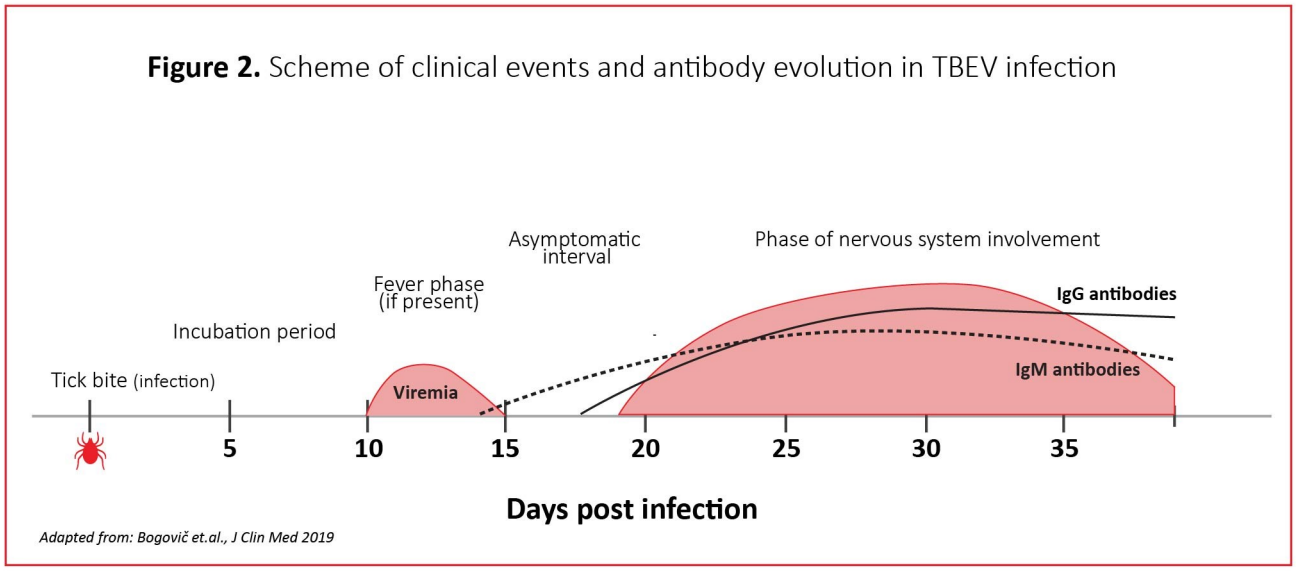
Infection with TBEV may be symptomatic or asymptomatic. A symptomatic infection may manifest as a febrile illness without nervous system involvement or as TBE (Figure 1).[38]

Asymptomatic infection with TBEV is defined as TBEV IgG antibody seroconversion in an asymptomatic person.

Febrile illness resulting from infection with TBEV is defined by the presence of fever and constitutional symptoms, the absence of signs/symptoms of CNS involvement at the time of actual illness, and the presence of TBEV RNA in serum and/or later seroconversion to TBEV. According to the later appearance (or absence) of neurologic involvement, the febrile illness is further sub-classified as either the **initial phase of TBE** (defined as a febrile illness that, after a clinical improvement, is followed by neurologic involvement occurring within at least a 1-month follow-up period and fulfilling criteria for TBE) or as **febrile illness resulting from infection with TBEV in a narrow sense** (abortive form of TBE, febrile headache, summer flu, fever form) when no signs/symptoms of CNS involvement are present at the time of actual illness or within at a least 1-month follow-up period.[38]

TBE is defined as the presence of clinical signs or symptoms of nervous system involvement (i.e. meningitis, encephalitis, myelitis, radiculitis, or a combination), with increased CSF leukocyte counts (>5 × 10^6 cells/L), and demonstration of a recent infection with TBEV indicated by serum specific IgM and IgG antibodies or IgG seroconversion in paired serum samples.[13,39] This definition partly contradicts the ECDC case definition for TBE, which does not explicitly require CSF pleocytosis to diagnose TBE;[40] however ECDC definitions are intended for epidemiological monitoring and are not necessarily optimal

Figure 2: Scheme of clinical events and antibody evolution in TBEV infection



for clinical use. The approximate time course of TBE is shown in Figure 2.[41]

Pathogenesis - clinical highlights

After the bite of an infected tick, TBEV replication occurs locally in the subcutaneous tissue. DCs of the skin (Langerhans cells) play an essential role since they bind with antigens and subsequently induce an immune response by producing proinflammatory cytokines. Langerhans cells are the most relevant cell group for local viral replication, transporting the virus to the regional lymph nodes where further replication occurs. After release into the bloodstream from lymph nodes, TBEV disseminates to other organs, particularly the reticulo-endothelial system (mainly bone marrow, spleen, and liver), where the virus continues to multiply and maintain viremia for several days. Probably during the second viremic phase (which clinically matches with febrile illness without CNS involvement), the virus reaches the brain.[42,43] The precise mechanism of viral passage through the blood-brain barrier is unclear but depends on the presence of viremia. There are four candidate routes:

i) direct axonal retrograde transport from infected peripheral nerves;

ii) infection of highly susceptible olfactory neurons;

iii) virus entry into vascular endothelial cells of brain capillaries, transcytosis, and release of virus into the brain parenchyma; and

iv) diffusion of virus between capillary endothelial cells.

There is also a so-called "Trojan horse" mechanism, which assumes that the virus is transported by infected immune cells to the CNS.[42,44,45] The primary targets of TBEV infection in CNS are neurons. Rarely, oligodendrocytes are infected.[42]

The pathogenesis of asymptomatic infections in humans is poorly defined. It seems logical that, on the one hand, the virus enters the body similarly to symptomatic infections and, on the other hand, does not enter the CNS. Still, it is not clear whether the development of the disease is deterred or interrupted after multiplication in the lymph nodes before or following penetration into the blood.

The characteristics of the TBEV subtype, the quantity of virus copies, and the host immune response influence the pathogenesis. The immune response is necessary not only for controlling TBEV infection but is also thought essential for the resulting clinical manifestations, but knowledge of such responses is incomplete.[41,46] Immune responses during TBEV infection are described in a separate chapter.

Presentations of tick-borne virus infection

1. Asymptomatic infections

Seroepidemiological studies suggest that most TBEV infections (70%–98%) are asymptomatic; however, the exact proportion of such cases is unknown because probably part of those with mild clinical presentation may remain below the diagnostic threshold.[47-49]

2. Symptomatic infections

The time interval from a tick bite to the beginning of the illness is usually 7–14 days, but it may be as short as two days and as long as four weeks. With the alimentary route

of infection, there is usually a shorter incubation period of 3 to 4 days; however, the reports are not unanimous.[50-55]

2.1. Febrile illness due to TBEV infection (abortive form of TBE, febrile headache, summer flu, fever form)

Information on febrile illness due to TBEV infection also called the abortive form of TBE, febrile headache, summer flu, or fever form, is limited. Clinically and serologically, abortive from TBE has been postulated to match the initial phase of TBE, except that subsequent CNS involvement does not occur. Because clinical symptoms and signs of the illness are non-specific, and because, in parallel to the initial phase of TBE, serum antibodies to TBEV are not yet expected to have developed, the only option for diagnosis at the time of actual illness is demonstrating the presence of TBEV RNA in the blood. However, this approach is not routine and might have a low diagnostic yield owing to several other known or unknown causes of fever, even in a highly endemic region for TBE. Therefore, the possibility that a febrile illness results from TBEV infection is usually tested for and established only after signs or symptoms of CNS involvement appear, which does not happen in the case of the fever form. In that case (and if PCR detection of viral RNA in blood is unavailable), further clinical and microbiologic (serologic) follow-up after improvement is needed to establish the diagnosis.

Data on the frequency of this clinical manifestation of the disease caused by European TBEV subtype are conflicting. TBEV infection manifesting as febrile illness without later CNS involvement is considered frequent[55-57], although not in all reports.[52,58-60], but the scientific basis for such a conclusion is unclear. According to some reports, it represents more than half of all clinically manifested TBEV infections.[55,56] However, this is not confirmed by the results of prospective clinical trials on the etiology of acute febrile illness after a tick bite. In the study by Lotric-Furlan and co-workers, among 56 patients diagnosed with TBEV infection by the presence of TBEV RNA in blood by PCR during febrile illness that developed after a tick bite, in 55 (98.2%) CNS involvement with pleocytosis later appeared.[61,62] In contrast, only one (1.8%) had an isolated febrile illness without later CNS involvement. A more recent, similarly designed study from Slovenia revealed that illness progressed to TBE in 52/62 (84%) adult patients within 18 days after defervescence.[38] In the Russian literature, this clinical manifestation is named “fever form” and is reported to represent up to 50% of all clinical presentations of TBEV infections.[63]

The current view is that febrile illness caused by TBEV infection most frequently presents as a moderate fever, headache, fatigue, and other non-specific symptoms and clinically corresponds to the initial phase of the TBE. The fever usually resolves in a few days, and the disease does not have long-term consequences.[38,64,65] The outcome of symptomatic TBEV infection without CNS involvement is believed to be favorable; however, very little reliable information on the outcome has been published.[38]

2.2. Tick-borne encephalitis

In 56–87% of symptomatic patients infected with the European subtype of TBEV, CNS inflammation is preceded by a febrile illness, resulting in a biphasic course of the disease.[4,12,19,52,53,60,66-69] The initial illness (first phase of TBE), which corresponds to viremia, presents with fever, fatigue, malaise, headache, and muscle and joint pain that occurs without CNS inflammation. It usually lasts less than one week, followed by improvement lasting several days.[38,53,70] The hallmark of the second phase of TBE is CNS involvement: in approximately 50% of adult patients, it presents as meningitis, in about 40% as meningoencephalitis, and around 10% as meningoencephalomyelitis.[49] The frequency of different neurological presentations has been somewhat variable.[9,53,60,68,71]

Some patients with TBE have no (obvious) initial phase of the disease and present directly with CNS involvement. Data on the monophasic course of the disease are incomplete. Some studies showed that patients with monophasic presentation of TBE have a more severe clinical course of the disease than those with biphasic course.[12,52,53] In addition, some reports on patients with severe TBE who needed intensive care management show an unusually high proportion of those with monophasic course (15/31, 48.4% and 21/33, 63.6%, respectively).[72,73] A direct comparison of the clinical presentation and laboratory findings in 705 adult TBE patients, of whom 283 had monophasic and 422 had biphasic course, revealed that patients with the monophasic course were significantly older, more often vaccinated against TBE (7.4% vs. 0.9%), more often had comorbidities (52% vs. 37%), and were more often treated in the intensive care unit (12.4% vs. 5.2%). However, the long-term outcome 2–7 years after TBE was comparable.[74]

Case fatality rate in TBE caused by the European subtype of TBEV is 0.5–2% and generally increases with age.[49,70]

TBE caused by Far-Eastern TBEV subtype has been characterized with more severe disease and a case fatality rate of up to 40%, while in TBE caused by Siberian virus subtype the reported case fatality rate is 2–3%, and cases of chronic and progressive forms have been described.[48,70,75,76]

The initial phase of tick-borne encephalitis

Information on the initial phase of TBE is limited. Characterization of 98 adult patients who had TBEV RNA in their blood but no CNS involvement at the time of evaluation revealed that incubation (time from tick bite to onset of the illness) was six days, median duration of illness was seven days, and that 37 (38%) patients were hospitalized for a median three days. The most frequent findings were malaise or fatigue (98%), fever (97%), headache (86%), and myalgia (54%), followed by arthralgia (43%), gastrointestinal symptoms (46%; abdominal pain 2%, nausea/vomiting 38%, loose stools 16%), respiratory symptoms (18%; sore throat 11%, cough 10%) and chills (19%). Typical laboratory findings were leukopenia (88%), thrombocytopenia (59%), and abnormal liver function test results (63%). At the time of positive PCR findings, 0/98 patients had serum IgG TBEV and seven serum IgM TBEV; all patients later seroconverted. Viral RNA load was higher in hospitalized patients with more severe illness than in those who did not need hospitalization but did not differ substantially according to age, sex, duration of illness before testing, or total duration of the actual febrile illness, or for patients with undetectable viral IgM in serum samples when compared with patients in whom antibodies were detectable. Illness progressed to TBE in 84% within 18 days after defervescence.[38] Clinical and laboratory findings in patients with TBEV febrile illness did not distinguish between patients in whom TBE later develops and those in whom it does not.[38]

Clinical spectrum of neurological manifestations

Meningitis is characterized by fever, headache, nausea, vomiting, and meningeal signs. These symptoms and signs are present in most patients but not all. 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.[68]

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 rarely with brain stem symptoms and/or cranial nerve abnormalities. Impaired consciousness, ranging from mild to severe, concentration disturbances, and cognitive function disturbances are rather frequent; amnesia, behavioral changes, psychosis, and delirium may also occur.

Myelitis manifests with flaccid paralyses that are occasionally preceded by severe pain in the affected muscle groups. The involvement is usually asymmetrical. Most often, the 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.[13,39,52,53,60]

Radiculitis is a rare manifestation of TBE.[77] In patients with TBE who have radiculitis it is reasonable to look for concomitant *Borrelia* infection.

Other manifestations in the acute phase of tick-borne encephalitis

Involvement of cranial nerves. Involvement of cranial nerves is rare (usually in less than 5% of patients), mainly asymmetrical, and usually has a favorable outcome. Ocular, facial, and pharyngeal muscles are most often affected, but hearing and vestibular defects are also encountered.[4,9,52,53,60] In a series of 1218 adult patients diagnosed with TBE at a single center, 11 (0.9%) developed peripheral facial palsy (two bilateral, nine unilateral);and occurs late in the course of acute illness(10-20 days after the onset of the neurological phase and more frequent in patients with an encephalitic than a meningitis manifestation of TBE. However, 3 out of 11 patients had associated borrelial infection 10.1111/j.1469-0691.2011.03719.x. 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 borreliosis has to be taken into account.[78]

Autonomic nervous system disorders. Occasionally, autonomic nervous system disorders occur in patients with TBE. These include cardiac and enteric nervous system disturbances. [79,80]

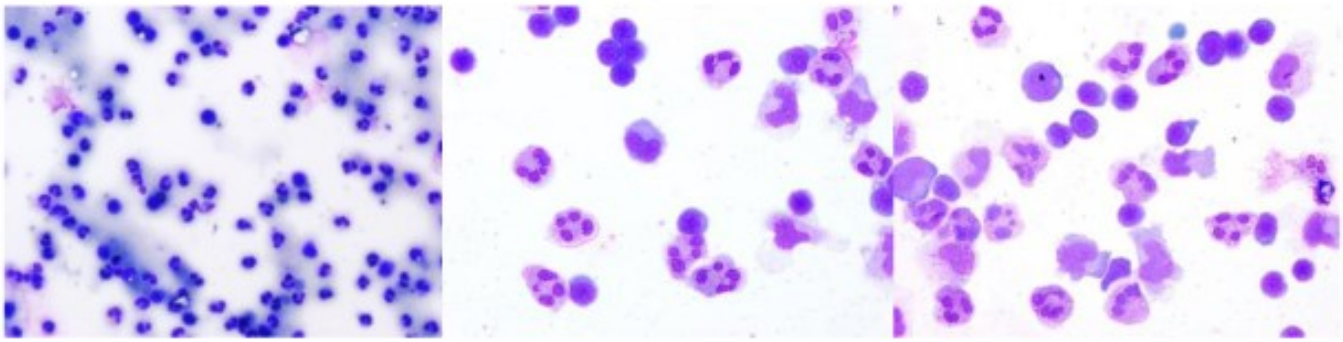
Encephalitis with normal CSF cell count

There are a few reports on a serologically confirmed TBEV infection in TBE but without CSF pleocytosis.[81,82] This observation disagrees with the large series of serologically proven TBE patients in which CSF pleocytosis was found in all cases.[13,39,53] However, the latter findings might result from a selection bias because CSF pleocytosis was one of the essential inclusion criteria for the diagnosis of TBE.

3. Chronic progressive tick-borne encephalitis

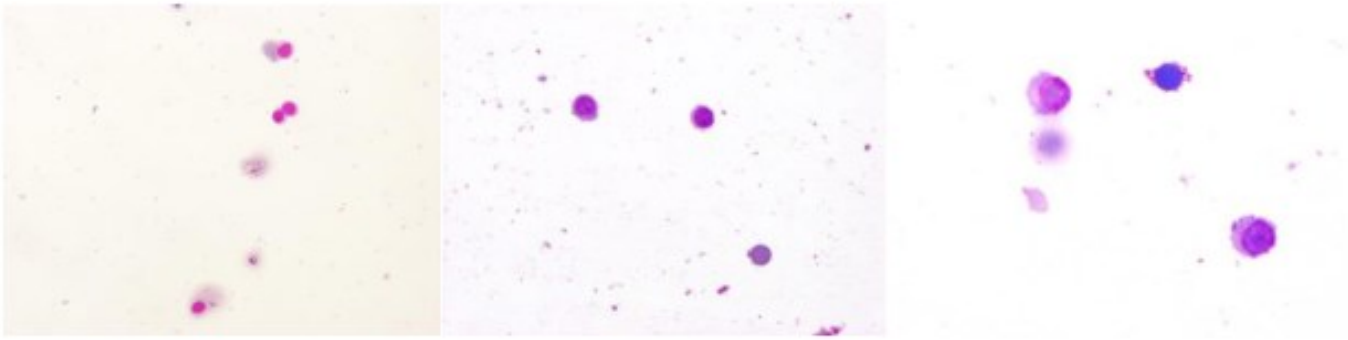
There is no agreement on the existence of chronic TBE. Cases of a chronic progressive form of TBE were reported from Siberia and the Russian Far East, caused by the Siberian TBEV subtype. Both mutations in the TBEV NS1 gene and an inappropriate T-cell immune response are implicated in chronic progressive disease.[70] According to information from Western Siberia, 1.7% of patients with acute TBE develop a chronic progressive form of the disease.[83] Clinical presentations include Kozshevnikov's

Figure 3: Evaluating pleocytosis in TBE (early)



Lymphocyte populations in CSF during acute TBE: The pleocytosis is dominated by mononuclear cells (lymphocytes and monocytes). Polymorphonuclear cells may predominate at an very early stage. (1 x 100; 1 x 400; 1 x 400.)

Figure 4: Evaluating pleocytosis in TBE (later)



During recovery, after acute phase, control LP. x 100, single lymphocytes, some monocytes, lack of granulocytes x 200 x 400.

epilepsy, lateral sclerosis, progressive neuritis, progressive muscle atrophy, and a Parkinson-like disease. A broad spectrum of incubation periods, time to the onset of individual neurological signs/symptoms, and survival after the onset of the disease have been reported.[84,85] Progressive TBE is probably not present or uncommon in diseases caused by European TBEV subtype. In the study carried out in Lithuania, where only European TBEV subtype has been recorded, the progressive course was noted in two out of 133 consecutive patients with acute TBE.[53,86]

TBE in particular situations (in immunocompromised persons, during pregnancy, in persons vaccinated against the disease) is presented in another chapter(s).

Laboratory findings

CSF pleocytosis

CSF pleocytosis is a dominant laboratory finding in patients with TBE. In 2 large studies, encompassing 731 and 717 adult patients with TBE, respectively, the median leukocyte values were 60 × 10^6/L and 86 × 10^6/L, with a maximal count of 1200 ×10^6/L.[13,87] Some studies indicate that CSF leukocyte count is lower in persons with TBE who are older than 60 years than in younger adults.[68] Lymphocytic predominance in CSF is typical for TBE; however, granulocytes may prevail during the first few days (Figures 3 and 4). Most patients have mild to moderately elevated protein and albumin concentrations in CSF and elevated albumin and IgG indexes, indicating disruption of blood-brain barrier.[13,68,70,88]

Peripheral blood

Laboratory abnormalities in the blood are more pronounced in the initial phase of TBE (and in the abortive form of the disease) than in the meningoencephalitic phase. In the first phase of TBE, the number of leucocytes in the peripheral blood is frequently reduced, while in the second phase, it is normal or slightly elevated. Furthermore, the initial phase is characterized by thrombocytopenia and elevated liver enzymes, while the second phase is not; moreover, inflammatory markers are usually within normal limits in the first phase of the disease but may be slightly elevated in some patients in the second phase.[38,39,52,70,89,90] The differences are best shown by comparing the results in patients assessed for laboratory abnormalities in the first

Table 1: Comparison of laboratory findings in patients with the initial and the second (meningoencephalitic) phase of tick-borne encephalitis[89]

Parameter	Initial phase*	Second phase**	*P* value
Leukocytes (× 10^9/L)	2.30 (1.20)	9.30 (3.80)	<0.001
<4 × 10^9/L	76/86 (88.4, 79.7–94.3)	0/87 (0, 0–4.2)	<0.001
Neutrophils (× 10^9/L)	1.17 (0.81)	7.00 (3.09)	<0.001
<1.5 × 10^9/L	49/74 (66.2, 54.3–76.8)	0/86 (0, 0–4.2)	<0.001
Lymphocytes (× 10^9/L)	0.80 (0.50)	1.50 (0.80)	<0.001
<1.1 × 10^9/L	56/74 (75.7, 64.3–84.9)	0/85 (0, 0–4.3)	<0.001
Monocytes (× 10^9/L)	0.28 (0.20)	0.70 (0.40)	<0.001
<0.21 × 10^9/L	32/74 (43.2, 31.8–55.3)	1/85 (1.2, 0–6.4)	<0.001
Thrombocytes (× 10^9/L)	132 (49.0)	249 (108)	<0.001
<150 × 10^9/L	55/86 (64.0, 52.9–74.0)	5/87 (5.7, 1.9–5.9)	<0.001
CRP (mg/L)	5.00 (2.00)	5.00 (4.00)	0.006
≥5 mg/L	13/86 (15.1, 8.3–24.5)	28/86 (32.6, 22.8–43.5)	0.012
AST (µkat/L)	0.60 (0.36)	0.33 (0.14)	<0.001
≥0.53 µkat/L	42/70 (0.60, 47.6–71.5)	13/73 (17.8, 9.8–28.5)	<0.001
AST (µkat/L)	0.52 (0.39)	0.48 (0.34)	0.583
≥0.58 µkat/L	28/70 (0.40, 28.5–52.4)	25/73 (34.2, 23.5–46.3)	0.590
GGT (µkat/L)	0.36 (0.30)	0.57 (0.52)	<0.001
≥0.64 µkat/L	16/69 (23.2, 13.9–34.9)	31/73 (42.5, 31.0–54.6)	0.024

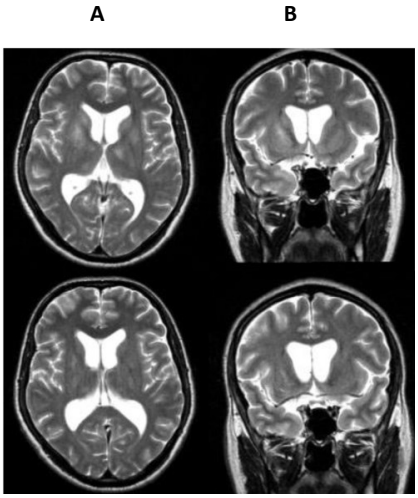
Data are given as median (interquartile range) or proportion (%, 95% confidence interval). CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase. * Median duration of illness 5 days, range 1–10 days; ** Median duration of meningoencephalitic phase of illness 2 days, range 1–10. Median symptom free interval 8 days.

and second phases of the disease. An example of such an approach is an analysis of 88 patients with biphasic course of TBE, in whom TBEV RNA in blood was established during the initial phase of illness and who later developed CNS inflammation and seroconversion. Comparison of laboratory findings in the initial and the second (meningoencephalitic) phase of TBE in this study revealed significant differences in peripheral blood leukocyte counts (including neutrophil, lymphocyte, and monocyte counts) and platelet counts, as well as serum concentrations of C-reactive protein, aspartate aminotransferase, and gamma-glutamyl transferase but not for alanine aminotransferase (Table 1).[89] A recent study exposed that in addition to previously known leukopenia, thrombocytopenia, and increased liver enzymes, the initial phase of TBE is relatively often associated also with elevated muscle enzyme activities: 33% of patients had elevated serum creatine kinase, 26% myoglobin and 22% troponin activity; at least one of the muscle enzymes was elevated in 42% of patients. Leukopenia, thrombocytopenia, elevated liver enzymes, and elevations of creatine kinase and myoglobin were present in the initial phase but resolved later, while mild troponin abnormalities were also found in the second phase of TBE.[91]

Neuroimaging

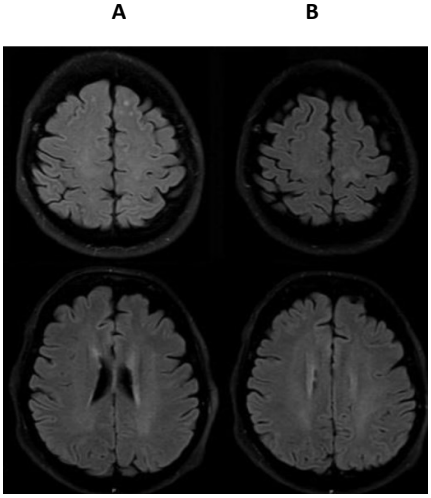
Neuroimaging enables rapid, non-invasive visualization of the central and peripheral nervous system. In clinical practice, neuroimaging is indispensable to corroborate clinical suspicion of nervous system inflammation, rule out mimics, provide hints for the causative pathogen, and assess for complications. Magnetic resonance imaging (MRI), with its excellent soft tissue contrast, is superior to

Figure 5: MRI visualization of TBE-related abnormalities



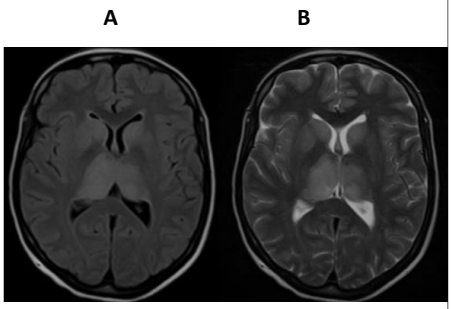
Axial (A) and coronal (B) T2-weighted MRI images show high signal intensity in the basal ganglia and thalami. The second scans (C, D) obtained several months later, show partial resolution of the lesions. Patient with chorea presentation.

Figure 6: Further visualization of TBE-related abnormalities



Axial FLAIR images. There is abnormal signal intensity in the left frontal (A) and left parietal lobe (B) and confluent, poorly visible abnormal bilateral hyperintensity in the periventricular white matter (C) and in the centrum semiovale (D). Parkinsonism as residual sequelae.

Figure 7: Additional visualization of TBE-related abnormalities



Axial fluid-attenuated inversion recovery (FLAIR) image (A) and T2-weighted MR image (B) show bilateral hyperintensity of the caudate nuclei, putamina and thalamus. The right side is slightly more involved than the left side. Patient with immunosuppression.

computed tomography (CT). CT is used for exploratory examination of the brain on admission, in case of rapid clinical deterioration, and before lumbar puncture.

The nervous system manifestations of TBEV infection include meningitis, encephalitis, myelitis, and radiculitis.[4] Most changes in neuroimaging of viral encephalitis are unspecific. They can be observed with several other pathogens and neurological disorders.[92] some radiological features are shared across infectious, immune-mediated, and non-inflammatory causes of nervous system disorders.[93] Moreover, radiological signs may be absent despite clinical signs and symptoms of meningeal, parenchymal, spinal cord, or peripheral nervous system dysfunction. Studies on the correlation of clinical severity with imaging findings are not available in TBE.

Meningitis

Clinical features of meningitis encompass the classic triad of fever, nuchal rigidity, and nausea/vomiting. Meningitis primarily involves the leptomeninges, which consist of the inner arachnoid and the pial meningeal layers. Unenhanced CT can display mild dilatation of the ventricles with effaced subarachnoid spaces, suggesting diffuse cerebral swelling.[94] MRI is more sensitive for detecting radiological features of meningitis than CT.[95] T1-weighted MR imaging may show obliteration of the basilar cisterns. Fluid-attenuated inversion recovery (FLAIR) sequences may demonstrate hyperintensity in the subarachnoid space, even when T1-weighted images appear normal. Postcontrast T1-weighted images may show linear continuous sulcal or cisternal enhancement, with predilection at the basal meninges and cerebellar folia.[96] Enhanced and thickened cranial nerves may also be observed.[97]

Encephalitis

Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction. MRI is essential in diagnosing encephalitis, evaluating the disease course and complications, and prognosis.[98] Encephalitic lesions of TBE are present as areas of increased signal intensity on T2/FLAIR-imaging (Figures 5, 6 and 7), which may also enhance upon administration of contrast agents.[99,100] In TBE, the enhancement is mainly restricted to the lesion margins.[96]

The sensitivity of MRI to detect brain lesions despite clinical symptoms of encephalitis due to TBEV infection is low. In a Swiss study of patients with encephalitis or meningoencephalitis by TBE and MR imaging performed after a median of 10 days, 27% had lesions on FLAIR and 6% diffusion restrictions.[100] Leptomeningeal enhancement was

detected in 44% and brain hemorrhage in 5%. Even with repeated scans, the yield for detecting parenchymal damage in patients with an encephalitic syndrome was 46%, according to an Austrian study.[18] The time point of imaging could play a significant role in this regard. Brain lesions were detected in two patients on day 21 from hospital admission in the latter study, whereas these were not present on the scans on days 5 and 8, respectively. Contrast enhancement is found only in the minority of patients.[18]

The predilection sites of brain lesions in TBE on FLAIR were the thalamus (50%) and the pontine area (29%) in the Swiss study.[100] Thalamic lesions can be uni- or bilateral. Lesions were less frequent in the limbic regions (amygdala and hippocampus, each 21%), the mesencephalon, and the cerebellum (each 21%). In the Austrian study, the predilection sites were the periaqueductal grey (17%), the thalamus, and the brainstem (each 12%).[18] Among the patients in whom a brain lesion was detected, the median number of lesions was 2. In a pilot study of patients with an encephalitic TBE course, glucose hypometabolism was present in 7 out of 10 TBE patients at sites prone to lesion development.[101] Glucose hypometabolism reflects neuronal dysfunction and did not correlate with MRI brain lesions due to TBEV. In line, MR spectroscopy of TBE lesions during the acute phase of the disease shows changes indicative of necrosis. The presence of brain lesions on MRI and lesion expansion may determine prognosis.[18,100] The persistence of lesions over time has not been studied systematically so far. There is anecdotal evidence of a complete resolution of cerebral, brainstem, and spinal cord lesions within six months.[102] A Polish study of patients with encephalitic lesions during acute TBE studied structural brain changes 12 months later.[103] On follow-up, there was marked brain atrophy with a widening of the anterior horns and lateral ventricles, indicating grey and white matter loss.

Myelitis and radiculitis

Myelitis and radiculitis with TBEV infection can occur isolated or in combination. Spinal cord and nerve root MRI findings were studied only in smaller patient series and case reports. TBEV has a propensity for the anterior horn cells of the grey matter in the spinal cord.[96] These lesions are commonly longitudinally extensive, defined as an expansion over three or more vertebral segments, and can expand to the brainstem.[104] Both uni- and bilateral lesions of the grey matter have been reported and are associated with a Polio-like syndrome characterized by acute flaccid paresis.[105,106] There can be a swelling of the grey matter and lesional and leptomeningeal contrast enhancement.[104] Spinal cord lesions often enhance markedly.[96] Rarely, the posterior horns may also be involved.[96] In radiculitis, the roots of the spinal nerves may be thickened and display contrast enhancement.[77,107]

Electroencephalography (EEG)

For viral encephalitis, electroencephalography (EEG) is a valuable adjunct to clinical neurological examination. It can detect subtle or subclinical disturbances of cerebral function and enables the detection and monitoring of seizure activity over time.[108] In most cases, the EEG findings are non-specific and denote global compromise of the brain function but may also provide information about prognosis and therapeutic response. Abnormal EEG findings were reported in 77% of patients with TBE.[69] In most cases, an initially abnormal EEG normalizes within a few weeks. However, a small study of children with TBE reported a higher likelihood of impaired attention and psychomotor speed and that the EEGs were significantly slower on follow-up than control EEGs.[109]

Epileptic seizures can occur as the initial manifestation or during TBE.[71,110] Continuous EEG monitoring for at least 48 hours is recommended in patients with persistent unconsciousness to evaluate intermittent non-convulsive seizures or even persistent non-convulsive status epilepticus.[39] The 10-year risk of epilepsy after TBE is 1.7% (95% CI 0.7-2.7).[111]

Prognosis and long-term sequelae

The analysis of the standardized mortality ratio (SMR) in Sweden from 2004–2017 revealed a mortality rate for TBE infection to be ≈4-fold higher than that of the matched control population.[112] The SMR was 3.96 (95% CI 2.55–5.90). The case fatality rate (CFR) was 0.75% in this study, and in the range of previously reported rates of 0.5% in Europe.[113] No cases in patients <40 years of age were fatal. CFR for diseases caused by the two non-European TBEV subtypes is generally higher, but the data are very limited. In lethal cases, death occurs within 5–10 days after the onset of neurological symptoms in the context of diffuse brain edema or bulbar involvement.

TBE is associated with individual and societal disease burden. The need for hospital care is increased, with protracted in-hospital stays and admission to the intensive care unit during acute TBE.[39] Moreover, the study of the Swedish National Health Data Register for TBE cases diagnosed during 1998-2014 revealed that patients with TBE were hospitalized for more days during the first year after disease onset (11.5 vs. 1.1 days) and had more specialist outpatient visits (3.6 vs. 1.2 visits).[114] They also had more sick leave days (66 vs. 10.7 days) than a reference cohort without TBE, indicating significant productivity losses.

The high proportion of patients with persistent post-TBE symptoms is another strong argument for preventive strategies. Sequelae can be categorized as neurological

Table 2: Overview of main sequelae and affected domains in TBE, adapted from[5]

Neurologic	Cognitive	Neuropsychiatric
Dizziness, paresis, tremor, hearing loss, shoulder girdle paralysis, headache, coordination impairment	Memory disorders, decreased concentration, executive dysfunction, impaired learning abilities	Fatigue, depression, sleep disorder

(e.g., paresis, limb paresis, aphasia, ataxia, sensory impairment, epilepsy, tremor, hearing disorder), neuropsychiatric symptoms (e.g., concentration and memory deficits), and general/unspecific (fatigue, headache, general weakness, poor sleep quality, sweating disturbances), as summarised in Table 2. Previous prospective studies disclosed that neurological and neuropsychological sequelae persist in 40–46% of the patients one year after the acute phase of the disease.[53,60] A study from Slovenia reported that the rate of persistent symptoms was higher at six months than at 12 months, which points to some improvement and regenerative capacity within the first year after TBE.[115] Recent studies corroborate the rate of incomplete recovery beyond 12 months. A study from Southern Germany performed telephone interviews after 18 months from TBEV infection; the period was 2018 to 2020.[14] Full recovery was reported by 67.3% (children: 94.9%, adults: 63.8%). Sequelae included fatigue (17.0%), weakness (13.4%), concentration deficit (13.0%), and impaired balance (12.0%). The recovery rate was 64% lower after severe TBE (compared to mild; HR: 0.36, 95%CI 0.25-0.52) and 22% lower with comorbidities (HR: 0.78, 95%CI 0.62-0.99). Substantial healthcare use was reported (90.1% hospitalization, 39.8% rehabilitation). A study from Lithuania evaluated long-term neurological and neurocognitive sequelae after TBE in adults.[116] This prospective study from 2018-2019 revealed that 25.5% of the patients had moderate or major impairment (Glasgow Outcome Scale, GOS) and various levels of disability in 34.7% (Rankin-Scale, RS) at discharge. Up to 18 months from the onset of TBE, over 20% remained with slight to moderate disability (modified RS, mRS). GOS, RS, and mRS scores correlated with disease severity.

There is also evidence for the development of post-encephalitic syndrome (PES). Some authors define PES as the presence of ≥ 2 subjective symptoms that developed or worsened since the onset of TBE and had no other known medical explanation and/or ≥ 1 objective neurological sign.[115]

The reporting of sequelae is affected by a lack of standardized reporting. Consensus criteria for classifying sequelae of TBE and its severity are eagerly awaited. Such a reporting system should include neurological and neuropsychological examinations for the evaluation of cerebral symptoms as well as a scoring system for spinal cord and peripheral nervous system disturbances. A harmonized classification system would also be helpful for a better understanding and monitoring of PES.

Treatment

No specific antiviral therapy is currently available and approved for TBEV infections. Some antiviral agents, specific immunoglobulins, and other potentially protective substances are under investigation for their anti-TBEV efficacy[117]; however, a detailed review of these 'pipeline' agents is beyond the scope of this chapter.

Treatment is supportive and symptomatic. Fever is associated with increased metabolic consumption and dehydratation. Antipyretics, or other physical measures like cooling blankets, or infusion of cooled fluids, should be employed to reduce body temperature. TBE can be accompanied by hypovolemia due to a decreased intake and a secondary loss of fluids. Hyponatremia is a common condition in patients with TBE, including the syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral saltwasting syndrome, and reduced sodium supplementation.[118] Mental and behavioral disturbances, delirium, and psychotic signs and symptoms may justify treatment with neuroleptics. In line with other types of brain injury, primary prophylaxis of seizures is currently not recommended, and treatment of clinical seizures is based on general guidelines for the management of seizures/ status epilepticus. Pain and arousal cause intracranial pressure peaks by increasing the cerebral blood flow; therefore, sedatives and careful clinical monitoring are key factors in the prevention of intracranial hypertension and its complications.

Encephalitis often requires ICU admission to ensure oxygenation, airway protection, circulatory support, and prevention and treatment of secondary complications that may impact outcomes. These include cerebral edema, seizures/status epilepticus, and systemic complications, such as fever, aspiration pneumonia, and respiratory failure requiring mechanical ventilation is also needed in patients with severe respiratory muscle paresis, in some cases lifelong..[119] Early recognition of complications and admission to the ICU is crucial for improving prognosis.

Most survivors do not recover fully and often require extended posthospitalization rehabilitation and care to regain their functional abilities.[5] A comprehensive assessment of neurological, cognitive, and psychiatric functions after hospital discharge is mandatory. Moreover, referral to rehabilitation services and psychiatric support, as with other neurological disorders, is indicated to improve the quality of life of both the patient and their caregivers.

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