Tickborne Encephalitis in an Area of High Endemicity in Lithuania: Disease Severity and Long-Term Prognosis

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Of 250 consecutively admitted patients with central nervous system (CNS) infections who were treated during a 1-year period, all 133 patients with tickborne encephalitis (TBE) were included in a prospective follow-up study. TBE presented as mild (meningeal) in 43.6% of patients and as moderate or severe (encephalitic) in 43.6% and 12.8% of patients, respectively. Paralytic disease was observed in 3.8% of the subjects, and cranial nerve injury was observed in 5.3%. One patient died of TBE. Permanent CNS dysfunction after 1 year was found in 30.8% of patients; in 8.5% of all TBE cases, severe disabilities required adjustment of daily activities. Corticosteroid treatment did not seem to improve outcome. A progressive course of TBE was noted in 2 patients. The risk of incomplete recovery was significantly higher among patients with the encephalitic form of TBE (odds ratio, 4.066; 95% confidence interval, 1.848–8.947). In conclusion, TBE is an important pathogen in CNS infection in the Kaunas region of Lithuania, and it causes long-lasting morbidity in one-third of cases.

Tickborne encephalitis (TBE) virus is a complex of closely related viruses within the Flaviviridae family. Like St. Louis encephalitis virus, West Nile virus, and Japanese encephalitis virus, TBE virus is one of the major neurotropic flaviviruses. TBE virus is endemic in many parts of Europe and Asia, and it is transmitted by Ixodes ricinus and Ixodes persulcatus ticks [1, 2]. Occasionally, milkborne TBE virus infections have been observed [2, 3].

The clinical picture of TBE has previously been described from different geographic regions in Europe and Asia [1, 4]. TBE in Europe is considered to be a milder disease than TBE in the Far East, where even relapsing and chronic courses of infection have been reported [5, 6]. It is not clear whether these findings are true differences in the clinical presentation or a result of patient selection in studies.

Since 1993, a dramatic increase in the number of TBE cases has been observed in Lithuania, with a peak of 645 cases in 1997 (17.4 cases per 100,000 population) [7]. This increase may be partially explained by improved diagnostic methods, but a genuine increase in the number of cases was also reported in most areas of endemicity during the 1990s [8].

In Lithuania, I. ricinus is the only vector of TBE virus, and virus can be isolated from ticks in all districts of Lithuania. An increase in tick abundance has been observed annually since 1993, with the highest numbers being found in central parts of Lithuania [7]. Recently, the first molecular characterization of TBE virus from Lithuania was reported [9]. No recent data on seroprevalence in Lithuania are available.
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PATIENTS AND METHODS

Patients. The study was approved by the local ethics committee, and appropriate informed consent was obtained from all participating patients. After providing informed consent, 250 patients (144 male and 106 female patients; age, ≥16 years) who were consecutively admitted to the Clinic of Infectious Diseases at Kaunas University Hospital (Lithuania) from June 1998 through May 1999 were enrolled in the study. All patients had clinical signs of neuroinfection and pleocytosis (≥8 × 10⁶ cells/L) in CSF. Sixteen patients declined to participate (6 patients with TBE, 6 with aseptic meningitis other than TBE, and 4 with bacterial meningitis).

CSF and serum specimens were obtained on 2 occasions, which were a median of 1 day (range, 0–11 days; 120 patients) and 8 days (range, 3–18 days; 91 patients) after enrollment. Additional serum samples were obtained a median of 12 weeks (range, 4–33 weeks) and 16 months (range, 10–23 months) after enrollment. At least 1 CSF sample and ≥1 serum sample were obtained from each patient. For 13 patients with TBE, spinal tap was performed before admission to the Clinic of Infectious Diseases at Kaunas University Hospital and was not repeated. Samples were stored at −25°C.

Clinical examination was performed at enrollment and on day 7–10, at week 12, and at month 16 of the study by 1 of 3 investigators. After instruction by one of the investigators, 1 year after the onset of TBE, all patients with TBE answered a neuropsychiatric questionnaire [10] that was designed for evaluation of organic brain disease (median, 16 months; range, 10–23 months). The questionnaire had 33 “yes” or “no” questions for which an affirmative answer always indicated presence of a symptom. The subjects of the questions were classified into 4 groups: (1) intellectual disorders, (2) personality changes, (3) disorders in the control of balance and movement, and (4) other specified symptoms, such as headache and sensory disturbances. Healthy individuals who had been vaccinated for TBE and hepatitis B completed the same questionnaire and served as control subjects (94 adults; 51 male and 43 female subjects; mean age, 41.2 years; age range, 20–77 years).

Microbiological diagnosis. TBE was diagnosed by the demonstration of specific IgM activity (by use of 2-step ELISA IgM, Immunozym Frühsommermeningoenzephalitis IgM, Immuno AG; Heidelberg, Germany) in serum samples [11]. For patients who had recently received TBE vaccine, CNS infection was diagnosed by demonstration of intrathecally produced TBE IgM antibodies [12]. For demonstration of IgM and IgG antibodies against Lyme borreliosis in serum and CSF specimens, a capture ELISA (DAKO) was used for 2 cases of TBE with progressive disease. The diagnosis of bacterial meningitis was made on the basis of CSF findings compatible with bacterial meningitis, the results of CSF culture for bacteria, or positive results of CSF latex antigen tests for Neisseria meningitidis, Streptococcus pneumoniae, or Haemophilus influenzae B.

No further attempts were made to establish specific etiological diagnosis in the remaining patients. Patients without a verified TBE diagnosis who did not have bacterial meningitis were classified as having non-TBE aseptic meningoencephalitis.

Clinical classification. The clinical presentation of meningoencephalitis at admission was classified as “mild,” “moderate,” or “severe.” Mild disease was defined as disease with predominantly meningeal symptoms, including fever, headache, rigidity of the neck, and nausea. Moderate disease was defined as disease with monofocal symptoms of the CNS and/or moderate diffuse brain dysfunction. Severe disease was defined as disease with multifocal symptoms of the CNS and/or severe diffuse brain dysfunction. Encephalitic symptoms were defined as altered consciousness, ataxia, dysphasia, tremor, seizures, and mono- or multifocal symptoms. All patients with signs of encephalitis at admission were classified as having moderate or severe disease.

Sequelae were classified as “mild,” “moderate,” or “severe,” depending on their influence on the patient’s quality of life [13]. Minor complaints—that is, those without any real impact on quality of life—were considered to be mild sequelae. Moderate sequelae were defined as residual symptoms or signs that affected quality of life but that did not require adjustments of daily activities. Severe sequelae were defined as symptoms or signs that led to an inability to continue previous activities or that required adjustments of daily activities.

Statistical methods. Independent samples were analyzed using the Mann-Whitney U test, the Kruskal-Wallis test, and the Student’s t test. Proportions were compared using χ² or Fisher’s exact tests. Spearman’s rank correlation test was used to calculate correlations. Outcomes at 12 weeks and 1 year after onset of disease were examined using a logistic regression model. P < .05 was considered to be statistically significant.

RESULTS

Demographic and epidemiological data. Of a total of 250 patients, 133 (53.2%) had TBE diagnosed, 99 (39.6%) had non-
TBE aseptic meningoen cephalitis diagnosed, and 18 (7.2%) had bacterial meningitis diagnosed. The first TBE case was admitted on 7 May and the last on 9 November; 65.4% of cases were diagnosed in August and September. Of 250 consecutive patients with CNS infection, 211 patients (84.4%; 202 with aseptic meningoen cephalitis and 9 with bacterial meningitis) were admitted to the hospital during the TBE season. Demographic and epidemiological data are shown in table 1. Sixty-two (46.6%) of the 133 patients with TBE were 36–55 years of age. The patients were divided into those with mild, moderate, or severe forms of TBE (table 1) according to clinical symptoms and signs (table 2, figure 1). Disturbances of consciousness were observed in 26 (27.7%) of the 94 patients, and gastrointestinal complaints were recorded for 20 (21.3%). Double infections with TBE virus and clinical signs of borrelia infection (as an early, localized form of erythema migrans) were seen in 2 (1.5%) of 133 patients with TBE. Another 2 patients reported having erythema migrans 2–3 months before the onset of TBE.

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Table 2. Neurological symptoms in patients with tickborne encephalitis (TBE) during the acute stage, 12 weeks after onset, and 1 year after onset.

<table>
<thead>
<tr>
<th>Neurological symptom</th>
<th>Acute stage of TBE (n = 133)</th>
<th>12 Weeks after onset (n = 120)</th>
<th>1 Year after onset (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>35 (26.3)</td>
<td>6 (5)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>5 (3.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>127 (95.5)</td>
<td>38 (31.7)</td>
<td>24 (20.5)</td>
</tr>
<tr>
<td>Tremor</td>
<td>29 (21.8)</td>
<td>18 (15)</td>
<td>10 (8.5)</td>
</tr>
<tr>
<td>Emotional instability</td>
<td>20 (15)</td>
<td>28 (23.3)</td>
<td>22 (18.8)</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>15 (11.3)</td>
<td>24 (20)</td>
<td>18 (15.4)</td>
</tr>
<tr>
<td>Decreased memory</td>
<td>13 (9.8)</td>
<td>25 (20.8)</td>
<td>23 (19.7)</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>25 (18.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>3 (2.6)</td>
<td>4 (3.3)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Cranial nerve paralysis</td>
<td>7 (5.3)</td>
<td>1 (0.8)</td>
<td>—</td>
</tr>
<tr>
<td>Spinal nerve paralysis</td>
<td>5 (3.8)</td>
<td>4 (3.3)</td>
<td>3 (2.6)</td>
</tr>
</tbody>
</table>

On physical examination, persistent neurological deficits were found in all 10 patients with severe sequelae after 1 year, and intensive postencephalitic complaints were noted by 8 patients. Of the 8 patients with paresis of the extremities, including patients with hemiparesis, after 1 year the muscular weakness and atrophy persisted in all but 2 patients, who had only slight or no improvement. Mental disorders progressed to dementia in 1 patient who initially had the severe form of disease.

In 2 patients, a progressive form of disease was found. A 37-year-old woman with moderate disease and paraparesis of the lower extremities during the acute stage developed mild right-side hemihyperaesthesia and hemiparesis within 3 months after the onset of TBE. Her cognitive disability also progressed to severe apathy. A 44-year-old man presented with diplopia due to injury of the brain stem 13 months after the onset of TBE. He was moderately ill in the acute stage, and he had only minor complaints of cognitive dysfunction at a follow-up visit. Internuclear ophtalmoplegia as well as right-side hemiplegia gradually developed. MRI revealed widespread gray- and white-matter lesions. Marked improvement was observed after treatment with high-dose methylprednisolone and plasma exchange. Intrathecal antibody production against Lyme borreliosis could not be demonstrated in either of these 2 cases.

Figure 1. Outcome at 1 year after onset of tickborne encephalitis (TBE), according to clinical classification during the acute stage of disease. See Patients and Methods for definitions of clinical classifications.
The overall morbidity at 1 year after onset of TBE in relation to the initial clinical presentation is presented in figure 1. We found a correlation between the form of disease during the acute stage and outcome at both 12 weeks ($r = 0.412; P < .001$) and 1 year ($r = 0.358; P < .001$) after onset of TBE.

The risk of incomplete recovery at 12 weeks after onset was significantly higher for patients with moderate or severe TBE (OR, 4.046; 95% CI, 1.745–9.384; $P < .0001$). Age did not correlate to the outcome at either 12 weeks or 1 year after the onset of TBE. Female patients had a higher risk of incomplete recovery at 12 weeks (OR, 2.513; 95% CI, 1.045–6.044; $P = .04$) but not at 1 year after onset. At 1 year after onset, the risk of incomplete recovery was significantly higher for patients who had moderate or severe TBE (OR, 4.066; 95% CI, 1.848–8.947; $P < .001$).

**Corticosteroid treatment and outcome of TBE.** Corticosteroids were used for 81 (60.9%) of the 133 patients with TBE. Hospitalization was significantly prolonged among these patients, compared with patients who received only treatment for symptoms (mean duration of hospitalization, 15.9 days and 13.1 days, respectively; $P < .001$). Of the patients who presented with mild, moderate, and severe disease, 39.7%, 70.7%, and 100% received corticosteroids, respectively; the differences between the groups were significant ($P = .0007$, $P < .001$, and $P = .0006$, respectively). No significant differences in age, sex, or dosage or duration of treatment were found between those...
treated with corticosteroids and those who were not nor between patients with complete versus incomplete recovery.

The risk of incomplete recovery at 12 weeks after onset was significantly higher for patients with moderate TBE (OR, 2.932; 95% CI, 1.239–6.940; P < .05) and if corticosteroids were used (OR, 2.704; 95% CI, 1.146–6.380; P < .05; figure 4). The use of corticosteroids was not an independent predictor of incomplete recovery at 1 year after onset (P = .70).

Neuropsychiatric questionnaire. Answers to the neuropsychiatric questionnaire were divided into 3 groups: patients with complete recovery after TBE (n = 45), patients with sequelae after TBE (n = 47), and healthy control subjects (n = 94). The mean ages of persons who did not recover (44.7 years), those who did recover (46.1 years), and the control subjects (41.2 years) did not differ significantly (P = .127). The results of the questionnaire are shown in figure 5. The proportion of positive answers in the group of patients with sequelae was significantly higher than was the proportion for control subjects for all questions but question number 6 (P = .167). The highest proportions of positive answers for

![Figure 3](image-url)

**Figure 3.** Cumulative follow-up results for 133 patients with tickborne encephalitis (TBE) at discharge from the hospital, 12 weeks after onset of TBE, and 1 year after onset of TBE. *Patients who reported recovery and who were thereafter lost to follow-up 12 weeks (n = 9) or 1 year (n = 1) after onset of TBE were considered to have had recovery and are therefore included in the calculations.

![Figure 4](image-url)

**Figure 4.** Probability of incomplete versus complete recovery at 12 weeks after onset of tickborne encephalitis (TBE), as a function of the form of TBE and the use of corticosteroids.
incompletely recovered patients were found for questions concerning personality changes and headache (numbers 14, 28, and 31).

Differences in the answers of the neuropsychiatric questionnaire reached statistical significance for 32 of 33 questions, when answers by completely recovered individuals are compared with those by incompletely recovered individuals ($P < .01$ for 31 questions and $P < .05$ for 1 question). For 4 questions, the group of recovered patients had a higher proportion of positive answers than did the control group ($P = .009$ for question number 12, $P = .014$ for number 14, $P < .001$ for number 19, and $P = .045$ for number 26).

**DISCUSSION**

In this study, we have shown that TBE accounts for more than one-half of all CNS infections in the Kaunas district of Lithuania. For the majority of patients, the convalescence period was long, and permanent CNS dysfunction was found in one-third of patients. Severe disability that required adjustment of daily activities was observed in almost 10% of patients. The mortality rate was only 0.75%, which corresponds to the findings of previous European studies (0%–3.9%) [14–23]. Spinal nerve paresis during the acute stage of TBE was found in 3.8% of cases in our study. Earlier European studies have found paresis during the acute stage of TBE in 3%–23.5% of cases [14–23]. The proportion of patients with permanent paresis found in our study (2.6%) is in agreement with the results of other European studies (0%–9.8%) [14–23].

Despite the fact that areas where TBE is endemic are widely spread over many countries of Europe and Asia, information about the long-term morbidity associated with TBE is lacking. To our knowledge, this is the second prospective follow-up study of consecutive patients with TBE and the first study of its kind from Eastern Europe.

Our study included 133 (24.3%) of 548 cases of TBE registered in Lithuania in 1998 [8]. The sample size of this study and the fact that it included consecutively admitted patients.
enabled us to draw important conclusions about the morbidity associated with TBE in our region, where <1% of the population is believed to have been vaccinated against TBE (Center for Communicable Disease Prevention and Control of Lithuania, Vilnius).

A positive correlation between age and severity of illness was found. In a prospective study from Sweden, however, no such correlation was found [24], although our study confirms the findings of several retrospective studies [4, 22, 23]. In central Europe and Scandinavia, infection with TBE virus is mainly acquired during leisure time or after the occasional visit to the forest [23, 25]. In contrast to these findings, we have shown that retired and unemployed people are the major risk group for infection with TBE virus in Lithuania, which is in agreement with findings from other Baltic states [26]. Therefore, TBE in this region constitutes a socioeconomic problem, and, in view of the aggravated course of TBE in elderly persons, this epidemiological feature of TBE in Lithuania is important to consider when prophylactic measures are discussed.

Minor complaints that did not influence the quality of life (classified as “mild sequelae”) were observed 1 year after onset of TBE in 15.4% of patients. The similarities between our findings and those of previous consecutive studies on long-term morbidity are striking [23, 24]. More-pronounced sequelae associated with impaired quality of life were seen in 30.8% of subjects in our study. Cognitive CNS dysfunction was the dominant symptom in this group of patients. Retrospective studies of TBE provide information mainly on the persistence of paresis and other marked residual symptoms; the prevalence of neuropsychiatric complaints was probably underestimated in these studies. The complete spectrum of the symptoms of post-TBE syndrome is described in one prospective study [24]. In our study, we found that an almost identical type and number of patients presented with permanent sequelae.

We also found that bad outcome was closely related to the severity of illness in the acute stage, which has not been previously shown in either prospective or retrospective studies, probably because of the lower number of patients included in those studies. The previous observation that meningitis has a good prognosis and that it usually clears up without sequelae [1, 4, 27] was partially verified in our study. However, 19% of the patients who initially had a meningeal form of TBE still had some cognitive dysfunction that affected the quality of life after 1 year.

The use of corticosteroids is not standard therapy for TBE. However, administration of corticosteroids, which is done on the basis of the impression that their use produces a rapid clinical response, is common in Lithuania. It was extremely difficult to evaluate the role of corticosteroids in the outcome of TBE in our study, because corticosteroids were used for all patients with the severe form of TBE. To obtain conclusive evidence, controlled studies are needed. However, the data obtained in this study do not support the use of corticosteroids for patients who have mild or moderate TBE.

To control for postencephalitic complaints, a special questionnaire was used in this study. The same questionnaire has been used in previous studies of HIV and TBE [10, 25]. We found a significant difference between patients with incomplete recovery and control subjects, as well as between patients with incomplete recovery and those with complete recovery, but there were no differences found between patients who recovered and control subjects. Therefore, we are convinced that the postencephalitic symptoms were related to TBE.

A progressive course of TBE was found in 2 patients in our study. In both cases, the disease was moderate during the acute stage. According to our knowledge, chronic or progressive forms of TBE have not been observed outside the former Soviet Union [1, 4–6]. With 1 exception [28], TBE virus RNA has not been found in CSF specimens obtained from persons during the acute stage of TBE. TBE virus replication is probably inhibited in the CNS when protective antibodies appear. Although they are rare, these chronic progressive forms of TBE raise questions about the pathogenesis of severe forms of TBE [29, 30].

The severity of TBE has been reported to vary in different geographic regions, and, according to these reports, TBE is described as a milder disease in Europe than it is in the Far East [1, 4]. Whether the explanation for these differences lies in the existence of 2 subtypes of TBE virus (a European form, which is transmitted by I. ricinus, and a Far Eastern form, which is transmitted by I. persulcatus) remains to be shown [31, 32]. Differences in the clinical picture of TBE in some closely neighboring areas of various regions have been reported [4]. In a recent study from Croatia, marked differences in the severity of TBE between eastern and other parts of Croatia were found [33]. On the other hand, in European and Russian reports, there are differences in the diagnostic criteria used. Therefore, data obtained from different countries vary to such an extent that comparison of the results is often not possible. In view of the similarities between our study and the Swedish study, with regard to study design and patient classification, we have not found any data supporting a higher disease severity in Eastern Europe, compared with central Europe and Scandinavia.

In conclusion, TBE is the major cause of CNS infection in adults in Lithuania. TBE causes considerable morbidity with long-lasting sequelae. The situation concerning TBE in Lithuania closely resembles the situation in Austria before Austria began its mass vaccination campaign in 1982 [8, 34]. The high morbidity associated with TBE in Lithuania shown in this study...
supports active preventive measures against TBE in regions of this country where TBE is endemic.

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References