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Original article

The long-term outcome of tick-borne encephalitis in Central Europe

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ABSTRACT

Background: Information on the long-term outcome of tick-borne encephalitis (TBE) is limited.
Objectives: To assess the frequency and severity of post-encephalitic syndrome (PES) at different time points after TBE, and to determine the parameters associated with unfavourable outcome.
Methods: Adult patients diagnosed with TBE in Slovenia in the period 2007–2012 were followed-up for 12 months and also examined 2–7 years after TBE. Each patient was asked to refer a person of similar age without a history of TBE to serve as control.
Results: A total of 420 patients and 295 control persons participated in the study. The proportion of patients with PES (defined as the presence of ≥ 2 subjective symptoms that newly developed or worsened since the onset of TBE and which had no other known medical explanation, and/or ≥ 1 objective neurological sign) was higher ($P < 0.001$) at the follow-up visit 6 months after the acute illness (127/304, 42%, 95% CI: 36–47%) than at 12 months (68/207, 33%, 95% CI: 26–40%); the proportion at 12 months was the same as at 2–7 years after TBE (137/420, 33%, 95% CI: 28–37%). However, the proportion of severe PES at the last two time points differed (9.7% vs 4.3%, $P = 0.008$). Multivariate logistic regression showed that unfavourable outcome at 6 months was associated with CSF leukocyte count (OR = 1.003, 95% CI: 1.001–1.005%, $P = 0.017$), at 12 months with the disease outcome at 6 months (OR = 115.473, 95% CI: 26.009–512.667%, $P < 0.001$), and at the final visit with disease outcome at 6 months (OR = 3.808, 95% CI: 1.151–12.593%, $P = 0.028$) and 12 months (OR = 26.740, 95% CI: 8.648–82.680%, $P < 0.001$). Unspecific symptoms that occurred within the four weeks before the final examination were more frequent and more constant in patients than in the control group.
Conclusions: The frequency of PES diminished over time and stabilized 12 months after the acute illness, whereas the severity of PES continued to decline. Unfavourable outcomes at 12 months and at the final visit were strongly associated with the presence of PES at previous time points.

1. Introduction

Tick-borne encephalitis (TBE), which is endemic in many European countries and in central and eastern parts of Asia, is one of the most important vector-borne viral infection of the central nervous system and is responsible for more than 10,000 hospitalizations every year (Heinz et al., 2013). Because of the severe acute illness and a considerable proportion of patients with long-lasting sequelae, TBE represents a substantial medical burden with high costs for the healthcare system and society (Anonymous, 2011; Dobler et al., 2012; Süss, 2011).

TBE is caused by three subtypes of TBE virus: European, Siberian and Far-Eastern. Clinical presentation of the disease differs in some respects according to the virus subtype. In Europe, the clinical manifestations of the acute illness, presumably due to the European virus subtype, have been investigated in numerous studies and are well defined (Günther et al., 1997; Haglund and Günther, 2003; Jereb et al., 2002; Jereb et al., 2006; Kaiser, 1999; Kaiser, 2002; Lesnicar et al., 2003; Logar et al., 2000; Logar et al., 2006; Lotric-Furlan et al., 2002; Lotric-Furlan et al., 2008; Lotric-Furlan and Strle, 2012; Lotrič-Furlan et al., 2017; Mickiene et al., 2002; Wahlberg et al., 2006). In contrast, much less is known about the convalescent phase and the risk of contracting long-term or permanent sequelae.

A large part of Slovenia is endemic for TBE and notification of cases has been mandatory since 1977. The incidence in Slovenia is among the

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highest in Europe (Kraigher et al., 2016). Several studies on TBE epidemiology (Durmiši et al., 2011), aetiology (Fajs et al., 2012), clinical presentation (Jereb et al., 2002; Jereb et al., 2006; Lesnicar et al., 2003; Logar et al., 2000; Logar et al., 2006; Lotric-Furlan et al., 2002; Lotric-Furlan et al., 2008; Lotric-Furlan and Strle, 2012; Lotrič-Furlan et al., 2017) and diagnosis (Saksida et al., 2005) have been published, together with a study on the estimation of the annual burden of TBE in Slovenia (Fafangel et al., 2017). However, only two articles on the long-term morbidity are available, and these were reported 37 (Radšel-Medvešček et al., 1980) and 21 years ago (Tomažič et al., 1996).

The aims of the present study were to assess the frequency and severity of post-encephalitic syndrome (PES) at different time points after TBE, to determine the clinical and laboratory parameters associated with an unfavourable (long-term) outcome, and to evaluate the long-term morbidity in a questionnaire-based case-control study.

2. Patients and methods

The study was approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia (No. 152/06/13, No. 178/02/13, No. 37/12/13). Each study participant provided written informed consent.

2.1. Patients

Patients aged ≥ 18 years who were diagnosed with TBE at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia, between January 2007 and December 2012, qualified for enrolment in the study. TBE was defined as a febrile illness with symptoms and/or signs of meningitis or meningoencephalitis, cerebrospinal fluid (CSF) pleocytosis ($> 5 \times 10^6$ cells L^{-1}), and demonstration of acute TBE virus infection through the presence of serum IgM and IgG antibodies to the virus or demonstration of intrathecal production of specific IgM and/or IgG antibodies in patients previously vaccinated against TBE. Antibodies to the virus were assessed using the Enzygnost® Anti-TBE Virus (IgM, IgG) test (SiemensGmbH, Marburg, Germany) in accordance with the manufacturer's protocol. Intrathecal IgM and/or IgG TBE antibody production was measured as described by Reiber and Peter; values > 1.4 were considered to indicate local antibody synthesis (Reiber and Peter, 2001).

Prospectively acquired demographic, epidemiological, laboratory and clinical data were obtained for all patients, enabling detailed appraisal of the course and severity of the acute illness, and included daily evaluation of the presence and intensity of TBE signs and symptoms during the hospital stay. The outcome of TBE was assessed at follow-up visits 6 and 12 months after hospitalization. At each visit patients were asked (with open questions) about the presence of subjective symptoms; symptoms that newly developed or worsened since the onset of TBE and which had no other known medical explanation were regarded as new or increased symptoms (NOIS) and qualified as a criterion for PES symptoms. In clinical examination particular attention was paid to signs of neurological involvement (tremor, ataxia, cranial and spinal nerve paralysis, etc.).

To assess the longer term outcome of TBE, patients diagnosed with the disease in the period 2007–2012 were invited to a final follow-up visit in 2014, i.e. 2–7 years after TBE (1–6 years after the last regular follow-up visit). Those who responded to the invitation qualified for the study.

At the final visit, in addition to standard history and clinical examination, and after responding to the open question on NOIS, patients were asked to complete two questionnaires: 1) A form in which they were asked about the frequency of six nonspecific symptoms (fatigue, arthralgias and/or myalgias, headache, memory disturbances, concentration disorders, and irritability) within the preceding four weeks; and 2) A quality of life questionnaire to measure functional health and wellbeing –SF-36 Health Survey, version 2 [SF-36v2] (SF-36v2 Health Survey, 2017) and comprising 36 items to evaluate eight domains of health (physical functioning, social functioning, body pain, general health perceptions, vitality, role limitations due to emotional, and due to physical health problems, and mental health) clustering into two global overall components: physical and mental (Ware and Gandek, 1998). Scores range from 0 to 100, with higher scores representing better health-related quality of life; 50 is the mean score of the norm with a standard deviation of 10. The SF-36v2 data were analysed and scored according to the guidelines of Ware et al. (Ware, 1993; https://campaign.optum.com/optum-outcomes.html).

2.2. Control group

Each patient who attended the final visit in 2014 was asked to refer a spouse, another family member, or a friend of the same age ± 5 years, living in the same region, to serve as a control subject. The exclusion criteria were age under 18 years or a history of TBE.

Each control subject was evaluated at the time of the 2014 follow-up visit of the corresponding patient, within a 14-day time span. Basic demographic, epidemiological and clinical data were obtained using a structured questionnaire asking the same questions as for the patients on frequency of the six nonspecific symptoms within the preceding four weeks; some of the control group participants also completed the quality of life questionnaire (SF-36v2).

2.3. Categorization of severity of acute illness

Patients with TBE were categorized as having either i) meningitis when they had only symptoms/signs of meningeal inflammation (fever, headache, rigidity of the neck, nausea, vomiting); ii) meningoencephalitis when they had symptoms/signs indicating brain tissue damage (impaired consciousness, concentration and cognitive function disturbances, tongue fasciculations, tremor of extremities, focal or generalized seizures, etc.) in addition to the findings of meningitis; or iii) meningoencephalomyelitis when they also had clinical signs of alpha motor neuron injury (flaccid paresis). Patients were considered as having mild disease when they were diagnosed with meningitis, and severe disease when they had meningoencephalitis or meningoencephalomyelitis.

2.4. Assessment/Definition of outcome

Sequelae of TBE were defined as subjective symptoms (fatigue, headache, arthralgias and myalgias, memory and concentration disorders, emotional lability, sleep disorders, dizziness, etc.) fulfilling criteria for NOIS and as objective neurological signs (tremor, ataxia, cranial and spinal nerve pareses, etc.).

An unfavourable long-term clinical outcome (PES) was defined as the presence of ≥ 2 subjective symptoms fulfilling criteria for NOIS and/or ≥ 1 objective neurological sign at the 6-month follow-up or later.

According to the number and type of sequelae, PES severity was classified as: i) mild – the presence of 2 symptoms fulfilling criteria for NOIS; ii) moderate – the presence of ≥ 3 symptoms fulfilling criteria for NOIS, and iii) severe – the presence of ≥ 1 objective manifestation with or without subjective symptoms.

2.5. Statistical methods

Data were summarized as medians and interquartile ranges (IQRs) for numerical variables and as frequencies and percentages for categorical data; 95% confidence intervals (CIs) for percentages were based on exact binomial distributions. Univariate comparisons were based on the Mann–Whitney test for numerical variables and on Yates' corrected chi-square test for categorical data. The uniformity of distribution regarding the length of time from the disease onset to the final visit was