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Magnetic resonance imaging and clinical findings in adults with tick-borne encephalitis

Alexander Pichler [a,*], Johann Sellner [b], Gayane Harutyunyan [b], Astrid Sonnleitner [c], Daniela Sabine Klobassa [c], Juan-Jose Archelos-Garcia [a], Hannah Rock [a], Thomas Gattringer [a], Franz Fazekas [a]

[a] Department of Neurology, Medical University of Graz, Auenbruggerplatz 22, 8036 Graz, Austria
[b] Department of Neurology, Paracelsus Medical University of Salzburg, Ignaz-Harrer-Straße 79, 5020 Salzburg, Austria
[c] Department of Pediatrics and Adolescent Medicine, Medical University Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria

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ABSTRACT

Background: Magnetic resonance imaging (MRI) in tick-borne encephalitis (TBE) is often performed for differential diagnosis, but only a few reports on the morphologic changes in TBE patients and their relation to the disease severity exist.
Methods: We retrospectively searched for all TBE patients who were admitted to the Departments of Neurology of the Medical University of Graz (Austria) and the Paracelsus Medical University of Salzburg (Austria) between 2003 and 2014. We recorded the clinical and demographic variables and rated overall disease severity as mild, moderate, severe or leading to death due to TBE. MRI scans were screened for morphologic abnormalities.
Results: Of an initial cohort of 88 patients with TBE, 45 patients with an available MRI of the brain were included in this study (median age 58.0 years, range: 18–80; men n = 28). Their median time spent in the hospital was 18 days (range: 4–174 days). 16 patients had a mild, 18 a moderate and 10 a severe disease course. One patient died due to TBE.
TBE related brain abnormalities could be identified in 4 cases. They consisted of diffuse areas of T2–signal hyperintensity, which were located in the crura cerebri in three patients and in the right centrum semiovale in one patient. No contrast enhancement was observed in any of the lesions and their presence was not related to specific clinical findings or the severity of TBE.
Conclusion: MRI brain lesions in TBE are rare and do not correlate with the course of the disease. Diffuse areas of signal hyperintensity in the crura cerebri appear suggestive of TBE.

1. Introduction

In central Europe, tick-borne encephalitis (TBE) is a common viral infection of the brain with a potentially life threatening disease course. The TBE virus (TBEV) encompasses 3 subtypes (European, Siberian and Far Eastern type), and belongs to the family of Flaviviridae. In Europe, the most common vector for the TBEV is *Ixodes ricinus* [1]. The clinical manifestation of TBE shows a wide spectrum ranging from mild meningitis to severe meningoencephalomyelitis and can lead to death in about 1% of the infected [2]. Up to 40% of all patients suffer from long-term neurological deficits [2,3]. Even though Austria is known as a highly endemic area for the TBEV [4] reports about the clinical characteristics and the course of the disease in adults are sparse.

The diagnosis of TBE is typically confirmed by detection of specific IgM and IgG antibodies in the serum and/or the cerebrospinal fluid (CSF). Magnetic resonance imaging (MRI) can serve to differentiate TBE from other viral forms of encephalitis, which are characterized by typical imaging findings such as herpes simplex encephalitis [5]. However, there are only a few reports on morphologic changes in TBE itself. These studies suggest that 10–18% of all TBE patients show abnormalities commonly affecting the thalami, basal ganglia and cerebellum [6–8]. While several case reports suggest that TBE associated lesions are related to a more severe disease course [7,9] and long-term neurological deficits [10], systematic analyses to answer this question are sparse.

The aim of this study was to provide clinical data of TBE patients in Styria and Salzburg, both known as highly endemic regions for the TBEV in Austria [4] with a special focus on MRI morphologic brain abnormalities and their potential association with demographic and clinical characteristics.

Abbreviations: TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FLAIR, fluid attenuated inversion recovery; ICU, intensive care unit.

* Corresponding author.
E-mail address: alexander.pichler@medunigraz.at (A. Pichler).

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2. Methods

We retrospectively identified 88 patients diagnosed with TBE, who were admitted to the Department of Neurology of the Medical University of Graz (Austria, province of Styria) (n = 56) and the Department of Neurology of the Paracelsus Medical University of Salzburg (Austria, province of Salzburg) (n = 32) between 2003 and 2014. The diagnosis of TBE was confirmed in all patients by the enzyme-linked immunosorbent assay (ELISA) verifying TBE-specific IgM and IgG antibodies in the serum and/or CSF.

All patients had a fully documented clinical history: clinical variables including age at disease onset, sex, duration of hospitalisation, days in the intensive care unit (ICU), and clinical symptoms were recorded.

Brain MRI was available in 45 (51.1%) of the 88 patients, who were then included for further analysis.

The severity of the neurological deficits of investigated patients was grouped into four categories consisting of a mild, moderate and severe disease course and death due to TBE (see Table 1) as suggested by earlier investigations on the severity and disease course of TBE [3,11] (Table 1). We also recorded laboratory parameters including the leukocyte count, protein and lactate levels of the cerebrospinal fluid.

The study was approved by the ethics committee of the Medical University of Graz.

2.1. Magnetic resonance imaging

Standard imaging was obtained using T2, fluid attenuated inversion recovery (FLAIR), diffusion and, in most cases, T1 plus gadolinium sequences. All scans were carefully and independently reviewed by two trained neuro-radiologists who were blinded to clinical data. We recorded all morphologic changes and categorized them as TBE related or non-specific lesions. TBE related lesions constituted signal abnormalities not explained by known pathologies or those reported to occur in TBE such as ill-defined, patchy lesions on T2-sequences [7,12]. Any other morphologic abnormalities, such as small white matter hyperintensities suggestive of ageing or vascular disease [13] or wide ventricles, were rated as non-specific and are not reported in the following. Linear dural enhancement was also categorized as non-specific as it might be associated with prior lumbar puncture [14].

2.2. Statistical analysis:

All statistical analyses were performed using SPSS, version 20 (SPSS Inc., Chicago, IL, USA). Data were tested for distribution, using histograms and the Kolmogorov-Smirnov test. In case of a non-parametric distribution of data, we used the Mann-Whitney *U* test and the Kruskal Wallis test. In the other cases, we applied the 2-tailed student's *t*-test and analyses of variance (ANOVA). Correlations between clinical variables and conventional MRI parameters were assessed by Pearson and Spearman correlation coefficients. Fisher's exact test was used to analyse contingency tables.

Table 1
Classification of the disease course of the investigated cohort according to prior investigations [3,11].

Mild disability	Meningeal symptoms including fever, headache, rigidity of the neck, nausea
Moderate disability	Monofocal deficits of the CNS and/or moderate dysfunction of the brain including tremor, ataxia, dysphagia, single cranial nerve affection and moderate decline of vigilance
Severe disability	Multifocal deficits of the CNS and/or severe brain dysfunction including seizures, central paralysis, multifocal cranial nerve deficits, affection of the spinal cord.
Death	

3. Results

3.1. Clinical and demographic variables

Demographic and clinical variables are shown in Table 2. There were no differences between the two centres regarding all clinical and laboratory findings.

The median age of the 45 patients at disease onset was 58.0 years (range 18–80 years). About two-thirds of all patients were male (n = 28). The median hospitalisation time was 18 days (range 4–174 days). No sex specific difference could be shown for any clinical or laboratory variables.

3.2. Disease severity

Patients were subdivided into four groups according to their neurological deficits as described above (Table 1). 16 patients (35.5%) had a mild, 18 (40.0%) a moderate and 10 (22.2%) patients a severe disease course. Individuals with a severe disease course had a longer median interval between the admission and the MRI scan (mild 3.5 days, moderate 2 days and severe 7.5 days, $p = 0.011$) (see Table 2).

Altogether, 21 patients were treated in the ICU with a median stay of 8 days (range 3–166 days); 2 of them needed mechanical ventilation. A 49-year-old female patient died due to respiratory failure as a direct consequence of TBE. In total, this patient spent 153 days in the hospital with 143 days in the ICU.

3.3. Magnetic resonance imaging findings and clinical associations

Brain MRI was available for 45 patients. The median interval between hospital admission and the first MRI scan was 2 days (range 0–18 days). The median interval between the first symptoms and the first MRI scan was 9 days (range 2–41 days).

In comparison to those patients of the initial group of 88 patients without a brain MRI (n = 43), the 45 patients, of whom a brain MRI was available, had a longer median hospitalisation time (18 vs. 12 days; $p < 0.001$) and tended to be older at disease onset (61 vs. 50 years, $p = 0.13$). All other demographic variables were comparable between patients with and without MRI.

TBE related brain abnormalities could be identified in four cases with diffuse signal changes in the area of the crura cerebri as the most frequent finding in three of them (see Figs. 1–3). One patient showed a diffuse area of signal hyperintensity in the right centrum semiovale. None of the abnormalities showed contrast enhancement.

The presence of TBE related signal abnormalities was not associated with disease severity and there was no difference regarding any clinical or demographic variable between patients with and without lesions. Also, the patient who died because of TBE did not have any TBE related lesions on MRI neither at disease onset nor three months after admission. Post mortem analysis of the brain showed pronounced post-encephalitic changes accentuated in the basal ganglia in terms of reactive proliferation of micro- and astroglia and a focal inflammation around small cerebral vessels.

No associations could be observed between the laboratory parameters both in serum and CSF and the presence of TBE related MRI lesions.

4. Discussion

Austria and especially the regions of Styria and Salzburg are highly endemic areas for the TBEV [4]. We were able to collect clinical and imaging data of a cohort of 45 patients with a definite diagnosis of TBE, who were admitted to the Department of Neurology of the Medical University of Graz and the Department of Neurology of the Paracelsus University of Salzburg between 2003 and 2014. We focused on morphologic brain abnormalities using MRI and their potential