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Original article

Clinical outcome and cerebrospinal fluid profiles in patients with tick-borne encephalitis and prior vaccination history

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ABSTRACT

Background: Tick-borne encephalitis (TBE) is endemic in southern and eastern districts of Germany. Approximately 10–14% of the infected individuals suffer from long-term disability and in 1.5–3.6% the course is fatal. Two well-tolerated vaccines are available, which provide high protection and which have been confirmed in several field studies. Here we investigate clinical course, long-term outcome and cerebrospinal fluid (CSF) characteristics of TBE cases with a prior history of any vaccination as well as real vaccination breakthrough (VBT).

Methods: A case series of 11 patients with a prior history of vaccination, part of a recently published lager cohort of 111 TBE cases. Evaluation included clinical data, degree of disability (modified RANKIN scale, mRS) and analysis of CSF and serum samples. Furthermore, metadata for extended analysis on clinical outcome of TBE with VBT were analysed.

Results: One patient had a clear VBT and ten of them had irregular vaccinations schedules (IVS). Infection severity did not differ in patients with IVS as compared to a non-vaccinated control cohort (median mRS: both 3.0) but these patients showed a stronger cellular immune response as measured by CSF pleocytosis (IVS, 205 cells/µL *versus* non-vaccinated control, 114 cell/µL, $P < 0.05$) and by differential pattern of CSF (intrathecal) immunoglobulin synthesis. However, shift analysis of VBT metadata using linear-by-linear association revealed a more serious course of TBE in patients with VBT than in a non-vaccinated control cohort ($\chi^2 = 9.95$, $P = 0.002$). Furthermore, ordinal logistic regression analysis showed that VBT patients had an age-corrected, 2.65 fold (CI: 1.110–6.328; $\chi^2 = 4.813$; $p = 0.028$) significant higher risk to suffer from moderate or severe infections, respectively.

Conclusion: A history of IVS surprisingly seems to have no impact on the clinical course of TBE but may leave marks in the specific brain immune response. VBT patients, however, carry an age-independent, significant risk to experience a severe infection.

1. Introduction

Tick-borne encephalitis (TBE) is the most frequent *Flavivirus* infection in Europe and Russia. In Europe, the European-type tick-borne encephalitis virus (TBEV-Eu) accounts for TBE whereas related Sibirian and Far Eastern subtypes (TBEV-Sib, TBEV-Fe) are prevalent in the Baltics, the European part of Russia, and eastward to the Ural mountains (Suss, 2011). In endemic areas and countries in Europe, TBE represents the most frequent viral CNS infection in general. Incidences in some southern regions of Germany or in Slovenia reach up to 29 infections per 100,000 of the population in Germany and up to 47 per 100,000 in Slovenia (Donoso Mantke et al., 2008; SurvStat@RKI, 2012).

Efficient primary infection prophylaxis can be reached by a specific anti-TBE vaccination. Two vaccines have been approved in Europe and shown to be safe and effective: FSME-Immun®, Baxter in 1976 (now

Abbreviations: CSF, cerebrospinal fluid; IVS, irregular vaccination schedule; mRS, modified RANKIN scale; RKI, Robert Koch Institute; TBE, tcik-borne encephalitis; TBEV, tick-borne encephalitis virus; VBT, vaccination breakthrough

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Pfizer), and Encepur®, GlaxoSmithKline (formerly Chiron-Behring) in 1991 (Kunz et al., 1976; Lindquist and Vapalahti, 2008). Although both vaccines are generated from TBEV-Eu strains, a cross-protection against TBEV-Sib and TBEV-Fe could be shown (Hayasaka et al., 2001; Holzmann et al., 1992). Despite the lack of controlled trials, high vaccination coverage has reduced annual infection rates to one seventeenth in Austria since the beginning of 1980 (Kunz, 2002, 2003). Thus, the high efficacy of the TBE vaccination has been approved in the field and the protection rate has been estimated to be 99% (Heinz et al., 2007).

In Germany, the vaccination committee (STIKO) at the Robert Koch Institute Berlin (RKI), the central institute for national infection surveillance, has proclaimed general vaccination recommendations for TBE in Germany. Accordingly, a vaccination is recommended for any individual exposed to ticks, for any job-related risk of TBE infection, and for travelers visiting TBE-risk areas in Germany or in other TBE-risk countries. On the basis of reported TBE cases, a classification of the federal territory into TBE non-risk and TBE risk areas has been defined at the district level. In 2017, a total of 146 administrative districts were classified as TBE risk areas in Germany (Robert-Koch-Institut, 2017). However, motivation to be vaccinated is insufficient in the exposed population in the risk areas in Germany. Vaccination coverage in risk areas in Germany ranges from 6.9% up to 60.7% (mean: 20–30% depending on the individual federal state) (Seedat and Marcus, 2013).

In Germany, 3997 TBE cases were reported to the RKI between the years 2000 and 2012 (Gilsdorf, 2000–2012). Within this period, 226 patients were infected in five districts of the Odenwald hills, a high-risk area in southwestern Germany. Of these, we have previously reported a cohort of 111 TBE patients who acquired autochthonic infection (Lenhard et al., 2016). The aim of the present study was to analyse patients with any vaccination history concerning the acute clinical infection course, including the related CSF inflammation profile and the long-term outcome of those patients. In addition, we report on a clear, verified vaccination breakthrough (VBT) and have analysed metadata of VBT by means of clinical outcome measures and predictors for unfavorable outcome.

2. Methods

2.1. Study population

We recently published epidemiological, clinical and neuroimage data of a cohort of 111 TBE patients. Epidemiological data associated with TBE were collected by means of a medical history questionnaire at admission and for long-term outcome by a follow-up telephone interview. For a detailed description of the study population we refer to previous published work (Lenhard et al., 2016). Of this cohort, 11 patients had a history of vaccination by any means and were further analysed in the present study. Vaccination was verified by a copy of the vaccination card. The study was approved by the ethical committee of the University of Heidelberg.

2.2. CSF analysis and immunoassays

CSF data consists of cell number count and cell differentiation (microscopic evaluation of CSF sediments), analysis of blood-CSF barrier function and of CSF chemistry (protein, glucose, and lactate). Anti-TBEV antibodies (IgG, IgM) were analysed in serum and CSF with an enzyme immunoassay assay (EIA; IMMUNOZYM FSME IgG, IgM, Progen Heidelberg, Germany). TBE IgG antibody-specific index (AI) was calculated as follows:

$$AI = \frac{Q_{\text{specific IgG}}}{Q_{\text{total IgG}}} = \frac{[\text{anti} - \text{TBE IgG}]^{CSF} \times [\text{anti} - \text{TBE IgG}]^{serum}}{[\text{total IgG}]^{serum} \times [\text{total IgG}]^{CSF}}$$

2.3. Case definition of vaccination breakthrough and irregular vaccination, database search strategy and analysis of metadata

VBT was defined according to the definition of Grgic-Vitek et al. (2010) as follows: confirmed TBE case (for definition, see Lenhard et al., 2016) and confirmed history of a complete vaccination schedule or complete vaccination and timely booster vaccination and infection within 3 years after last vaccination. Irregular vaccination schedule (IVS) was defined either as incomplete vaccination (two of three recommended vaccinations) or as insufficient vaccination (one of three recommended vaccinations) and as lack of regular booster vaccination according to the general recommendations.

A PubMed search to identify published cases of VBT and vaccination failure as well as of cases of any vaccination history with TBE was performed by using the following broad Boolean search strategy: "((vaccine*[ti] OR vaccination*[ti] OR immunization*[ti]) AND (tick-borne-encephalit*[ti] OR central-European-encephalit*[ti] OR TBE [ti]))". Hits for any vaccination-associated reports of TBE were preselected from the results. Only cases/studies that met the criteria for real VBT were included in the further analysis (Grgic-Vitek et al., 2010). Metadata for clinical outcome in vaccination failure were compared to our control cohort, which was published previously in detail (Lenhard et al., 2016). To establish comparability of the selected metadata for VBT with our case of VBT and our control cohort, the clinical outcome data of our cohort, measured as modified RANKIN scale (mRS), were transformed into a simplified common severity score as follows: mRS 0 (healthy) were assigned as "0" for further analysis; mRS 1–2 as "1" (mild), mRS 3–4 as "2" (moderate), and mRS 5–6 as "3" (severe).

2.4. Statistics

All statistical analyses were performed using the SPSS software package (SPSS version 21; SPSS Inc). Nominally scaled data (infection type: bi- versus monophasic) were analysed by Fisher's exact test, ordinally scaled data (age categories, clinical outcome score, cell number, age) were analysed by Mann–Whitney *U* test, and parametric data (CSF protein) were analysed by Student's *t*-test. Shift analysis for the degree of severity of infection (clinical outcome score) within the control (TBE-Co)- and the VBT TBE group, respectively, was performed with linear-by-linear association. Finally, to estimate the likelihood to suffer from a more severe TBE infection course in VBT, an ordinal logistic regression analysis was performed. For all variables, probability values as well as the odds ratios (OR) and 95% confidence intervals (CI) were determined. To receive odds ratios and probability values, a syntax command was included in the ordinal regression analysis, since SPSS do not perform this analysis routinely (for illustration, see e.g. https://statistics.laerd.com/spss-tutorials/ordinal-regression-using-spss-statistics.php) Significance was accepted at the P level < 0.05 for all calculations.

3. Results

3.1. Baseline data and clinical outcome of TBE cases with any vaccination history

Eleven patients (10%) of the total cohort of 111 TBE cases had a history of any kind of prior vaccination. Table 1 summarizes the baseline data of this subgroup compared to the main data of the control group (TBE cases without vaccination history) (Lenhard et al., 2016). Of them, 1 patient (Table 1, number 1) had a clearly verified VBT with TBE onset 3 months after completing a full vaccination schedule. For detailed description of this case, see Section 3.2. Ten patients had a vaccination with an IVS, among whom two had an insufficient vaccination (one of three recommended vaccinations), five had an incomplete (two of three recommended vaccinations), and three patients had a complete vaccination but forgot timely booster vaccination. The