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# The clinical and epidemiological profile of tick-borne encephalitis in southern Germany 1994–98

## A prospective study of 656 patients

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## Summary

**Seven hundred and nine patients fell ill in southern Germany (Baden-Württemberg) after infection with the tick-borne encephalitis (TBE) virus between 1994 and 1998. Detailed clinical and epidemiological data on TBE were available for 656 patients. A biphasic course of the disease occurred in 485 patients (74%). TBE presented as meningitis in 320 patients (49%), as meningo-encephalitis in 270 (41%) and as meningo-encephalomyelitis in 66 (10%). Eight of the patients (1.2%) died from TBE. Four hundred and forty-five patients (68%) had noticed a tick bite and the first symptoms occurred, on average, 7 days later. The most frequent neurological symptoms were impairment of consciousness (31%), ataxia (18%) and paresis of the extremities (15%) and cranial nerves (11%). Laboratory investigations revealed leucocytosis in the peripheral blood in 224 out of 392 patients (74%), elevation of the erythrocyte sedimentation rate in 223 out of 245 (91%), increased C-reactive protein in 127 out of 155 (82%), pleocytosis in the CSF of all patients tested, damage of the blood–CSF barrier in 255 out of 322 (79%), abnormalities in EEG in 165 out of 214 (77%) and abnormalities in MRI in 18 out of 102 (18%). In general, adolescents up to 14 years of age had a more favourable course of the disease than adults. Of 230 patients who were re-examined at a later time, 53 (23%) had moderate or severe sequelae. Patients with sequelae presented more frequently ($P < 0.001$) with impaired consciousness (Glasgow Coma Scale < 7), ataxia, pareses of the extremities or cranial nerves, a need for assisted ventilation, abnormal findings in MRI, pleocytosis > 300 cells/μl and impairment of the blood–CSF barrier (total protein > 600 mg/l). In view of the severity of the illness and the high frequency of sequelae, active immunization against TBE is recommended for all subjects living in and travelling to areas of risk. Prevention of TBE by post-exposure prophylaxis with hyperimmunoglobulins is less effective and therefore should be performed only when absolutely necessary.**

**Keywords**: TBE; active immunization; meningoencephalomyelitis

**Abbreviations**: GCS = Glasgow Coma Scale; TBE = tick-borne encephalitis

## Introduction

Tick-borne encephalitis (TBE) is caused by an RNA virus belonging to the flavivirus family. Based on antibody adsorption experiments, peptide mapping and nucleotide sequencing, two subtypes of TBE virus have been identified and designated as western and eastern (Heinz and Kunz, 1981, 1982; Mandl *et al.*, 1988, 1989; Pletnev, 1990). The western subtype is endemic in large parts of Northern, Central and Eastern Europe, while the eastern subtype can be found in the European and Asian regions of the Commonwealth of Independent States (former Soviet Union) (WHO, 1986; Anonymous, 1997). In Germany, TBE is prevalent in Baden-Württemberg, Bavaria and South Hessen (Roggendorf, 1996; Anonymous, 1997). During the years 1991 to 1998, at least 1230 cases of TBE were reported in Germany, with a mean incidence in Baden-Württemberg of 1.2 per 100 000 inhabitants per year and a case fatality rate of 1% (Kaiser, 1996). In a highly endemic focus in Baden-Württemberg a seroprevalence of 9% has been found (Kaiser *et al.*, 1997*a*).

TBE typically takes a biphasic course. After an incubation period, usually between 7 and 14 days, the prodromal

symptoms (uncharacteristic influenza-like illness with fever, headache, malaise and myalgia) are followed by CNS involvement. After an afebrile interval of ~1 week the second stage develops. TBE may manifest as isolated meningitis, meningoencephalitis or meningoencephalomyelitis (Duniewicz, 1976; Ackermann *et al.*, 1986; Köck *et al.*, 1992; Kaiser, 1995). Reports describing the clinical course and outcome of large series of patients with TBE are sparse.

In 1994 a dramatic increase in the number of TBE virus infections occurred in the area of Freiburg (southern Germany). At the time there was a lack of information regarding the risks associated with and the outcome of TBE virus infection in southern Germany, which includes Baden-Württemberg, an important tourist area. A prospective study to investigate the clinical course, prognosis and epidemiology of TBE in Germany was undertaken. Results of this study support a policy of active immunization against TBE for all subjects who stay in or travel to areas of risk and are likely to be exposed to ticks.

## Patients and methods

### *Patient population*

This prospective multicentre study was performed in Baden-Württemberg, a federal state in southern Germany, between 1994 and 1998. Data from patients were recorded by the Departments of Neurology ($n = 25$), Internal Medicine ($n = 101$) and Paediatrics ($n = 14$) in Baden-Württemberg and by 50 diagnostic laboratories and 40 health authorities which were invited to participate in this study. Patients in medical departments were examined by consulting neurologists. EEG was carried only in hospitals that had EEG machines, and MRI was carried out in patients with impaired consciousness. Findings in EEG were considered only in patients who were studied within the first 3 days after admission to hospital. Data were acquired by means of a questionnaire in which the following information was requested: initials of patients, date of birth, sex, postal code of the place of residence, the probable place of infection, information about a tick-bite (date and activity at the time of the tick-bite), prior vaccination against TBE, yellow fever or Japanese encephalitis, the occurrence, date and duration of prodromal symptoms and detailed clinical and serological data. In addition, the clinicians were asked to send an anonymous record of the patients, which included laboratory data. Patients were asked to give their informed consent to participate in the study. Data were made anonymous to satisfy the German data protection law.

### *Immunodiagnostic tests for TBE virus-specific antibodies*

TBE was diagnosed by the demonstration of specific IgM and IgG activity in the serum by routine serological tests (IMMUNOZYM FSME IgG, IgM; IMMUNO AG, Heidelberg, Germany) (Roggendorf *et al.*, 1981*b*). In patients recently immunized with TBE vaccine, CNS infection was diagnosed by demonstration of intrathecally produced viral TBE IgM activity. Patients with a prior vaccination against yellow fever or Japanese encephalitis were excluded from the study.

### *Definition of areas of risk for TBE virus infection*

According to the recommendations of a national conference on tick-borne diseases held in Freiburg in March 1998, the areas of risk in Germany for TBE virus infection are defined as administrative districts with at least five cases of TBE within 5 years (Kaiser, 1998). Areas of high risk are defined as districts with $\geqslant 25$ cases of TBE within 5 years.

### *Clinical case definition of TBE*

Patients were classified as suffering from ‘meningitis’ (fever, headache, rigidity of the neck, nausea, vomiting, pleocytosis in the CSF), ‘meningoencephalitis’ (abnormal findings in EEG and/or altered consciousness, and/or focal neurological symptoms in addition to findings of meningitis) or ‘meningoencephalomyelitis’ (flaccid mono-, para- or tetraparesis in addition to findings of meningoencephalitis). Myelitis, never the sole form of presentation of TBE, only occurred in association with meningoencephalitis. Impairment of consciousness was assessed using the Glasgow Coma Scale (GCS) (Teasdale *et al.*, 1974). Pareses were classified according to the Medical Research Council (Medical Research Council, 1976).

### *Follow-up examinations*

Follow-up data were available from 230 patients. One hundred and ten patients were studied for sequelae up to 5 years after the acute illness (median 12 months, range 1–60 months). Sixty-three patients were examined clinically, by neuropsychological testing and by EEG, and these data have been presented recently (Kaiser *et al.*, 1997*b*). One hundred and twenty patients were treated for further periods of between 2 and 12 months in rehabilitation centres. Information about the clinical condition at the follow-up examinations was provided by the attending physician. Sequelae were classified according to Bohr and colleagues (Table 1) (Bohr *et al.*, 1985).

### *Statistics*

Independent samples were analysed by means of the *t* test and Levene’s test for equality of variances. The frequency of positive findings was examined by the $\chi^2$ test. The significance level considered was 1% ($P \leqslant 0.01$)

**Table 1** *Sequelae due to tick-borne encephalitis lasting at least 3 months (modified according to Bohr and colleagues (Bohr* et al.*, 1985)*

| | |
|---|---|
| Nil | No sequelae |
| Mild | Presence of one or more mild symptoms such as dizziness, memory deficits, headache, tiredness and slight hearing impairment, minor psychological problems or unsteady gait. Daily life and working abilities not markedly affected. |
| Moderate | Presence of many or more severe symptoms, ataxia of gait, paresis of the extremities, pronounced dementia or severe deafness. Patient affected in daily life and working ability. |
| Severe | More pronounced clinical disabilities, often seriously affecting social life and working capability, and in a few cases requiring institutional care. |

## Results

### *Epidemiological data*

Between 1994 and 1998 a total of 709 patients fell ill after infection with TBE virus in Baden-Württemberg and South Hessen and detailed epidemiological and clinical data were available for 656 of these patients. Figure 1 shows the areas of risk for TBE in Baden-Württemberg and South Hessen, established from reports between 1994 and 1998. Most of the infections were acquired within the valleys of the Black Forest and in the vicinity of Lake Constance. In the present study no infections were registered in regions >800 m above sea level. Areas of high risk were the districts of Ortenau, Emmendingen, Freiburg, Breisgau-Hochschwarzwald, Waldshut and Enz.

Out of 656 individuals, 445 (68%) had noticed a tick bite before admission. In 576 patients (88%) infection took place during leisure-time activity and only 80 (12%) had an occupation associated with outdoor activities (forest workers, farmers). No obvious association between geographical region and the severity of the disease could be found. Admissions to hospital of patients with TBE were between March and December in each year (Fig. 2). On average, twice as many men ($n = 433$; 66%) as women ($n = 223$; 34%) fell ill but the mean ages of male (45 ± 19 years) and female patients (43 ± 21 years) did not differ. Figure 3 shows the age distribution of patients with TBE, of which 12% ($n = 77$) were children and adolescents aged up to 14 years. Thirteen patients had received a prior, incomplete, active vaccination against TBE (two rather than three immunizations within 18 months) and seven had received hyperimmunoglobulins (passive immunization) within 1–3 days after an observed tick bite.

### *Clinical findings*

#### *Incubation period*

Detailed data on the incubation period were available for only 73 subjects. The data were analysed only when patients had been exposed to ticks on just one occasion and when only one tick bite had been noticed in the 4 week period prior to the disease onset. On average, the period between a tick bite and the occurrence of the first clinical symptoms was 11 ± 6 days, the median 8 days and the range 4–28 days. There was no correlation between the length of the incubation period and the severity of subsequent illness.

#### *Prodromal symptoms*

A biphasic course of illness with a prodromal period occurred in 485 patients (74%). The first stage of illness, characterized by fever, headache and sometimes malaise, upper respiratory and/or abdominal symptoms, lasted a median of 4 days (range 1–7). Thereafter, most of the patients recovered for a median of 7 days (range 3–21). Diarrhoea was noticed in 36 patients (7.4%), elevated liver enzymes in 32 (6.6%), thrombopenia (<60 000/μl) and leucopenia (<4000/μl) in five patients (1%). A prodromal period was reported less frequently in patients with encephalomyelitis (59%, $P = 0.01$) than in patients with meningoencephalitis (75%) or isolated meningitis (76%).

#### *Clinical presentation*

Of the 656 patients, 320 (49%) presented with meningitis, 270 (41%) with meningoencephalitis and 66 (10%) with meningoencephalomyelitis. Patients with meningoencephalomyelitis were treated in hospital (mean 70 days, range 5–400 days) and in intensive care units (mean 30 days, range 5–400 days) for longer than patients with meningoencephalitis (hospital: mean 15 days, range 5–40 days; intensive care units: mean 7 days, range 4–10 days) or meningitis (hospital: mean 10 days, range 5–38 days). There was a tendency towards a more severe course of TBE with increasing age (Fig. 4).

Four patients with meningitis (2%) had transitory pareses of the abducent and vestibular nerve for several days. The diagnosis of meningoencephalitis was established from focal neurological symptoms in 213 patients (79%), from impaired consciousness and diffuse slowing patterns in EEG in 35 patients (13%) and from abnormal EEG alone in 22 patients (8%). The most frequent symptoms in patients with meningoencephalitis and meningoencephalomyelitis are presented in Table 2.

Patients with meningoencephalomyelitis were treated in intensive care units more frequently than those with meningoencephalitis (30 out of 66 versus 9 out of 270, $P < 0.001$). Impairment of consciousness was a frequent finding in both of these manifestations of TBE, but patients with meningoencephalomyelitis were more severely affected. Of the 158 patients with meningoencephalitis, low scores (<7) on the GCS were determined in only five patients (3%), 11 patients (7%) had levels between 7–11 and 142 (90%) had levels >11. On the other hand, of the 45 patients with meningoencephalomyelitis, 20 had levels <7 (44%), six

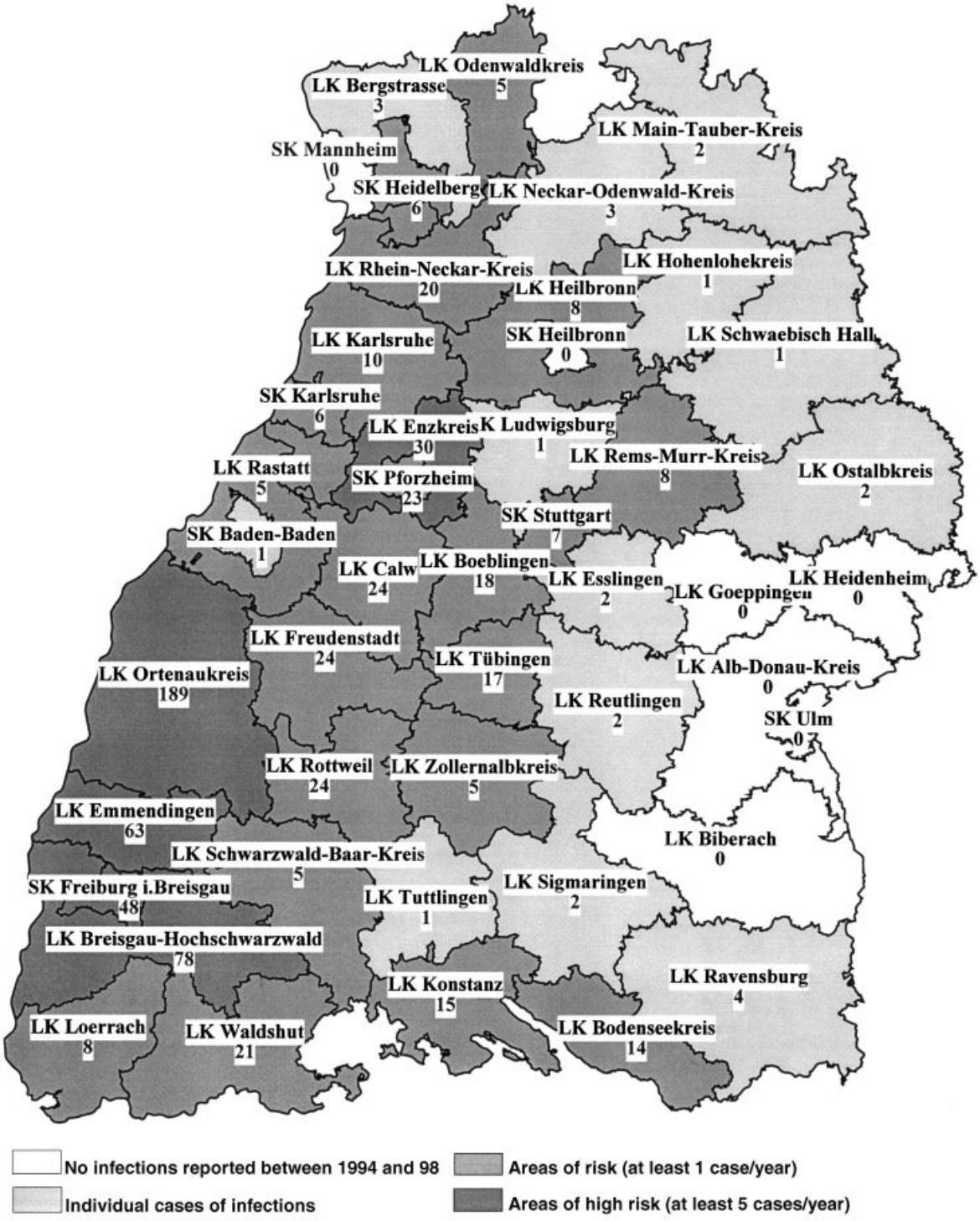


**Fig. 1** Areas of risk for TBE virus infections in Baden-Württemberg and South Hessen during 1994–1998.

(13%) had levels between 7 and 11 and 19 (42%) had levels >11. Eighty-six of the patients were disorientated and four reported having had hallucinations.

Flaccid paresis of the extremities (≤3/5) was the most prominent feature in all patients with meningoencephalomyelitis; 28 patients (43%) suffered from either monoparesis or tetraparesis and 10 patients (15%) from paraparesis of the lower extremities. In meningoencephalitis, paresis of the extremities was less frequent [monoparesis, 18 patients (6.8%); hemiparesis, 16 patients (6%)], less serious (>3/5) and mostly transitory, with a duration of a few days. A similar pattern was observed with pareses of the cranial nerves, which were more severe and relatively more frequent in patients with meningoencephalomyelitis (Table 3). In patients with meningoencephalitis, most pareses of the cranial nerves were transitory, lasting 3–10 days, except for hearing

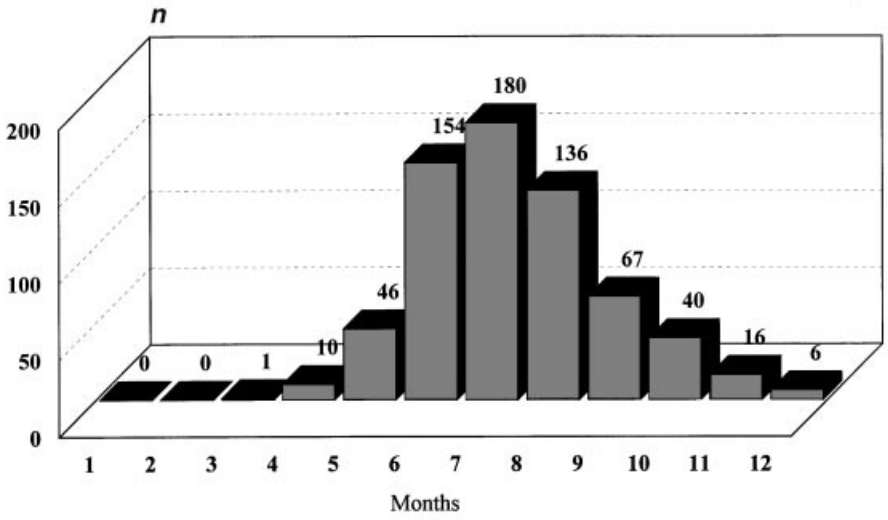


**Fig. 2** Seasonal distribution of 656 patients with TBE in Southern Germany during 1994–98.

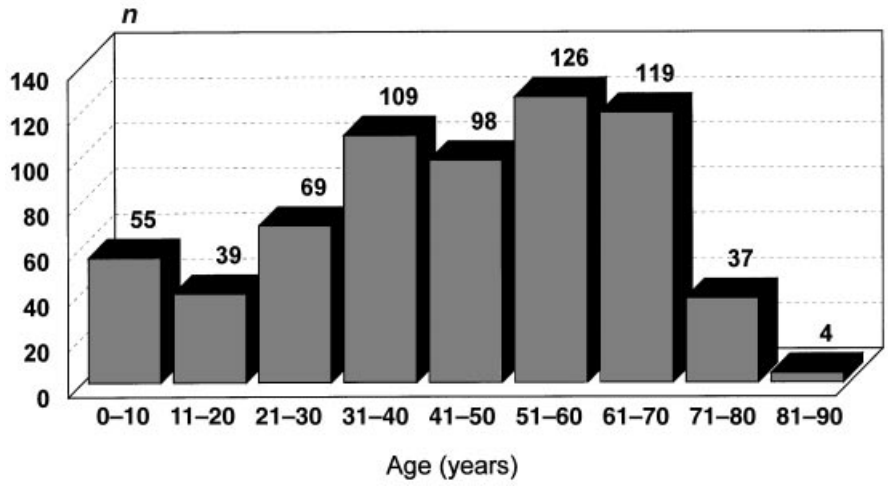


**Fig. 3** Age distribution of 656 patients with TBE.

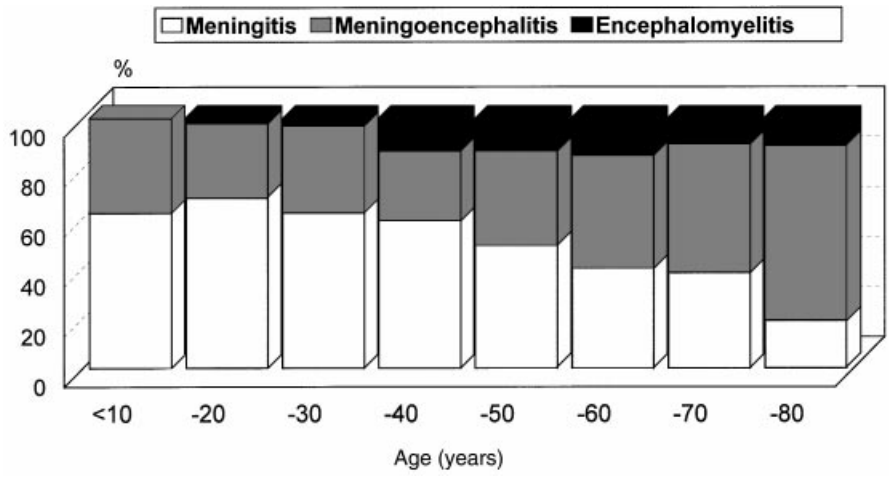


**Fig. 4** Relative frequency of meningitis, meningoencephalitis and meningoencephalomyelitis in patients with TBE virus infection related to age decades.

**Table 2** *Neurological symptoms in patients with TBE*

| | Meningitis $n = 320$ No. of patients (%) | Meningoencephalitis $n = 270$ No. of patients (%) | Meningoencephalomyelitis $n = 66$ No. of patients (%) | All patients $n = 656$ No. of patients (%) |
|---|---|---|---|---|
| Impaired consciousness | | 158 (59) | 45 (68) | 203 (31) |
| Ataxia | | 74 (27) | 45 (68) | 119 (18) |
| Paresis of the limbs | | 33 (12) | 66 (100) | 66 (15) |
| Paresis of the cranial nerves | 8 (2.5) | 36 (14) | 30 (45) | 74 (11) |
| Respiratory insufficiency | | 1 (0.5) | 30 (45) | 31 (4.7) |
| Tremor | | 14 (5) | 14 (21) | 28 (4.3) |
| Dysaesthesia | | 16 (6) | 3 (4.5) | 19 (2.9) |
| Dysphasia | | 15 (6) | 1 (1.5) | 16 (2.5) |
| Impaired bowel function | | 3 (1) | 9 (13.5) | 12 (1.8) |
| Seizures | | 7 (3) | 4 (6) | 11 (1.7) |
| Dysdiadochokinesia | | 5 (2) | 5 (7.5) | 10 (1.5) |

**Table 3** *Paresis of the cranial nerves in patients with meningoencephalitis and meningoencephalomyelitis*

| Cranial nerve | Meningitis $n = 320$ No. of patients (%) | Meningoencephalitis $n = 270$ No. of patients (%) | Meningoencephalomyelitis $n = 66$ No. of patients (%) | All patients $n = 656$ No. of patients (%) |
|---|---|---|---|---|
| III | | 1 (0.3) | 2 (3) | 3 (0.5) |
| V | | | 2 (3) | 2 (0.3) |
| VI | 4 (3) | 12 (4.4) | 5 (7.5) | 21 (3.2) |
| VII | 4 (3) | 7 (2.6) | 10 (15.1) | 17 (2.6) |
| VIII | | 11 (4.0) | 12 (18.2) | 27 (4.1) |
| IX, X | | 4 (1.5) | 12 (18.2) | 16 (2.5) |
| XI | | | 17 (25.7) | 17 (2.6) |
| XII | | | 9 (13.6) | 9 (1.4) |

impairment, dysphagia and dysarthria, which persisted for longer periods. Ten patients with meningoencephalomyelitis were continuously ventilated either to the present time ($n = 2$, ventilation for 2 and 5 years) or until death (eight patients; 1–52 weeks after onset of the disease). Tremor of the limbs mostly occurred as intention tremor (20 patients) and less frequently as resting tremor (eight patients). Other neurological symptoms occurred with a frequency of <3% (Table 2).

## *Laboratory findings on admission to hospital*

TBE virus-specific IgM-antibodies in serum were present in 653 out of 656 patients with TBE (99%); in three patients the diagnosis was established as the result of a significant rise in IgG antibodies in serum, and an accompanying increase in antibody avidity 3 weeks after the first testing (Gassmann and Bauer, 1997). All patients revealed IgG antibodies against TBE virus after a maximum of 2 weeks following admission to hospital.

Examination of the peripheral blood revealed leucocytosis (>10 000 cells/μl) in 224 out of 302 patients (74%) and elevation of the sedimentation rate in 223 out of 245 patients (91%) and of C-reactive protein in 127 out of 155 patients (82%). The frequency and extent of abnormal values (Table 4) did not correlate with the diagnosis or prognosis of TBE. Pleocytosis in the CSF was a general finding in all patients; the median cell count was 60/μl with a range of 6–1200/μl. Patients with meningoencephalomyelitis had significantly ($P < 0.001$) higher values than those with meningitis or meningoencephalitis (Table 4).

Impairment of the blood–CSF barrier was demonstrated in 255 out of 322 patients (79%). Abnormal values of total protein in the CSF were detected more frequently in patients with meningoencephalomyelitis (39 out of 44, 88%; $P = 0.021$) and meningoencephalitis (131 out of 159, 82%; $P = 0.025$) than in patients with meningitis (85 out of 119, 71%). Additionally, patients with meningitis had lower levels of total protein in the CSF than patients with other manifestations (Table 4).

## *EEG and MRI*

Of 214 patients who were examined by EEG, 165 (77%) presented with abnormalities (diffuse slowing and/or intermittent focal abnormalities). The frequency of abnormal EEG findings was similar in patients with meningoencephalitis (91%) and meningoencephalomyelitis (96%).

MRI studies were carried out on 102 patients, and 18 showed abnormal findings. Of 64 patients with meningoencephalitis and 25 with meningoencephalomyelitis, 11 (17%) and seven (28%), respectively, showed abnormalities on MRI. The MRI was unremarkable in 13

**Table 4** *Laboratory findings in TBE*

| | Meningitis ($n$ = 320) | Meningoencephalitis ($n$ = 270) | | Meningoencephalomyelitis ($n$ = 66) | | All patients ($n$ = 656) |
|---|---|---|---|---|---|---|
| Leucocytosis in peripheral blood (cells/μl) | 12600 ± 4500 | 12600 ± 5300 | n.s. | 12000 ± 4100 | n.s. | 12600 ± 4800 |
| Erythrocyte sedimentation rate (mm in 1st hour) | 31 ± 18 | 32 ± 21 | n.s. | 25 ± 13 | n.s. | 31 ± 19 |
| C-reactive protein (mg/dl) | 7.1 ± 10.5 | 5.8 ± 9.1 | n.s. | 5.3 ± 7.1 | n.s. | 5.5 ± 7.3 |
| Cell count in CSF (/μl) | 87 ± 119 | 103 ± 124 | n.s. | 223 ± 376 | $P < 0.001$ | 110 ± 150 |
| Total protein in CSF (mg/l) | 590 ± 280 | 720 ± 410 | $P = 0.002$ | 950 ± 450 | $P < 0.001$ | 720 ± 380 |

Patients with meningoencephalitis and meningoencephalomyelitis were compared individually with patients with meningitis.

patients with meningitis. In 15 out of 18 patients the findings were confined to the thalamus (Fig. 5), and in three patients further lesions were detected in the cerebellum, brainstem and caudate nucleus. One of these three patients was under immunosuppression with cyclosporin and corticosteroids following renal transplantation.

### *Comparison of adolescents and adults*

The age definition of adolescents and adults is arbitrary but in the present study individuals who were aged >14 years were classified as adults. This division takes into account the recommendation by the German medical authority (Paul Ehrlich Institute, Langen) that TBE-specific hyperimmunoglobulins should not be used in adolescents up to 14 years of age (see Discussion). The relevant data from both groups are shown in Table 5. In comparison with adults, adolescents suffered more frequently from isolated meningitis ($P$ = 0.002) but less frequently from meningoencephalitis, and they never presented with meningoencephalomyelitis. Adolescents always had a good prognosis, with no persisting deficits and no necessity for rehabilitation. The mean stay in hospital was much shorter for adolescents than for adults ($P$ = 0.006; Table 5). Abnormalities in EEGs were demonstrated more frequently in adolescents than in adults, but the differences were not significant. The high frequency of abnormal MRIs in adolescents (5 out of 9) may reflect the small number of patients investigated. Of the laboratory parameters, only the mean leucocyte count in the peripheral blood was significantly higher in adolescents than in adults ($P$ = 0.007). Adolescents showed reduced consciousness, ataxia and central and cranial nerve palsies less frequently than adults ($P < 0.001$).

### *Sequelae and outcome*

Of 230 patients who were re-examined, 80 (35%) had no problems, 88 (38%) had transitory, mild complaints (disturbances of memory, headache, tiredness or slight hearing impairment, minor psychological disturbances or unsteady gait), but 62 (27%) had sequelae lasting >3 months. Of the latter group, nine patients had mild, 23 moderate and 30 severe sequelae. The majority (90%) of patients with moderate (19 out of 23) and severe (29 out of 30) sequelae came down with meningoencephalomyelitis, while patients with mild sequelae suffered mainly from meningoencephalitis (7 out of 9). Of the 53 patients with moderate or severe sequelae, the majority ($n$ = 47) suffered from pareses of the extremities (⩽3 out of 5).

Selected clinical and laboratory findings, determined on admission to hospital, were analysed for their prognostic value. For this purpose findings in patients with moderate and severe sequelae ($n$ = 53) were compared with those without persisting sequelae ($n$ = 177). Significant correlations ($P < 0.001$) between the occurrence of sequelae and the following clinical symptoms were demonstrated (Table 6): impaired consciousness (GCS <7), ataxia, pareses (⩽3 out of 5) of the extremities and of the cranial nerves, and need for assisted ventilation. In general, these symptoms occurred at the latest 5 days after the onset of high-grade fever and headache marking the second stage of illness.

Patients with persisting sequelae more frequently showed abnormal findings on MRI, pleocytosis of >300 cells/μl in the CSF and impairment of the blood–CSF barrier, as demonstrated by an elevation of the total protein to >600 mg/l (Table 7). The mean cell count and the protein content of the CSF were significantly ($P < 0.001$) higher in patients with sequelae (230 ± 380/μl and 1060 ± 440 mg/l, respectively) than in those without deficits (85 ± 103/μl and 660 ± 350 mg/l, respectively). Persistence of sequelae did not correlate with the leucocyte count in peripheral blood, the sedimentation rate or C-reactive protein.

Eighteen per cent of the patients (120 out of 656) needed further treatment in rehabilitation centres; patients with meningoencephalomyelitis were admitted more frequently (60 out of 66, 91%; $P < 0.001$) than patients with meningoencephalitis (51 out of 270, 19%) or meningitis (9 out of 320, 3%), reflecting the severity of clinical symptoms at presentation.

## Discussion

The diagnosis of TBE is derived from epidemiological (a stay in an area of risk for TBE, facultative history of a tick bite) and clinical (biphasic course of disease and neurological symptoms with ataxia being most indicative for this infection) data, and the demonstration of TBE-specific IgM and IgG

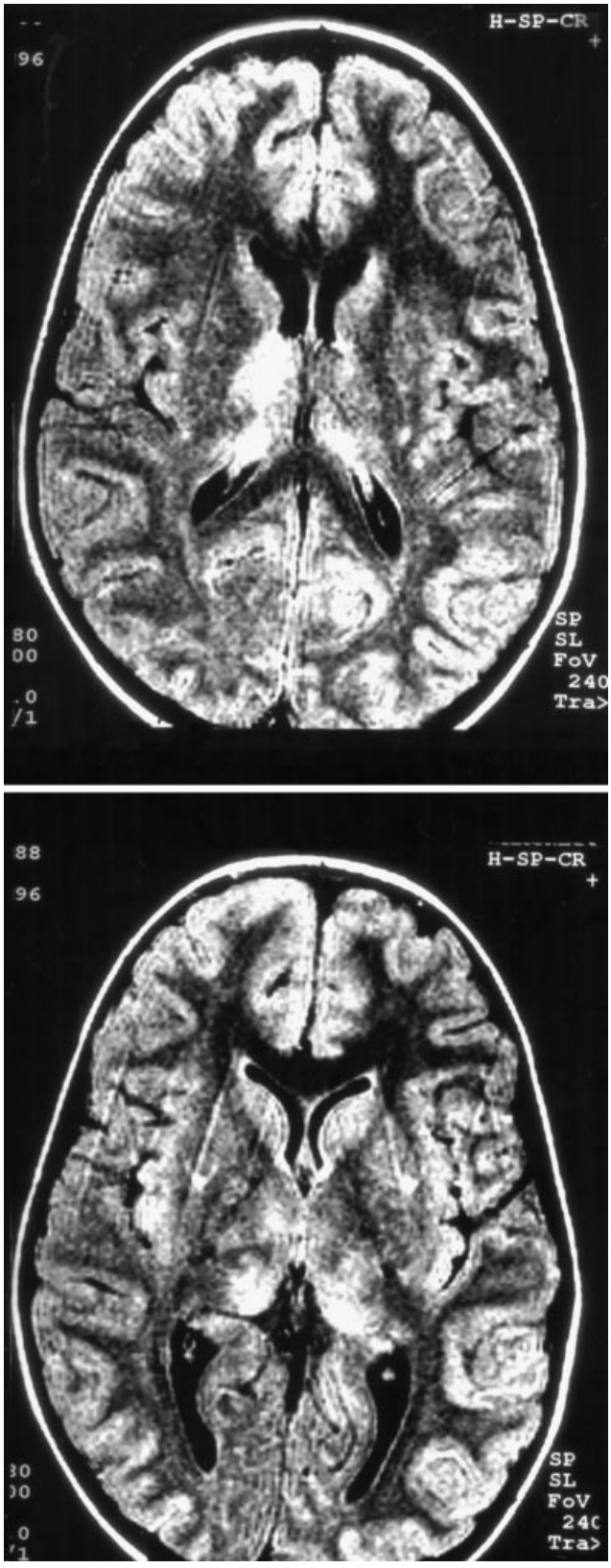


**Fig. 5** MRI of a patient with TBE: lesions predominantly in the thalamus.

antibodies in serum. In general, there is intrathecal synthesis of TBE-specific IgM and/or IgG antibodies in the CSF, at the latest, 3 weeks after admission to hospital. Although this latter criterion is the most specific serological method of confirming the diagnosis, the presence of specific IgM antibodies in serum is generally considered to be adequate evidence of recent TBE (Roggendorf *et al.*, 1981*b*). The patients of the present study were assumed to have been infected by the western subtype of TBE virus, as the eastern subtype has not yet been isolated from ticks or patients in Western Europe.

The frequent presence of signs of inflammation in serum (leucocytosis, elevation of the sedimentation rate and of C-reactive protein) is noteworthy, as it should not be forgotten that these findings, associated with headache, fever and meningism, are highly indicative of bacterial meningitis. Predominance of neutrophilic cells over lymphocytes in the CSF would also support such a presumptive diagnosis, and consequently most of the patients were treated with antibiotics, at least until the TBE serology was found to be positive. Combined infections with TBE virus and, for example, *Borrelia burgdorferi sensu lato* are very rare, but may result in a more severe course of disease (Oksi *et al.*, 1993)

The range of the incubation period was similar in this study to the 4–28 days reported previously. The first clinical symptoms occurred most frequently 8 days after a tick bite, which is also in line with previously reported data (Harasek, 1974; Falk *et al.*, 1981; Roggendorf *et al.*, 1981*a*; Kunz, 1992). In two published cases of infections occurring during laboratory work with TBE virus, the symptoms of the prodromal stage started 9 and 10 days after the presumptive infection (Moritsch, 1962; Bodemann *et al.*, 1980). After experimental infection of monkeys the first signs of illness also appeared on the ninth day (Verlinde *et al.*, 1955). In conclusion, the most probable incubation period lies between 7 and 14 days.

The most obvious feature of TBE, not only in patients but also in experimentally infected monkeys, is ataxia, followed by paresis or paralysis of one or more limbs (Duniewicz, 1976; Köck *et al.*, 1992; Gunther *et al.*, 1997). These and other neurological symptoms of TBE can be explained by the affinity of the TBE virus for certain regions of the CNS. Post-mortem examination of the brain and spinal cord from patients with a lethal course of TBE and from monkeys that were infected experimentally with the TBE virus showed similar findings (Grinschgl, 1955; Verlinde *et al.*, 1955; Moritsch and Krausler, 1957). The cerebral and spinal meninges usually show a diffuse infiltration with lymphocytes and sometimes leucocytes; the most extensive area of meningitis is around the cerebellum. The brain is oedematous and hyperaemic and microscopic lesions are present in almost all parts of the CNS, but particularly in the medulla oblongata, the pons, the cerebellum, the brainstem, the basal ganglia, the thalamus and the spinal cord. The lesions are localized in the grey matter and consist of lymphocytic perivascular

**Table 5** *Clinical and laboratory findings in adolescents and adults (percentage of patients studied)*

| | Adolescents (0.5–14 years) $n = 77$ | Adults (>14 years) $n = 579$ | All patients $n = 656$ |
|---|---|---|---|
| Meningitis | 64% | 47% | 49% |
| Meningoencephalitis | 36% | 41.5% | 41% |
| Meningoencephalomyelitis | 0 | 11.5% | 10% |
| Mean stay in hospital (days) | 7 ± 5 | 21 ± 39 | 19 ± 37 |
| Impaired consciousness | 11% | 26% | 24% |
| Ataxia | 5% | 16% | 18% |
| Paresis of the limbs | 2.6% | 17% | 15% |
| Paresis of the cranial nerves | 4% | 12.4% | 11% |
| EEG, abnormal findings | 27/31 (87%) | 138/183 (75%) | 165/214 (77%) |
| MRI, abnormal findings | 5/9 (56%) | 13/93 (14%) | 18/102 (18%) |
| Pleocytosis in the CSF (cells/μl) | 154 ± 158 | 106 ± 181 | 110 ± 150 |
| Total protein in the CSF (mg/l) | 520 ± 490 | 720 ± 370 | 720 ± 380 |
| Leucocytes (cells/μl) | 17 300 ± 5700 | 11 800 ± 4200 | 12 600 ± 4800 |
| Sedimentation rate (mm in 1st hour) | 41 ± 20 | 29 ± 19 | 31 ± 19 |
| C-reactive protein (mg/dl) | 7.2 ± 9.8 | 6.0 ± 9.2 | 5.5 ± 7.3 |

**Table 6** *Frequency of clinical findings in patients with and without sequelae*

| Sequelae | Impaired consciousness* | Confusion | Ataxia | Paresis of the extremities | Paresis of the cranial nerves | Extrapyramidal symptoms | Respiratory insufficiency |
|---|---|---|---|---|---|---|---|
| No ($n = 177$) | 4 (2%) | 30 (17%) | 39 (22%) | 18 (10%) | 18 (10%) | 11 (6%) | 1 (1%) |
| Yes ($n = 53$) | 19 (36%) | 15 (28%) | 40 (76%) | 51 (96%) | 29 (55%) | 5 (9%) | 30 (57%) |
| *P* | <0.001 | 0.055 | <0.001 | <0.001 | <0.001 | 0.296 | <0.001 |

*GCS score < 7.

**Table 7** *Frequency of laboratory findings in patients with and without sequelae*

| Sequelae | Abnormal findings in EEG | Abnormal findings in MRI | Pleocytosis in CSF >300/μl | Total protein in CSF >600 mg/l |
|---|---|---|---|---|
| No | 55/67 (82%) | 2/33 (6%) | 8/127 (6%) | 52/106 (49%) |
| Yes | 23/24 (96%) | 7/22 (32%) | 10/45 (22%) | 36/43 (84%) |
| *P* | 0.088 | 0.016 | 0.005 | <0.001 |

infiltrations, accumulation of glia cells, necrosis of nerve cells and neuronophagia. In particular, Purkinje cells in the cerebellum and the anterior horn cells in the spinal cord are frequently attacked. Infiltration and rarefaction of cells are also noted in the mesencephalon and diencephalon. Changes in the cerebral cortex are almost invariably restricted to the motor area, with degeneration and necrosis of the pyramidal cells and lymphocytic accumulation and glial proliferation near the surface.

It was obvious from the present study that there was a high frequency of sequelae in patients with TBE. While there are numerous reports on the clinical picture of TBE, there is little information available on the convalescent phase or on the risk of contracting permanent damage. Apart from 63 patients in this study, whose data have been presented in detail elsewhere (Kaiser *et al.*, 1997*b*), follow-up data for other patients with TBE have been published in only two studies, which were performed in Sweden. In the first study, which was done retrospectively, the frequency of sequelae was nearly 36% (40 out of 112 patients) (Haglund *et al.*, 1996). In the second study, a prospective study of 85 patients with TBE and 64 patients with meningoencephalitis of other viral aetiology (controls), the frequency of sequelae was significantly higher (40%) in patients with TBE than in the controls (Gunther *et al.*, 1997). The lower frequency of sequelae reported for patients in the present study (27%) probably reflects the selection of assessment criteria and the fact that mental disorders were not investigated intensively. The relatively high number of patients presenting with paresis on follow-up examination (47 out of 230, 20%) may exaggerate the true prevalence of sequelae. A majority of the patients ($n = 420$), not available for follow-up, were discharged from hospital without pareses. It might, therefore, be speculated that only 47 out of 656 patients had residual pareses (7%), which is in line with other reports (0.3–10%) (Holmgren *et al.*, 1959; Ziebart-Schroth, 1972; Duniewicz, 1976; Ackermann *et al.*, 1979; Falisevac and Beus, 1981; Jezyna *et al.*, 1984; Köck *et al.*, 1992). In these latter studies, the frequency of all sequelae at discharge from hospital ranged from 10 to 25%.

The predictive value of selected clinical and laboratory parameters concerning the prognosis was examined. The most striking signs of an unfavourable course of disease was the rapid development of unconsciousness (GCS $<7$) as well as paresis of the limbs and lower cranial nerves. Individual patients with meningoencephalomyelitis, who were initially admitted to hospital without paresis, showed paralysis and respiratory insufficiency within 24–48 h. In other patients, severe ataxia at presentation was associated with long-lasting disability after discharge from hospital. In general, the rapid evolution of severe symptoms was very likely to lead to a bad prognosis, especially in patients with meningoencephalomyelitis. Of the laboratory parameters, only the findings in MRI, cell count and total protein in the CSF correlated with the global outcome of disease.

The more favourable course and better outcome of TBE in adolescents than in adults documented in this study agrees with the findings of various other authors. Of 363 children up to 14 years of age, whose history was published between 1962 and 1993, 284 (78%) suffered from meningitis, 76 (21%) from meningoencephalitis and three (1%) from encephalomyelitis (Moritsch, 1962; Harasek, 1974; Falk and Lazarini, 1981; Messner, 1981; Helwig *et al.*, 1983; Rakar, 1993; Cizman *et al*., 1999). Most of the children, even the three children with encephalomyelitis who were reported by Harasek and Messner, had a favourable outcome (Harasek, 1974; Messner, 1981). Only Rakar reported on sequelae in 6 out of 160 children (paresis, seizures, emotional disturbance), who were studied between 1978 and 1992 in Slovenia (Rakar, 1993). Owing to the rarity of sequelae, the histories of children with an unfavourable prognosis have been presented mostly as individual reports. Roggendorf and colleagues mentioned a 12-year-old child with severe meningoencephalitis who was discharged from hospital after 9 months with epileptic seizures (Roggendorf *et al.*, 1981*a*). Failure to recognize abdominal symptoms as criteria of the prodromal stage of TBE occurred in the only fatal case of TBE in adolescents so far reported in the literature (Messner, 1981). An 11-year-old boy who lived in an area of risk but had no history of a tick bite and presented with symptoms of vomiting, diarrhoea and marked abdominal pain was operated on under general anaesthesia for suspected appendicitis, but the appendix was normal. Three days later brainstem encephalitis and respiratory insufficiency evolved and 10 days later the boy died. Autopsy showed brainstem haemorrhage and general sinus thrombosis. The general anaesthesia and the stress of the surgical intervention were discussed as contributing factors in the lethal course of the disease in this adolescent. In 1992, Grubbauer and colleagues reported on the youngest child so far (3.5 months of age) with severe meningoencephalitis resulting from TBE, which led to an epileptic state and required neurointensive care with intubation and assisted ventilation (Grubbauer *et al*., 1992). A 1 year follow-up examination showed no abnormalities. The authors recommended active immunization after the first year of life and prophylactic treatment with hyperimmunoglobulin after a tick bite (post-exposure prophylaxis) in endemic areas. However, between 1981 and 1993 this post-exposure prophylaxis was associated with an unfavourable course of disease in at least five children between 1 and 14 years of age (C. Laub and G. Wündisch, unpublished data). MRI of four of these children revealed enhancement of the thalamus (Waldvogel *et al.*, 1996), but similar findings were also demonstrated in five of the nine children of this study. These data and the findings from a further 13 adults who had abnormalities in MRI but had not received post-exposure prophylactic treatment suggest that a causal association between prophylaxis and abnormalities in MRI is rather unlikely. The proof of a causal relationship between post-exposure prophylaxis and a more severe course of TBE in adolescents up to 14 years of age is rather difficult since individual children had received high doses of corticosteroids, antibiotics and antiviral drugs and in all children an unobserved—and possibly causal—earlier tick bite could not be excluded. Due to the risk of a causal relationship between the administration of hyperimmunoglobulin and a severe course of disease, this prophylaxis after a tick bite is not recommended in adolescents up to 14 years of age (Arras *et al.*, 1996). Indeed, in most children and adolescents the natural course of TBE is associated with a favourable outcome, and only in a minor proportion of these patients is the long-term prognosis bad.

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