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Tick-borne encephalitis in Sweden in relation to aseptic meningo-encephalitis of other etiology: a prospective study of clinical course and outcome

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Abstract A total of 149 patients with clinical symptoms of acute viral meningo-encephalitis were enrolled in this study from June 1991 to December 1993. Tick-borne encephalitis (TBE) was diagnosed in 85 of the 149 patients (males 54%, median age 42 years (range 15–78)). The initial clinical appearance of TBE was classified as mild (mainly meningeal; (n = 47), moderate (n = 31) or severe (n = 7), more or less encephalitic. The most common acute symptoms of encephalitis were ataxia (26%), altered consciousness (20%), decreased concentration or memory (9%), irritable response to light and sound (28%), tremor (9%) and dysphasia (9%). Spinal nerve paralysis (11%) occurred in all three clinical stages and did not correlate with the severity or duration of encephalitis. The duration of hospitalisation, the time on the sick-list and the time to recovery were significantly longer in TBE patients. All patients survived, but many patients with TBE suffered an extended period of neurological dysfunction. Of patients with TBE 80% (68/85) showed persisting symptoms of CNS dysfunction on follow-up at week 6, compared with 55% (35/64) of the patients with aseptic meningitis of other aetiology. The corresponding figures after 1 year were 40% (33/83) and 20% (13/64). One year after TBE 13 (28%) patients with initially mild, meningeal symptoms had decreased memory and decreased concentration capacity, dysphasia or ataxia. Spinal nerve paralysis persisted after 1 year in 5 of 9 patients with TBE. In conclusion, TBE in Sweden is associated with a significant morbidity and a post-TBE syndrome existed after 1 year in more than one third of the patients.

Key words Tick-borne encephalitis · Meningo-encephalitis · Viral disease · Cerebrospinal fluid

Introduction

Tick-borne encephalitis (TBE) is caused by a flavivirus related to dengue fever, Japanese B encephalitis and yellow fever viruses. Two subtypes of TBE virus (TBEV) have been identified, one western and one eastern [13, 21, 23]. The TBEV western subtype is transmitted through bites by *Ixodes ricinus* and appears endemic in the Swedish eastern archipelago, the Baltic sea area, Russia and parts of central Europe [20]. The disease has been known in Scandinavia since the early 1940s and the first case was described in Sweden in 1954 [15, 18, 29, 31]. During the last decade the annual incidence in Sweden has been between 40 and 116 reported cases and the seroprevalence in endemic areas is 4–22% [11]. It is estimated that about 0.1–1% of the ticks in endemic areas in Sweden and Finland are carrying the virus [32]. TBEV constitutes a major human pathogenic agent among tick-borne flaviviruses and many patients suffer an extended period of

neurological and cognitive dysfunction [12, 15, 25]. The understanding of pathogenic mechanisms in TBE is incomplete. In a few fatal human cases neuronal necrosis, inflammatory reaction involving blood vessels and spongiform focal necrosis of white and predominantly grey matter have been described [16, 17, 22].

The aim of this prospective study was to describe the clinical course and outcome of TBE in relation to other types of aseptic meningo-encephalitis both during the acute phase and long-term follow-up. A main objective was to investigate the possibility of a definitive post-TBE syndrome.

Patients and methods

After giving informed consent 149 patients (male/female: 70/79) with clinical symptoms and signs of acute viral meningitis with or without encephalitis were enrolled in the study from June 1991 to December 1993. The patients were treated at the Department of Infectious Diseases at Danderyd and Huddinge Hospital, Stockholm. The study comprised 85 of 108 (79%) consecutive patients with a confirmed TBE diagnosis who gave informed consent and a reference group of 64 of 488 patients with aseptic meningo-encephalitis of non-TBE aetiology diagnosed during the study period. Established diagnoses were enteroviral infection in 27 patients (ECHO 30 $n = 6$, ECHO 5 $n = 1$, ECHO 6 $n = 1$, ECHO 11 $n = 1$, Coxsackie A9 $n = 4$, Coxsackie B5 $n = 1$, and not specified $n = 13$), herpes simplex virus type 2 infection (HSV 2) in 11 patients, herpes simplex virus type 1 infection (HSV 1) in 1 patient, and cytomegalovirus infection in 1 patient. In 24 patients the aetiology remained unknown.

Cerebrospinal fluid (CSF) and serum specimens were obtained after a median of 2 days after admission ($n = 131$), range 0–6 (day 2); 9 days ($n = 59$), range 7–19 (day 9); 40 days ($n = 87$), range 21–67 (week 6) and 13 months ($n = 57$), range 11–19 (1 year) after onset of meningo-encephalitis. Samples were stored at –20°C. Clinical examination including neurological status was performed on admission, at week 6 and after 1 year, mainly by two investigators (G. G. and M. H.). In total 147 of 149 patients were followed for 1 year (TBE 83, non-TBE 64). One patient with TBE moved abroad and was lost to follow-up. The remaining TBE patient developed dementia and was excluded from long-term follow-up.

Sero-diagnostic criteria

TBE was diagnosed by the demonstration of specific IgM activity (μm-capture IgM ELISA) in serum [14], verified by a significant rise in complement fixing activity and ELISA IgG activity between acute and convalescent phase sera [19]. In patients recently immunised with TBE vaccine, CNS infection was diagnosed by demonstration of intrathecally produced viral TBE IgM activity.

Enteroviral infection was diagnosed by isolation of virus from CSF ($n = 6$) and/or faecal sample ($n = 11$) in GMK-AH1/RD cells [7], or by demonstration of enteroviral RNA ($n = 11$) by polymerase chain reaction (PCR) in CSF [8]. Extraction was as described for the method "GuSCN-DNA/RNA" [4]. Alternatively, infection was diagnosed by a significant rise in, or high, IgG ($n = 4$) activity in combination with a significant change in paired IgM titres ($n = 22$) [26] or a significant rise in complement fixing activity ($n = 9$).

HSV 1 and 2 CNS infections were diagnosed by the demonstration of HSV DNA in CSF by PCR ($n = 9$) and/or intrathecal production of anti-HSV activity by capture-ELISA in CSF and serum [1, 2, 6]. HSV PCR-DNA analyses were performed in patients with negative TBE IgM analysis.

Extended diagnostic test were performed, including serological tests for *Borrelia burgdorferii* IgM and IgG antibodies in all CSF and serum samples [28], without revealing any dual CNS infections with TBE and borrelia.

Albumin (normal value 0.1–0.3 g/l) and IgG levels in CSF and serum samples were measured by a nephelometric method, and IgG index was calculated as the ratio of albumin (CSF albumin/serum albumin, normal upper limit < 0.006) to IgG (CSF IgG/serum IgG, normal value < 0.65) [30].

Clinical classification of patients with meningo-encephalitis

The acute phase of meningo-encephalitis was classified as mild, moderate or severe depending on meningeal symptoms and the severity of clinical signs of encephalitis and presence of focal CNS signs (Table 1). Mild disease (I) was defined as causing primarily meningeal symptoms. Defined as meningeal symptoms were fever, headache, rigidity of the neck, nausea, vomiting. Moderate disease (II) was defined as the presence of monofocal symptoms and/or moderate diffuse dysfunction of the CNS. Considered as encephalitis were such symptoms as altered consciousness, ataxia, tremor, and dysphasia. The disease was considered severe (III) if multifocal symptoms and/or a severe diffuse dysfunction of the CNS were present at the onset of the disease. The two latter groups (II and III) included patients with primarily signs of encephalitis on admission to the hospital (Table 1). All patients were examined and clinically categorised by the same investigators, at admission, at week 6 and at long-term follow-up.

Table 1 Clinical classification of meningo-encephalitis in patients with tick borne encephalitis (*TBE*, $n = 85$) and aseptic meningoencephalitis of other aetiology (*non-TBE*; $n = 64$) on admission to the hospital and persistence of symptoms of disease at follow up after 6 weeks (median 40 days, range 21–67) and 1 year (median 13 months, range 11–19 months)

Classification of disease	TBE *n* (%)	Not recovered		Non-TBE *n* (%)	Not recovered	
		Week 6 *n* (%)	1 year *n* (%)		Week 6 *n* (%)	1 year *n* (%)
I. Mild	47 (55.3)	36/47 (76.6)	13/47 (27.7)	56 (87.5)	29/56 (51.8)	8/56 (14.3)
• Spinal nerve paralysis	3	2	1	–	–	–
II. Moderate	31 (36.5)	26/31 (83.9)	16/30 (53.3)	5 (7.8)	3/5 (60)	3/5 (60)
• Spinal nerve paralysis	4	4	3	–	–	–
III. Severe	7 (8.2)	6/7 (85.7)	4/6 (66.7)	3 (4.7)	3/3 (100)	2/3 (66.7)
• Spinal nerve paralysis	2	2	1	–	–	–
Total:	85	68/85 (80)	33/83 (39.8)	64	35/64 (54.7)	13/64 (20.3)
Spinal nerve paralysis:	9 (10.6)	8/9 (88.9)	5/9 (55.6)	–	–	–

Statistics

Independent samples were analysed by means of the Mann-Whitney *U*-test; proportions were compared using Fisher's exact test and Spearman rank correlation was used in calculating correlation. Kaplan-Meyer curves were plotted for time to recovery and duration of absence from work (sick list) and Cox regression was used for life-table analysis.

The study was approved by the local ethical committee.

Results

Demographic and epidemiological data

A history of tick-bite during 1–4 weeks before onset of disease was presented by 65 of 85 (77%) of the patients with TBE. Of the TBE patients 74 of 85 (87%) showed a biphasic course of illness with a median duration between first and second onset of disease of 13 days (range 3–40). The first stage of illness, characterised by fever and headache, lasted a median of 4 days (range 1–8) and the latency phase before first onset of meningo-encephalitis was a median of 8 days (range 1–33). Most of the patients had been bitten by ticks in the Swedish eastern archipelago. No certain association between geographical region and severity of disease could be found. Two patients were vaccinated with two injections of inactivated TBE vaccine (FSME vaccine; Immuno, Austria) before the onset of TBE. One patient with severe meningo-encephalitis was immunised the first time 32 days before and the second time 3 days after onset of the first prodromal phase of disease. The other patient was immunised twice, 5 and 2 months before the onset of meningo-encephalitis.

Patients with TBE were significantly older than non-TBE patients ($P < 0.001$), with a median age of 42 years in TBE (range 15–78) and of 34 years (range 16–69) in non-TBE patients. Patients with enteroviral disease ranged in age between 17 and 69 years (median 32 years) and patients with HSV type 2 infection were between 19 and 50 years of age (median 35 years). Among patients with TBE 54% were males; 38% of the non-TBE patients were male. In enteroviral and HSV 2 infections males constituted 44% and 27% of 27 and 11 patients respectively.

Clinical course during acute phase of disease

Of the 85 TBE patients, 55% had mild or predominantly meningeal symptoms; this figure was 88% for the 56 non-TBE patients (Table 1). Encephalitic symptoms, observed in 38 (45%) of the TBE patients and in 8 (13%) of the non-TBE patients, were classified as moderate in 31 TBE patients and in 5 non-TBE patients or severe in 7 and 3 patients respectively. Patients with moderate TBE disease had 1.5 encephalitic symptoms, of which 0.8 were focal, and patients with severe TBE disease had 2.4 encephalitic symptoms, of which 2.0 were focal. Common symptoms in patients with TBE were altered consciousness, decreased concentration and memory, ataxia, tremor, dysphasia and dysaesthesia (Table 2). This complex of symptoms could also be seen in non-TBE patients, though with considerably lower frequency (Table 2). Other symptoms associated with TBE in the acute stage were an irritable response to light and sound, aggressive behaviour, emotional instability, sleep disturbances and pain in the lower limbs. Seizures or hemiparesis were not observed in any of the diagnostic groups. Autonomic dysfunction such as impaired bowel function was not seen.

Among patients with non-TBE disease all enteroviral infections were classified as mild. In the group with moderate to severe encephalitic disease 3 had HSV infections and in 5 cases the aetiology was unknown. Neither in TBE nor in non-TBE patients was there a correlation between higher age and aggravated disease ($P = 0.1$, $P = 0.06$ respectively). Gender did not correlate with the clinical course in TBE or non-TBE patients.

Table 2 Neurological symptoms during acute stage of meningo-encephalitis and at long-term follow-up in patients with TBE and patients with aseptic meningo-encephalitis of other aetiology (non-TBE)

Neurological symptoms	No. of patients (%)					
	Week 1		Week 6		1 year	
	TBE ($n = 85$)	Non-TBE ($n = 64$)	TBE ($n = 85$)	Non-TBE ($n = 64$)	TBE ($n = 83$)	Non-TBE ($n = 64$)
Ataxia	22 (25.9)	1 (1.6)	11 (12.9)	1 (1.6)	6 (7.2)	1 (1.6)
Altered consciousness[a]	17 (20.0)	4 (6.3)	1 (1.2)	–	–	–
Light and sound irritability	24 (28.2)	38 (59.4)	4 (4.7)	7 (10.9)	1 (1.2)	–
Decreased concentration	5 (5.9)	2 (3.1)	14 (16.5)	3 (4.7)	7 (8.4)	2 (3.1)
Decreased memory	3 (3.5)	–	14 (16.5)	3 (4.7)	9 (10.8)	3 (4.7)
Dysphasia	8 (9.4)	–	10 (11.8)	–	5 (6.0)	–
Tremor	8 (9.4)	1 (1.6)	13 (15.3)	2 (3.1)	2 (2.4)	1 (1.6)
Dysaesthesia	11 (12.9)	1 (1.6)	5 (5.9)	3 (4.7)	2 (2.4)	1 (1.6)
Seizures	–	–	–	–	–	–
Cranial nerve paralysis[b]	2 (2.4)	–	1 (1.2)	–	2 (2.4)	–
Spinal nerve paralysis[c]	9 (10.6)	–	8 (9.4)	–	5 (6.0)	–

[a] Somnolence, slow cerebration, mental confusion, irritability

[b] Two patients with acute diplopia, one patient with hearing loss after 6 weeks and two patients with hearing loss after 1 year

[c] Including two patients with tetraparesis and one patient with paralysis of the urinary bladder

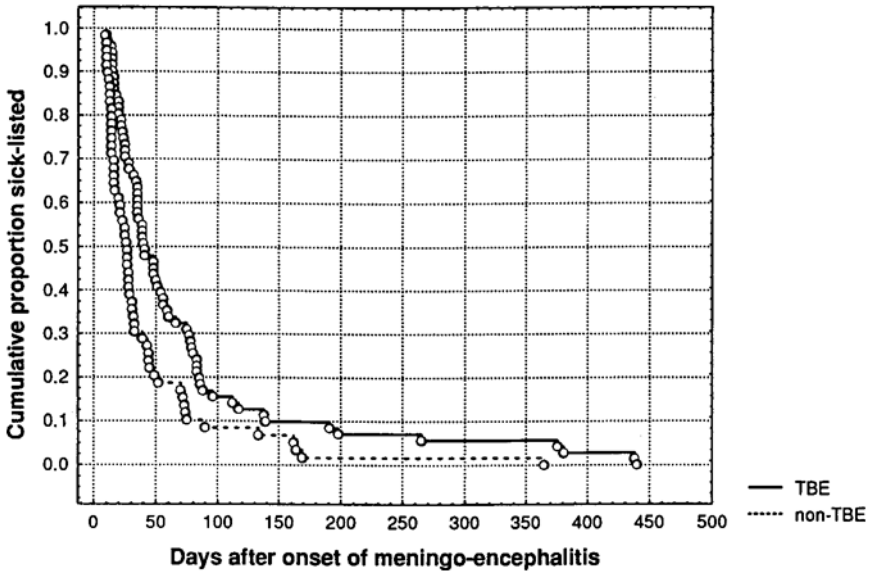

Fig. 1 Kaplan-Meyer life-table analysis of the cumulative proportion of patients sick-listed (out of work) in tick-borne encephalitis (*TBE*, $n = 71$) versus the non-TBE ($n = 59$) group. Students and pensioners excluded. The difference between groups was significant ($P = 0.0019$)

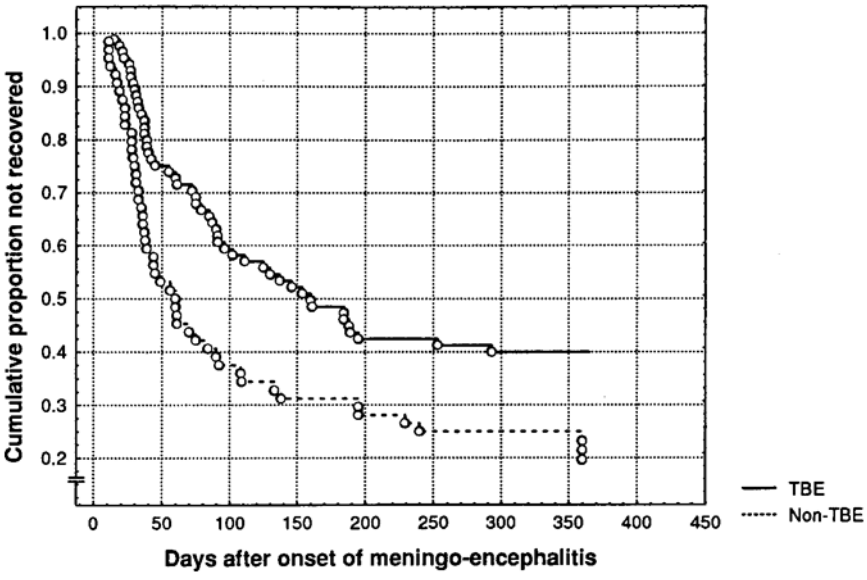

Fig. 2 Kaplan-Meyer life-table analysis of the cumulative proportion of patients who did not recover in the TBE ($n = 85$) versus the non-TBE ($n = 64$) group. The difference between groups was significant ($P = 0.0028$)

Nine of 85 patients with TBE (11%) developed severe myelitis and/or radiculitis followed by paralysis of the spinal nerves during the acute phase of disease after a median of 6 days (range 1–17). Spinal nerve paralysis together with mild disease, without obvious clinical signs of encephalitis, was found in 3 patients and in 2 and 4 patients with severe or moderate disease respectively (Table 1). Six patients developed paralysis of shoulder muscles, in 2 cases bilaterally. One patient had paralysis of the urinary bladder that resolved within 14 days. Tetraparesis occurred in 2 patients, in 1 patient combined with paralysis of the intercostal muscles and diaphragm requiring assisted ventilation and in the other combined with aphasia. The appearance of spinal nerve paralysis following myelitis and/or radiculitis in TBE patients did not seem to be associated with the severity of disease (defined as mild, moderate or severe); paralysis could occur together with minor or extensive symptoms of encephalitis. Spinal nerve paralysis was not seen in non-TBE patients.

Outcome and long-term follow-up

The duration of hospital treatment was significantly longer ($P < 0.001$) in TBE patients (median 7 days, range 0–262 days) than in non-TBE patients (median 3.5 days, range 0–20 days). It was observed that women with TBE required a longer hospital stay than men ($P = 0.002$). In TBE patients, increasing age correlated with the length of hospital treatment ($P = 0.003$, $r_s = 0.33$), but not in non-TBE patients. Three patients with TBE and one with non-TBE were treated as out patients.

Table 3 Symptoms 1 year after onset of meningo-encephalitis in patients (n = 83) with TBE in relation to clinical classification in acute stage of disease

Neurological symptoms	Severity of disease		
	Mild (n = 13/47) No of patients	Moderate (n = 16/30)	Severe (n = 4/6)
Ataxia	2	4	–
Decreased concentration	3	4	0
Decreased concentration/ memory	3	4	2
Dysphasia	2	2	1
Dysaesthesia	1	1	0
Tremor	–	2	–
Sound and light irritability	–	–	1
Seizures	–	–	–
Headache	4	4	1
Hearing loss	1	1	–
Spinal nerve paralysis	1	3	1

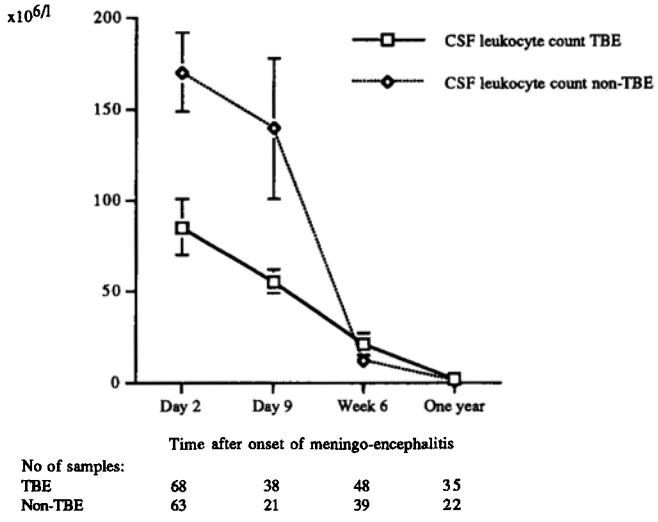

Fig. 3 CSF leucocyte count (× 10^6/l) in patients with TBE (n = 72) and non-TBE patients (n = 61). Mean and SEM

The time off work (students and pensioners excluded) was significantly longer in TBE patients (Fig. 1). The further increased risk (overrisk) of returning to work in non-TBE versus TBE patients was 68%. The relative risk to remain on the sick list after TBE compared with non-TBE was 0.41, with a lessened risk of 59% (subrisk) of returning to work in TBE patients relative to non-TBE patients (P = 0.0019). The time to total recovery, i.e. asymptomatic state, was longer in TBE than in non-TBE patients (Fig. 2). There was an overrisk to recover completely from non-TBE of 82% relative to TBE. The relative risk not to recover totally from TBE versus non-TBE during the follow-up period was 0.45. That means a subrisk of 55% to

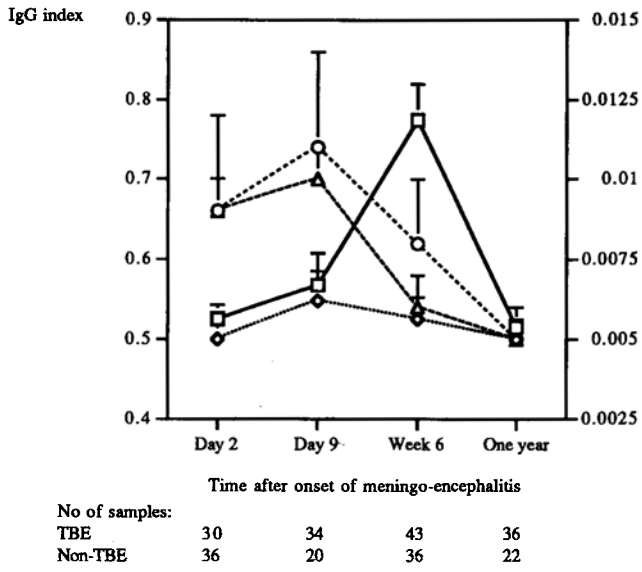

Fig. 4 CSF/serum IgG index and albumin ratio in patients with TBE (n = 85) and non-TBE patients (n = 64). Geometric mean and SEM; —□— IgG index TBE, ---◇--- IgG index non-TBE, ---○--- Albumin ratio TBE, —△— Albuminum ratio non-TBE

recover from TBE relative to non-TBE (P = 0.0028). Within 2 months 26.5% of the TBE patients and 48% of patients with non-TBE recovered totally.

Clinical follow-up after 6 weeks was possible in 149 patients and after 1 year in 147 patients (Tables 1, 2). Clinical symptoms at follow-up, such as impairment of memory and concentration capacity, ataxia, tremor, dysphasia and in TBE persisting spinal nerve paralysis, were significantly more common at week 6 (P < 0.001) and after 1 year (P = 0.006) in TBE than in other types of aseptic meningo-encephalitis. All patients who had recovered after 6 weeks were still healthy at 1 year follow-up.

Clinical symptoms at follow-up after 1 year

The most frequent symptoms at 1 year after TBE were decreased memory, impaired concentration capacity, ataxia, dysphasia and tremor. No mortality was observed during the study period. Even though the TBE patients with moderate or severe disease had recovered less at 1 year, it should be mentioned that 13 (28%) of the TBE patients with mild disease had symptoms at 1 year. The symptoms of the latter were decreased memory and concentration capacity, but also dysphasia or ataxia in 2 patients each (Table 3). In TBE patients with initially moderate or severe disease 16 (53%) and 4 (67%) respectively of the patients had not recovered at 1 year follow-up (Table 1). Tetraparesis in 2 patients and bilateral paralysis of the shoulder muscles in 3 patients persisted after 1 year (Table 3). In the non-TBE group, 4 patients with HSV type 2, 1 with HSV type 1, 4 with enteroviral disease and

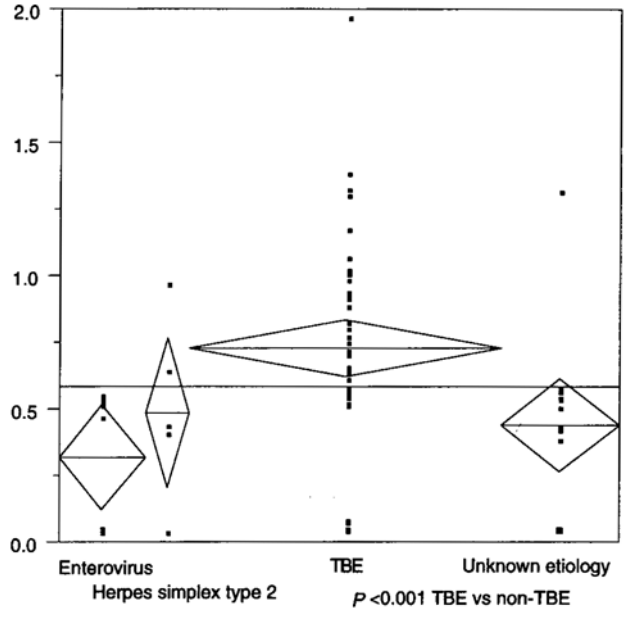

Fig. 5 IgG index at week 6 in patients with TBE (n = 43), enteroviral disease (n = 12), herpes simplex type 2 meningo-encephalitis (n = 5) and aseptic meningo-encephalitis of unknown aetiology (n = 17). Icons: the *central bar* represents the group mean, the *height* represents 95% confidence interval and the *width* represents the sample size. The Mann-Whitney U-test was used for the statistics

4 with disease of unknown aetiology still had symptoms after 1 year, the most prominent being decreased memory and concentration capacity but no other focal abnormalities. Relapses with headache and meningeal symptoms were common in patients with HSV 2 infection. Frequent headache persisted after 1 year in 9 of 83 (11%) of the patients with TBE and in 5 of 64 (9%) of the non-TBE patients.

There was a positive correlation between age and protracted symptoms after 1 year in non-TBE but not in TBE patients ($P = 0.003$). TBE patients who had completely recovered within 6 weeks showed a longer interval between first illness and onset of meningo-encephalitis ($P < 0.05$).

In 4 patients with spinal nerve paralysis, the paralysis had disappeared in a median of 96.5 days, range 14–197. Tetraparesis in 2 patients and bilateral shoulder paralysis persisted after 1 year.

CSF findings in TBE compared with non-TBE patients

The CSF leucocyte counts during TBE and non-TBE are shown in Fig. 3. TBE patients had significantly lower CSF leucocyte counts during the acute stage of disease than non-TBE patients ($P = 0.0002$). Only 27% (18/68) of patients with TBE had a CSF leucocyte count exceeding 100×10^6/l in CSF during the first 6 days of meningo-encephalitis compared with 51% (32/63) of the non-TBE patients ($P = 0.002$). The initial mean proportion of mononuclear cells was 60% in TBE and 76% in non-TBE. The proportion increased in both TBE and non-TBE during the course of disease and was 87% and 94% after 9 days respectively.

CSF albumin was initially higher in non-TBE (geometric mean 0.49 g/l, range 0.15–2.0) than in TBE (geometric mean 0.43 g/l, range 0.19–2.0). The difference was not statistically significant. However, in TBE CSF albumin increased during the course of disease and still remained elevated at week 6. In non-TBE, on the other hand, levels were normal at 6 weeks (geometric mean 0.24 g/l, range

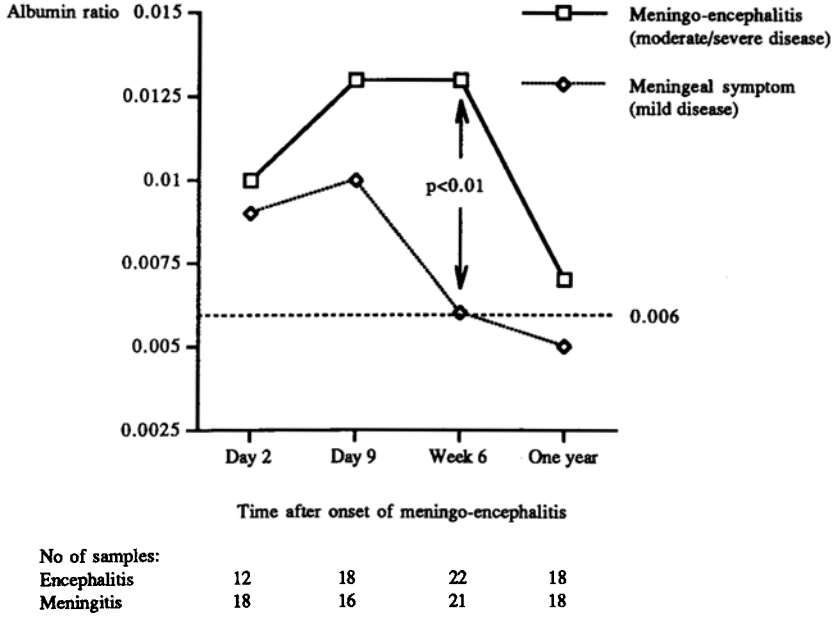

Fig. 6 CSF/serum albumin ratio in TBE patients with severe or moderate disease (primarily encephalitis; n = 38) and patients with mild disease (primarily meningeal symptoms; n = 47). Reference value < 0.006. Geometric mean and SEM. The Mann-Whitney U-test was used for the statistics

0.1–0.46) and significantly lower ($P < 0.01$) than in TBE (geometric mean 0.34 g/l, range 0.14–1.55).

During the first weeks of disease the majority of patients in both groups showed damage of the blood-brain barrier as demonstrated by the CSF/serum albumin ratio (Fig. 4). TBE patients had a significantly higher albumin ratio at week 6 compared with the non-TBE group (Fig. 4), indicating a more intense and serious degree of blood-brain-barrier damage ($P = 0.03$). Intrathecal IgG synthesis, expressed by the IgG index, showed no differences between the groups in the acute phase of disease (day 2 and 9, Fig. 4). At week 6, 27 of 43 (63%) TBE patients and 3 of 35 (9%) patients in the non-TBE group showed an elevated IgG index, verifying an intense IgG synthesis intrathecally with a significantly higher index in TBE than in non-TBE patients ($P < 0.0001$) (Fig. 4). The distribution of IgG synthesis between established viral diagnoses is shown in Fig. 5. There was a significant difference between TBE and other types of aseptic meningo-encephalitis and enteroviral disease ($P < 0.001$), indicating a prominent intrathecal IgG synthesis in TBE. Patients with clinical neurological signs of moderate or severe TBE disease, primarily encephalitis, had a higher albumin ratio during the acute phase of disease at day 2, day 9, week 6 and at long-term follow-up (Fig. 6). Week 6 geometric mean levels of albumin ratio were significantly higher in patients with obvious encephalitis than in those without ($P < 0.01$).

There was no correlation between blood-brain-barrier damage (albumin ratio) and IgG index or encephalitis and elevated IgG index. No significant differences could be observed between mild or moderate to severe disease in TBE during the course of disease with regard to any other CSF parameters described, with the exception of the albumin ratio at week 6. There was no significant correlation between CSF leucocyte count, IgG index or CSF/serum albumin ratio and outcome after 6 weeks and 1 year in TBE or non-TBE patients.

Discussion

The present prospective study confirmed that TBE causes long-lasting, mainly cognitive CNS dysfunction. TBE showed persisting morbidity after 6 weeks in as many as 4 out of 5 and after 1 year in more than one third of the patients. The corresponding morbidity figures for non-TBE patients were lower, 55% and 20% respectively. There was no mortality in either group. Three different clinical courses in TBE may be identified according to the results of this study. One is with complete recovery in 2 month (1/4 of the patients), as found in most types of enteroviral meningo-encephalitis and other non-TBE disorders. A second group has a protracted course with cognitive symptoms and other neurological dysfunctions of longer duration and a third group has prolonged spinal nerve paralysis, probably due to myelo-radiculitis.

The results of our study were based on a carefully defined and controlled group of consecutive TBE patients. It allows conclusions concerning the rate of symptoms and sequelae, as well as comparisons with aseptic meningo-encephalitis of other aetiology. The vast majority of patients in this study were diagnosed as having TBE. Patients with other types of aseptic meningo-encephalitis were included prospectively as controls and do not reflect the real incidence over the time period studied. Non-TBE patients with mild disease did not agree to participate in the study more often than TBE patients. This selection bias probably resulted in an underestimation of the differences between TBE and non-TBE.

In viral CNS infections, depending on the causative agent and individual immune response, there is a scale from more or less serious symptoms and signs of meningitis to apparent encephalitis with focal or multifocal symptoms. We found that the clinical course in TBE was dominated by encephalitis in nearly half of the patients, as compared with one out of eight of the patients with non-TBE aetiology. This clinical observation was consistent with the fact that damage of the blood-brain barrier was more protracted in TBE patients than in non-TBE patients and still persisted after 6 weeks of disease. Furthermore, the CSF leucocyte count was lower in TBE than in non-TBE patients. This indicated a disparity between the T-cell response that causes meningeal reaction and the response to other inflammatory mediators in TBE compared with non-TBE. Long-term sequelae are frequently encountered in HSV type 1 meningo-encephalitis [27] as a result of a lytic viral infection, viral replication in the CNS but, in particular, a long-lasting inflammatory reaction. In TBE it is difficult to detect viral RNA during the encephalitic stage of disease [24], indicating that the main pathogenic mechanism may be due to inflammatory mediators [10], even if TBEV may be concealed in the neurons without leaking into the CSF.

Paralysis of the spinal nerves may be considered as a separate entity distinguished from symptoms dominated by diffuse, more or less severe, CNS dysfunction. The course of myelitis and/or radiculitis was different independent of the presence of encephalitic symptoms. The pathogenic pathway of these entities is not clear. Our knowledge, based on previous literature, comprises data from a few autopsies in rapidly fatal cases. The primary pathological changes were found in mesencephalon, brain stem, cortex of the cerebellum and the spinal cord, predominantly involving grey matter, but also white matter. Neuronal degeneration could be demonstrated post mortem in the spinal cord in rapidly fatal cases not easily distinguishable from poliomyelitis [3, 5, 9].

Long-lasting cognitive and serious neurological dysfunctions, such as spinal nerve paralysis, induced by TBE have been described previously in retrospective studies [12, 15]. Permanent sequelae have been considered unusual. This opinion was contradicted by our findings:

40% of the patients showed encephalitic symptoms after 1 year and 56% of the patients with spinal nerve paralysis were still paretic at long-term follow-up. This indicated that patients with TBE may develop a post-TBE syndrome characterised by cognitive dysfunctions such as impairment of memory and decreased ability to concentrate, both expressive and impressive dysphasia and sometimes persisting spinal nerve paralysis. This was not seen in aseptic meningitis of other origins. The previous observations in a retrospective follow-up study that headache and hearing loss was of special significance in TBE [12] could not be verified by data in the present study. Only 9 of our 33 patients suffered from long-term headache and 2 from hearing loss after 1 year. However, the difference in follow-up time between these two studies must be taken into consideration. Cognitive dysfunctions and sleep disturbances persisting for many years may result in headache and other secondary impairments. The observation, in two recent studies, that severity of TBE increased with age [12, 18] was not apparent in this study, although the median age of the TBE patients was more than a decade higher than in the non-TBE patients. Instead, a greater proportion of elderly patients in the non-TBE group suffered from persistent symptoms at long-term follow-up. Increasing age and male gender seem to be risk factors for acquiring TBE disease. Nevertheless, patients suffering from cognitive and neurological dysfunction for 3–10 weeks or 1 year were significantly more common in TBE patients than in patients with aseptic meningitis of other aetiologies. Patients infected with HSV 2 had a tendency to relapse with predominantly meningeal symptoms. Documented enteroviral infection had a more benign course. Only 4 of 27 patients showed symptoms after 1 year, indicating that clinical follow-up in this category of patients is not required on a routine basis.

The results of the present study strongly support previous observations from non-controlled and retrospective studies that a post meningo-encephalitic syndrome, impairing quality of life, occurs after TBE. Thus, in the endemic areas, TBE causes high costs for the health care system with long periods of hospitalisation, inability to work as well as long-lasting neurological symptoms and social distress of the patients. The need for further investigations concerning the pathogenesis of TBE is obvious in order to translate neuropsychological findings into biomedical terms to allow the exploration of future treatment possibilities, besides active immunisation programmes.

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