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RESEARCH

Cerebrospinal fluid findings and their temporal pattern in patients with different clinical presentations of tick-borne encephalitis; a cohort study

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Abstract

Objectives There is a lack of systematic data on cerebrospinal fluid (CSF) findings in the different clinical manifestations of tick-borne encephalitis (TBE) and according to the duration of neurological involvement. This study aims to evaluate and compare routine CSF parameters in TBE patients presenting with meningitis, meningoencephalitis, or meningoencephalomyelitis, and to assess temporal changes in CSF during the first 10 days after the onset of neurological symptoms.

Methods We analysed 15 CSF parameters in 717 consecutive adult patients hospitalized for TBE at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia. Among these patients, 230 (32%) had meningitis, 446 (62%) meningoencephalitis, and 41 (6%) meningoencephalomyelitis.

Results CSF findings differed significantly among the three clinical presentations. Leukocyte count, neutrophil proportion, protein levels, immunoglobulin concentrations (IgM, IgG, IgA), and intrathecal synthesis quotients were highest in meningoencephalomyelitis and lowest in meningitis. These differences remained largely significant after adjusting for confounding factors. CSF abnormalities were detectable from day one of neurological symptoms, peaked around days 4–5, and then stabilized or showed mild improvement. Neutrophils predominated during the first two days, followed by a predominance of lymphocytes and monocytes from day 3 onward. This pattern was consistent in meningitis and meningoencephalitis but less pronounced in meningoencephalomyelitis.

Conclusions Clinical manifestations of TBE exhibit distinct CSF profiles. Abnormalities are most pronounced in meningoencephalomyelitis and least in meningitis. These alterations appear early, peak within the first days, and then stabilize or improve, although this pattern is less predictable in meningoencephalomyelitis.

Keywords Tick-borne encephalitis · Meningitis · Meningoencephalitis · Meningoencephalomyelitis · Cerebrospinal fluid

Introduction

Tick-borne encephalitis (TBE) is an inflammation of the central nervous system caused by the TBE virus. Among the three main subtypes that infect humans, the European TBE virus subtype is predominantly found in Europe and is the only confirmed cause of TBE in Slovenia [1, 2].

In 56–87% of patients infected with the European subtype, the disease follows a biphasic course, where a febrile illness precedes the inflammation of the central nervous system [3–12]. However, some patients do not exhibit an apparent initial phase and present directly with neurological involvement. In adults, TBE manifests as meningitis in approximately 50% of cases, as meningoencephalitis in about 40%, and as meningoencephalomyelitis in around 10% [13]. Nonetheless, the frequencies of these neurological forms vary across studies [3, 6, 7, 14, 15]. In children, meningitis is more common, whereas meningoencephalitis and meningoencephalomyelitis occur less frequently than in adults [16, 17]. The case fatality rate for TBE caused by the European TBE virus subtype is between 0.5% and 2%,

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and it generally increases with age [13, 18]. At least one-third of patients experience postencephalitic syndrome, and approximately 5% suffer from permanent paresis [3, 6, 19].

Although the clinical presentation of TBE is well described, there is a lack of precise, systematic data on cerebrospinal fluid (CSF) findings across different clinical forms of the disease, as well as in relation to the duration of neurological involvement.

The aim of this study was to evaluate and compare routine CSF findings in patients with the main clinical forms of TBE (meningitis, meningoencephalitis, and meningoencephalomyelitis), and to gain insight into the temporal dynamics of CSF changes during the first 10 days after the onset of neurological symptoms.

Patients and methods

Patients

Fifteen CSF parameters, obtained as a part of routine clinical diagnostics, were analyzed in 717 consecutive adult patients hospitalized for TBE at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia, between 2007 and 2012. The clinical presentation of this prospectively followed cohort has been reported previously [20]. The findings were compared: i) according to the three main clinical forms of the disease—meningitis, meningoencephalitis, and meningoencephalomyelitis; and ii) according to the duration of neurological signs and symptoms.

Definitions

TBE

All patients met the following three criteria: clinical symptoms/signs of central nervous system involvement, CSF pleocytosis ($>5\times10^6$/L leukocytes), and evidence of recent TBE virus infection, confirmed by the presence of both IgM and IgG antibodies to the virus in serum.

Main forms of TBE

Patients were categorized as having [19, 20]:

a) *Meningitis*—if they presented only with symptoms/signs of meningeal inflammation (fever, headache, nausea, vomiting, neck stiffness);
b) *Meningoencephalitis*—if they exhibited signs of brain tissue involvement (e.g., impaired consciousness, cognitive or concentration disturbances, tremor of extremities, tongue fasciculations, seizures) in addition to signs of meningitis; or
c) *Meningoencephalomyelitis*—if they also had flaccid pareses.

Biphasic and monophasic course

A biphasic course was defined as neurological involvement preceded by a nonspecific febrile illness followed by an improvement lasting at least one day and up to one month. A monophasic course was defined as the direct onset of central nervous system involvement without a preceding febrile phase.

Duration of neurological signs/symptoms

The duration of signs and symptoms suggesting central nervous system involvement was defined as the number of days from the onset of neurological manifestations (meningitis, meningoencephalitis or meningoencephalitis) to CSF examination, which typically took place upon hospital admission.

Antibodies to TBE virus

Serum IgM and IgG antibodies against the TBE virus were determined using Enzygnost® Anti-TBEV (IgM, IgG) kits (Dade Behring Marburg GmbH, Marburg, Germany), following the manufacturer's instructions.

CSF parameters

CSF was analyzed for cell counts, protein, and glucose concentrations. A leukocyte count $>5\times10^6$/L (pleocytosis) and protein concentration >0.45 g/L were considered abnormal. The concentrations of neutrophils and mononuclear leukocytes in CSF were determined, and the percentage of neutrophils was calculated. CSF glucose levels and the CSF-to-blood glucose ratio were also recorded. Immunoglobulin classes M, G, and A (IgM, IgG, and IgA, respectively) and albumin levels were measured in both serum and CSF, with corresponding quotients calculated. Elevated quotients were interpreted as indicative of blood–brain barrier disruption.

Methods used for the determination of these parameters, and corresponding reference values, are provided in the Supplementary File.

Statistical analyses

Continuous variables were summarized using medians and interquartile ranges (IQRs), while categorical variables were presented as counts and percentages. Comparisons among disease forms were assessed using the Kruskal–Wallis test by ranks for overall differences in continuous variables, followed by the Wilcoxon rank-sum test for pairwise

comparisons between TBE forms. Fisher's exact test was used for categorical variables.

Multinomial logistic regression analyses were conducted to assess associations between TBE form and selected clinical and CSF parameters. Covariates included in the models were preselected by clinical experts (P.B. and F.S.) and selected independently of outcome data. Patients with meningitis served as the reference group in all regression models. Results were reported as odds ratios (ORs) with 95% CIs, and corresponding p-values were calculated using Wald tests. A p-value < 0.05 was considered statistically significant. Where appropriate, p-values were adjusted for multiple comparisons. All analyses were performed using R software [21].

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Republic of Slovenia (No. 0120–441/2025–2711-3). The Ethics Committee waived the need for written informed consent.

Results

Among 717 patients with TBE (408 males, 309 females; median age 54 years, interquartile range [IQR] 41–64 years), 230 (32.1%) presented with meningitis, 446 (62.2%) with meningoencephalitis, and 41 (5.7%) with meningoencephalomyelitis. A total of 26 patients (3.6%) had received at least two doses of the TBE vaccine.

The median duration of neurological symptoms before hospital admission and lumbar puncture was 5 days in patients with meningitis, and 4 days in those with meningoencephalitis or meningoencephalomyelitis (p = 0.008). Patients with meningitis were significantly younger (median 50 years) compared to those with meningoencephalitis (54 years) and meningoencephalomyelitis (59 years); p < 0.001. Vaccine breakthrough TBE was least common in patients with meningitis (1.7%) and more frequent in those with meningoencephalitis (4%) or meningoencephalomyelitis (9.8%); p = 0.031. There were no statistically significant differences in sex distribution (55%, 57%, and 66% males in the meningitis, meningoencephalitis, and meningoencephalomyelitis groups, respectively; p = 0.448) or in the proportion of patients with a biphasic disease course (64%, 59%, and 49%, respectively; p = 0.121) (Table 1).

Significant differences were observed among the three groups in CSF findings, including leukocyte count, neutrophil proportion, glucose concentration, total protein and albumin levels, as well as concentrations of IgM, IgG, and IgA, and albumin and immunoglobulin indexes (Table 2). These abnormalities were most pronounced in patients with meningoencephalomyelitis and least severe in those with meningitis (Fig. 1). Most of these differences remained statistically significant in a multinomial regression model adjusted for sex, age, biphasic disease course, and duration of neurological involvement prior to lumbar puncture (Table 3).

Table 1 Basic findings in a cohort of 717 patients with tick-borne encephalitis

Parameter	All n = 717	M n = 230	ME n = 446	MEM n = 41	p
Age (years)	54 (41–64)	50 (38–60)	54 (41–66)	59 (52–68)	< 0.001
Sex (female)	309 (43.1)	103 (44.8)	192 (43.0)	14 (34.1)	0.448
Biphasic course*	422 (59.9) 705	146 (64.3) 227	257 (58.5) 439	19 (48.7) 39	0.121
Duration of neurological symptoms (days)*	4 (3–6) 655	5 (3–7) 210	4 (3–6) 408	4 (2–5) 37	0.008
Vaccinated against TBE**	26 (3.6)	4 (1.7)	18 (4.0)	4 (9.8)	0.031
Concommitant Lyme neuroborreliosis***	22/661 (3.3)	8/213 (3.8)	13/413 (3.1)	1/35 (2.9)	0.911

All numeric values are presented as median (IQR) or number (%)

M Meningitis, *ME* Meningoencephalitis, *MEM* Meningoencephalomyelitis, *TBE* Tick-borne encephalitis

*The second row in each cell indicates the number of valid cases

**At least 2 doses of TBE vaccine: 16 patients with complete and 10 patients with incomplete basic vaccination with FSME-IMMUN®. Of 16 patients with complete basic vaccination, 12 had received three doses of TBE vaccine, the others at least one booster; in 5 (31.3%) patients the time interval was longer than recommended. In the subgroup of 10 patients with incomplete basic vaccination the median time interval between the last dose of TBE vaccine and illness onset was 3 (1–120) months

***Of 661 patients for whom information was available, 22 fulfilled laboratory criteria for confirmed LNB, i.e., demonstration of borrelial intrathecal antibody synthesis and/or isolation of *Borrelia* from cerebrospinal fluid

Table 2 Cerebrospinal fluid findings in patients with three different clinical manifestations of tick-borne encephalitis

CSF findings	All n = 717	M n = 230	ME n = 446	MEM n = 41	p M vs ME	p M vs MEM	p ME vs MEM
Leukocytes ($\times 10^6$/L)	86 (44–154) 717	85 (42–137) 230	84 (42–155) 446	144 (90–309) 41	> 0.999	< 0.001	0.005
Neutrophils	30 (11–57) 713	23 (10–43) 229	32 (14–59) 443	75 (11–164) 41	0.002	0.002	0.105
Lymphocytes	42 (17–87) 713	48 (20–87) 229	37 (16–85) 443	64 (27–127) 41	0.624	0.502	0.152
Neutrophils/Leukocytes	0.38 (0.20–0.60) 713	0.31 (0.13–0.54) 229	0.41 (0.23–0.62) 443	0.53 (0.25–0.78) 41	< 0.001	0.024	0.807
Protein (g/L)	0.70 (0.54–0.92) 716	0.66 (0.53–0.83) 230	0.71 (0.54–0.95) 445	0.91 (0.60–1.17) 41	0.228	0.004	0.077
Glucose CSF (mmol/L)	3.00 (2.70–3.30) 711	2.90 (2.60–3.20) 230	3.00 (2.70–3.40) 442	3.10 (2.70–3.50) 39	0.078	0.366	> 0.999
Glucose CSF/blood	0.53 (0.47–0.58) 690	0.53 (0.47–0.59) 222	0.53 (0.47–0.58) 432	0.53 (0.48–0.58) 36	> 0.999	0.836	> 0.999
IgM (mg/L)	2.88 (1.52–4.92) 536	2.61 (1.47–4.44) 175	2.90 (1.54–4.77) 331	6.74 (3.08–12.5) 30	> 0.999	< 0.001	< 0.001
IgG (mg/L)	55.2 (41.8–77.3) 538	53.1 (40.7–72.2) 175	55.1 (41.7–79.2) 332	67.9 (48.0–102) 31	> 0.999	0.015	0.096
IgA (mg/L)	7.23 (4.59–10.9) 536	6.58 (4.75–9.52) 175	7.07 (4.46–11.3) 331	16.1 (7.74–24.1) 30	> 0.999	< 0.001	< 0.001
Albumin (mg/L)	428 (336–562) 538	408 (324–527) 175	433 (337–558) 332	542 (382–816) 31	> 0.999	0.012	0.056
IgM quotient	2.16 (1.29–3.74) 535	1.98 (1.30–3.12) 175	2.19 (1.24–3.86) 330	4.36 (2.15–9.97) 30	> 0.999	< 0.001	< 0.001
IgG quotient	5.15 (3.98–6.89) 538	4.83 (3.90–6.25) 175	5.20 (3.97–7.30) 332	6.61 (4.79–10.8) 31	0.522	0.003	0.050
IgA quotient	3.30 (2.37–4.54) 534	3.15 (2.25–4.10) 175	3.35 (2.42–4.60) 329	5.45 (3.51–9.26) 30	0.462	< 0.001	< 0.001
Albumin quotient	10.3 (7.89–13.9) 538	9.95 (7.70–12.5) 175	10.5 (7.88–14.2) 332	13.8 (9.25–21.1) 31	0.462	0.003	0.050

All numeric values are presented as median (interquartile range), rounded to three significant digits. The second row in each cell indicates the number of valid cases. p-values are corrected for multiple comparisons using the false discovery rate (FDR) method

CSF Cerebrospinal fluid, *M* Meningitis, *ME* Meningoencephalitis, MEM Meningoencephalomyelitis, *IgM* Immunoglobulin class M, *IgG* Immunoglobulin class G, *IgA* Immunoglobulin class A

The duration of neurological symptoms before hospital admission and lumbar puncture ranged from 1 to 21 days, with most patients enrolled between days 2 and 5 after symptom onset (Fig. 2). The temporal evolution of CSF parameters during the first 10 days of illness is shown in Fig. 3. Most CSF abnormalities were already evident on the first day of neurological symptoms, worsened during the first 4–5 days, and then either stabilized or gradually improved. One notable exception was the proportion of neutrophils in CSF: neutrophils predominated during the first two days, while from day 3 onward, lymphocytes and monocytes were more common (Fig. 4). This general pattern was observed in patients with meningitis and meningoencephalitis, but was less consistent in those with meningoencephalomyelitis (Figs. 3, 5).

Discussion

Although TBE was first reported as early as 1931 [22], and its clinical presentation is well characterized, precise and systematic data on CSF findings across different clinical manifestations or according to the duration of central nervous system involvement remain scarce. A PubMed literature search revealed only a few reports that link routine CSF parameters, predominantly protein concentration, to

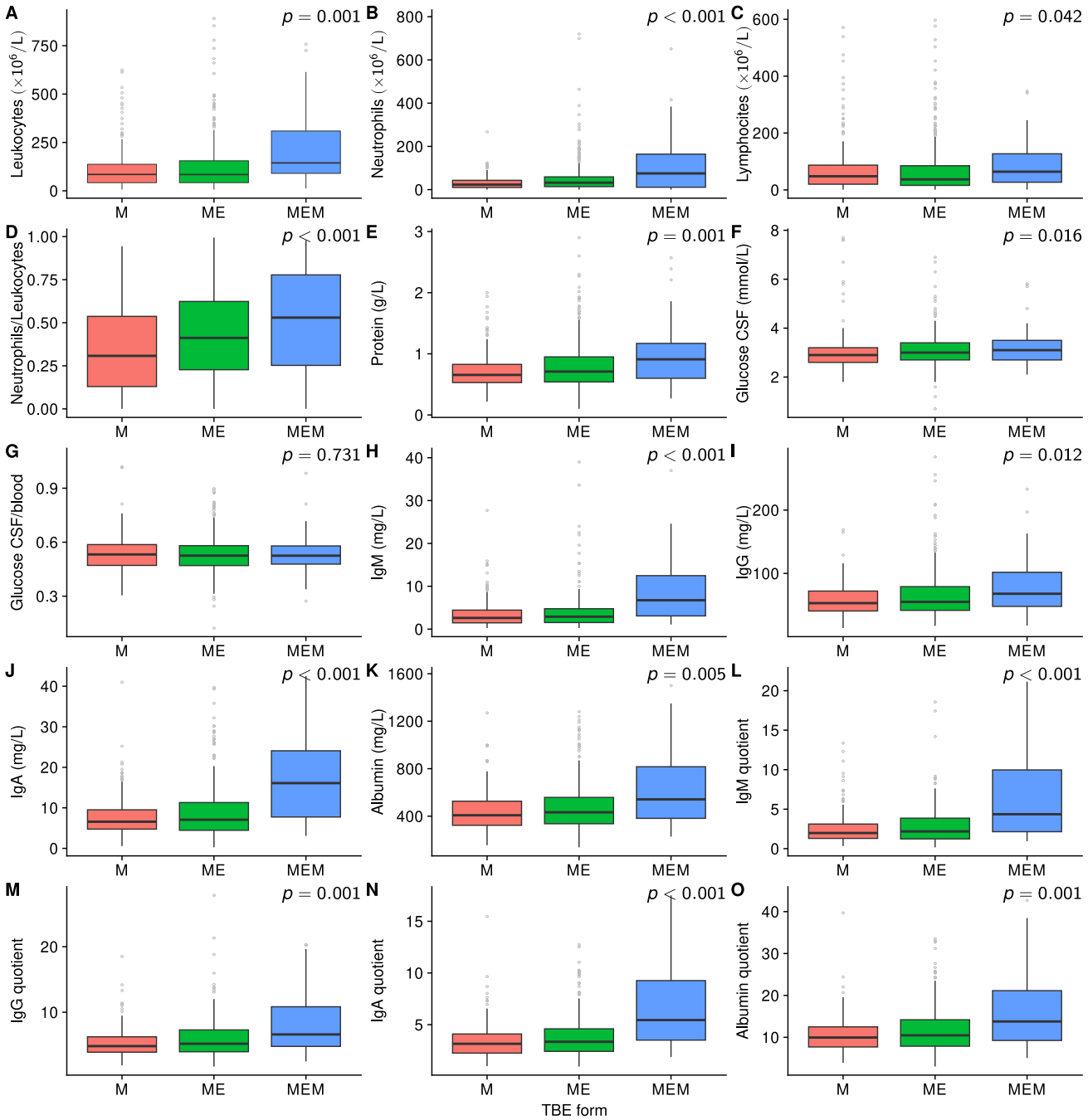

Fig. 1 Comparison of 15 routine cerebrospinal fluid parameters in patients with the main clinical manifestations of tick-borne encephalitis (TBE): meningitis (M), meningoencephalitis (ME) and meningoencephalomyelitis (MEM)

the severity of TBE [4, 5, 14, 23]. However, the severity of acute illness only roughly correlates with clinical manifestations. While meningitis is generally considered the mildest form of TBE, both meningoencephalitis and meningoencephalomyelitis can vary substantially in severity. As meningoencephalitis is considerably more common than meningoencephalomyelitis (with a ratio of nearly 11:1 in our cohort), its features dominate when findings

Table 3 Summary of multinomial logistic regression models for crude and adjusted odds ratios across outcome categories

	Crude			Adjusted		
Term	OR	95% CI	p	OR	95% CI	p
TBE form: Meningoencephalitis						
Leukocytes ($\times 10^6$/L)	1.001	(1.000, 1.002)	0.201	1.002	(1.000, 1.003)	0.099
Neutrophils ($\times 10^6$/L)	1.010	(1.005, 1.015)	< 0.001	1.011	(1.006, 1.016)	< 0.001
Lymphocytes ($\times 10^6$/L)	0.999	(0.997, 1.001)	0.391	1.000	(0.998, 1.002)	0.791
Neutrophils/Leukocytes	1.450	(1.225, 1.717)	< 0.001	1.444	(1.190, 1.753)	< 0.001
Protein (g/L)	1.282	(1.066, 1.541)	0.018	1.345	(1.097, 1.648)	0.009
Glucose, CSF (mmol/L)	1.121	(0.884, 1.423)	0.391	1.012	(0.792, 1.293)	0.924
Glucose, blood (mmol/L)	1.103	(0.968, 1.257)	0.181	1.050	(0.914, 1.206)	0.541
Glucose CSF/blood	0.955	(0.812, 1.123)	0.579	0.961	(0.805, 1.146)	0.700
IgM (mg/L)	1.017	(0.967, 1.070)	0.523	1.025	(0.966, 1.088)	0.477
IgG (mg/L)	1.008	(1.002, 1.014)	0.030	1.010	(1.003, 1.018)	0.009
IgA (mg/L)	1.036	(1.002, 1.070)	0.060	1.032	(0.997, 1.069)	0.104
Albumin (mg/L)	1.001	(1.000, 1.002)	0.092	1.001	(1.000, 1.002)	0.033
IgM quotient	1.050	(0.963, 1.144)	0.317	1.086	(0.982, 1.200)	0.144
IgG quotient	1.090	(1.012, 1.174)	0.039	1.128	(1.035, 1.229)	0.012
IgA quotient	1.123	(1.014, 1.243)	0.043	1.169	(1.044, 1.310)	0.012
Albumin quotient	1.048	(1.008, 1.090)	0.034	1.061	(1.015, 1.108)	0.014
TBE form: Meningoencephalomyelitis						
Leukocytes ($\times 10^6$/L)	1.005	(1.003, 1.007)	< 0.001	1.006	(1.003, 1.008)	< 0.001
Neutrophils ($\times 10^6$/L)	1.015	(1.010, 1.020)	< 0.001	1.016	(1.010, 1.021)	< 0.001
Lymphocytes ($\times 10^6$/L)	1.002	(0.999, 1.005)	0.180	1.004	(1.001, 1.007)	0.017
Neutrophils/Leukocytes	1.790	(1.280, 2.503)	0.002	1.703	(1.160, 2.500)	0.012
Protein (g/L)	1.887	(1.429, 2.490)	< 0.001	1.996	(1.456, 2.736)	< 0.001
Glucose, CSF (mmol/L)	1.471	(0.991, 2.182)	0.084	1.303	(0.853, 1.992)	0.283
Glucose, blood (mmol/L)	1.211	(0.984, 1.490)	0.099	1.138	(0.899, 1.442)	0.347
Glucose CSF/blood	1.130	(0.812, 1.574)	0.500	1.175	(0.835, 1.655)	0.420
IgM (mg/L)	1.147	(1.079, 1.219)	< 0.001	1.208	(1.110, 1.314)	< 0.001
IgG (mg/L)	1.018	(1.009, 1.027)	< 0.001	1.021	(1.010, 1.032)	< 0.001
IgA (mg/L)	1.142	(1.089, 1.196)	< 0.001	1.128	(1.073, 1.186)	< 0.001
Albumin (mg/L)	1.004	(1.002, 1.005)	< 0.001	1.004	(1.002, 1.006)	< 0.001
IgM quotient	1.353	(1.205, 1.518)	< 0.001	1.556	(1.331, 1.818)	< 0.001
IgG quotient	1.280	(1.156, 1.417)	< 0.001	1.372	(1.209, 1.557)	< 0.001
IgA quotient	1.524	(1.320, 1.759)	< 0.001	1.612	(1.366, 1.903)	< 0.001
Albumin quotient	1.158	(1.096, 1.224)	< 0.001	1.171	(1.097, 1.249)	< 0.001

For each predictor, both crude (unadjusted) and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) are presented. Adjusted models account for potential confounding variables, including age, sex, biphasic course, and duration of neurologic symptoms. The reference category for the dependent variable is meningitis. p-values are corrected for multiple comparisons using the false discovery rate (FDR) method

TBE Tick-borne encephalitis, *CSF* Cerebrospinal fluid, *IgM* Immunoglobulin class M, *IgG* Immunoglobulin class G, *IgA* Immunoglobulin class A

are grouped by disease severity. Consequently, the question of which factors are associated with more severe acute illness is not equivalent to identifying factors linked to specific clinical forms of TBE.

The aim of this study was to assess and compare routine CSF findings in a large cohort of consecutive, well-defined adult patients hospitalized for TBE at a single institution, according to their principal clinical manifestations (meningitis, meningoencephalitis, or meningoencephalomyelitis). A further objective was to provide a detailed description of CSF abnormalities during the first 10 days after the onset of neurological signs or symptoms.

Clinical characteristics of the 717 consecutive TBE patients included in this study have been described elsewhere [20] and generally align with previously published data. However, compared with earlier reports [3, 6, 7,

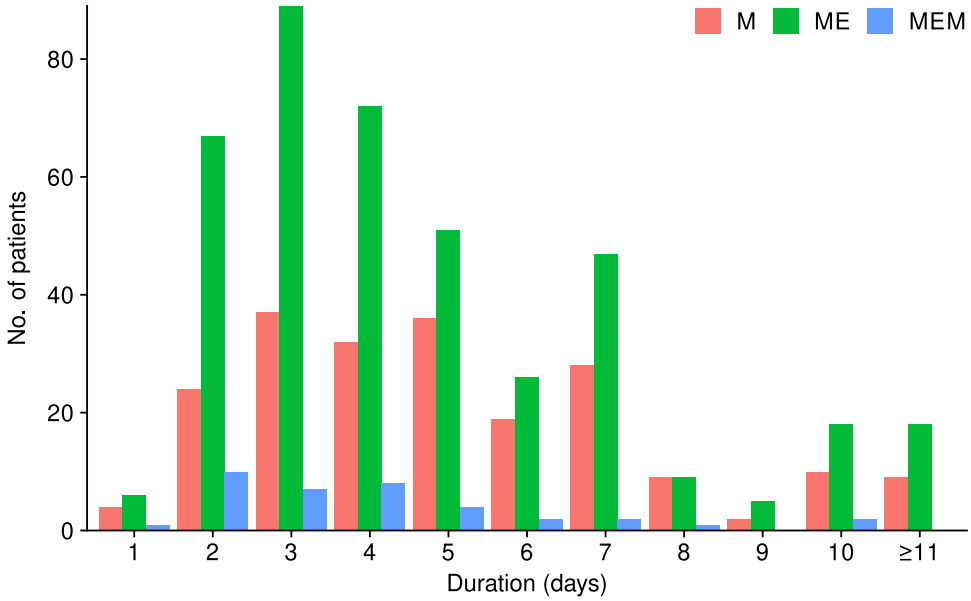

Fig. 2 Number of patients with different clinical manifestations of tick-borne encephalitis according to the duration of neurological signs/symptoms (in days) at lumbar punction (CSF examination): meningitis (M), meningoencephalitis (ME) and meningoencephalomyelitis (MEM)

14, 15], our cohort had a higher proportion of patients with meningoencephalitis and a lower proportion with meningitis.

The present analysis demonstrated that patients with meningitis were the youngest, had the lowest male predominance, were least likely to present with a monophasic disease course, and were least likely to have been vaccinated against TBE. In contrast, patients with meningoencephalomyelitis were the oldest, predominantly male, more likely to have a monophasic disease course, and most likely to present with breakthrough TBE.

Among 15 routinely measured CSF parameters, significant differences were observed across the three clinical groups for all but the CSF/blood glucose ratio. Overall, CSF abnormalities were most pronounced in the meningoencephalomyelitis group and least in patients with meningitis. Notably, the CSF profiles of patients with meningoencephalitis more closely resembled those of patients with meningitis than those with meningoencephalomyelitis (Table 2, Fig. 1). Many differences between the groups were not only statistically significant but also clinically notable, with patients with meningoencephalomyelitis exhibiting 1.3- to over two-fold higher or more abnormal values in most CSF parameters. The mechanisms underlying these differences are not yet understood. Two main explanations could account for the differences in CSF findings between different clinical manifestations of TBE: variations in pathophysiology and/or differences in the duration of neurological symptoms across groups. The median interval between the onset of neurological symptoms and lumbar puncture with CSF analysis was 5 days in patients with meningitis, and 4 days in both the meningoencephalitis and meningoencephalomyelitis groups. Although these between-group differences in symptom duration were small, they reached statistical significance, driven primarily by the longer duration in patients with meningitis. If the observed CSF differences were predominantly a consequence of symptom duration, one would expect the meningitis group to differ from both the meningoencephalitis and meningoencephalomyelitis groups, but not to observe differences between the latter two. For the abnormalities to be most pronounced in patients with shorter symptom duration (i.e., those with meningoencephalitis and meningoencephalomyelitis), they would need to peak within the first few days and then decline. However, most CSF abnormalities showed a different pattern: they increased over the first 4–5 days of neurological symptoms and subsequently either plateaued or gradually improved. Moreover, adjusting for sex, age, disease course (biphasic vs. monophasic), and duration of neurological involvement did not substantially alter the findings, suggesting that these variables are not the primary drivers of the observed distinctions.

A plausible, though simplified, explanation is that more pronounced inflammatory changes in meningoencephalomyelitis reflect the broader anatomical extent of central nervous

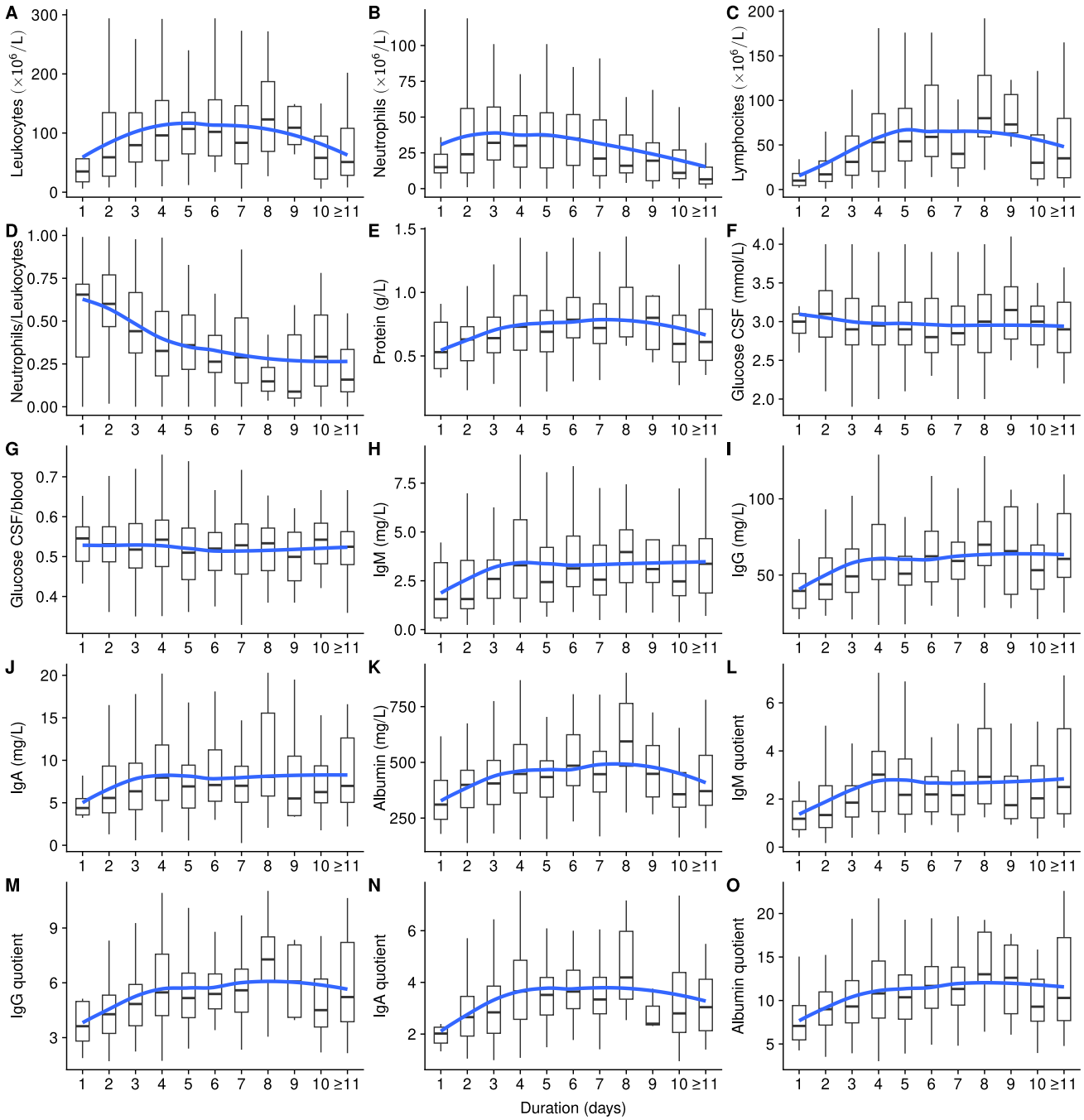

Fig. 3 Temporal evolution of cerebrospinal fluid parameters during the first 10 days of neurological signs/symptoms of tick-borne encephalitis

system involvement – namely, that inflammation affects not only the meninges and brain but also the spinal cord. This may also be associated with differences in CSF flow dynamics in the spinal region. While this hypothesis could account for higher CSF protein, albumin, immunoglobulin levels, and corresponding indices, it does not fully explain the elevated leukocyte counts and, particularly, the more persistent and pronounced neutrophilic predominance observed in this group. These findings suggest that meningoencephalomyelitis may involve a distinct immunological

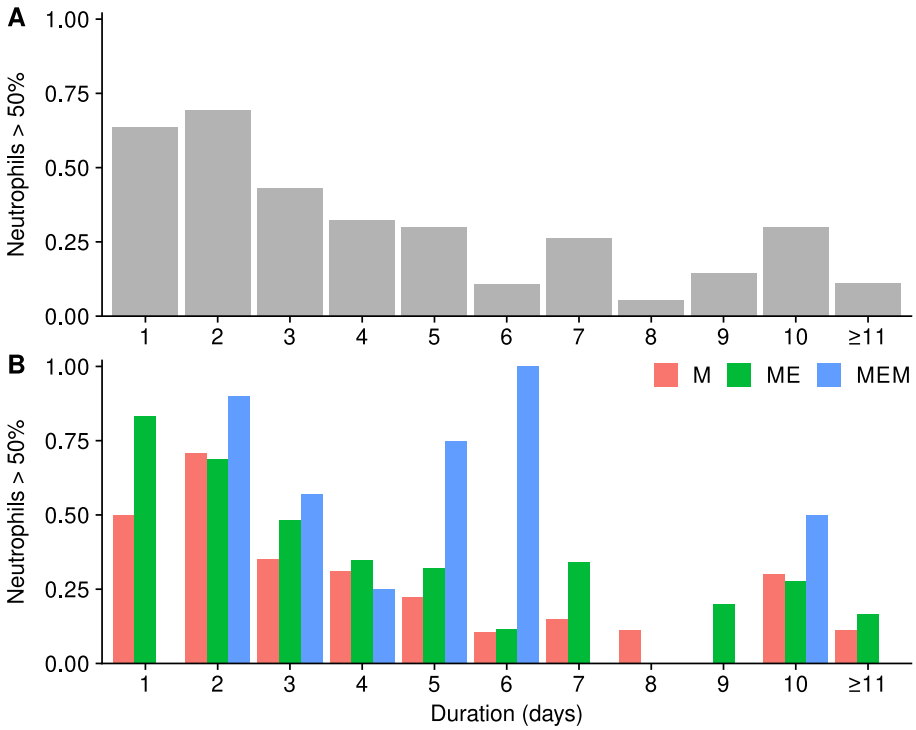

Fig. 4 Proportion of patients with neutrophil predominance in cerebrospinal fluid according to duration of illness. **A** All patients with tick-borne encephalitis. **B** Patients stratified according to clinical manifestations: meningitis (M), meningoencephalitis (ME) and meningoencephalomyelitis (MEM)

or pathophysiological response compared to meningitis or meningoencephalitis.

When CSF findings were analyzed according to the duration of neurological symptoms, a consistent pattern emerged: most parameters were already abnormal on day 1, peaked between days 4 and 5, and then either plateaued or gradually declined through day 10. An exception was the proportion of neutrophils in the CSF. In the overall TBE cohort, as well as in patients with meningitis and meningoencephalitis, neutrophils predominated during the first two days, after which lymphocytes/monocytes became predominant (Fig. 4A). However, in patients with meningoencephalomyelitis, neutrophilic predominance persisted until day 5 and at higher absolute levels (Figs. 4B and 5), which indicates a different temporal evolution of CSF parameters in this subgroup. Nevertheless, on each day analyzed, CSF abnormalities were generally least pronounced in meningitis, slightly to moderately more pronounced in meningoencephalitis, and most pronounced in meningoencephalomyelitis.

The strengths of our study include the large number of TBE patients, prospectively collected clinical data, and rigorous application of clinical definitions. Nonetheless, despite the overall cohort size, the relatively small number of patients with meningoencephalomyelitis limits the robustness of day-by-day CSF analyses in this subgroup. Another limitation of the present study was concomitant *Borrelia* infection. Of 611 patients for whom the corresponding information was available, 22 (3.3%) patients with TBE also fulfilled criteria for concomitant definite Lyme neuroborreliosis [24]. Although rare, this concomitant *Borrelia* infection could potentially influence CSF findings in the present study; however, since *Borrelia* infections were approximately equally distributed among the three clinical presentations of TBE it is unlikely to have affected the comparative analyses between clinical groups. Additionally, because our study included only patients aged ≥ 15 years, findings may not be generalizable to pediatric populations. Lastly, all patients were from an endemic area where only the European subtype of TBE virus circulates; thus, our results may not fully apply to cases caused by other TBE virus subtypes.

Conclusions

The main clinical manifestations of TBE—meningitis, meningoencephalitis, and meningoencephalomyelitis—differ not only in clinical presentation but also in routine CSF findings. CSF abnormalities are most pronounced in patients with meningoencephalomyelitis and least in those with meningitis, with meningoencephalitis patients exhibiting intermediate profiles

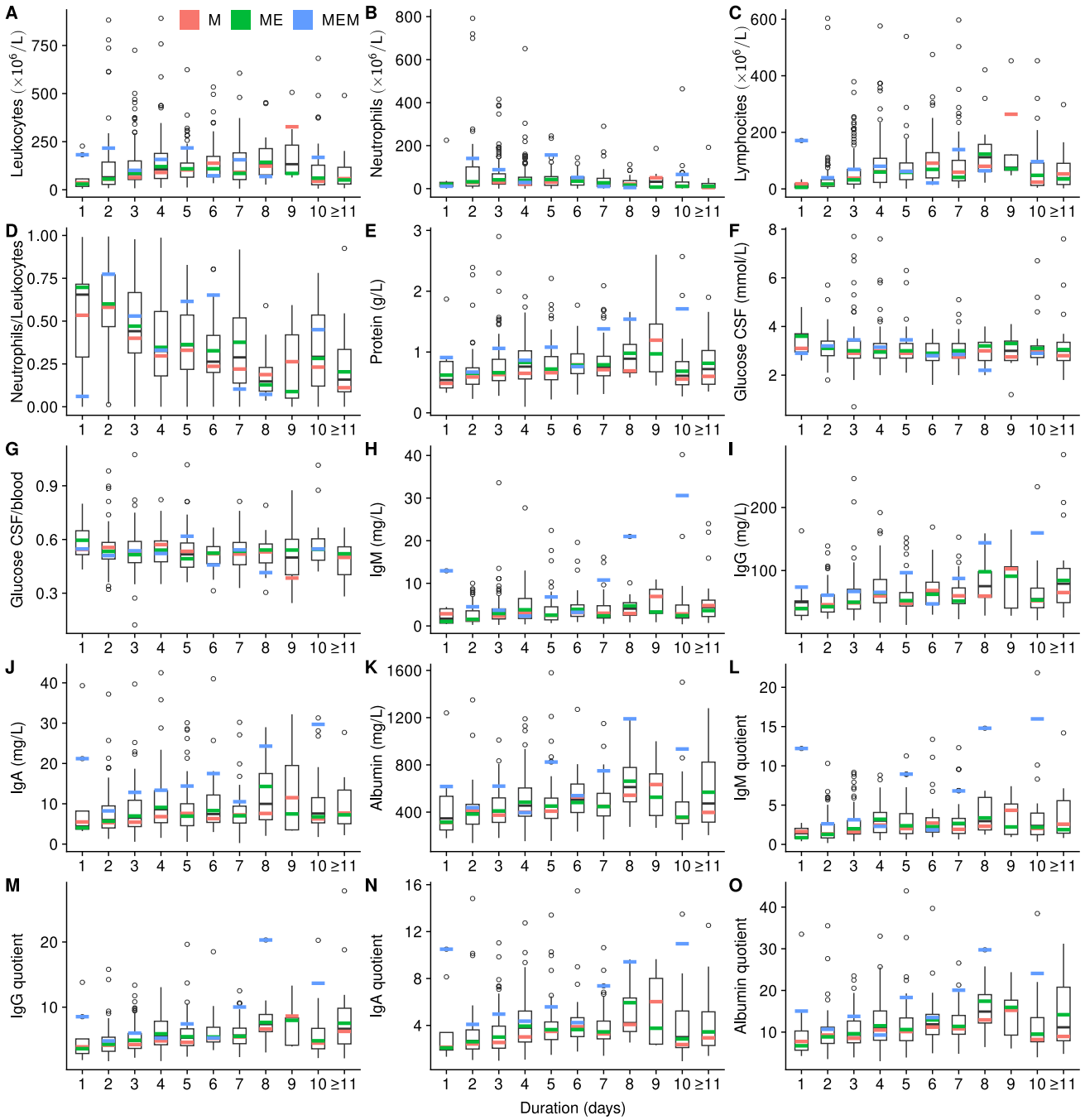

Fig. 5 Temporal evolution of cerebrospinal fluid parameters during the first 10 days of neurological signs/symptoms of tick-borne encephalitis according to clinical manifestations: meningitis (M), meningoencephalitis (ME) and meningoencephalomyelitis (MEM)

more similar to meningitis. Most CSF parameters are already abnormal on the first day of neurological symptoms, worsen over the initial 4–5 days, and then stabilize or gradually improve until day 10. However, this temporal pattern is less evident in patients with meningoencephalomyelitis, suggesting a distinct pathophysiological course.

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Data availability The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest Conflict of interest declaration: F.S. is an unpaid member of the steering committee of the European Society of Clinical Microbiology and Infectious Disease Study Group on Lyme Borreliosis (ESGBOR). Other authors declare no conflict of interest.

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