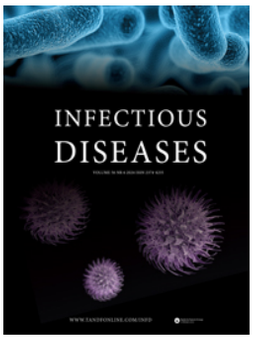

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BRIEF REPORT

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Elevated levels of serum muscle enzymes in the initial phase of tick-borne encephalitis

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ABSTRACT

Purpose: Since some patients with tick-borne encephalitis (TBE) have pronounced myalgias, and since myositis is reported in *Flavivirus* diseases such as dengue, we performed systematic search for abnormalities of muscle enzymes in a group of patients in whom the presence of tick-borne encephalitis virus (TBEV) RNA in the first phase of the disease was demonstrated and who developed second phase of TBE.

Methods: Total leukocyte and platelet blood counts were determined routinely at the initial examination during the first and the second phase of TBE. Activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), myoglobin and troponin was determined from the available stored serum specimens; the first and second phase disease specimens were tested simultaneously.

Results: Of 24 patients with biphasic course of TBE, 83% had leukopenia, 65% thrombocytopenia, 83% elevated AST and 4% elevated ALT level. Furthermore, 33% had elevated serum CK, 26% myoglobin and 22% troponin activity; at least one of the muscle enzymes was elevated in 42% of patients. Leukopenia, thrombocytopenia, elevated liver enzymes and elevations of CK and myoglobin were present in the initial phase but resolve later, while troponin abnormalities were also found in the second phase of TBE.

Conclusions: The present study exposes that in addition to previously known leukopenia, thrombocytopenia and increased liver enzymes activity, the initial phase of TBE is relatively often associated also with elevated muscle enzymes. Clinical relevance of these findings remains to be determined.

KEYWORDS
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Introduction

Tick-borne encephalitis (TBE) is the most frequent tick-transmitted infection of the central nervous system (CNS) in Europe and Asia. It is caused by tick-borne encephalitis virus (TBEV), which belongs to the *Orthoflavivirus* genus of the family *Flaviviridae*. Most human cases are due to the European, Siberian or Far-Eastern subtypes of TBEV [1]. In Slovenia, TBE viruses have been sequenced from ticks, rodents and human clinical samples, and in all cases the European subtype was confirmed [2,3]. Symptomatic infections with the European subtype often have a biphasic disease course. The first phase, which corresponds to viremia, presents with fever, fatigue, malaise, headache and muscle and joint pain. It lasts approximately one week and is followed by a few-day improvement. The hallmark of the second phase is CNS inflammation, i.e. meningitis, meningoencephalitis or meningoencephalomyelitis [4,5].

Since clinical symptoms and signs of the initial phase of TBE are nonspecific, and since serum antibodies to TBEV are not yet present, the diagnosis at this time is seldom achieved in practice. It is enabled by demonstration of TBEV RNA in the blood [6]. However, this is not a routine approach and may have a low diagnostic yield even in regions highly endemic for TBE, in large part due to several other known or unknown causes of fever. Therefore, the possibility that a febrile illness is the result of TBEV infection is usually tested and eventually established only after the appearance of signs/symptoms of CNS involvement. Consequently, knowledge on the initial phase of TBE is limited and comparisons of results in the same patients in the first and second phase of the disease are even more restricted.

Laboratory abnormalities such as leukopenia, thrombocytopenia and abnormal liver tests during the first phase of the disease are well-known [5,7,8]. Since some patients have pronounced myalgias early in the course of TBE, we decided to systematically search for abnormalities of muscle enzymes in a group of patients in whom the presence of TBEV RNA in the first phase of the disease was demonstrated and who developed second phase of TBE.

Methods

Adult patients examined for febrile illness at the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia, during 2005–2022, in whom the presence of TBEV RNA was identified by real-time reverse transcription-polymerase chain reaction (RT-PCR) in their serum specimens, and who later developed CNS inflammation, qualified for the study. The serum samples were obtained either during a prospective study on the pathogenesis of TBE and on the etiology of febrile illness after a tick bite/exposure to ticks or represented remnant samples collected as a part of routine diagnostic testing of patients with a febrile illness in whom TBE later developed. Serum specimens were stored at −80 °C until further processing.

The initial phase of TBE was defined as the presence of fever and constitutional symptoms, demonstration of viral RNA in serum or blood, and the absence of signs/symptoms of CNS involvement at the time of actual illness, followed by symptoms/signs of CNS involvement that fulfilled criteria for TBE.

TBE was defined as the presence of clinical signs/symptoms of meningitis or meningoencephalitis, cerebrospinal fluid pleocytosis ($>5 \times 10^6$ leukocytes/L), and demonstration of IgM and IgG antibodies to TBEV in serum.

In all patients, the presence of TBEV RNA in serum was ascertained during the initial phase of illness and complete TBEV genome was sequenced as reported previously [3,9].

The presence of TBEV antibodies in serum samples was determined using the Enzygnost Anti-TBE/FSME Virus (IgM, IgG) test (Siemens AG, Munich, Germany) in accordance with the manufacturer's instructions.

Total leukocyte and platelet blood counts were determined routinely at the initial examination during the first and the second phase of TBE. Activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), myoglobin and troponin was determined from the available stored serum specimens; the first and second phase disease specimens were tested simultaneously.

Elevated muscle enzyme activity was defined as mild (>1–$2 \times$ upper limit of normal, ULN), moderate (>2–$3 \times$ ULN) or severe ($>3 \times$ ULN).

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Patients whose specimens were obtained in the study on the pathogenesis of TBE and on the etiology of febrile illness after a tick bite/exposure to ticks (approved by the National Medical Ethics Committee of Slovenia, numbers 152/06/13, 0120-281/2019/10) signed an informed consent form while the Ethics Committee waived the need for written

informed consent for patients for whom remnants of routinely collected serum specimens were used (number 0120-418/2020-3).

Statistics

Continuous variables were summarized as median values and ranges, and discrete variables as counts and percentages with 95% confidence intervals. Comparisons between disease phases (i.e. initial vs. meningoencephalitic) were evaluated using Wilcoxon's rank sum tests for continuous variables and Fisher's exact tests for discrete variables. Pairwise associations between variables were estimated using the Kendall rank correlation. Observations below a lower limit of quantification were treated as left-censored, and a censored linear model was used to impute observations where necessary.

Results

Demographic and clinical data on 24 patients are shown in Table 1 while laboratory findings are depicted in Tables 2 and 3. None of the patients had been previously vaccinated against TBE. Complete genome sequencing confirmed European TBEV subtype in all cases. Comparison of laboratory blood parameters between the initial and meningoencephalitic phase of TBE confirmed previous findings on the presence of leukopenia, thrombocytopenia and increased liver enzymes activity in the initial phase of TBE. However, the present study additionally showed that: (i) in the initial phase of TBE 8/24 (33%) patients had elevated CK serum activity, 6/23 (26%) elevated myoglobin levels and 5/23 (22%) elevated troponin levels; at least one of the muscle enzymes was elevated in 10/24 patients (42%); (ii) the majority (but not all) of these elevations were mild to moderate; and (iii) the abnormalities of CK

Table 1. Demographic and clinical data on 24 patients with the initial as well as meningoencephalitis phase of tick-borne encephalitis.

Characteristic	Number (%, 95% CI) or median (IQR, range)
Male sex	8 (33.3, 15.6–55.3)
Age (years)	52 (41–61, 28–84)
Underlying illnesses	10 (41.7, 22.1–63.4)
Immune deficiency	2 (8.3, 1.0–27.0)
Ischemic heart disease	2 (8.3, 1.0–27.0)
Treatment with statins	5 (20.8, 7.1–42.2)
Clinical presentation of initial phase	
Fever ≥37.5 °C	22 (91.7, 91.3–99.4)
The highest temperature (°C)	38.5 (37.8–38.7, 37.5–40.0)
Chills	4 (16.7, 4.7–37.4)
Headache	22 (91.7, 91.3–99.4)
Myalgias	14 (58.3, 36.6–77.9)
Arthralgias	8 (33.3, 15.6–55.3)
Abdominal pain	4 (16.7, 4.7–37.4)
Nausea, vomiting	12 (50.0, 29.1–70.9)
Malaise and fatigue	24 (100, 85.8–100)
Duration of initial phase[a] (days)	7 (6.5–8.5, 5–10)
Number of hospitalized patients during initial phase	7 (29.2, 12.6–51.1)
Duration of hospitalization (days)	2 (1.5–4, 1–9)
Clinical presentation of meningoencephalitic phase	
Meningitis	6 (25.0, 9.8–46.7)
Meningoencephalitis	14 (58.3, 36.6–77.9)
Meningoencephalomyelitis	4 (16.7, 4.7–37.4)
Number of hospitalized patients during meningoencephalitic phase	24 (100, 85.8–100)
Duration of hospitalization (days)	9 (7–13, 2–112)

[a]Exact information available for 15 patients.

Table 2. Laboratory dynamics in 24 patients with the initial and meningoencephalitic phase of tick-borne encephalitis.

	Phase of illness		
Laboratory parameters	Initial*	Meningoencephalitic**	*p* Value
Leukocytes ($\times 10^9$/L)	2.2 (1.0–8.9)[a]	9.3 (5.9–18.6)	<.001
Decreased (<4.0)	19 (82.6%)	0	<.001
Elevated (>10.0)	0	10 (41.7%)	<.001
Platelets ($\times 10^9$/L)	113 (58–201)[a]	266 (138–441)	<.001
Decreased (<140)	15 (65.2%)	1 (4.2%)	<.001
Elevated (>510)	0	0	NA
ALT (μkat/L)	0.14 (<0.10–3.11)	0.14 (<0.10–0.53)	.597
Elevated (≥0.57)	1 (4%)	0	>.999
AST (μkat/L)	0.68 (0.27–8.88)	0.34 (0.24–0.62)	<.001
Elevated (≥0.52)	20 (83%)	3 (12.5%)	<.001
CK (μkat/L)	0.94 (0.51–47.96)	0.63 (0.16–1.8)	.001
Elevated (≥2.41)	8[b] (33%)	0	.004[c]
Myoglobin (μg/L)	58 (14.8–629.7)[a]	28 (12.8–87.3)	<.001
Elevated (≥107)	6[c] (26.1%)	0	.009
Troponin (ng/L)	<10 (<10–33)[a]	<10 (<10–44)	.853
Elevated (≥16)	5[d] (21.7%)	5[e] (21%)	>.999
At least one muscle enzyme elevated[f]	10 (41.7%)	5[g] (20.8%)	.213

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase.
Data are shown as ratio (%) or median (interquartile range).
*Day of illness, when blood was collected: median 4.5 (IQR 3–6), range 2–8.
**Day of the second phase of illness, when blood was collected: median 2 (IQR 2–2), range 1–6.
[a]Data for 23 patients.
[b]In three out of eight patients, elevations were mild (>1–2 upper limit of normal, ULN), in three moderate(>2–3 ULN) and in three severe (>3 ULN).
[c]In two out of six patients, elevations were mild (>1–2 ULN), in three moderate (>2–3 ULN) and in one severe (>3 ULN).
[d]In three out of five patients elevations were mild (>1–2 ULN), in one moderate (>2–3 ULN).
[e]In three out of five patients elevations were mild (>1–2 ULN), in two moderate (>2–3 ULN).
[f]CK, myoglobin, troponin.
[g]Only troponin.

Table 3. Laboratory dynamics in 24 patients with the initial and meningoencephalitic phase of tick-borne encephalitis.

	Number (%) of patients with >10% change in the ratio of levels (initial vs. meningoencephalitic phase)		
Laboratory parameter	>10% decrease	>10% increase	*p* Value
Leukocytes ($\times 10^9$/L)	0[a]	23 (100%)[a]	<.001
Platelets ($\times 10^9$/L)	0[a]	23 (100%)[a]	<.001
ALT (μkat/L)	11 (45.8%)	8 (23.3%)	.555
AST (μkat/L)	21 (87.5%)	2 (8.3%)	<.001
CK (μkat/L)	19 (79.2%)	5 (20.8%)	<.001
Myoglobin (μg/L)	18 (78.3%)[a]	3 (13.0%)[a]	<.001
Troponin (ng/L)	4 (17.4%)[a]	5 (21.7%)[a]	>.999

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase.
[a]Data for 23 patients.

and myoglobin were exclusively associated with the initial phase of illness but resolved later, while troponin abnormalities were also found in the second phase of illness.

The levels of muscle enzymes in the initial phase of TBE were not significantly associated with the presence of myalgias ($p = .457$ for CK, $p = .352$ for myoglobin and $p = .275$ for troponin) nor with the disease course including the duration of the initial phase ($p = .103$ for CK and $p = .241$ for myoglobin), hospitalization during the initial phase ($p = .965$ for CK and $p = .176$ for myoglobin) or clinical presentation of the second phase of TBE ($p = .434$ for CK and $p = .217$ for myoglobin). Moreover, concentrations of muscle enzymes were not significantly associated with TBEV-RNA levels ($p = .214$ for CK, $p = .884$ for myoglobin and $p = .114$ for troponin).

Discussion

Among infectious causes, bacteria, parasites and viruses, such as influenza viruses, HIV, SARS-CoV2 and several others, have been associated with muscle involvement [10,11]. However, in viral infections, myositis is rarely the sole or the most prominent clinical presentation.

The main stimulus for the present study was pronounced myalgias in some of our patients with the initial phase of TBE and the information on the presence of myositis in *Flavivirus* diseases such as dengue [11]. PubMed literature search on myositis in TBE revealed only two pertinent individual case reports in the last 40 years, suggesting rareness of such events. Both reported patients were characterized with clinically overt acute myositis that developed early in the course of TBE, was associated with highly elevated muscle enzyme levels in serum (CK and aldolase in one report [12]; CK and myoglobin in the other [13]), and spontaneously vanished.

Systematic search for several blood parameters in the initial as well as meningoencephalitic phase of 24 patients with well-defined TBE, performed in the present study, confirmed previous results indicating that leukopenia, thrombocytopenia and increased liver enzyme activity are associated with the initial phase of TBE [5,7,8]. However, the present study also exposed that in the initial phase of TBE 33% of patients had elevated CK serum levels, 26% elevated myoglobin levels and 22% elevated troponin levels; at least one of the muscle enzymes was elevated in 42% of patients. Although the majority of these abnormalities were mild to moderate, some were quite pronounced. Furthermore, the elevations of CK and myoglobin levels were exclusively associated with the initial phase of illness but resolved later, while troponin abnormalities were also found in the second phase of illness.

While several of our patients had myalgia with elevated CK, myoglobin and/or troponin levels, none had clinically overt myositis, none reported chest pain or symptoms suggesting heart involvement, and none of the routinely recorded ECGs during the meningoencephalitic phase of illness revealed any substantial abnormalities. Furthermore, none of the patients with elevated muscle enzymes, including troponin, had a known underlying heart disease or were receiving drugs potentially associated with laboratory abnormalities such as statins.

Mechanisms of muscle involvement in viral infections are unclear. Absence of a direct viral effect in most biopsies suggests immune-mediated pathogenesis [14]. However, in our patients, transient leukopenia, thrombocytopenia, increased activity of (some) liver enzymes as well as laboratory indicators of muscle involvement in the first phase of TBE, when viremia is present, and their normalization in the meningoencephalitic phase of the disease, when viremia disappears, suggest the importance of the presence of the virus. The most likely mechanism seems to be an immune mediated damage: the presence of TBEV in blood triggers the secretion of immune mediators that damage bone marrow, liver and muscles. However, data on the presence of cytokines/chemokines in the blood of human patients in the initial phase of TBE are very scarce – PubMed literature search revealed only one report [15].

The main advantage of our study is systematic assessment of the muscle enzyme abnormalities in the initial as well as meningoencephalitic phase of well determined cases of TBE. In the present study, the proportion of males among the enrolled patients was lower (8/24, 33%) than usually reported for TBE (slight male predominance would be expected), and the proportion of patients with meningitis (6/24, 25%) was lower than usually seen in adult patients with TBE (approximately 50%) [4,16]. We do not have a reliable explanation for these discrepancies. However, the selection of patients was based on the requirement that they had a biphasic course of disease, evidence of TBEV RNA in the blood and stored biological samples for laboratory analyses; this selection may not provide the distribution expected in a general cohort of TBE patients. Our findings were obtained in adults and additional studies will be needed

to determine if similar findings are observed in children. Furthermore, the findings are valid for TBE caused by the European TBEV subtype but may not be valid for other subtypes such as Siberian and Far-eastern. While no statistically significant associations were found between elevated muscle enzyme levels and the presence of myalgias, severity and duration of the initial phase of illness, clinical presentation of the second phase of TBE or TBEV-RNA blood levels, the number of patients enrolled in the present study was relatively small which could limit the ability to detect significant differences. Although our data on relatively common muscle enzyme abnormalities in the first phase of TBE are pronounced, clinical relevance of elevated muscle enzymes, including troponin which suggests heart involvement, remains to be determined in detailed further clinical studies. Nevertheless, the main message of the present study to clinicians in the TBE endemic area is to consider the possibility of the initial phase of TBE not only in the case of unspecific febrile illness associated with leukopenia, thrombocytopenia and/or abnormal liver tests, but also in the presence of elevated muscle enzyme activity.

In conclusion, our study revealed that in the initial phase of TBE, 33% of patients have elevated CK serum levels, 26% elevated myoglobin levels and 22% elevated troponin levels; at least one of the muscle enzymes is elevated in 42% of patients. The elevations of CK and myoglobin are associated with the initial phase of illness but resolve later, while troponin abnormalities are also found in the second phase of illness. Clinical relevance of these findings remains to be determined.

Author contributions

Conceptualization: PB and FS; methodology: PB, TAŽ, MK and ATB; validation: PB and FS; formal analysis: PB, KO, AK and FS; resources: PB and FS; writing original draft preparation: PB, KS and FS; writing review and editing: PB, SLF, KO, TAŽ, MK, AK, ATB, KS and FS; funding acquisition: PB and FS. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

KS served as a consultant for T2 Biosystems, Roche, bioMerieux and NYS Biodefense Fund, for the development of a diagnostic assays in Lyme borreliosis. FS served on the scientific advisory board for Roche on Lyme disease serological diagnostics and on the scientific advisory board for Pfizer on Lyme disease vaccine and is an unpaid member of the steering committee of the ESCMID Study Group on Lyme Borreliosis/ESGBOR. Other authors report no conflict of interest.

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