

AUTONOMIC INVOLVEMENT IN TICK-BORNE ENCEPHALITIS (TBE): REPORT OF FIVE CASES

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Abstract

Background: Tick-borne encephalitis (TBE) is a viral infection of the CNS with significant acute and long-term morbidity. Dysfunction of the autonomic nervous system may be a potentially harmful complication of TBE.

Material and Methods: In a retrospective case series, 5 patients with acute TBE were evaluated for clinical signs of autonomic dysfunction and subject to autonomic testing. Heart rate variability (HRV) with 6 per minute deep breathing was performed between day 9 to 31 after onset of meningitis. Follow-up data were available in three cases.

Results: All patients showed clinical signs of autonomic dysfunction, including upper and lower gastrointestinal tract symptoms, orthostatic hypotension, and urinary retention. A reduced HRV was observed in 4 patients, with sustained sinus tachycardia in 2 of them. The minimum of the HRV was reached 9 to 20 days after onset of meningitis. In one patient, normalization of the HRV occurred within 3 months.

Conclusion: Acute TBE can be associated with autonomic dysfunction including reduced HRV and tachycardia. Prospective studies are needed to analyze the incidence of autonomic dysfunction in TBE, and to clarify which patients have the highest risk for autonomic failure.

Key words: Tick-borne encephalitis; autonomic nervous system; dysautonomia; heart rate variability; tachycardia

Abbreviations: ANS, autonomic nervous system; HRV, heart rate variability; TBE, Tick-borne encephalitis; TBEV, Tick-borne encephalitis virus

INTRODUCTION

Tick-borne encephalitis (TBE) is a mostly benign, but potentially life-threatening virus-mediated infection of the CNS [2, 6, 10]. It is caused by the TBE virus (TBEV), which belongs to the flavivirus family, and is transmitted in Central and Eastern Europe by ticks of the species *Ixodes ricinus*. TBE is characterized by a typical biphasic disease course. After a short febrile prodromal period, frequently followed by an asymptomatic interval, acute CNS symptoms occur along with high fever. Based on the clinical presentation three forms of TBE are differentiated: meningitis, menin-

goencephalitis, and meningoencephalomyelitis, often accompanied by radiculitis [10]. A poliomyelitis-like syndrome has been described in severe cases, resulting in significant mortality and disabling sequelae [17]. Diffuse brain edema and involvement of the medulla oblongata and the central portions of the brain are thought to be the main causes of mortality [2]. Overall, the fatality rate in Europe is probably less than 1% [6, 10].

Dysfunction of the autonomic nervous system (ANS), a potentially life-threatening complication [25], has rarely been noted to occur in TBE [14]. We report 5 patients with acute TBE, who developed clinically evident autonomic dysfunction including a decrease in heart rate variability (HRV).

PATIENTS AND METHODS

PATIENTS AND LABORATORY PROCEDURES

This study was conducted at a tertiary referral center in eastern Bavaria, an area endemic for TBE. We investigated all consecutive patients with suspected TBE who were admitted to our department in the year 2001. During the acute phase of meningitis standard diagnostic and therapeutic procedures were carried out in all patients. Detailed patient characteristics, epidemiological and clinical data were recorded. Thorough general and neurological examination was done. Routine blood and cerebrospinal fluid (CSF) parameters were examined. Heart rate and blood pressure, which was measured oscillometrically in supine position, were recorded at least every 4 h. At the time of this retrospective analysis, medical records were surveyed for descriptions of dysautonomic symptoms and cardiovascular function.

The diagnosis of TBE infection was established in all patients by the demonstration of specific immunoglobulin (Ig)M and IgG antibodies in serum and CSF [8]. Antibodies against TBEV were determined by an enzyme-linked immuno-sorbent assay (ELISA) following the manufacturer's protocol (Enzygnost Anti-TBE Virus; Dade Behring, Marburg, Germany). Coinfection with *Borrelia burgdorferi* was tested by specific IgG and IgM antibodies in serum and CSF using both ELISA (Enzygnost Borreliosis; Dade Behring) and a western blot against *Borrelia*-specific recombinant OspA (31kD), OspC (22kD), p100, p39, p18, and p41 (flagellin) (recomBlot *Borrelia* IgG/IgM; Mikrogen, Martinsried, Germany). Intrathecal produc-

tion of TBEV and *Borrelia*-specific antibodies was assessed using the respective specific antibody index, which is defined as the ratio between the CSF/serum quotient for specific antibodies and the quotient of total IgG concentrations in CSF and serum [16]; values > 4.0 were considered positive.

AUTONOMIC TESTING

All patients who were clinically suspected to have autonomic dysfunction were subject to autonomic testing. Standard procedures and equipment (Multiliner electromyograph, Toennies, Höchberg, Germany) were used for the evaluation of heart rate variability with respiration. For 18 hours prior to the test no alcohol, caffeine or nicotine was consumed. The examination was started after the participants had rested for at least 15 minutes in a half-sitting position in a comfortably warm room. R-R intervals with an accuracy of 1 ms were recorded during normal breathing and during deep breathing at 6 respirations per minute. Artifact-free periods of 1 minute were analyzed by calculation of mean heart rate, expiration to inspiration (E-I)-ratio, and R-R intervals. For R-R interval analysis the RR4 algorithm $[(RR_{max} - RR_{min}) \times 100/RR_{mean}]$ according to Stalberg and Nogués was used [19]. Values were normalized against in-house age-matched controls [18]. Tachycardia was defined as a heart rate of above 100 beats/min. Autonomic testing was performed in all patients within day 7 to 31 after the onset of the neurological symptoms and - when pathological - repeated at least biweekly until discharge from hospital. One patient was followed for 1 year.

RESULTS

Between May 2001 and November 2001 a total of 8 adult patients (male: 6; female: 2; age: median: 55

years, range: 28-71 years) referred to our center for acute meningitis were given the definite diagnosis of TBE. Autonomic dysfunction was suspected on clinical grounds in 5 patients (male: 4; female: 1; age: median: 56 years, range: 48-71 years). These patients were subject to autonomic testing and further analysis.

Four of them had a history of tick bite, with multiple tick bites in patients 1 and 3. Patient 1 had received a booster vaccination against TBE 39 months before onset of meningitis. Two patients (cases 1, 3) had an IgG-antibody response against *Borrelia burgdorferi* in the serum without a specific intrathecal IgG-production or an IgM-response. Apart from achalasia two years ago in patient 1, mild alcohol consumption in patients 3 and 5, and a gastrectomy for unknown reason in patient 3, there was no comorbidity with relevance for ANS function. In particular, no patient had a history or laboratory abnormalities suggesting diabetes, cardiac arrhythmia, or a cardiopathy. No patient was on drugs known to affect the ANS.

Table 1 summarizes the patients' general characteristics and the clinical symptoms. All of them showed clinical signs of autonomic dysfunction (Table 2). Four patients had a reduced HRV with respiration, one patient (case 1) a fixed heart rate. In cases of pathological HRV, minimum values were measured at days 9 to 20 after onset of the initial neurological symptoms. The sympathetic skin responses were recorded from both hands of patients 1 and 4, and showed no abnormalities.

Clinically, a delayed onset of dysautonomic symptoms was found, evolving 5 to 12 days after onset of neurological symptoms and 10 to 19 days after the first febrile episode of the TBEV infection. Sustained sinus tachycardia with a mean 24 hour heart rate of above 100 beats/min was apparent in 2 patients and started at days 9 (patient 4) and 14 (patient 1), respectively, after onset of the meningitis. At this time both

Table 1. Demographic and clinical features of patients.

Case	Sex	Age (yrs)	Cerebrospinal fluid ^a		Clinical characteristics ^b	Clinical classification ^c	Neurological sequelae ^d
			WBC	Protein			
1	M	54	122	216	Fever, meningism, somnolence, ataxia, dysarthria, right-sided facial palsy, myelitis/radiculitis (UE bilateral)	3	Muscular atrophy and paresis (UE bilateral), cerebellar ataxia, facial palsy, neuropsychological deficits (attention deficit, short-term memory impairment, emotional lability)
2	F	56	109	111	Fever, headache, meningism, nausea, vomiting, disorientation	2	Unknown
3	M	71	11	52	Fever, nausea, headache	1	No
4	M	48	162	69	Fever, headache, meningism, ataxia, diplopia, dysarthria, left-sided facial palsy	3	Cerebellar ataxia, neuropsychological deficits (attention deficit, mild memory impairment)
5	M	66	14	96	Fever, myelitis/radiculitis (LE bilateral)	3	Muscular atrophy and paresis left LE

^a White blood cell count (WBC) is expressed as number of cells/mm³ and the protein concentration as mg/dl.

^b During the course of acute TBE; LE, lower extremities; UE, upper extremities.

^c 1, 2, 3 represents meningitis, meningoencephalitis, and meningoencephalomyelitis/-radiculitis, respectively.

^d As present 3-12 months after acute TBE.

Table 2. Autonomic function in patients with TBE.

Case	Clinical signs of autonomic dysfunction ^a	Heart rate variability with deep breathing ^b					Assessment of HRV
		Day	Mean HR [1/min]	E-I-ratio	RRIA (normal range)	n	
1	Tachycardia, UGI, LGI	20	111.6	1.02	2.51 (>10.5)	12	Reduced (d19-21, 29-39), remission after 3 months
2	Orthostatic hypotension (slurred speech, confusion, nausea when upright)	9	98.7	1.04	6.08 (>10.1)	5	Reduced (d9-17)
3	UGI, LGI	12	81.8	1.04	6.36 (>7.0)	1	Reduced (d12)
4	Tachycardia	12	110.9	1.03	4.69 (>12.2)	6	Reduced (d12-22)
5	Urinary retention, LGI, orthostatic hypotension (dizziness, slurred speech, nausea when upright)	31	93.8	1.16	21.22 (>7.8)	1	Normal

^aRetrospectively retrieved from clinical records; LGI, lower gastrointestinal tract symptoms; UGI, upper gastrointestinal tract symptoms.

^bAs measured at the indicated day after onset of meningitis; HR, heart rate; E-I-ratio, expiration to inspiration ratio; RRIA, R-R interval analysis, normalized against in-house age-matched controls; n, number of tests.

Table 3. Time course of heart rate variability and vital capacity in patient 1. From day 20 to 24 after onset of meningitis an experimental therapy with intravenous immunoglobulins (IVIg) was administered.

Day	RRIA ^a	VC [L] ^b	Treatment
19	7.04	-	
20	2.51	2.6	0.4 g/kg IVIg
21	4.94	2.8	0.4 g/kg IVIg
22	13.30	2.6	0.4 g/kg IVIg
23	-	3.1	0.4 g/kg IVIg
24	-	2.9	0.4 g/kg IVIg
25	11.03	3.2	
30	6.39	-	
33	9.33	3.0	
36	7.68	3.1	
39	7.68	3.2	
103	20.61	-	
327	21.30	-	

^aRRIA = R-R interval analysis, normalized against in-house age-matched controls (normal >10.5). Dash indicates missing value, pathological values are in bold print.

^bVC = vital capacity, mean (n > 2; normal >3.4).

patients had already recovered from acute febrile disease. Patient 2 shortly missed the criteria for tachycardia with a maximum heart rate of 99 beats/min measured on day 9. Patient 1 had a sustained hypertonia with a mean 24 hour systolic blood pressure of above 150 mm Hg from day 14 to day 21 after the onset of meningitis (maximum mean systolic blood pressure: 177 mm Hg). Except for sinus tachycardia, routine ECG was normal in all patients.

Further dysautonomic symptoms included upper and lower gastrointestinal tract symptoms, like dysphagia, severe postprandial abdominal pain and vomiting, reduced bowel motility, and constipation (Table 2). Fecal impaction was found in patients 1 and 5. Two patients (cases 2, 5) complained of dizziness, confusion,

slurred speech, and nausea when sitting up. One patient (case 5) had a normal HRV although showing clinical signs of dysautonomia, e. g. a urine retention, which occurred 10 days after the onset of meningitis and required a suprapubic catheter.

Patients with a compromised cardiovagal function were submitted to cardiorespiratory monitoring and received symptomatic treatment. No lability of blood pressure or episodes of bradycardia occurred and all patients remained clinically stable. Because of a fixed heart rate and a pronounced tachycardia patient 1 received an experimental treatment with intravenous immunoglobulins at a dose of 0.4 g/kg/day from day 20 to 24, followed by an improvement of HRV (Table 3), hypertonia, and tachycardia. On day 6 after the end of the treatment, the HRV deteriorated again with ultimate resolution first seen at the 3-month follow-up visit.

Magnetic resonance imaging (MRI) was performed in 4 patients. MRI was normal in two of them while showing non-enhancing unspecific lesions in the subcortical and deep white matter in patients 1 and 2. No lesions were found in the brainstem or the hypothalamus. In patient 5, MRI of the complete spinal cord was normal.

Follow-up visits were done in 3 patients (cases 1, 4, 5) at 3 to 12 months after discharge from hospital. Autonomic sequelae were neither reported nor found on neurological examination. In patient 1, HRV remained normal at the 1-year follow-up visit. The other patients were not subjected to autonomic testing or lost for follow-up.

DISCUSSION

Our results suggest an association between ANS dysfunction and TBE. The patients described showed symptoms and signs of a dysregulated cardiovascular control, particularly reduced HRV and tachycardia. In addition, further dysautonomic symptoms in the gas-

trointestinal and urinary system were reported. The clinical course and the results of the electrodiagnostic testing suggest a secondary autonomic failure with predominant involvement of the parasympathetic system. Furthermore, symptoms that – according to the clinical records – were most likely attributable to orthostatic hypotension, i. e. sympathetic failure, were also part of the spectrum of dysautonomia seen in these patients.

Due to the retrospective setting of the study, sympathetic and further parasympathetic functions, as well as the distinction between preganglionic and postganglionic involvement of the ANS, were not assessed. Therefore, autonomic dysfunction observed in TBE may principally be caused by a disorder of the peripheral autonomic nerves, central connections of the autonomic system, or both.

Clinical symptoms of dysautonomia in TBE have occasionally been mentioned before [9, 14, 22]. Within his cohort of 656 patients, Kaiser reported on an impaired bowel function in 1.8% of all cases and in 13.5% of meningoencephalomyelitis cases [10]. Sweating was noted as a persisting sequel in 5.5% of 492 Slovenian patients [21]. An impairment of cardiovascular control was reported in a fatal case from Slovenia [22].

Measurement of the HRV is a standard method for the evaluation of the parasympathetic control of the heart. It has been used extensively to study the cardiovagal function in patients with various disorders, including myocardial infarction [20], diabetic neuropathy [24], and Guillain-Barré-syndrome [11]. R-R interval analysis upon deep breathing can be performed by recording 1 minute periods or even one single deep breath and is a highly sensitive test [15, 19].

It is assumed that the HRV is frequently decreased in patients treated in the ICU, e.g. patients with sepsis or with severe head and brain injuries [3]. However, virtually nothing is known about HRV in patients with acute meningoencephalitis. Among the patients described herein, only one (patient 1) was critically ill and required ICU treatment.

The mild myeloradiculitis seen in some of our patients is unlikely to compromise the diagnostic value of HRV measurements. In patient 1, a transient improvement of the HRV occurred despite constantly reduced vital capacity. Furthermore, it is well known that the R-R variation is not significantly affected by even a wide variation of the tidal volume [19].

TBEV is a neurotropic virus [13] and invasion into central or peripheral neural tissue along with a local inflammatory reaction may explain the ANS dysfunction. Recently, a selective distribution of TBEV antigen in spinal cord, brainstem, cerebellum, and basal ganglia has been demonstrated by immunohistochemistry from postmortem CNS tissue [4]. The tegmentum of the medulla and the pons, including raphe nuclei and the locus coeruleus, i.e. regions relevant to the ANS, were infected in over 50% of fatal cases. MRI of the brain has shown an involvement of the thalamus, hypothalamus, cerebellum, basal ganglia, and the brainstem in approximately 20% of TBE cases [10, 12]. In our patients, no specific lesions were found in these regions by MRI, which does not exclude an infection of the central autonomic network by TBEV.

Cranial nerve lesions are common in severe cases of TBE. Particularly, glossopharyngeal and vagal nerve paresis occurs in 1.5% of cases with a meningocephalitic and in 18.2% of cases with a meningoencephalomyelitic disease course [10]. Patients 1 and 4 had an involvement of cranial nerves with clinical signs of a vagal nerve lesion, e. g. dysarthria, however, this occurred several days before frank dysautonomia. In the remaining patients no impairment of cranial nerves was found.

As an alternative explanation for the ANS dysfunction seen in our patients, the delayed onset approximately 2 weeks after the initial neurological symptoms may point to an immune-mediated mechanism. Postinfectious dysautonomia is common in Guillain-Barré-syndrome [11] and has been described in association with other viral CNS-infections, including those by Human Immunodeficiency virus [5], Epstein-Barr virus [1], and mumps virus [23]. Interestingly, immunotherapy with intravenous immunoglobulins had an effect on the HRV in one of our patients and has previously been reported to be beneficial in postinfectious [1, 23] and idiopathic [7] dysautonomia.

Despite its frequently asymptomatic presentation, dysregulation of the cardiovagal and cardiac sympathetic function leading to bradycardia and sudden cardiac arrest are main causes of death in diabetes and Guillain-Barré-syndrome [24, 25]. We did not observe a marked lability of blood pressure or episodes of bradycardia in our cases. Since cardiorespiratory monitoring represents standard care for patients with severe meningoencephalitis, malignant cardiac arrhythmias should be easily detected. However, conclusions drawn from this study are limited because of the retrospective design and the small patient number. The role of ANS dysfunction in the morbidity and mortality of acute TBE and its sequelae needs to be further elucidated.

In summary, we have observed an abnormal function of the ANS in 5 out of 8 consecutive patients with TBE occurring within one year. Cardioneuropathy as assessed by HRV was the main dysautonomic symptom seen in this series. Monitoring of the cardiorespiratory function is required for severe TBE. Knowledge and symptomatic treatment of autonomic failure in patients with TBE might help to further improve clinical care. Prospective studies are needed to confirm the role of ANS dysfunction in TBE and to identify patients at risk of serious cardiovascular complications.

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