

Clinical features of double infection with tick-borne encephalitis and Lyme borreliosis transmitted by tick bite

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Background: In Latvia and other endemic regions, a single tick bite has the potential to transmit both tick-borne encephalitis (TBE) and Lyme borreliosis.

Objective: To analyse both the clinical features and differential diagnosis of combined tick-borne infection with TBE and Lyme borreliosis, in 51 patients with serological evidence, of whom 69% had tick bites.

Results: Biphasic fever suggestive of TBE occurred in 55% of the patients. Meningitis occurred in 92%, with painful radicular symptoms in 39%. Muscle weakness occurred in 41%; in 29% the flaccid paralysis was compatible with TBE. Only two patients presented with the bulbar palsy typical of TBE. Typical Lyme borreliosis facial palsy occurred in three patients. Typical TBE oculomotor disturbances occurred in two. Other features typical of Lyme borreliosis detected in our patients were distal peripheral neuropathy (n = 4), arthralgia (n = 9), local erythema 1–12 days after tick bite (n = 7) and erythema chronicum migrans (n = 1). Echocardiogram abnormalities occurred in 15.

Conclusions: Patients with double infection with TBE and Lyme borreliosis fell into three main clinical groups: febrile illness, 3 (6%); meningitis, 15 (30%); central or peripheral neurological deficit (meningoencephalitis, meningomyelitis, meningoradiculitis and polyradiculoneuritis), 33 (65%). Systemic features pointing to Lyme borreliosis were found in 25 patients (49%); immunoglobulin (Ig)M antibodies to borreliosis were present in 18 of them. The clinical occurrence of both Lyme borreliosis and TBE vary after exposure to tick bite, and the neurological manifestations of each disorder vary widely, with considerable overlap. This observational study provides no evidence that co-infection produces unusual manifestations due to unpredicted interaction between the two diseases. Patients with tick exposure presenting with acute neurological symptoms in areas endemic for both Lyme borreliosis and TBE should be investigated for both conditions. The threshold for simultaneous treatment of both conditions should be low, given the possibility of co-occurrence and the difficulty in ascribing individual neurological manifestations to one condition or the other.

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The Baltic region is an endemic focus for both tick-borne encephalitis (TBE) and Lyme borreliosis transmitted by ticks.^{1–4} In Latvia, 7061 cases of TBE and 3566 cases of Lyme borreliosis were registered between 1994 and 2003, out of a population of 2.4 million. Both tick species present in Latvia, *Ixodes ricinus* and *persulcatus*, can transmit the encephalitis virus, the borreliosis spirochete and more rarely erlichiosis. A single tick bite has the potential to transmit both infections.⁵ Despite their different clinical courses, TBE and Lyme borreliosis have neurological features in common: lymphocytic meningitis, flaccid or spastic limb weakness and cranial nerve involvement. Thus, differentiating between these disorders is important, given different approaches to treatment.

Of the two infections, only TBE runs a biphasic course with the initial prodromal period of influenza-like symptoms usually developing 1–2 weeks after the tick bite. Hence, after an asymptomatic period lasting 2–10 days, about a third of infected patients enter a second phase with aseptic meningitis.² Subsequently, 2–10% in Western TBE subtype or 10–25% in Eastern TBE subtype develop encephalitis, myelitis or meningoencephalomyelitis typically manifesting as combinations of flaccid paresis of the limbs, usually arms and neck, bulbar dysfunction, disorientation, aphasia and spastic paresis.^{1,2} A poliomyelitis-like syndrome is described in central European TBE.⁶ Manifestations of TBE in the Baltic may be heterogeneous, given that infection with the Western, Far Eastern and Siberian subtypes all cause human infection

in Latvia.⁷ Although severe manifestations usually subside after 3–6 weeks, the convalescence period of TBE may be very long, with nearly 40% having a postencephalitic syndrome at 4 years.⁸ The uptake of TBE vaccination is increasing in the Baltic region.

Classical Lyme borreliosis differs considerably from TBE and produces local and generalised forms, systemic involvement, and development over several stages. Its acute and chronic courses pose problems of diagnosis and management.^{1,9} Diagnosis of neuroborreliosis requires a definite or possible tick bite, erythema migrans or seropositivity, and typical peripheral or central nervous system involvement.¹⁰ In early neuroborreliosis (2–10 weeks after tick bite) the most common neurological abnormalities are meningitis, meningoradiculoneuritis and cranial neuritis, particularly facial palsy.^{1,9–11} Progressive chronic encephalomyelitis, polyneuritis and cerebrovascular disorders are later manifestations of Lyme borreliosis, usually occurring months after the initial infection. Neurological features are noted in 10–12% of all patients with Lyme borreliosis in Europe¹ and in 10–15% of patients in Northern America.¹¹ Neurological manifestations in 330 European patients with Lyme borreliosis included radicular pain (70%), headache (18%), peripheral paresis (45%), central paresis (4%), sensory disturbances (44%) and facial palsy (39%).¹ *Borrelia* infection takes a subclinical or minimally symptomatic course in up to 80% of the population

Abbreviations: CSF, cerebrospinal fluid; TBE, tick-borne encephalitis

after tick bites.¹² Importantly, borreliosis is treatable with antibiotics.

TBE infection can be proven by specific and sensitive ELISA detection of antibody in cerebrospinal fluid (CSF), or by detection of genome through polymerase chain reaction.¹³ Serum IgM antibodies can remain positive for ≥ 10 months.^{2, 14} By contrast, serological tests for Lyme borreliosis infection are less sensitive and specific to variable onset and occurrence of specific IgM and IgG antibodies, with recognised persistent seronegatives; direct detection of a pathogen is rarely possible, and reliance must be placed on interpreting the laboratory investigations in the light of the clinical picture.^{13, 15, 16} Demonstration of intrathecal antibody production provides a specific test,¹⁷ but is not sensitive in detecting all forms of neuroborreliosis.¹⁵ Despite their different clinical courses, TBE and Lyme borreliosis have neurological features in common: lymphocytic meningitis, flaccid or spastic limb weakness, and cranial nerve involvement. Pain, particularly in a radicular distribution, and sensory disturbance are regarded as features more typical of Lyme borreliosis than TBE.

Only limited information on double infection with TBE and Lyme borreliosis is available. Single cases, small series or serologically defined series with limited clinical information are described from Germany, Slovenia, Central Russia and Finland.^{18–24} This retrospective clinical observational study analyses the clinical features and problems of differential diagnosis in patients with evidence of both TBE and Lyme borreliosis infection in Latvia.

PATIENTS AND METHODS

Fifty one patients (30 men and 21 women aged 18/80 (mean 50) years) were diagnosed with combined TBE and Lyme borreliosis in the Neurological Departments of P Stradin's Clinical Hospital and Clinical Hospital Gailezers, Riga, Latvia, and in the Latvian Infectology Centre, Riga, Latvia, from 1994 to 2002. None had been vaccinated against TBE. Clinical and laboratory features were analysed retrospectively. TBE was diagnosed on the basis of epidemiological circumstances (tick bite or likely contact with ticks), a febrile illness, meningitis and meningoencephalomyelitis, and serological confirmation by ELISA (Boehringer Ingelheim, Germany) detection of specific TBE IgM antibodies in sera or CSF. Diagnosis of early or later systemic Lyme borreliosis was based on confirmed tick exposure, clinical evidence of erythema migrans, and neurological, cardiac or joint disturbances with serological detection of IgM or IgG antibodies in serum or CSF (indirect immunofluorescence (n = 1) method until 1994, subsequently ELISA (Boehringer Ingelheim)) on testing in the days after hospital admission. In all, 42% of patients were hospitalised for more than 2 weeks after first symptoms.

RESULTS

Presentation

All patients presented between May and November, and most recalled a tick bite (69%) or had visited a forest (14%) in the preceding weeks. The incubation period to first symptoms could be determined for 36 patients (71%) averaging 17 days (1–44). On admission, 98% had an acute febrile illness. The usual initial symptoms were tiredness or fatigue, headache, nausea or vomiting. Fever was biphasic in 28 (55%). Seven (14%) had local erythema after tick bite.

Neurological features

Forty seven patients had meningism at presentation. Lumbar puncture was carried out in 44 patients, usually showing CSF lymphocytic pleocytosis (median 180 cells/mm³; range 78–924); in a minority (n = 8), polymorphs predominated. A broad range of neurological features were noted. Muscle

weakness occurred in 21 (41%), usually consisting of flaccid paralysis of arms and shoulder girdle (n = 14) or legs (n = 8). One patient died after severe bulbar dysfunction combined with flaccid paralysis of arms and respiratory muscle weakness; two others had less severe bulbar or respiratory difficulties. Non-bulbar cranial nerve abnormalities occurred in five. Twenty one patients (41%) had migrating or radicular pain in limbs. Clinical features of distal polyneuropathy (distal sensory disturbance and Achilles reflex loss) occurred in four patients, and nerve conduction studies carried out in seven patients showed evidence of radiculopathy or axonal polyneuropathy in six.

Systemic abnormalities

Joint swelling occurred in two patients. One of them with early local erythema went on to develop formal erythema chronicum migrans (diameter >5 cm²). No patient presented with newly symptomatic cardiac disease. Asymptomatic atrioventricular or His bundle cardiac conduction abnormalities were noted electrocardiographically in 15 patients, but in the absence of premonitory echocardiograms, these cannot all be definitively related to infection (table 1).

Syndromes

The patients with evidence of combined TBE and Lyme borreliosis infection fell into three main clinical groups: febrile illness (n = 3; 6%), meningitis (n = 15; 30%) and neurological deficit (meningoencephalitis, meningomyelitis, meningoradiculitis and polyradiculoneuritis) (n = 33; 65%). Patients with predominantly cerebral features were categorised as "meningoencephalitic" (n = 10) even if they showed other neurological (peripheral, myelitic) or systemic features. Flaccid pareses reflecting anterior horn cell damage categorised patients in the meningomyelitis group (n = 12). Patients with meningitis with migrating limb pain or other signs of peripheral neuropathy or radiculopathy or abnormal nerve conduction studies were classified as meningopolyradiculoneuritic (n = 11; table 2).

DISCUSSION

Most of our patients started with an acute febrile illness compatible with either TBE or Lyme borreliosis. The biphasic fever that occurred in more than half of our patients with double infection is a more typical occurrence in TBE and was noted in >70% of the patients.¹ Meningitis occurred in most of our patients and is equally typical of both TBE and Lyme borreliosis. Meningoradiculoneuritis affects three quarters of all patients with neuroborreliosis,¹ and painful radicular symptoms accompanied meningitis in 41% of our patients, strongly suggesting Lyme borreliosis. Flaccid limb paralysis occurs similarly in both TBE and Lyme borreliosis, but with a particular predilection for the shoulder in TBE; this site was affected in 28% of our patients. Bulbar dysfunction is more typical of TBE; only three of our patients presented with bulbar or respiratory palsy and one died. The facial palsy considered typical of Lyme borreliosis occurred in only three patients and the oculomotor disturbances more typical of TBE occurred in two.

Non-neurological abnormalities are a particular pointer to Lyme borreliosis rather than TBE. Erythema after tick bite is recorded in up to 40% of patients with Lyme borreliosis,^{1, 11} but occurred in only 7 (14%) of our doubly infected patients. When it occurs, arthritis is a pointer to Lyme borreliosis. Echocardiogram evidence of atrioventricular block or intra-ventricular conduction abnormalities occurs in Lyme borreliosis, often without cardiological symptoms.^{1, 11} By contrast, TBE rarely manifests outside the central nervous system.

It is difficult to ascribe neurological symptoms to either condition when there is evidence of double infection with

	Number (n=51)	%	LB-IgG positive	LB-IgM positive	Systemic features LB	LB-IgM and systemic LB	
Meningeal symptoms:							
Headache or Meningism	47	92	30	34	23	17	
CSF pleocytosis	42	95*					
Lymphocytic	26	62†					
Polymorphonuclear	8	19†					
mixed	8	19†					
Neurological features:							
Tremor	22	43	15	10	4	4	
Nystagmus	12	24	8	7	2	2	
Muscle weakness	21	41	13	16	11	8	
Flaccid paresis arms and shoulders	14	28	10	11	6	6	
Flaccid paresis legs	8	16	6	7	5	4	
Spastic paresis	6	12	3	5	4	3	
Bulbar or respiratory dysfunction	3	6	2	1	2	1	
Facial palsy	3	6	1	3	1	1	
Oculomotor disturbances	2	4	1	1			
Distal polyneuropathy	4	8	3	2	2	2	
Migrating, radicular, limb pains	21	41	13	16	10	8	
Systemic features:							
Biphasic fever	28	55	23	17	12	8	
Early local erythema (>5 cm)	7	14	4	4			
Erythema chronicum migrans	1	2	1	1			
Joint involvement	9	18	6	7			
Arthralgias	7	14	4	5			
Swelling	2	4	2	2			
Atrio-ventricular block	5	10	5	3			
His Bundle block	10	20	5	8			
Seropositivity:							
TBE	IgM	51	100	33	35	25	18
Borrelia	IgM	35	69			18	
	IgG	33	65			15	
	IgM and IgG	18	35			7	

CSF, cerebrospinal fluid; Ig, immunoglobulin; LB, Lyme borreliosis.
 *Of the 44 lumbar punctured.
 †Of those with pleocytic CSF.

TBE and Lyme borreliosis, or indeed in any patient with a neurological disorder after tick bite in areas endemic for both conditions. Patients exhibiting neurological features clearly and simultaneously attributable to Lyme borreliosis and TBE seemed to be unusual. However, many patients exhibited neurological features compatible with either condition alone, despite manifesting additional serological or systemic involvement of the other condition. There are good reasons for suspecting that one or other disorder might not be manifesting in the nervous system; for instance, only about a third of patients with TBE infection go on to develop prodromal or neurological illness.² Furthermore, we cannot exclude the possibility that some of our patients IgG ELISA positive for Lyme borreliosis showed separate prior Borrelia exposure or that the Borrelia inoculation had merely provoked antibodies without clinical disease, or that patients with systemic skin, joint or heart manifestations were not simultaneously manifesting neurological forms of Lyme borreliosis. Up to 8% of residents and 15% of outdoor workers in endemic areas

may have IgG antibodies to Borrelia, of whom 50% have never had symptoms attributable to the disease.¹¹ These studies emphasise that patients with tick exposure presenting with an acute neurological symptom in an area endemic for both Lyme borreliosis and TBE should be investigated for both conditions. Severe TBE can occur despite completed active vaccination.¹⁸ We observed no clear evidence of novel or exceptionally severe neurological manifestations suggesting unpredicted interaction between TBE and Lyme borreliosis.

In a TBE ELISA-positive patient with neurological illness after exposure to tick, in a region also endemic for Lyme borreliosis, we advise simultaneous consideration of both conditions given the possibility of co-infection and the difficulty in clinical differentiation. The precision of serological detection of Lyme borreliosis is known to be poor and a pragmatic early decision about antibiotic treatment needs to be taken in patients with possible Lyme borreliosis supported by ELISA seropositivity, the best screening test. Lyme

Neurological syndrome	Total (n)	Systemic features of LB (n)	IgM positive for LB (n)	IgG positive for LB (n)	IgM and IgG positive for LB (n)	Systemic features* of LB and IgM positive (n)
Meningitis alone	15	5	10	11	6	3
Meningopolyradiculoneuritis	11	8	8	8	5	6
Meningomyelitis	12	4	10	8	6	4
Meningoencephalitis	10	6	6	5	1	4
Febrile illness†	3	2	1	1	0	1

Ig, immunoglobulin; LB, Lyme borreliosis.
 *Systemic features of LB are local erythema, erythema chronicum, migrans, arthralgias, joint swelling, AV block or His bundle block.
 †3 patients: migrating limb pain and joint pain; distal polyneuropathy; erythema.

borreliosis is more likely if the patient has systemic features in the skin, joint or myocardium, and a meningopolyradiculoneuritis, especially if there is IgM antibody positive for Lyme borreliosis. TBE is most likely in an isolated meningoencephalitis. Meningitis or meningomyelitis is equally compatible with either Lyme borreliosis or TBE. Overall, there should be a low threshold for antibiotic treatment for putative Lyme borreliosis in any of these clinical presentations, given the overlap of neurological features with TBE and the possibility that any systemic features reflect Lyme borreliosis infection even if borreliosis is not causing the neurological illness. Currently the antibiotics recommended for neuroborreliosis are ceftriaxone, with penicillin or doxycycline as alternatives. No specific antiviral treatment for TBE is available yet. No consensus opinion exists about the effectiveness of steroids or specific immunoglobulins, and the often rapid onset of coma or neuromuscular respiratory failure warrants intensive care.²

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