Fatal outcome of tick-borne encephalitis – a case series

Zgon w przebiegu kleszczowego zapalenia mózgu – opis serii przypadków

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Abstract

Tick-borne encephalitis (TBE) is a disease which may present as meningitis, encephalomeningitis and myeloencephalomeningitis. The course of the disease is usually mild although it may result in the patient's death in 1-4% of cases. Patients with myeloencephalomeningitis are the most endangered group, but also encephalomeningitis may have a fatal outcome. There are many risk factors which influence the severity of TBE, including patient's age, immunosuppression and concomitant diseases. We present four cases of patients who died because of TBE. The aim of the paper was to underline that in elderly patients or patients suffering from chronic diseases and additional infections, special attention should be paid to their treatment, including mechanical ventilation and steroid use.

Key words: tick-borne encephalitis, sequelae, encephalitis, fatal outcome.

Streszczenie

Kleszczowe zapalenie mózgu (KZM) może przebiegać pod trzema postaciami: zapalenia opon mózgowo-rdzeniowych, zapalenia mózgu i opon mózgowo-rdzeniowych oraz zapalenia rdzenia, mózgu i opon mózgowo-rdzeniowych. Przebieg choroby jest zazwyczaj łagodny, jednak w przypadku 1–4% pacjentów choroba może zakończyć się zgonem. Grupami najbardziej narażonymi na zgon są pacjenci z zapaleniem rdzenia, mózgu i opon mózgowo-rdzeniowych oraz z zapaleniem mózgu i opon mózgowo-rdzeniowych. Istnieje wiele czynników wpływających na ciężkość KZM, m.in. wiek pacjentów, upośledzenie układu odpornościowego i współistnienie innych chorób. W pracy zaprezentowano opisy czterech przypadków pacjentów, którzy zmarli z powodu KZM. Celem pracy jest podkreślenie, iż w przypadku starszych pacjentów lub pacjentów z chorobami przewlekłymi czy z innymi zakażeniami towarzyszącymi, chorujących na KZM należy zwrócić uwagę na leczenie, w tym respiratoro- i steroidoterapię.

Słowa kluczowe: kleszczowe zapalenie mózgu, powikłania, zapalenie mózgu, zgon.

Introduction

Tick-borne encephalitis (TBE) virus consists of 3 subtypes: European, Siberian, and Far-Eastern. The Siberian and Far-Eastern subtypes are considered to cause more severe disease than the European subtype [1]. The mortality rate of Far-Eastern subtype infection is 15-20% versus 1-4% in European subtype infection [1-3]. Recently, TBE has become a growing public health problem in Europe and other parts of the world [1]. Worldwide, at least 10-12 thousand cases of TBE are reported each year. What is even more interesting, the virus is

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spreading to new areas [4-7]. TBE is a relatively frequent infectious disease in Poland. Data from the National Health Institute show that on average 250 persons develop symptoms of TBE annually. Most cases are registered in the North-Eastern part of the country, which is considered to be an endemic region for TBE [8]. TBE presents as meningitis in about 50% of patients, as meningoencephalitis in about 40%, and as meningoencephalomyelitis in about 10% [1]. Meningitis is usually accompanied by high fever, headache, nausea, vomiting and vertigo. Signs of meningeal irritation usually occur but may not be pronounced. All patients exhibit cerebrospinal fluid pleocytosis. Specific serological tests are used in diagnosis. The treatment is symptomatic.

Forest workers and people with a relatively high work-related risk of acquiring a TBE infection are usually vaccinated. The most endangered groups are elderly people. It is a consequence of their habits, e.g. collecting mushrooms, leisure activity in forests. Epidemiological data from various European countries demonstrate that the incidence of TBE is higher in elderly people than in younger age groups. In some countries (e.g. Germany, Austria, Sweden, Lithuania) more than 50% of TBE patients are over 50 years old [9]. In Poland, among 710 patients with TBE hospitalized in the Department of Infectious Diseases and Neuroinfections in Białystok in 1993-2008, 235 patients (33%) were > 50 years old.

TBE is a disease with a usually mild course. However, there may be some risk factors which may lead to the patient's death. In this paper, four cases of patients who died because of TBE are described.

Case reports

Patient 1

A 49-year-old man with a history of tick bite (two weeks before) was admitted to the Department of Infectious Diseases and Neuroinfections because of severe headache with vertigo and fever. The symptoms had lasted for about two days.

At admission the patient was conscious. In physical examination, full neck stiffness and Oppenheim sign were observed. The cerebrospinal fluid (CSF) examination revealed inflammatory features (Table 1). Anti-TBE antibodies in the IgM class were found in serum and CSF (Table 1). One day after admission dysphagia and loss of palatal reflexes were observed. The patient was not able to lift his head. He complained of abdominal pain. The patient's history indicated that he had recently undergone an operation because of pyelonephritis. The next day, despite steroid administration the patient had high fever (40°C), and dysphagia became more severe. The patient was transferred to the intensive care unit (ICU), because of breathing difficulties.

At admission to the ICU the patient presented with increasing respiratory failure, nystagmus, ankle clonus, and Babinski sign. He required mechanical ventilation. He was treated with antibiotics (cefotaxime 2 g t.i.d.) and antioedematous drugs (mannitol, dexamethasone). On the sixth day of therapy, the patient's state stabilized. On the ninth day, severe hyponatraemia was observed. On the thirteenth day of hospitalization, Guillain-Barré syndrome and polyneuritis were considered. Control lumbar puncture was performed. In CSF, cytosis and protein concentration were normal (Table 1). Immunoglobulins were introduced to the therapy. The steroid daily dosage was increased to 60 mg of prednisone. On the 21st day of hospitalization, treatment with vancomycin and cefoperazone with sulbactam was implemented because of positive culture from the respiratory tract (MRSA, *Acinetobacter baumannii*). The patient underwent intensive physical rehabilitation. He was also consulted by a psychiatrist (paroxetine was introduced to the therapy). On the 49th day, the patient did not require mechanical ventilation and was transferred to the Department of Neurology.

Despite treatment, his status gradually worsened and the patient died two months after admission.

Patient 2

A 70-year-old man with a history of tick bite was admitted to the Department of Infectious Diseases, because of headaches and fever for 2 days. He had no history of any chronic diseases.

At admission neck stiffness was observed. The CSF had inflammatory features (Table 1). On the third day of hospitalization the patient's general status worsened. He was disoriented and agitated. There were no abnormalities in brain CT. On the fourth day the patient in comatose state was transmitted to the Department of Infectious Diseases and Neuroinfections. At admission the patient had neck stiffness (3 cm) and positive Kernig's sign. On the skin of his thigh, scrotum and in the sacral bone region three ticks were found. Anti-TBE antibodies in IgM and IgG class in serum and CSF were present.

Table 1. Results of laboratory tests in reported cases

	Patient no. 1	Patient no. 2	Patient no. 3	Patient no. 4
Serological tests				
Tick-borne encephalitis (U/mL)*				
Serum IgM	300 (positive)	140 (positive)	73 (positive)	200 (positive)
Serum IgG	negative	35 (positive)	700 (positive)	40 (positive)
CSF IgM	17 (positive)	not examined	50 (positive)	not examined
CSF IgG	negative	not examined	700 (positive)	not examined
Borreliosis (BBU/mL)**				
Serum IgM	33 (positive)	negative	negative	negative
Serum IgG	negative	76 (positive)	56 (positive)	negative
CSF IgM	negative	not examined	10 (positive)	not examined
CSF IgG	negative	not examined	81 (positive)	not examined
Plasma/serum				
Erythrocyte sedimentation rate [mm/h]	26/52	18	20/70; 30/80	5/12
C-reactive protein [mg/dL]	0.4	–	173.3; 203.7; 133	12.4; 2.4
White blood cell count [1000/mm^3]	11.57	8.9; 16.9	16.73; 15.99	5.4; 19.07
Na [mmol/L]	139	136	129	135
K [mmol/L]	4.0	3.85	3.6	4.5
Glucose [mg/dL]	79	100	297; 226	281; 459
Other tests	–	CK: 942 U/L	alkalosis	CK: 52 U/L
		LDH: 639 U/L	D-dimers: 2195.66 μg/mL	LDH: 262 U/L AST: 77 U/L ALT: 77 U/L
CSF				
Colour and transparency	aqueous, clear	aqueous, clear	yellow, transparent	aqueous, clear
Cytosis [1/mm^3]	73; 1	12	310	322
Glucose [mg/dL]	49; 74	67	49	97
Protein [mg/dL]	49.6; 221	52	265.5	49.8
Chloride [mEq/L]	125	120	120	(–)
Nonne-Apelt test	(–); (+/–)	(–)	(+++)	(–)
Pandy test	(+/–); (+/–)	(–)	(+++)	
Other			CSF culture: *Listeria* spp.	

CSF – cerebrospinal fluid

**Cut-off values: 15 U/mL (IgM), 28 U/ml (IgG) (for serum and CSF)*

***Cut-off values (IgM and IgG): 11 BBU/mL (serum), 5 BBU/mL (CSF)*

On the day of admission respiratory insufficiency occurred which resulted in the patient's death.

Patient 3

A 76-year-old woman was admitted to the Department of Infectious Diseases and Neuroinfections with suspected meningitis. The patient's history revealed that two weeks before she had flue-like symptoms: general weakness and fever.

At admission her general status was poor; she was unconscious, without reaction to external stimuli, with fever (39.8°C). In physical examination, neck stiffness (3 cm) and positive Oppenheim sign were found along with paleness, abnormal breathing sounds in both lung fields, tachycardia, atrial fibrillation, and hypertension (180/120, 220/110, 200/100 mm Hg). In laboratory tests, increased inflammation parameters (leukocytosis, erythrocyte sedimentation rate, C-reactive protein), alkalosis, increased D-dimer concentration, hyperglycaemia and abnormalities in electrolyte concentrations were observed (Table 1).

The CSF showed inflammatory features (Table 1). Anti-TBE antibodies and anti-*Borrelia burgdorferi* in IgM and IgG class in serum and CSF were found (Table 1). Antibiotics (rifampicin, amikacin, streptomycin, ceftriaxone), acyclovir, anti-oedematous drugs (dexamethasone, mannitol), intravenous fluids, antihypertensive drugs (captopril, metoprolol) and analgesics were used.

On the fourth day of hospitalization, the general state of patient worsened. The patient died because of cardiopulmonary insufficiency. In microbiological culture of CSF acquired after the patient's death, *Listeria* spp. were observed.

Patient 4

A 73-year-old woman with a history of tick bites was admitted to the Department of Infectious Diseases because of headaches, nausea, vomiting, and malaise. At admission the patient was conscious with slightly expressed meningeal signs and left upper limb paresis.

In laboratory tests, increased activity of aminotransferases, inflammation parameters (C-reactive protein), and hyperglycaemia were observed (Table 1). The CSF showed inflammatory features (Table 1). Anti-TBE antibodies in serum were found (Table 1).

Despite treatment, the patient's status worsened. Right hemiparesis was observed. After a week of therapy with ceftriaxone (2 g daily), mannitol (400 ml daily), and dexamethasone (32 mg daily) the patient was transmitted to the Department of Infectious Diseases and Neuroinfections. At admission the patient was in a severe state with limited contact. In physical examination, tachycardia, hypertension, and arrhythmia were revealed, as well as Cheyne-Stokes respiration and neck stiffness. Laboratory tests showed leukocytosis (19 000 per mm^3), hyperglycaemia (459 mg%), and hypoxaemia (67 mm Hg). Despite intensive insulin therapy, glucose concentration did not decrease. Dyspnoea and tachycardia became more severe and the patient died at the fifth hour after admission.

Discussion

Tick-borne encephalitis is a disease which should be taken into consideration in every case of encephalitis in endemic areas. TBE caused by the European virus subtype is a disease with a usually mild course. However, it may take a severe course with fatal outcome in 1-4% of cases. According to Tomazic *et al*., fatal outcome occurs in the acute status of severe encephalitis due to causes that can be related to direct lesions resulting from the virus in the CNS. The involvement of vital centres (respiratory, vasoactive) may also lead to death. The patient in a severe state is usually treated in the ICU where he/she is additionally endangered by nosocomial infections [10-12].

According to Pikelj *et al*., other factors influencing the course of a TBE infection are early alteration of consciousness (Glasgow Coma Scale score < 7), development of limb paralysis together with respiratory insufficiency within 24-48 hours from the beginning of phase II of the disease and pleocytosis > 300 cells [13,14]. According to Mickiene *et al*., a single-phase course of the disease is also an ominous predictive factor [15]. Late onset of specific anti-TBE virus IgM antibodies in CSF is related to the severity of acute encephalitis symptoms.

In the cases described here, similar risk factors were observed. Three patients were diagnosed with encephalomeningitis and one with meningoencephalomyelitis. The most common factor which contributed to a severe course of the disease and death was the patient's age, as seen in cases 2, 3, and 4. Also one-phase course of TBE was present in 3 of the 4 described cases (1, 2, and 4). Death of 3 patients (2, 3, and 4) occurred in the acute phase of the disease. In case 1, long-term hospitalization in the ICU resulted in nosocomial infection, which also increased the risk of a fatal outcome. In cases 3 and 4, pleocytosis with >300 cells was present in CSF, although

in cases 1 and 2 the cell amount was considerably lower. According to our clinical observations, pleocytosis over 300 cells/mm^3 does not correlate with severity of the disease [8]. Inflammatory indicators do not seem to be relevant for the prediction of the course of the disease, although they may rise in the acute phase of the disease (cases 1, 2, and 4). Concomitant chronic diseases seem to be an important risk factor. Patient 3 suffered from hypertension and diabetes and patient 4 from diabetes. Although not described in this paper (not enough data), it is worth mentioning that a patient also hospitalized in the Department of Infectious Diseases and Neuroinfections with diagnosis of TBE died because of long-term (> 10 year) steroid therapy (rheumatoid arthritis).

In the case of patient 3, coinfection with *Listeria monocytogenes* played an important role in the fatal outcome. Infection with *L. monocytogenes* alone has a mortality rate of 20%. In this case, TBE was the factor that lowered the patient's immunological defence and enabled *L. monocytogenes* infection. The result of CSF culture was acquired after the patient's death; therefore no ampicillin treatment was implemented. It has to be emphasized that the most common coinfection in patients suffering from TBE is Lyme disease [16]. It is rarely fatal, but the risk of sequelae seems to be higher than in patients infected only with TBE virus.

To sum up, patients who develop encephalitis, encephalomyelitis, and those with pareses are at high risk of fatal outcome as a direct consequence. It has to be emphasized, however, that in the case of elderly patients or in those suffering from chronic diseases and additional infections, special attention should be paid to their treatment, including mechanical ventilation and steroid therapy. A vaccination programme offered to this group of people could greatly reduce the risk of fatal TBE outcome in Poland.

We conclude that the fatal outcome of TBE may be a consequence of coexisting risk factors such as age and concomitant chronic disorders or coinfection, e.g. *L. monocytogenes* or others. Pleocytosis may not be used as a predictive factor of severity of the course of TBE.

Special efforts should be made to vaccinate elderly people (> 50 years of age), who constitute the main group endangered by the development of severe TBE sequelae.

Disclosure

Authors report no conflict of interest.

References

1. Kaiser R. Tick-borne encephalitis. *Infect Dis Clin N Am* 2008; 22: 561-575.
2. Lindquist L., Vapalahti O. Tick-borne encepalitis. *Lancet* 2008; 371: 1861-1871.
3. Barrett P.N., Dorner F., Ehrlich H.J. Tick-borne encephalitis virus vaccine. In: Plotkin S., Orenstein W. [eds.]. Vaccines. 4th edition. *WB Saunders*, Philadelphia 2004.
4. Ruscio M. Tick-borne encephalitis: a case with fatal outcome. *Wien Med Wochenschr* 2009; 11-12: 296-300.
5. International Scientific Working Group on TBE: Epidemiology of TBE. [serial online; cited 10 January 2011]; www.tbe-info.com.
6. Donoso M.O., Schadler R., Niedrig M. A survey on cases of tick-borne encephalitis in European countries. *Euro Surveill* 2008; 13: 18848.
7. Randolph S.E. Tick-borne encephalitis incidence in Central and Eastern Europe: multi-factorial environmental and socio-economic causes. *Microbes Infect* 2008; 10: 209-216.
8. Czupryna P., Moniuszko A., Pancewicz S., et al. Tick-borne encephalitis in Poland in years 1993-2008 – epidemiology and clinical presentation. A retrospective study of 687 patients. *Eur J Neurol* 2011; 18: 673-679.
9. Kunze U., Baumhackl U., Bretschneider R., et al. Tick-borne encephalitis in the golden agers: A conference report of the International Scientific Working Group on Tick-Borne Encephalitis (ISW TBE). *Vaccine* 2006; 24: 1236-1237.
10. Tomazic J., Poljak M., Popovic P., et al. Tick-borne encephalitis: possibly a fatal disease in its acute stage. PCR amplification of TBE RNA from post-mortem brain tissue. *Infection* 1997; 25: 41-43.
11. Kunz C. Tick-borne encephalitis in Europe. *Acta Leidensia* 1992; 60: 1-14.
12. Herzing R., Patt C.M., Prokes T. An uncommon severe clinical course of European tick-borne encephalitis. *Biomed Papers* 2002; 146: 63-67.
13. Pikelj F., Tomazic J., Maticic M., et al. Severe forms of tick-borne meningoencephalitis in Slovenia. *J Infect* 1995; 31: 83-85.
14. Haglund M., Gunther G. Tick-borne encephalitis – pathogenesis, clinical course and long-term follow-up. *Vaccine* 2003; 21: S11-S18.
15. Mickiene A., Laiskonis A., Günther G., et al. Tick borne encephalitis in an area of high endemicity in Lithuania: disease severity and long-term prognosis. *Clin Infect Dis* 2002; 35: 650-658.
16. Zajkowska J., Kondrusik M., Świerzbińska R., et al. Zmiany stężenia interferonu gamma w płynie mózgowo-rdzeniowym chorych na kleszczowe zapalenie mózgu. *Neurol Neurochir Pol* 2005; 39: 108-113.