THE COURSE OF TICK-BORNE ENCEPHALITIS BASED ON A CASE REPORT

Przebieg kleszczowego zapalenia mózgu na podstawie opisu przypadku

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Streszczenie: Kleszczowe zapalenie mózgu jest najczęstszą wirusową chorobą przenoszoną przez kleszcze w Polsce. Dokładna liczba przypadków jest znacznie niedoszacowana z powodu rzadko wykonywanych badań w tym kierunku podczas diagnostyki chorób infekcyjnych wskazujących na zajęcie ośrodkowego układu nerwowego. Objawy kleszczowego zapalenia mózgu są niespecyficzne. Badanie stężenia przeciwciał w surowicy krwi w kierunku kleszczowego zapalenia mózgu należy rozważyć w sytuacji wystąpienia choroby w okresie czerwiec-październik oraz dodatniego wywiadu w kierunku ukłucia przez kleszcza. Lepsza wykrywalność zakażenia wirusem kleszczowego zapalenia mózgu pozwoliłaby na redukcję liczby wykonywanych badań oraz stosowanego leczenia farmakologicznego, w tym zbędnej antybiotykoterapii.

Abstract: Tick-borne encephalitis (TBE) is the most common viral disease transmitted by ticks in Poland. The exact number of cases is significantly underestimated due to the fact that patients presenting with infectious diseases and signs of the involvement of the central nervous system are rarely tested for TBE. The symptoms of tick-borne encephalitis are non-specific. Determination of the blood serum concentration of TBE antibodies in patients who develop the disease in June–October and have a positive history of tick bite should be considered. Better detection of TBE infection would make reduction of the number of tests performed and the amount of pharmacotherapy applied possible, including unnecessary antibiotic therapy.

Słowa kluczowe: neuroinfekcja, kleszczowe zapalenie mózgu, choroby odkleszczowe, wirus kleszczowego zapalenia mózgu.

Key words: neuroinfection, tick-borne encephalitis, tick-borne encephalitis virus, tick-borne diseases.

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Introduction

Tick-borne encephalitis (TBE, Lat. *encephalitis ixodica*) is a disease caused by Central European encephalitis virus. It belongs to the *Flaviviridae* family, which consists of RNA viruses. It is introduced into the human body via a bite by an infected tick. In Poland, the TBE virus is transmitted by the castor bean tick (*Ixodes ricinus*). The virus reservoir are small rodents and ticks themselves [1, 2]. The infection is also spread by the oral route through consumption of thermal untreated milk from infected animals, mainly goats and sheep and less frequently cows, in the viraemic phase. The virus becomes inactivated during pasteurisation [3, 4, 5]. There is no possibility of human-to-human transmission [1].

In 2019, according to the data of the National Institute of Public Health – National Institute of Hygiene, the incidence of TBE in Poland was 0.69 cases/100,000/year [6]. According to the WHO definition, TBE-endemic areas are districts where more than 5 cases/100,000 persons/year are detected [7]. In our country, this definition is met only by the Podlaskie province. The actual number of cases is probably higher due to rare TBE testing, because the incidence is higher in most of Poland's neighbouring countries [8, 9]. For this reason, the entire area of Poland should be considered to be threatened by the occurrence of TBE. The highest TBE incidence in Poland occurs from May to October with a characteristic increase in July followed by October [10, 11].

Table 1. Comparison of the frequency of tick-borne diseases in Poland. Status as of 2017 [13].

Tick-borne diseases in Poland (number of cases)				
Lyme disease	**TBE**	**tularaemia**	**anaplasmosis**	**babesiosis**
21,516	282	30	4	1

Ticks are transmitters of various diseases. In Poland, these include Lyme disease, TBE and occasionally tularaemia, anaplasmosis and babesiosis [12] – Table 1.

The TBE virus initially multiplies in the skin and surrounding lymph nodes. It is delivered with the lymph to the cells of various organs. This is the phase of primary viraemia, which is responsible for the symptoms of the first phase. Then, cytotoxic lymphocytes eliminate the virus from the body. In some cases, the body's response is inadequate and secondary viraemia occurs. As a result, the virus enters neurons and glial cells through the endothelium of blood vessels in the brain [1].

The incubation period is 4–28 days, with an average of 7 days. In endemic areas, it is estimated that 70–95% of persons passes the infection subclinically or completely asymptomatically. Most often, the disease occurs suddenly and has two phases [1, 8, 10]:

- **First (prodrome) phase**: flu-like symptoms lasting up to 7 days: malaise, weakness, apathy, fever (usually not exceeding 38°C), upper respiratory tract inflammation, headache, muscle and joint pain, vomiting, nausea, diarrhoea. In laboratory tests: leukopenia, thrombocytopenia and slightly elevated transaminases.
- **Second (neurological) phase – neuroinfection**: symptoms of central nervous system involvement, such as fever up to 40°C, malaise, vomiting, nausea, headache and dizziness, meningeal symptoms, convulsions, consciousness disorders, focal signs, unilateral hearing loss, tinnitus – Table 2.

Table 2. Comparison of the frequency of occurrence of particular symptoms in patients with TBE in the group of adults and children. Own compilation based on [14].

Prevalence of symptoms in adults and children		
Symptom	**Adults**	**Children**
Headache	98%	90%
Vomiting	50%	60%
Fatigue	90%	40%
Malaise	83%	15%
Muscle pains	38%	10%
Joint pains	27%	0%
Dizziness	47%	10%
Photophobia	55%	10%
Fever > 38°C	98%	100%
Meningeal symptoms	85%	90%
Tremor	50%	25%
Paresis	3%	0%

The neurological phase can take the form of the following medical conditions [8, 10, 14, 15]:

- **meningitis** (45–49% of adults, 69–78% of children): occurs most often and is the mildest form. It develops with typical manifestations of lymphocytic meningitis: fever, headache, nausea, vomiting.
- **meningoencephalitis** (45% of adults, 21–30% of children): with a more acute course and symptoms of encephalitis. The most common manifestation is ataxia as a result of cerebellar involvement. In addition, symptoms such as impaired consciousness and cranial nerve palsy may occur.
- **meningoencephalitis + myelitis** (5% of adults, 1% of children): the most severe form. In addition to the symptoms listed above, there are symptoms of injury to the anterior horns of the spinal cord and flaccid paralysis of the limbs. Prognosis is worse in the case of involvement of the medulla oblongata and brainstem. The most severe complication of this form is respiratory muscle paralysis.
- **meningoencephalitis + myelitis with spinal nerve root involvements** (5% of adults): characterised by meningeal symptoms and focal damage of the CNS, nerve roots and peripheral nerves. In most cases, brachial plexus injury occurs, causing paresis of the upper limb, which regresses slowly and is not always completely relieved.

Criteria for the diagnosis of TBE are presented in Table 3.

There is no specific treatment for TBE. Despite ongoing research on an antiviral drug against TBE, no product has been registered to date [15, 17].

The prognosis in most patients is good, with complete resolution of symptoms. In severe cases of encephalomyelitis, pareses, sensory disturbances and impairment of intellectual functions, such as focussing attention and memory, may persist for several months [1, 8]. Mortality in adults in Europe is estimated at 1–4% [18], in Poland at less than 2% [11].

Prophylaxis of tick-borne encephalitis involves, first of all, protection against tick bites by avoiding the areas of increased risk of TBE, the use of repellents (preferably containing DEET or permethrin) and appropriate clothing with long sleeves and legs, hats, high shoes and socks. Light-coloured clothing is recommended. After returning from a forest or meadow, the skin of the whole body should be inspected each time. In the case of a tick bite, the tick should be mechanically removed as soon as

possible, because the virus is contained in its salivary glands and infection can occur within minutes after the bite [1, 2].

Table 3. Criteria for the diagnosis of TBE according to the National Institute of Public Health (PZH) [16].

Criteria for diagnosis of TBE	
Clinical criteria of TBE	symptoms of CNS inflammation
Epidemiological criteria	exposure through the same source (non-pasteurised dairy products)
Laboratory criteria for a confirmed case	• presence of serum IgM- and IgG-specific antibodies • presence of serum IgM and IgG antibodies in the cerebrospinal fluid • seroconversion or a 4-fold increase in the titre of TBE-specific antibodies in two serum samples • detection of TBE virus nucleic acid in clinical specimens • isolation of the virus from clinical specimens
Laboratory criteria for a probable case	detection of TBE-specific IgM antibodies in a single serum sample

Probable case of TBE: clinical criteria and at least one of two criteria, epidemiological or laboratory criteria of a probable case.
Confirmed case of TBE: clinical criteria and one of the five criteria for a confirmed case.

The most effective way to avoid infection is to undergo preventive vaccinations. It is recommended for people living in endemic areas or planning to travel to these regions (in such a case a vaccination cycle should start several months beforehand). There are two inactivated vaccines available in Poland, that provide protection for several years. Both can be administered to children from the age of one. They are administered in two doses, 4–12 weeks apart, followed by a third dose after 9–12 months. A booster dose is recommended after three years [8, 11, 19, 20].

Case study

A 5-year-old boy with autism and allergy was admitted to the Department of Pediatrics, Nephrology, and Paediatric Allergology of the Military Institute of Medicine in July 2021 because of low-grade fever, weakness, headache lasting a week, and decreased appetite over the previous month. A tick bite was observed in early June. In mid-June 2021, the child was hospitalised in another hospital for mild acute myositis in the course of a viral infection accompanied by fever and signs of upper respiratory tract infection. At that time, tests showed leukopenia and elevated creatine kinase values. Symptomatic treatment was administered and improvement was achieved. Two weeks after hospitalisation, fever recurred, accompanied by headache and vomiting. Sinusitis was suspected on an outpatient basis and cefuroxime axetil was introduced.

On admission to the Department of Paediatrics, the child was in good general condition, no significant abnormalities were found. On neurological examination: meningeal signs, Romberg's test and finger-nose test were negative. Muscle strength in the upper and lower limbs was normal. On examination of the visual organ, the eye movements were normal, the pupils were equal, round and responsive to light. Somaesthesia was preserved. The 5th nerve outlets were not painful.

In laboratory tests, inflammatory markers were not elevated (CRP <0.1mg/dl, ESR 11 mm, leukocytes 10,120). Serum electrolyte and water balance were normal (sodium 134 mmol/L, potassium 5.0 mmol/L). Blood count showed no significant abnormalities (WBC 10,120, RBC 4.62 million, HGB 12.5 g/dl, HCT 36%, MCV 78fL, PLT 378,000, LYMPH 25.8%, NEUT 61%, MONO 9.5%, EO 2.8%, BASO 0.5%). Liver and kidney function tests were normal (ALT 16 U/l, AST 28 U/l, ALP 129 U/L, urea 34 mg/dl, creatinine 0.5 mg/dl). Creatine kinase CK-MB concentration was elevated (32 U/l). Other markers of myocardial damage were not elevated. Serology (ELISA method) excluded *Borrelia*, *Yersinia enterocolitica* and *Mycoplasma pneumoniae* infections. No signs of infection were detected in the urine test. No abnormalities were seen on chest radiography. The ultrasound examination of the abdominal cavity showed single reactive lymph nodes up to 8.5 mm in size, otherwise without any abnormalities. Parasitic infestation of the gastrointestinal tract was excluded. The PCR test for SARS-CoV-2 was negative.

A contrast magnetic resonance (MR) scan of the head was performed. Focal lesions in the brain, cerebellum and brainstem and features of increased cerebrospinal fluid pressure were excluded. The only abnormality detected on MR was thickening of the mucosa of the left nasal concha. Because of the lack of abnormalities on imaging examinations and in the presence of symptoms and positive history of tick bite, a serum antibody test for tick-borne encephalitis virus was performed after consultation with a neurologist. A positive result of IgM class antibodies against tick-borne encephalitis [4.4 Ratio (>1.1)] was obtained.

After a seven-day hospitalisation and symptomatic treatment, the complaints reported on admission subsided. The boy was discharged home in good general condition with recommendations for further multispecialist care.

Discussion

In many respects, the presented case fits a typical picture of tick-borne encephalitis. In 90% of children, the disease has a biphasic course [8]. In the patient, the first phase of the disease began in June with flu-like symptoms, fever and leucopenia. The time between the first and second phase in children is on average 6–14.5 days. The second phase began after about two weeks, which also corresponds with the typical picture of the disease [8, 14]. The symptoms of the second phase coincide with those most commonly reported by patients: low-grade fever, weakness, lack of appetite, headache, vomiting.

In addition, the time from the tick bite to the first symptoms of the disease in the described patient also fits the typical picture of the disease. In children, the average TBE incubation period is 12 days [8, 14].

The course of tick-borne encephalitis in children is usually milder than in adults; however, severe forms develop in one third of cases [8, 10, 14]. The most common form in children is asymptomatic, meningitic or meningoencephalitic [21]. In the past, the disease was considered benign due to rare cases of acute complications, death or significant disability. More recent studies indicate that only a proportion of children are completely cured [8].

In children, the infection often presents non-specifically with malaise and fever, which makes diagnosis difficult. We should keep in mind that children may suffer from that disease as early as in the first year of life, which also complicates the diagnosis due to limited communication. The youngest reported case of a child suffering from TBE is a 17-day-old infant in Austria [22]. A case of a child with atypical severe course in the form of epileptic seizures and productive symptoms has also been described [21]. The heterogeneity of the clinical picture should make physicians particularly vigilant when diagnosing paediatric patients. It is estimated that 10% of meningitis cases in children in endemic regions are caused by the TBE virus [22].

Complications in the paediatric population tend to be cognitive-behavioural, in contrast to adults with predominating neurological complications [23]. Cognitive dysfunction and subjective complaints have been proven to occur one year after the illness [24]. Parents of children who have contracted TBE note fatigue, headache, irritability and memory impairment in long-term follow-up [22]. Studies have also shown that children who have suffered from TBE have poorer psychomotor performance and impaired attention, which may translate into poorer school results [24, 25, 26]. Younger children may have difficulty describing their symptoms. After-effects of TBE in children and adults are summarised in Table 4.

Table 4. Incidence of complications post-TBE infection in adults and children [8].

Complications in adults and children %		
Complication	**Adults**	**Children**
Chronic headache	10.8–22.6	11–14
Palsies	2.6–11	no data/not tested
Ataxia and tremor	2.4–14.5	<1
Post encephalitic Syndrome (PES)	40–50	no data/not tested
memory disorders	10.8–19.7	50
concentration disorders	8.4–15.4	26–43
mood disorders	18.8	45
cognitive disorders	11	12–69
fatigue	21.7	45
hearing loss	2.4	no data/not tested
sensory impairment	2.4	no data/not tested
hypersensitivity to sounds and light	1.2	3–11

Because of possible long-term complications, a child with TBE should be placed under paediatric, psychological, and otolaryngologic care to monitor their psychological development and possible hearing loss.

A serum test for specific antibodies to the TBE virus is a relatively simple and inexpensive test. Therefore, it should be performed in the differential diagnosis of neuroinfection. This is especially true when accompanied by the characteristic history of TBE: typical symptoms, biphasic nature of the disease, onset of the disease in June–October, spending time in a heavily forested area, and tick bite. It should be kept in mind that 1/3 of the patients do not remember a tick bite [8].

A positive test result can reduce the number of procedures and examinations performed, shorten the time until diagnosis and prevent the patient from being exposed to unnecessary pharmacological treatment. Such management undoubtedly improves patient comfort and reduces the cost of diagnostics and treatment.

The best solution is universal application of the principle: prevention is better than cure. Children – as young,

developing organisms exposed to complications in the form of neurological developmental disorders – should be covered by vaccine prophylaxis. Both vaccines available in Poland can be used in children from the age of one. The vaccine protects also against food-borne infection [20]. Data from reports from sanitary and epidemiological stations in 2015–2019 in Poland show an increasing number of vaccinated people among both adults and children, but the vaccination rate in Poland still remains low [11].

Conclusions

In case of characteristic symptoms and history indicating a tick bite, TBE needs to be excluded. This may contribute to a reduced number of unnecessary procedures, lower treatment costs, and implementation of appropriate care aimed at diagnosing and treating complications of TBE.

Literature:

1. Flisiak R, Szechiński J, Jaroszewicz J. Choroby przenoszone przez kleszcze [Tick-borne diseases] In: Gajewski P. et al.: Interna Szczeklika [Szczeklik's Internal Medicine] Krakow, 2020, p. 2469–2477. ISBN 978-83-7430-627-0
2. Baumann A, Popczyk U, Sadkowska M. Choroby zakaźne i pasożytnicze – Epidemiologia i profilaktyka [Infectious and parasitic diseases – Epidemiology and prevention]. 2014; 7th edition, Alfa Medica Press; 216–220.
3. Cisak E, Wójcik-Fatla A, Zajac V. Prevalence of tick-borne encephalitis virus (TBEV) in samples of raw milk taken randomly from cows, goats and sheep in Eastern Poland. Ann. Agric. Environ. Med. 2010; 17 (2): 283–286
4. Król ME, Borawski B, Nowicka-Ciełuszecka A. Outbreak of alimentary tick-borne encephalitis in Podlaskie voivodeship, Poland. Przegl. Epidemiol. 2019; 73 (2): 239–248
5. Hudopisk N, Korva M, Janet E, Tick-borne encephalitis associated with consumption of raw goat milk, Slovenia, 2012. Emerg. Infect. Dis. 2013; 19 (5): 806–808, https://doi.org/10.3201/eid1905.121442
6. National Institute of Public Health – National Institute of Hygiene, Department of Epidemiology and Surveillance of Infectious Diseases. Institute, Warsaw 2019 [quoted 26 October 2021]. Zachorowania na wybrane choroby zakaźne w Polsce od 1 stycznia do 31 grudnia 2019 r. oraz w porównywalnym okresie 2018 r. [Incidence of selected infectious diseases in Poland from 1 January to 31 December 2019 and the comparable period in 2018] Address: http://wwwold.pzh.gov.pl/oldpage/epimeld/2019/INF_19_12B.pdf
7. World Health Organization. Geneva 2011 [quoted on 26 October 2021]. Vaccines against tick-borne encephalitis: WHO position paper. Address: https://www.who.int/wer/2011/wer8624.pdf?ua=1
8. Kuchar E, Zajkowska J, Flisiak R, et al. Epidemiologia, diagnostyka i profilaktyka kleszczowego zapalenia mózgu w Polsce i wybranych krajach europejskich- Stanowisko Polskiej Grupy Ekspertów [Epidemiology, diagnostics and prophylaxis of tick-borne encephalitis in Poland and selected European countries – Position of the Polish Group of Experts], Medycyna Pracy 2021; 72 (2): 193–210. Online access [26.10.2021]: https://doi.org/10.13075/mp.5893.01063
9. Tick-borne encephalitis, Annual Epidemiological Report for 2019 ECDC online access: https://www.ecdc.europa.eu/sites/default/fles/documents/AER-TBE-2019.pdf
10. Zajkowska J, Czupryna P. Kleszczowe zapalenie mózgu – epidemiologia, patogeneza, obraz kliniczny, diagnostyka, profilaktyka i leczenie [Tick-borne encephalitis – epidemiology, pathogenesis, clinical picture, diagnosis, prevention and treatment]. Forum Zakażeń 2013; 4 (1): 43–51.
11. Paradowska-Stankiewicz I, Zbrzeźniak J. Kleszczowe zapalenie mózgu w Polsce i na świecie. Ocena sytuacji epidemiologicznej KZM w Polsce w latach 2015–2019 w oparciu o dane pochodzące z nadzoru epidemiologicznego [Tick-borne encephalitis in Poland and worldwide. Epidemiological analysis of TBE in Poland in 2015–2019 based on epidemiological surveillance]. Report of the National Institute of Public Health. Online access: https://www.pzh.gov.pl/wp--content/uploads/2021/03/KleszczoweZapalenieMozgu-raport-PZH_2021.pdf
12. Kmieciak W, Ciszewski M, Szewczyk EM. Choroby odklesz-czowe w Polsce – występowanie i trudności diagnostyczne [Tick-borne diseases in Poland – prevalence and diagnostic difficulties, Medycyna Pracy 2016; 67 (1): 73–87, online access: http://dx.doi.org/10.13075/mp.5893.00264
13. National Institute of Public Health: Infectious diseases and poisonings in Poland in 2017. [Access 19.07.2018]. [archived from the address: http://wwwold.pzh.gov.pl/oldpage/epimeld/2017/Ch_2017_wstepne_dane.pdf].
14. Arnez M, Kolbl J. Comparison of the epidemiological and clinical features of tick-borne encephalitis in children and adults. Infection. 2000; 28 (2): 74–77, https://doi.org/10.1007/s15010 0050050
15. Pancewicz S, Garlicki A, Moniuszko-Malinowska A. Diagnostyka i leczenie chorób przenoszonych przez kleszcze. Rekomendacje Polskiego Towarzystwa Epidemiologów i Lekarzy Chorób Zakaźnych [Diagnosis and treatment of tick-borne diseases. Recommendations of the Polish Society of Epidemiology and Physicians of Infectious Diseases]. Przegl. Epidemiol. 2015; 69: 421–428
16. National Institute of Public Health – National Institute of Hygiene, Department of Epidemiology and Surveillance of Infectious Diseases. Instytut, Warsaw 2019. Defnicje przypadków chorób zakaźnych na potrzeby nadzoru epidemiologicznego [Infectious disease case definitions for epidemiological surveillance]: http://wwwold.pzh.gov.pl/oldpage/epimeld/inne/ Def_PL2_5.pdf
17. Taba P, Schmutzhard E, Forsberg P. EAN consensus review on prevention, diagnosis and management of tick-borne encephalitis. Eur. J. Neurol. 2017; 24 (10): 1214–1261, https://doi.org/10.1111/ene.13356
18. Zajkowska J, Czupryna P, Pancewicz S. Fatal outcome of tick-borne encephalitis – a case series. Neurol. Neurochir. Pol. 2011; 45 (4): 402–406.
19. Program Szczepień ochronnych 2021, online access [26.10.2021]: http://dziennikmz.mz.gov.pl/DUM_ MZ/2020/117/akt.pdf
20. Charakterystyka produktów leczniczych szczepionek przeciw KZM dostępnych w Polsce, dostęp internetowy [Characteristics of the medicinal products for vaccines against TBE available in Poland, online access] [26.10.2021] https://szczepienia.pzh.gov.pl/dla-lekarzy/lista-szczepionek-oraz-chpl-do-pobrania-2/
21. Szenborn L, Kuchar E, Wołkowska-Mączka M. Napady padaczkowe jako dominujący objaw kleszczowego zapalenia mózgu u 14-letniego chłopca-opis przypadku [Epileptic seizures as the predominant symptom of tick-borne encephalitis in a 14-year-old boy – case report], Forum Zakażeń 2014; 5 (2): 61–65
22. Palyga-Bysiecka I, Kręcisz B, Szczepańska B. Clinical course and neurological sequels after tick-borne encephalitis in children – case report. Ann Agric Environ Med. https://doi: 10.26444/aaem/133206
23. Steffen R. Tick-borne encephalitis (TBE) in children in Europe: Epidemiology, clinical outcome and comparison of vaccination recommendations. Ticks Tick Borne Dis. 2019;10 (1): 100–110, https://doi.org/10.1016/j.ttb-dis.2018. 08.003
24. Engman ML, Lindström K, Sallamba M. One-year follow-up of tick-borne central nervous system infections in childhood. Pediatr. Infect. Dis. J. 2012; 31 (6): 570–574, https://doi.org/10.1097/INF.0b013e31824f23c0
25. Schmolck H, Maritz E, Kletzin I. Neurologic, neuropsychologic, and electroencephalographic findings after European Tick-borne Encephalitis in children. J. Child. Neurol. 2005; 20 (6): 500–508,

https://doi.org/10.1177/088307380502 00060601
26. Ullman H, Fowler A, Wickström R. Increased working memory related fMRI signal in children following Tick Borne Encephalitis. Eur. J. Paediatr. Neurol. 2016; 20 (1): 125–130, https://doi.org/10.1016/j.ejpn.2015.09.004