FATAL OUTCOME OF TICK-BORNE ENCEPHALITIS IN AN IMMUNOSUPPRESSED PATIENT FROM THE ENDEMIC AREA IN SLOVAKIA

FATÁLNY DOPAD KLIEŠŤOVEJ ENCEFALITÍDY U IMUNOSUPRIMOVANÉHO PACIENTA Z ENDEMICKEJ OBLASTI SLOVENSKA

LITVOVÁ Slavka[1,2], ŠTEFKOVIČOVÁ Mária[1], KOPILEC GARABÁŠOVÁ Mária[3*], KRAJČOVIČOVÁ Zdenka[1], KAŠLÍKOVÁ Katarína[1], KOLOŠOVÁ Andrea[4,5]

[1] *Faculty of Healthcare, Alexander Dubček University in Trenčín, Trenčín, Slovakia*
[2] *Regional Public Health Authority in Trenčín, Trenčín, Slovakia*
[3] *Dolnooravian Hospital of Dr. L. N. Jégé in Dolný Kubín, Dolný Kubín, Slovakia*
[4] *Slovak Medical University in Bratislava, Bratislava, Slovakia*
[5] *University Hospital Bratislava, Bratislava*
[*] *Corresponding author*

ABSTRACT
Tick-borne encephalitis is an infectious disease of the central nervous system caused by the TBEvirus, that is commonly transmitted by a tick-bite, however, the route of transmission via raw milk is also common. The aim of this disease case report is to present a severe clinical case of TBE in a patient with immunosupressive treatment due to kidney transplantation with fatal outcome. This case in a middle-aged male was accompanied by a second TBE case in his immunocompetent son with a typical bi-phasic illness course and rapid recovery. They both lived in the endemic area Strážovské vrchy in the middle Váh Valley area in Slovakia. Immunosuppresive treatment can in the patient decreased the patients' immunological response to tick-borne encephalitis virus with risk of fatal outcome.

Key words: Tick-borne encephalitis. Immunosuppression. Fatal case. Transplantation. Alimentary transmission. Milk products.

ABSTRAKT
Kliešťová encefalitída (KE) je infekčné ochorenie postihujúce centrálny nervový systém vyvolané vírusom KE. Vírus je zvyčajne prenesený pri uhryznutí kliešťom, avšak častá je aj alimentárna cesta prenosu - konzumáciou surového mlieka. Cieľom tejto kazuistiky je prezentovať závažný klinický prípad KE s fatálnym koncom. Išlo o ochorenie u muža v strednom veku s imunosupresívnou liečbou po transplantácii obličky. Prípad bol sprevádzaný druhým ochorením KE u jeho imunokompetentného syna s typickým dvojfázovým priebehom s rýchlym zotavením. Obaja žili v endemickej oblasti Slovenska Strážovské vrchy na strednom Považí. Imunosupresívna liečba môže u pacienta znížiť imunitnú odpoveď na prítomnosť vírusu kliešťovej encefalitídy s rizikom fatálneho dopadu ochorenia.

Kľúčové slová: Kliešťová encefalitída. Imunosupresia. Fatálny prípad. Transplantácia. Alimentárny prenos. Mliečne výrobky.

INTRODUCTION

Tick-born encephalitis (TBE) is one of the most frequent flavoviral infection of the central nervous system in Europe. TBE is becoming a growing public health challenge because the number of cases has increased substantially, especially in northern and Eastern Europe and Asia. In the last two decades, the incidence of TBE has increased due to climate change, which is leading to a change in geographic distribution of ticks genus *Ixodes* [1].

The disease is the most often transmitted by saliva of infected ticks, but it can also occur through unpasteurized cow's, goat's or sheep's milk or their products. The largest known outbreak of foodborne TBE occurred in 1951 in Czechoslovakia. More than 600 individuals became infected by the TBE-virus contaminated cow's and goat's milk [2]. Later the outbreaks of TBE after the consumption of raw goat's milk have been reported in various countries in Europe and in Russia [3-8]. Slovakia is among the countries with the highest incidence of alimentary tick-borne encephalitis in Europe associated with consumption of unpasteurized milk and cheese from domestic ruminants. None of the European countries report a comparable number of TBE alimentary outbreaks with probable and laboratory confirmed food transmission factor as Slovakia [9]. In the period of years 2017–2020 alimentary infections represented 16.3% of all recognized TBE cases. The countries with the highest reported numbers of TBEV alimentary cases in addition to Slovakia are the Czech Republic [2] and Hungary [2, 10]. Review of TBE alimentary infections (outbreaks) is presented in Table 1.

The TBE disease typically shows a biphasic course. During the approximately one weeklong viremic phase, influenza-like symptoms and typical symptoms of neuroinfection as headache, fever, fatigue, myalgia, nuchal rigidity, postural instability, nausea and vomiting, photophobia and confusion

Table 1 Selected outbreaks of alimentary TBE in European countries

Year of outbreak	Country	Number of alimentary cases	Epidemiologic factor	Comments	Ref.
1951	Slovakia, Rožňava	660 cases - 271 of them hospitalized	goat's milk	goat's milk was shuffled to cow's milk	[4]
1974	Slovakia, Závada	10 hospitalized cases	sheep's milk	-	[16]
1994	Slovakia, Považská Bystrica	7 cases	goat's milk	family outbreak	[4]
1997 – 2008	Czech Republic	64 cases	goat's milk, cow's milk sheep's cheese	goat's milk (56,3%), cow's milk (10,9%) sheep's cheese (32,8%)	[2]
2012	Slovenia	3 out of 4 exposed	goat's milk	biphasic course in 2 persons - the favorable conditions, 4th person healthy - vaccinated	[13]
2008	Austria	6 out of 7 exposed	goat's milk	-	[7]
2007	Hungary	25 out of 154 exposed	goat's milk	-	[6]
2005	Estonia, Tallinn and Harjumaa	27 out of 27 exposed – 24 hospitalized	goat's milk	all associated with consumption of the unonpasteurized goat's milk as a part of healthy diet campaigne	[7]
2011	Hungary	11 cases (7 confirmed, 4 suspected),103 exposed	cow's milk	unpasteurized cow's milk from the farmer without authorization. The first report of TBE after drinking cow's milk in the EU	[8]
2015	Croatia	7 out of 10 exposed	raw goat's milk or cheese	none had been vaccinated nor had a tick bite observed.	[17]
2016	Germany	2 out of 32 exposed	goat's dairy products	possible link to raw milk and cheese from a goat farm	[18]
2017	Germany	13 out of 27 exposed	raw goat's milk	exposed and non-vaccinated people developed clinical illness and were serology confirmed as TBE cases.	[19]
2017	Poland	4 cases	raw goat's milk	-	[20]
2019	Croatia	6 cases	possible link to raw goat's milk	case-control analysis - individuals with TBE (cases) had 25 (95 % CI 0.8-1410.2, p = 0.021) times higher odds of raw goat's milk consumption compared to healthy controls.	[21]

occur. Neurological manifestations are the hallmark of the second phase, with a clinical spectrum ranging from mild meningitis to severe encephalitis. Frequently are described long-term neurological sequelae.

The course of disease varies from non-symptomatic which are likely to remain undiagnosed to encephalitis with mortality rates between 0.5 and 2 % [11].

A more severe course is caused by the presence of risk factors such as higer age, immunodeficiency and genetic factors. TBE can be fatal, especially in immunosuppressed patients [12-15]. In our disease case report, we present severe clinical case of TBE

in a patient with immunosupressive treatment due to kidney transplantation with fatal outcome.

CASE REPORT

We are describing two cases of TBE in a family of 5 members that occured in July 2015, under the mountain range Strážovské vrchy in the valley stredné Považie. The disease was diagnosed in father and son. The patients lived in an endemic area of Slovakia with a high prevalence of TBE and were not vaccinated against TBE.

The first case: A 14 year old boy with a biphasic course of illness. On the 21st of June 2015 the patient presented with a red-tinged throat and headache, was prescribed antibiotic treatment with Cefuroxime axetil. After little improvement high fevers rising up to 39 °C were noted along with further headaches, photophobia, phonophobia and repeated vomiting. On the 1st of July the patient was admitted to the regional hospital in the pediatric ward due to tongue tremor, trembling eye-lids, nausea, vomiting, weakness, somnolence and neuroinfection was suspected. The diagnosis of TBE was based on biochemical findings in the CSF showing aseptic meningitis as well as on positivity of IgM and IgG antibodies in serum by ELISA test. CSF was negative for anti-TBEV antibodies. On the 26th of June 2015, five days before admission to hospital and after the first phase of the disease, the patient had a tick extracted from the left scapular region. According to his mother he had occassionally consumed home produced raw goat's milk. The patient was discharged from the hospital 10 days later in a satisfactory condition.

The second case: A 48 year-old male patient with a history of cadaver kidney transplantation in 2013 and post-transplant immunosuppressive therapy with a history of glomerulonephritis was admitted to the regional hospital due to suspected neuroinfection on 3th of July 2015. One day prior to admission he had severe headache, shivering, fever 38 °C, myalgia, and arthralgia. Upon admission to the hospital with the following signs of neuroinfection - lucid but exhausted with unstable posture, walking with a wide based gait, shakiness, chanted speech, trembling eye lids, tongue and limb tremor and positive signs of meningeal irritation. The patient gradually deteriorated, despite a reduction in the dosage of used immunossupressive treatment became somnolent with intermittent episodes of coma. The initial MRI scan revealed high signal zones in the grey matter in both sides of the thalamus, midbrain, and basal ganglia. Successive epileptic attack, quadriparesis ascending on the left side and coma vigille were noted. The patient died 19 weeks later. Due to the severe course of the illness it was not possible to determine whether he had a viraemic illness phase at home before admission or if it was a grave monophasic course of illness. It is possible that early signs of the disease could have been mitigated by ongoing immunosuppresive treatment. CSF analysis revealed pleocytosis, as well as on positivity of IgM antibodies in serum by ELISA test. IgG antibodies in serum and IgM/IgG antibodies in CSF were negative shortly after admission. Although first sample of CSF was negative for TBE antibodies, 18 days later, IgM was detected in borderline amounts in CSF.

There was a history of a tick bite around 24th of June 2015. According to his wife, the patient had been drinking raw milk from a home-bred goat that was purchased to provide her husband with good quality milk to help with his renal problems. The other members of the household (two children 15 and 13 years of age) and their mother denied consumption of any of the raw goat's milk.

DISCUSSION

TBEV is the most significant tick-borne virus in Europe and important proportion of overall TBEV infections can be also mediated by the consumption of raw milk products. The clinical spectrum of tick-borne encephalitis ranges from a mild, short-lived illness to a more severe, life-threatening illness. The disease might have serious long-term consequences, especially mental, neurologic and psychiatric disorders. We present the familial occurence of the TBE in endemic area in a 48 year-old father and his son. In a father with history immunosuppressive treatment contributed to the fatal outcome caused by infections, while his immunocompetent 14-year-old son recovered with no consequences. Our disease case report has documented the tragic impact of TBE for the farmer´s family. The TBE outbreak caused by alimentary transmission of TBEV lack definitive evidence of the virus having been present in milk or dairy products. However, in others´ studies the source of infection was proven by direct demonstration of TBEV RNA and a corresponding virus load (concentration) in serum and milk samples from the goats whose milk was consumed. The outbreaks od alimentary TBE could have been

avoided if the milk had been pasteurized or boiled before consumption. There are two specific factors of alimentary transmission. One is an accumulation of the cases in one place over the short period and the second one is a short incubation time (3 – 4 days) similarly as in the transmission by the tick. Differences between TBE associated with the consumption of raw milk (goat's, sheep's) and tick bites there are several. Incubation period after a tick bite is on average 7 – 14 days whereas after exposure alimentary route is usually shorter and only 3 – 4 days and even short as 2 days [13, 22]. From the point of view of clinical course, biphasic form of TBE is more common in alimentary TBE and in case after a tick bite constitutes only 20 – 30 % of all cases [23]. In patients with alimentary TBE is more often observed non-severe meningoencephalitis and have a high probability of recovering without neurological sequelae compared with tick-associated TBE [22]. In presenting this TBE case report, the authors consider it is very likely to have been caused by alimentary transmission even though both patients had some history of a recent tick bite (in the case of the son, it was only documented after the initial phase of viraemia). Because only 0.1 to 5.0 % of ticks carry the TBE virus, it is unlikely for two members of the same family to be attacked by two infected ticks at the same time and place. The father was consuming his family's raw goat's milk regularly, his son less frequently. In infected goats, shortly after the viraemic phase, the TBE virus enters the milk with an average peristance time of around 7 days. The consumption of such milk may lead to the infection of more than one person at any one time. Alimentary outbreaks are therefore usually not sporadic as tick bite cases are but are present in outbreaks of varying size.

The TBE caused by the central European virus subtype has a biphasic course in 75 % of cases. Severe brain impairment occurs in 10 % and the case fatality rate is below 2 % [12, 24]. Several clinical studies proved that monophasic form of neuroinfection is associated with more severe outcome. Long term consequences are observed in around half of adults [24, 25]. In our case reports, the 14-year-old son had a typical biphasic course without serious problems. In his father's case, it was impossible to ascertain whether it was a monophasic disease or if the initial viraemic phase was not recognised because of immunosuppresive treatment. Because of his serious condition on admission, it was not possible to obtain a detailed history of the early stage of his illness. This fatal case of TBE presented here emphasises a serious prognosis when acute TBE is diagnosed in immunosuppresed patients. The number of immunosuppressed patients may be increasing due to improvements in medical care, as well as new indications for immunosuppressive agents which have been introduced over the past years [26]. Several fatal cases have been described in patients treated with rituximab, among whom one has been previously vaccinated against TBE [27]. Lethal TBE case was reported also in a patient with history rheumatoid arthritis with immunosuppressive treatment and in patient with lymphatic leukemia [28, 29]. Chmelik et al. (2016) present a fatal case of TBE in an immunosuppressed 12-year-old patient from Czech. A boy was hospitalized with suspected hemophagocytic lymphohistiocytosis without any sign of TBE. CSF was negative for anti-TBEV antibodies and TBE IgG and IgM (ELISA) were also negative. The immunosupressive therapy was initiated and after 8 days a relaps of high temperature accompanied with development of meningeal signs, progreding quadruplegia and coma followed. TBE serology at this time was highly positive in both IgG and IgM. In spite of the intensive care after 31 weeks the child died [14].

It is interesting that in the intial meningo-encephalitic phase of the disease the specific IgM and IgG serum antibodies are always present, while the antibodies in a spinal fluid are present only in about 50 % cases [12, 17]. The younger of our two patients was tested positive for both IgM and IgG at the begining of meningo-encephalitis, however, his father only for IgM in serum. Specific antibodies in father's CSF were not present after admission, but 18 days later, IgM was detected in borderline amounts in CSF. In both cases CSF analysis revealed pleocytosis. Delayed anti-TBE antibodies production may be observed in immunocompromised patients which might hinder the diagnosis [14, 15, 27]. Even though TBE can be prevented by vaccination, standard vaccine schedule may not provide enough cellular immunogenicity in these immunosuppressed patients [28].

The risk of developing TBE also increases with the consumption of dairy products especially in endemic areas. Milk and dairy products from domestic ruminants are popular because of the widespread belief that they are more healthy and better tasting. Milk from hundreds of animals is rather often mixed

together before filling bottles or before preparing dairy products. Therefore a disease carrying single animal may create a serious outbreak situation. Experimental data have revealed safe virus inactivating procedures in milk, such as pasteurization and boiling.

CONCLUSION

TBEV can cause serious infection of the central nervous system in humans, resulting in potential neurological complications and fatal outcomes. Immunocompromised patients are a risk group for severe TBE, and clinical course is unpredictable. Delayed production of anti-TBE antibodies is perceived in part of the immunocompromised patients which might inhibit the diagnosis of the disease. It is imperative to recognize and acknowledge that accurate and timely diagnosis of TBEV infection is vital due to the non-specific nature of the initial symptoms. For TBEV infection no specific antiviral therapy exists, treatment approaches primarily focus on symptomatic relief and support. Accurate diagnosis is essential for effective management, prevention of complications, and the implementation of control measures. Besides tick borne viral transmissions, alimentary infections are reported due to consumption of raw milk and unpasteurized dairy products originating from the natural foci of TBE. Traditional raw dairy products made in TBEV foci therefore represent a considerable risk to human health. The fashionable natural lifestyle encourages the consumption of raw milk and products made of unpasteurized milk. The risk of alimentary exposures could be reduced through education campaigns that encourage persons to consume only milk that has been boiled or pasteurized and only dairy products made from pasteurized milk. In Slovakia TBE is endemic and approximately more than 200 cases are reported each year. Cases of TBE can be underestimated since the diagnostic tests for this condition are not performed routinely in places where disease occurs rarely and in the abortive form of TBE.

Vaccination programs and public awareness campaigns could greatly reduce the number of patients affected by this potentially severe CNS infection esspecialy in endemic areas. It is necessary to encourage and achieve a co-ordinated response of both the veterinary and public health sectors to achieve a reduction TBE incidence and its public health impact.

The expanding risk areas, increasing incidence of TBEV infections, and emerging endemic regions emphasize the importance of gaining a better understanding of the factors influencing TBEV pathogenesis. By deepening knowledge of TBEV and its associated factors, it is necessary to improve strategies for timely diagnosis, appropriate management, and effective control measures against TBEV infections. In addition, TBE vaccination, should be encouraged in areas where TBEV is highly endemic.

Funding

This publication was produced with the support of the Project KEGA Nr. 004TnUAD-4/2022 „Imple-mentation of multimedia approaches into the education of healthcare professionals within the context of management of emergency epide-miological situations".

REFERENCES

[1] ALKISHE A. A., PETERSON A. T., SAMY A.M. Climate change influences on the potential geographic distribution of the disease vector tick Ixodes ricinus. *PLoS ONE*. 2017; 12 (12): e0189092.

[2] KRÍZ B., BENES C., DANIEL M. Alimentary transmission of tick-borne encephalitis in the Czech Republic 1997-2008. *Epidemiol Mikrobiol Imunol.* 2009; 58 (2): 98-103.

[3] BALOGH Z., FERENCZI E., SZELES K. et al. Tick-borne encephalitis outbreak in Hungary due to consumption of raw goat milk. *J Virol Methods*. 2010; 163 (2): 481-485.

[4] KOHL I., KOŽUCH O., ELECKOVÁ E. et al. Family outbreak of alimentary tick-borne encephalitis in Slovakia associated with a natural focus of infection. *Eur J Epidemiol*. 1996; 12 (4): 373-375.

[5] VERETA L.A., SKOROBREKHA V.Z., NIKOLAEVA S.P. et al. The transmission of the tick-borne encephalitis virus via cow's milk [in Russian]. *Med Parazitol (Mosk).* 1991; 3: 54-56.

[6] JUCEVICIENE A., VAPALAHTI O., LAISKONIS A. et al. Prevalence of tick-borne-encephalitis virus antibodies in Lithuania. *J Clin Virol.* 2002; 25 (1): 23-27.

[7] HOLZMANN H., ABERLE S.W., STIASNY K. et al. Tick-borne encephalitis from eating goat cheese in a mountain region of Austria. *Emerg Infect Dis*. 2009; 15 (10): 1671-1673.

[8] KERBO N., DONCHENKO I., KUTSAR K. et al. Tickborne encephalitis outbreak in Estonia

linked to raw goat milk, May-June 2005. *Euro Surveill.* 2005; 10 (6): E050623.2.
[9] KERLIK J., AVDIČOVÁ M., ŠTEFKOVIČOVÁ M. et al. Slovakia Reports Highest Occurrence of Alimentary Tick-Borne Encephalitis in Europe: Analysis of Tick-Borne Encephalitis Outbreaks in Slovakia during 2007–2016. *Travel Med Infect Dis*. 2018; 26: 37-42.
[10] CAINI S., SZOMOR K., FERENCZI E. et al. Tick-Borne Encephalitis Transmitted by Unpasteurised Cow Milk in Western Hungary, September to October 2011. *Eurosurveillance.* 2012; 17 (12): 20128.
[11] HANSSON K.E., ROSDAHL A., INSULANDER M. et al. Tick-borne encephalitis vaccine failures: a 10-year retrospective study supporting the rationale for adding an extra priming dose in individuals starting at age 50 years. *Clin Infect Dis*, 2020; 70 (2): 245-251.
[12] BOGOVIC P., STRLE F. Tick-borne encephalitis: A review of epidemiology, clinical characteristics, and management. *World J Clin Cases*. 2015; 3 (5): 430-441.
[13] HUDOPISK N., KORVA M., JANET E. et al. Tick-borne Encephalitis Associated with Consumption of Raw Goat Milk, Slovenia, 2012. *Emerg Infect Dis.* 2013; 19 (5): 806-808.
[14] CHMELÍK V., CHRDLE A., RŮŽEK D. et al. Fatal tick-borne encephalitis in an immunosuppressed 12-year-old patient. *J Clin Virol.* 2016; 74: 73-74.
[15] DE BRUIJN M., VAN DER LELY N., MARCELIS J. et al. Tick-borne' encephalitis in an immunocompromised patient. *Ned Tijdschr Geneeskd*. 2015; 159: A9067.
[16] GREŠÍKOVÁ M. *Kliešťová encefalitída – trvalý verejno-zdravotnícky problém*. Bratislava: VEDA, vydavateľstvo SAV, 1999. ISBN 80-224-0627-9, 100s.
[17] MARKOVINOVIĆ L., LIČINA M.K., TEŠIĆ V. et al. An Outbreak of Tick-Borne Encephalitis Associated with Raw Goat Milk and Cheese Consumption, Croatia, 2015. *Infection.* 2016; 44 (5): 661-665.
[18] BROCKMANN S.O., OEHME R., BUCKENMAIER T. et al. Cluster of Two Human Cases of Tick-Borne Encephalitis (TBE) Transmitted by Unpasteurised Goat Milk and Cheese in Germany, May 2016. *Eurosurveillance.* 2018; 23 (15): 17-00336.
[19] CHITIMIA-DOBLER L., LINDAU A., OEHME R. et al. Tick-borne encephalitis vaccination protects from alimentary TBE infection: Results from an alimentary outbreak. *Microorganisms*. 2021; 9 (5): 889.
[20] KRÓL M.E., BORAWSKI B., NOWICKA-CIEŁUSZECKA A. et al. Outbreak of Alimentary Tick Borne Encephalitis in Podlaskie Voivodeship, Poland. *Przegl Epidemiol.* 2019; 73 (2): 239-248.
[21] ILIC M., BARBIC L., BOGDANIC M. et al. Tick-Borne Encephalitis Outbreak Following Raw Goat Milk Consumption in a New Micro-Location, Croatia, June 2019. *Ticks Tick Borne Dis.* 2020; 11 (6): 101513.
[22] GRITSUN T.S., LASHKEVICH V.A., GOULD E.A. Tick-Borne Encephalitis. *Antiviral Res.* 2003; 57 (1-2): 129-146.
[23] PAULSEN K.M., STUEN S., DAS NEVES C.G. et al. Tick-borne Encephalitis Virus in Cows and Unpasteurized Cow Milk from Norway. *Zoonoses Public Health*. 2019; 66 (2): 216-222.
[24] KAISER R. Tick-borne encephalitis--still a serious disease? *Wien Med Wochenschr*. 2012; 162 (11-12): 229.
[25] LOTRIC-FURLAN S., AVSIC-ZUPANC T., STRLE F. An abortive form of tick-borne encephalitis (TBE) a rare clinical manifestation of infection with TBE virus. *Wien Klin Wochenschr.* 2002; 114 (13-14): 627-629.
[26] HARPAZ R., DAHL R.M., DOOLING K.L. Prevalence of Immunosuppression Among US Adults, 2013. *JAMA*. 2016; 316 (23): 2547-2548.
[27] KNIGHT A., PAUKSENS K., NORDMARK G. et al. Fatal outcome of tick-borne encephalitis in two patients with rheumatic disease treated with rituximab. *Rheumatology (Oxford)*. 2017; 56 (5): 855-856.
[28] SENDI P., HIRZEL C., PFISTER S. et al. Fatal Outcome of European Tick-borne Encephalitis after Vaccine Failure. *Front Neurol.* 2017; 8: 119.
[29] KUIVANEN S.,SMURA T., RANTANEN K. et al. Fatal Tick-Borne Encephalitis Virus Infections Caused by Siberian and European Subtypes, Finland, 2015. *Emerg Infect Dis*. 2018; 24 (5): 946-948.