Original paper

Retrospective clinical and serological studies of tick-borne encephalitis-indication for vaccination

Katarzyna Gustaw[1], Jolanta Chmielewska-Badora[2], Ewa Cisak[2]

[1]Department of Neurodegenerative Diseases, Institute of Agricultural Medicine, Lublin, Poland, Department of Logopedics and Applied Linguistics, UMCS, Lublin, Poland
[2]Department of Occupational Biohazards, Institute of Agricultural Medicine, Lublin, Poland

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Corresponding author:
Katarzyna Gustaw, MD PhD
Department of Neurodegenerative Diseases
Institute of Agricultural Medicine
Jaczewskiego 2
20-095 Lublin, Poland
Phone: +48 81 718 45 19
Fax +48 81 747 86 46
E-mail: kasiagu@yahoo.ca

Abstract

Introduction: Tick borne encephalitis (TBE) is a potentially debilitating disease caused by TBE virus. Tick born encephalitis has wide distribution. Natural foci of TBE had been localized in the Lublin region, Poland, with a growing prevalence of the incidence beginning in the 90s.
Material and methods: We have examined 108 patients who underwent tick-born encephalitis with a clinical manifestation of meningoencephalitis and encephalitis who had suffered from TBE in the years 1995-2001. Only 38 patients, however, fulfilled both clinical and serological criteria of TBEV and were included in further analysis.
Results: In all 38 patients specific TBE antigens in the cerebral spinal fluid (CSF) and serum were noticed at the level at least 300 Vu (Vienna unit) (ELISA) during the illness.
In 42% of cases seropositive high levels of specific immunoglobulins have still been noticed after the recovery. None of the patients suffered from TBEV for the second time. Moreover, we did not find any correlation of seropositive levels of immunoglobulins and neurological symptoms dynamics.
Conclusions: TBE, however, has to be taken into account in the history of the patient with acute neurological symptoms who have previously suffered from TBE. Besides, in patients suffering from TBEV the level of specific immunoglobulins may have a protective value.

Key words: tick borne encephalitis, TBE, serology, vaccination.

Introduction

Tick-borne encephalitis (TBE) is a disease transmitted by ticks and one of the most important human infections of the central nervous system (CNS). TBE is reported to be endemic in several European countries [1-4]. Humans are generally infected by the bite of an infected tick. Laboratory infections, as well as infections after consumption of nonpasteurized milk, have occasionally been reported [5, 6]. The infection typically takes a biphasic course. After an incubation period usually lasting 7 to 14 days, the precursor symptoms manifest. The first stage of the disease will last 1 to 8 days. After the febrile asymptomatic interval, the second stage develops. It is here that TBE may manifest as isolated meningitis, meningoencephalitis, meningoencephalomyelitis, and/or radiculitis. The mortality rate varies from 0.3 to 3% [1, 2, 7].

Clinical infections caused by TBEV are quite common in Poland and can cause significant disease burden not only as acute cases but also chronic [8-10]. Multiple strains of tick-born encephalitis virus (TBEV) have been observed, including the Lublin region [11]. Limited epidemiological data prevent a satisfactory appreciation of the prevalence, incidence, and outcomes of TBE [3, 12]. The authors suggest the possibility of natural foci of tick-borne encephalitis in the Lublin region [11, 13]. All diseases transmitted by ticks should be taken into consideration, because they represent a health problem [8-14].

Seroepidemiological studies on TBE virus infection in endemic areas of various European countries have demonstrated the possibility of untypical even asymptomatic infection [15-16]. Additionally, positive levels of specific immunoglobulins were noticed in sera of asymptomatic people working in forests [1, 5, 8, 14]. In some of these reports it was also suggested that there is an abortive form of TBE virus infection, which may be manifested only by a febrile headache without meningeal involvement (e.g., the initial phase of the illness without subsequent CNS involvement). Patients who have suffered from TBE are reported to be immune for the remainder of their lives. At present, there is no effective antiviral therapy, therefore management is strictly supportive. Passive immunization is recommended only within 48 hours. Due to this limitation, our study suggests that active immunization against TBE may be recommended for all subjects living in and traveling to areas of risk.

An important objective of our study was the evaluation of the risk of TBE incidence in the Lublin region. Incidence was assessed each year from 1995 to 2001. This retrospective study also evaluated the clinical and immunological characteristics of the patients who previously had suffered from the severe form of tick-borne encephalitis. Our evaluation of the occurrence and level of specific immunoglobulins in patients who contracted tick-borne encephalitis offers support for the consideration of active immunization.

Material and methods

Clinical and epidemiological data were collected from patients who had suffered from, and were diagnosed with, encephalitis from 1995 to 2001. Within that population, tick-borne encephalitis was diagnosed in 108 patients. Serological diagnostic procedures were performed by the Department of Occupational Biohazards, Institute of Agricultural Medicine in Lublin. Tick-borne encephalitis virus infection was confirmed by the demonstration of specific IgG antibodies in the serum and in the CSF. Antibodies against TBEV were measured by ELISA using IgG Kit IMMUNO (FSME IMMUNOZYM IgG, Vienna, Austria). Ig titer was expressed as Vienna units (Vu). Ig titer results less than 63 Vu are considered negative; 63-126 Vu are considered a border line; greater than 126 Vu are considered positive. The serological examination was performed twice with a gap of six months. For all the patients, levels of immunoglobulins higher than 300 Vienna units (Vu) in enzyme-linked immunoassay (ELISA) were measured, both in the serum and in the CSF. From the 108 patients, 38 were selected for their full clinical history and confirmed TBE diagnosis after a severe course of the disease (Table I).

Results

The 108 patients who had contracted tick-born encephalitis (1995-2001) came from the Lublin region, an area with a total population of 2,042,500 inhabitants. The incidence was estimated to 0.71 /100,000/year in farmers and 0.58 /100,000/year in

Table I. The characteristics of the examined group

	Number of patients (mean age 56.4)	%
Sex		
Women	22	57.9%
Men	16	42.1%
Place of living		
City	11	28.9%
Villages	27	71.1%

Table II. Analysis of the level of specific anti TBEV immunoglobulins

	IgG TBEVu first analysis	IgG TBEVu second analysis
Mean	214.3	215
SD	117.8	104.2

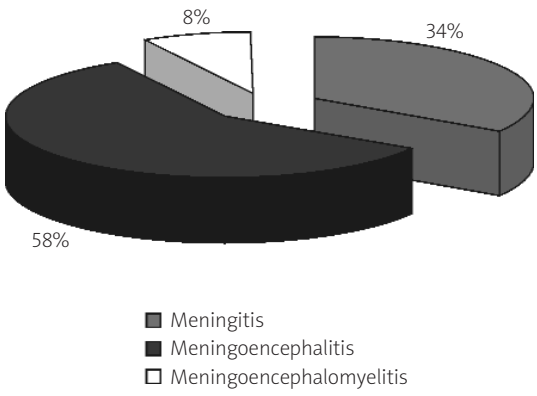

Figure. 1. The clinical picture of TBE

urban dwellers. The highest incidence was observed in 1996 (2.8/100,000/year). Ninety-eight percent of the patients were infected by the bite of the tick but only 70% remember the episode. Two patients (1.7%) were infected after consumption of nonpasteurized milk. The lowest incidence occurred in 2001 and was 0.45/100,000/year. There were no age or gender differences observed. The highest incidence (3.1/100,000/year) was observed in the Radzyń forestry region which corresponds with tick-study data [11].

The selected 38 (35%) had a serologically confirmed clinical history of TBE and had been properly treated before this study. For these, the typical biphasic course of the disease occurred for 75% of patients. Additionally, 34% presented with meningitis, 58% with meningoencephalitis, and 8% with meningoencephalomyelitis (Figure 1).

A subsequent evaluation was done after the 6-months observational period (laboratory testing duplicated to ensure accuracy; see Table II). In 42% of the group, the specific immunoglobulins at the positive levels (greater than 300 Vu) were noticed. In 54% the results were considered borderline. Only 4% patients had negative levels. Interestingly, in four cases levels greater than 300 Vu were noticed. Such a high level is ordinarily characteristic of an acute phase of the disease, however, for these patients it was without clinical symptoms of TBE.

It is unlikely that all of the patients modified their life-style to avoid future tick contact. Therefore, there would be a reasonable possibility for contact with infected ticks. Since none of the patients exhibited re-infection, it suggests that they developed a form of immunity.

Discussion

Data obtained from epidemiological studies on TBE virus infection in forestry areas of various European countries [9,14] indicates that the incidence of TBE in the Lublin region is consistent with other European regions. Those regions also exhibit endemic foci [3, 6, 7, 16, 17]. This paper showed the existence of such a focus in Poland in the Radzyń Podlaski district (greater Lublin area). The Radzyń epidemiological focus correlates with microbiological observation. Cisak et al. [11], measured the prevalence of TBEV in ticks in the Lublin region. Results of that study confirmed the presence of a focus of tick-borne encephalitis virus in ticks collected in different spots in the Lublin region. The highest prevalence of infection with TBEV among ticks was found in the Radzyń district [11]. Consistency between clinical and microbiological data from the Lublin region shown that the link between TBE and ticks being infected was the primary causative link between individuals becoming infected

Infection with the tick-borne encephalitis virus (TBEV) can result in various neurological complications. At present, there are little data available on laboratory findings that might help predict the clinical course and prognosis of tick-borne encephalitis (TBE).

In contrast to those with a moderate course of disease, patients with severe courses of TBE displayed higher cell counts in the CSF and lower concentrations of neutralizing antibodies in the serum, and more frequently revealed an intrathecal synthesis of total IgG [7, 16, 17]. It was reported that the severe course of the disease in individual patients with TBE may result from a slow or low production of neutralizing antibodies. [18, 19].

We did not find any difference in antibodies levels between those groups of patients.

There is a limited amount of data describing the retrospective analysis of the tick born encephalitis. Kaiser et al. [15] found that in Germany between 1991 and 2000, about 1500 patients became ill after infection with the tick-borne encephalitis virus.

Similar to our study, in Kaiser et al. (2002) a biphasic course of the disease occurred in 75% of patients. TBE presented as meningitis in 400 patients (47%), as meningoencephalitis in 356 (42%) and as meningoencephalomyelitis in 93 (11%) [15]. In this study, however TBE in a clinical form of meningoencephalitis dominated in the patients.

Moreover, there are major differences in the results obtained from patients suffering from meningitis alone and those suffering from meningoencephalitis [15, 19]. We did not observe such a difference between two clinical forms of the disease mentioned above.

In our study, more than 90% of patients who had previously suffered from TBE had still high anti-TBEV antibodies level without clinical symptoms of the infection. It is unlikely that all of the patients modified their life-style to avoid future tick contact. Therefore, there would be a reasonable possibility for contact with infected ticks. Since none of the patients exhibited re-infection, it suggests that they developed a form of immunity.

Diagnosis of human TBE is usually based on serology, which if performed late usually may have a number of pitfalls. Thus the diagnosis is still based on clinical findings. On top of that, the outcome of the disease can mimic many neurological diseases. Besides TBEV virus can possibly persist without symptoms. Thus active TBE has to be taken into account in the history of the patients with acute neurological symptoms who have previously suffered from TBE.

Bearing in mind all above-mentioned facts vaccination seems to be a good solution especially in the endemic aeries for TBEV besides the fact that adverse reactions to tick-borne encephalitis vaccine, however, were documented [20].

Regarding the higher risk of severe manifestations of TBE in the elderly patients and the higher risk of failure of immunization in this population, vaccina-

tion against TBE is more important in elderly subjects than in very young persons [18]. What is even more important, prevention of TBE by post exposure prophylaxis with immunoglobulins is less effective and should therefore not be performed [7, 21]. Active immunization against TBE nowadays is recommended for all subjects living in and traveling to areas of risk. Thus vaccination should be taken into consideration especially in regions endemic for TBE [21-23]. A level of specific immunoglobulins should, however, been carefully examined. Serological examination as well as medical history of tick transmitted diseases should be, however, carefully performed before vaccination.

Conclusions

Incidence of TBE in the Lublin region did not differ as compared to data obtained in other European countries. TBE endemic foci have been reported both in Poland and in different parts of Europe. Percentage of TBE in patients presenting with meningitis and meningoencephalitis differed, however, between studies.

It can also be concluded that the level of specific immunoglobulins against TBEV (tick borne encephalitis virus) following tick borne encephalitis can be of a protective value.

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