16th ISW-TBE Newsletter

October 2011

Dear colleague,

welcome back to another edition of the ISW-TBE Newsletter.

After a pleasant Indian Summer, with September temperatures up to 30°C in parts of Central Europe, it will be interesting to see the effects this year's weather has been having on the prevalence of TBEV-infected ticks. In terms of TBE incidence, of course, my hope is that many of those living in or traveling to TBE-endemic areas did not give the virus a chance.

Although it's only been a few months since the last newsletter, there's again a huge collection of pertinent pieces of news and fine studies from the wide and interdisciplinary field of TBE research.

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Enjoy reading!

With kind regards,

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1 TBE in Children Revisited

Rare, or Simply Underdiagnosed?

Long-term neurologic deficits in adults as a consequence of TBE are well documented.[1] In children, TBE has generally been considered a mild illness with a more favorable outcome than in adults, although neurological and neuropsychological consequences in children have been reported.[2, 3] The long-term consequences of TBE infection in children are still largely unknown, emphasizing the importance of accurate diagnosis. Specific antiviral treatment against TBE does not exist, but highly effective vaccination is available.

In a recent retrospective evaluation,[4] Hansson and colleagues analyzed 3635 anti-TBE–virus (TBEV) serologies from 2003–2008 in Sweden, 699 of which were from children <16 years of age. Of these, 170 (24%) were IgM- and/or IgG-positive, and 39 (5.5%) were IgM-positive, consistent with a diagnosis of TBE. Patients were asked to complete retrospective questionnaires regarding the symptoms they had experienced before serology.

The study showed that the symptoms of TBE in children are often vague and nonspecific, confirming previous studies which demonstrated that TBEV induces a more pronounced encephalitic presentation in adults than in children. Not only are the symptoms of TBE in childhood less telling, children also have greater difficulties verbalizing symptoms, a fact that further compounds the diagnosis of TBE in the very young. Overall, therefore, there is reason to believe that the diagnosis of TBE in children may often be missed and that children would benefit from more frequent TBEV serology.

Prospective Study Confirms Concerns Regarding Underdiagnosis of TBE in Children

The concerns raised by the retrospective study by Hansson[4] are supported by results of a recent prospective study from Sweden[5] estimating the incidence of symptomatic TBE and neuroborreliosis (NB) in children. In 2009, 124 children <18 years of age with neurologic symptoms from the highly tick-endemic southwestern region of Stockholm County were included. Anti-TBEV and anti-*Borrelia* serologies were performed and inflammation parameters in blood and cerebrospinal fluid analyzed.

31 of the 124 children (25%) with neurologic symptoms were found to have a tick-borne CNS infection, with TBE seen in 10 (8%) and NB in 21 children (16.8%). Most of these children presented with nonspecific signs, such as general malaise, fatigue, and headache; blood inflammation parameters failed to contribute to the diagnosis.

Headache and fever were most common in children with TBE, and malaise/fatigue was strongly associated with TBE (**Figure 1**). Seizures were not observed in any of the TBE or NB patients.

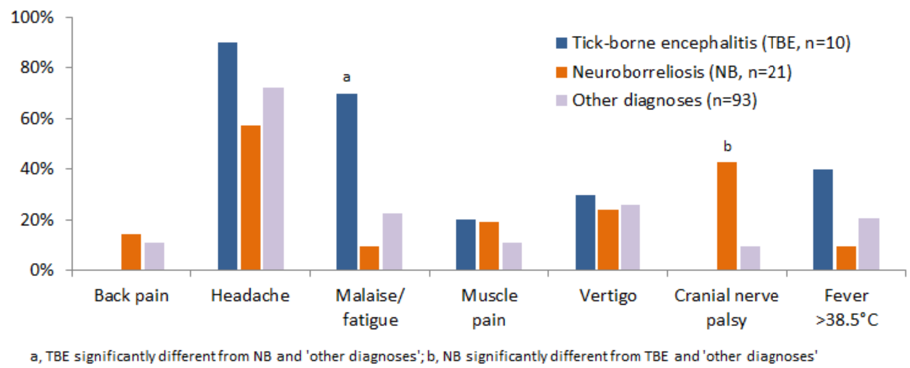

Figure 1. Common signs and symptoms in 124 children with neurologic symptoms (adapted from Sundin et al.[5])

Overall, tick-borne CNS infections in this unselected group of children with neurologic symptoms presenting for medical care were more common than had been expected.

- The southwestern region of Stockholm County covers about 100,000 children, resulting in a TBE incidence rate of roughly 10/100,000—a figure well above the incidence rate reported for Stockholm (3.71,[6] see below).
- Between 2004–2009, a mean of 18 children per year were reported to have developed TBE in the whole of Stockholm County, a region covering a pediatric population of about 420,000.
- The 2009 study by Sundin et al., covering only the southwest of Stockholm County, identified no fewer than 10 of the 15 children reported in the whole of Stockholm County in 2009. It is therefore conceivable that actively looking for TBE during the diagnostic work-up in children may result in substantially higher numbers of TBE diagnoses.
- The biphasic course considered a typical characteristic of TBE was relatively rare (20%), although it was more frequent in preschool children (40%).
- Of the 13 children requiring hospitalization, 2 underwent extensive and partly invasive examinations before the TBE diagnosis was established serologically. In these patients, invasive testing could have been prevented had TBEV serology been routinely performed.

TBE in children may be difficult to diagnose and, unless specifically tested for, may easily be missed. Therefore, in children having spent time in a TBE-endemic area and presenting with neurologic symptoms, more frequent TBEV serology appears warranted. And with underdiagnosis of TBE in the very young apparently more common than expected, the saying that ‘an ounce of prevention is worth a pound of cure’ may be even more pertinent than previously thought.

2 Number of TBE Cases in Sweden Approaching Record High

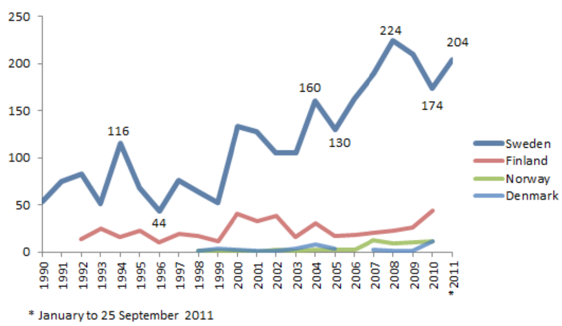

***Figure 2.** Number of TBE cases in Sweden, Finland, Norway, and Denmark since 1990*

The fact that Sweden has been taking a closer look at the effects of TBE on its children is most likely not a coincidence. In terms of TBE, Sweden has taken an exceptional place among its Scandinavian neighbors in that it has been the only country witnessing a more or less consistent increase in TBE incidence in recent years (**Figures 2 and 3**).

By September 2011, TBE case numbers in Sweden have again been among the highest recorded so far—a development thought to be due to a combination of thriving tick populations due to favorable weather conditions, a high density of important blood sources, such as rodents, and an increase in human outdoor activities.[6]

By August 2011, 161 cases of TBE had been registered, corresponding to a national incidence rate of 1.7 per 100,000 population. This might not sound like a terribly high risk.

However, TBE occurs in natural foci, whose formation relies on a complex interplay between the population dynamics of vector ticks, the presence of suitable hosts as a source of life-sustaining blood meals and a platform for virus transmission among ticks, the prevailing humidity and temperature conditions, as well as socioeconomic and leisure time activities.

In Sweden, too, TBE is restricted to specific regions of the country, reaching incidence rates as high as 9.29 in Södermanland, 6.55 in Uppsala, or 3.71 in Stockholm. In August 2011 alone, 83 TBE cases were reported, more than in any other month in the past 4 years. By September 25, the number of TBE cases had increased to 204[6]—and is headed for another record high.

***Figure 3.** Location of tick-borne encephalitis cases in Sweden, 2010*[6]

3 Slovenia: Incidence Rates in Specific Foci as High as 76.9

Yet, Vaccination Rates Lagging

Although vaccination against tick-borne encephalitis (TBE) was introduced in 1986, Slovenia remains one of the countries with the highest reported TBE incidence rates. A recent study by Grgic-Vitek and Klavs[7] analyzed TBE surveillance data of the past 20 years.

Although almost all of Slovenia is endemic for TBE, with national yearly incidence rates up to 26.7 per 100,000 population, 2 regions have been even more severely affected, i.e., Gorenjska and Koroska, with amazingly high incidence rates of up to 57.2 and 76.9, respectively. Also, the past decade saw a shift in the age distribution of reported TBE cases to older age groups, resulting in the highest national incidence rates in those aged 55–64 years.

These high incidence rates are in sharp contrast to the overall self-reported prevalence of TBE vaccination of only 12.4%.[8] Characteristics independently associated with higher odds for self-paid vaccination against TBE were high income, not being overweight, and ever being vaccinated against influenza.[8]

According to the authors, offering free vaccination against TBE would likely contribute to reducing the high disease burden related with TBE, with particular emphasis given to the two most affected regions, i.e., in Gorenjska and Koroska, and to the age groups found to be at highest risk.[7]

4 Animals: Sentinels for the Definition of TBE Risk Areas

Rodents: Reliable Surrogates for the Prevalence of TBE

In Germany, as in many other countries, TBE risk analysis has been based almost exclusively on the incidence of human cases. However, as vaccination rates increase, this approach may become increasingly misleading.

To test the suitability of rodents as surrogate markers for virus spread, laboratory-bred *Microtus arvalis* voles were experimentally infected with TBEV and analyzed over a period of 100 days by real-time quantitative polymerase chain reaction.[9] In addition, the prevalence of TBEV in rodents trapped in Brandenburg was determined and compared with that in rodents from German TBE risk and non-risk areas.

Experimentally infected *M. arvalis* voles developed a persistent TBE infection without clinical symptoms, with the TBE virus detectable in various organs for at least 3 months and in blood for 1 month. 10% of all rodents investigated were positive for TBEV. In TBE risk areas, the infection rate was higher than in areas with only single human cases or non-risk areas.

The study demonstrated that rodents are promising sentinels for use in defining TBE risk areas, including those with low TBEV circulation.

TBE virus seropositive dog detected in Belgium: screening of the canine population as sentinels for public health

In Belgium, a country considered non-endemic for TBE, TBEV surveillance is virtually nonexistent. Roelandt et al.[10] obtained serum samples of Belgian dogs from 3 diagnostic laboratories from Northern (n=688) and Southern Belgium (n=192). One dog was found to be TBEV seropositive. Several ELISA-positive and borderline sera underwent seroneutralization and hemagglutinin inhibition tests to rule out West Nile and Louping Ill viruses and tested negative. The clinical history of the seropositive dog failed to unequivocally explain where and when TBEV infection had been acquired, and further surveillance is necessary to determine whether this dog was a single, travel-related case or whether it is an early warning of a possible future emergence of TBEV.

5 When Nymphs and Larvae Gather for A Blood Meal…

Co-feeding Ticks: An Important Mode of Transmission of TBEV

The focal distribution of the TBE virus depends in large part on co-feeding transmission between infected *Ixodes ricinus* nymphs and uninfected larvae. This mechanism even works when the animal the ticks feed on is non-viremic.

To better understand the role of co-feeding ticks in the transmission of TBEV, a recent Swiss study[11] investigated the tick infestation of rodents and the influence of microclimate on the seasonality of questing *I. ricinus* ticks. The 3-year study was carried out at 4 sites, 2 of which are confirmed TBEV foci. Free-living ticks and rodents were collected monthly, and microclimatic data were recorded.

In 2007, the investigators observed a decrease in the density of questing nymphs in 3 of the 4 sites, associated with low relative humidity and high temperatures in the spring. In the same year, the proportion of rodents carrying co-feeding ticks was lower at sites with a low density of questing nymphs. The proportion of hosts with co-feeding ticks seemed to be one of the factors distinguishing a TBEV focus from a non-TBEV focus.

6 Conference Report: TTP7 in Zaragoza, Spain

By Univ.-Prof. Dr. Jochen Süss
Friedrich-Loeffler-Institute, Jena, Germany

Between 28 August and 2 September 2011, the **Seventh Ticks and Tick-borne Pathogens International Conference (TTP7)** was held in Zaragoza, Spain, assembling 331 scientists from all over the world, who had submitted a total of 402 abstracts.[12] In this brief report, I would like to summarize some of the many contributions that attracted my attention and are relevant to human medicine—a selection which, admittedly, is subjective and influenced by my own field of professional activity and research.

The Vaccines session was opened by an excellent key presentation by **Peter Willadsen** entitled *A review of commercial vaccine performance for control of tick infestations in cattle*, which provided a realistic assessment of the successes—and failures—seen so far. The session itself included 14 presentations dealing almost exclusively with new strategies and targets for the control of cattle ticks. Thus, significant progress has been made in the control of *Rhipicephalus microplus* and *R. appendiculatus* infestations, and various novel approaches to taking the bite out of a tick sting were presented. For example, **Christine Maritz-Olivier**, University of Pretoria, presented a systematic functional genomics approach for the identification of protective antigens from *R. microplus*. Using DNA microarray and a reverse vaccinology approach, the authors identified a number of novel membrane-associated proteins that may serve as new targets for vaccine development. **Ondrej Hajdusek** from the Czech Republic presented new insights into the iron metabolism of ticks, an aspect which may also serve as a new target for the development of vaccines.

In the Tick-Borne Diseases in Humans session, **Desmond Foley**, Maryland, USA, provided an introduction into TickMap, an online spatial database of tick species collection records, species distribution models, and disease models (www.tickmap.org). Users can zoom to anywhere in the world to view the locations of past tick collections and the results of models that predict the geographic extent of individual species.

The Roslin Wellcome Trust Tick Cell Biobank (http://tickcells.roslin.ac.uk) presented by **Lesley Bell-Sakyi**, University of Edinburgh, provides a much-needed and reliable source of validated cell lines from ticks of importance to medical and veterinary science. The biobank houses over 50 cell lines derived from 14 ixodid and 2 argasid species.

Based on my own field and laboratory data and comparisons with published data, I had the honor to explain why a scientifically founded characterization of TBEV foci is only possible if information on autochthonous human disease cases is combined and linked with data from vector and host investigations as well as the molecular epidemiology of the respective virus isolates.

Ashild Andreassen and colleagues from Norway presented a comparison of three TBEV-PCR methods. Based on the 5700 ticks they had collected, the prevalence of TBEV in the tick pools investigated varied between 0%–12%. The real-time PCR test they designed for the study was many times more sensitive than existing tests, allowing for rapid, cheap, and sensitive real-time PCR to detect TBEV in tick pools.

Piotr Cuber presented extensive data on tick activity (*I. ricinus*) and TBEV prevalence in the Polish province of Silesia. 4955 ticks were collected from 24 localities in Silesia. Tick activity peaked in the spring, but an autumnal peak was not seen in any of the localities. Tick activity and numbers were correlated with air humidity. The prevalence of TBEV in Silesia (1320 nymphs) was 1.52%.

Pontus Lindblom and colleagues investigated TBEV in ticks detached from humans in Sweden and Åland in 2008 and 2009 and were unable to reproduce the repeatedly published finding that virus prevalence in these ticks was statistically significantly higher than in field-collected ticks.

In another vivid key presentation, **Jean Tsao**, USA, presented a modern evaluation of the terms 'ecology,' 'epidemiology,' and 'ecoepidemiology,' using as main example Lyme disease in the USA.

Olaf Kahl and colleagues from Germany addressed the seasonal timing of tick development and questing as well as the life span of the different life stages of *I. ricinus*—crucial factors for estimating the circulation patterns of any pathogen vectored by these ticks. Using what are called field plots—artificial tick habitats—the authors found that the life cycle of *I. ricinus* takes 3.5 to 7 years (average, 5 years), which is distinctly longer than conventionally believed.

Joseph Piesman, US Centers for Disease Control, Colorado, presented data from an animal experiment in mice on the antibiotic prophylaxis of Lyme disease after a tick bite, which, if verified, may have important practical consequences for human medicine. The authors found that two treatments of doxycycline administered to mice by oral gavage on the day of removal of a single potentially infectious *I. scapularis* protected 78% of test mice compared to controls. When treatment was delayed until 24 hours after tick removal, only 30% of mice were protected. Prophylactic treatment was totally ineffective when delivered more than 2 days after tick removal. The results emphasize that prophylactic antibiotic treatment of tick bites to prevent Lyme disease must be delivered promptly after removal of potentially infectious ticks from patients.

TTP8 will be held in 2012 in Capetown, South Africa.

News in Brief

In June 2011, the **World Health Organization (WHO)** published its first ever position paper on vaccines against TBE.[13, 14] Recommendations on the use of TBE vaccines had been discussed by SAGE at its meeting in April 2011.

As a follow-up to its retrospective survey on tick borne-encephalitis (TBE) in 2008, the **European Network for Diagnostics of Imported Viral Diseases (ENIVD)** performed a new and expanded survey in 2010, the report of which was published in a September issue of 'Eurosurveillance'.[15]

A recent Polish study evaluated the performance of the national **surveillance system capturing information on aseptic central nervous system infections (ACI)**. Of the 1,994 reported ACI cases, 12%) were diagnosed with TBE virus, 2% with enterovirus, 2% with herpesvirus, and 2% had other viral causes. The frequency of suspected ACI cases referred for viral etiology investigation in 2008 ranged from 1.98 to 285.4 samples per mio inhabitants, and the proportion of hospitalized ACI cases reported to the surveillance system was 48% nationally, with major regional differences (range 30–91%). Based on these results, the frequency of central nervous system infections, including TBE, may have been seriously underestimated.[16]

Infectious diseases have been found to be the most frequent among occupational diseases. A recent Polish report presents the **case of a forest worker with borreliosis coexisting with TBE**. Despite nonconcurrent recognition of both diseases, the worker is likely to have contracted both infections at the same time or not long apart.[17] Another recent report presented a **case of TBE associated with an isolated reversible splenial corpus callosum lesion (IRSL)** in a 42-year-old. MRI demonstrated a single ovoid hyperintensity in T2 and DWI with reduction in ADC in the splenium of corpus callosum which had disappeared at the 6-week follow-up.[18]

Reference List

1. Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet 2008;371:1861-1871.
2. Fritsch P, Gruber-Sedlmayr U, Pansi H et al. Tick-borne encephalitis in Styrian children from 1981 to 2005: a retrospective study and a review of the literature. Acta Paediatr 2008;97.
3. Schmolck H, Maritz E, Kletzin I, Korinthenberg R. Neurologic, neuropsychologic, and electroencephalographic findings after European tick-borne encephalitis in children. J Child Neurol 2005;20:500-508.
4. Hansson ME, Orvell C, Engman ML et al. Tick-borne encephalitis in childhood: rare or missed? Pediatr Infect Dis J 2011;30:355-357.
5. Sundin M, Hansson ME, Engman ML et al. Pediatric tick-borne infections of the central nervous system in an endemic region of Sweden: a prospective evaluation of clinical manifestations. Eur J Pediatr 2011.
6. Lundkvist A, Wallensten A, Vene S, Hjertqvist M. Tick-borne encephalitis increasing in Sweden, 2011. Euro Surveill 2011;16.
7. Grgic-Vitek M, Klavs I. High burden of tick-borne encephalitis in Slovenia--challenge for vaccination policy. Vaccine 2011;29:5178-5183.
8. Grgic-Vitek M, Klavs I. Low coverage and predictors of vaccination uptake against tick-borne encephalitis in Slovenia. Eur J Public Health 2011.
9. Achazi K, Ruzek D, Donoso-Mantke O et al. Rodents as sentinels for the prevalence of tick-borne encephalitis virus. Vector Borne Zoonotic Dis 2011;11:641-647.
10. Roelandt S, Heyman P, De FM et al. Tick-borne encephalitis virus seropositive dog detected in Belgium: screening of the canine population as sentinels for public health. Vector Borne Zoonotic Dis 2011;11:1371-1376.
11. Burri C, Bastic V, Maeder G, Patalas E, Gern L. Microclimate and the zoonotic cycle of tick-borne encephalitis virus in Switzerland. J Med Entomol 2011;48:615-627.
12. Proceedings of the Seventh Ticks and Tick-borne Pathogens International Conference (TTP7), Zaragoza, Spain, 2011 (available from: www.unizar.es/ttp7/TTP7/Main.html).
13. WHO. Vaccines against tick-borne encephalitis: WHO position paper - Recommendations. Vaccine 2011.
14. WHO. Vaccines against tick-borne encephalitis: WHO position paper. Weekly Epidemiological Record 2011.
15. Donoso MO, Escadafal C, Niedrig M et al. Tick-borne encephalitis in Europe, 2007 to 2009. Euro Surveill 2011;16.
16. Stefanoff P, Rogalska J, Zajkowska J et al. Surveillance of aseptic central nervous system infections in Poland: is it meeting its objectives? Euro Surveill 2011;16.
17. Krzyczmanik D, Rybacki M, Wittczak T et al. [Coexistence of two occupational infectious diseases in one patient--borreliosis and tick-borne encephalitis--a case report]. Medycyna Pracy 2011;62:339-344.
18. Vollmann H, Hagemann G, Mentzel HJ et al. Isolated reversible splenial lesion in tick-borne encephalitis: a case report and literature review. Clin Neurol Neurosurg 2011;113:430-433.

This newsletter is intended to highlight interesting aspects and issues related to tick-borne encephalitis (TBE). It does not claim to be comprehensive or to provide medical advice. Should you have any questions on issues reported herein, please contact Professor Ursula Kunze at ursula.kunze@meduniwien.ac.at.

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