Tick-born encephalitis (TBE)

Clinical aspects

Webinar Lecture Sept 28, 2022, Lars Lindquist
Different subtypes of TBE and geographic distribution
My talk will focus on TBE-Eu

- **TBE-Eu**: Mainly a biphasic disease with the lowest tropism for the CNS among TBE subtypes
- **TBE-Sib**: Can in rare instances cause chronic persistent disease
- **TBE-FE**: Mainly a monophasic disease with the highest tropism for the CNS

*Ixodes persulcatus*

*Ixodes ricinus*
The natural life cycle of the TBE virus

1. 2000 eggs
2. Larva
3. Nymph
4. Adult
5. 3 yrs

Humans are accidental host

Man is not at all important for maintaining TBE virus in nature

Co-feeding transmission

Disease

Natural life cycle of TBE virus

2022

Humans are accidental host
Case definition of TBE in humans

CLINICAL CRITERIA
• Inflammation of the Central Nervous System (CNS) (including meningitis, encephalitis, myelitis or radiculitis)

LABORATORY CRITERIA
• Probable case:
  - Detection of serum TBE-specific IgM-antibodies. 96% are positive in the first serum sample.
• Confirmed case:
  - 4-fold increase of serum antibody levels (IgG)
  - Detection of specific intrathecal (spinal fluid) antibodies

If suspicion of vaccine breakthrough indication of testing intrathecal antibodies. If a vaccine breakthrough has occurred there is a risk of initial negative serum IgM-response and a boosted serum IgG-antibody response (second test taken after approx 10-14 days) is needed to confirm a TBE diagnosis. To speed up the diagnosis therefore intrathecal antibody is therefore a possible alternative.
TBE season in EU is April-November, peak month usually July but may vary. Example below Sweden 2007-2011

Source: Folkhälsomyndignheten
An increased risk of TBE is seen in many countries, example Sweden 1996-2020

This steady increase of TBE in Sweden is seen despite a continuous and major increase in numbers of vaccinated people.
There has also been a common regional spread of TBE over time. Below the situation in Sweden

1990

2017

Source: Folkhälsomyndigheten
The proportion of male (blue) and female (red) of TBE cases in Stockholm county 2000-2011

Source: Folkhälsomyndigheten
Reported TBE cases are significantly higher in adults, especially in male cases (Sweden 2021)
Different disease patterns of TBE

- Fever/an influenza like illness
- Only meningitis
- Encephalitis
- Myelitis

Less severe forms of TBE

Severe forms of TBE
The overall clinical course in meningoencephalitis caused by the European Subtype of TBE (TBE-Eu)

- **Prodromal phase:** An acute disease with usually a biphasic course in TBE-Eu with a prodromal **febrile phase** with 5-7 symptomless days before the second clinical phase. The Siberian and Far Eastern subtypes are more likely to have no prodromal phase and have a monophasic course.

- **Clinical infection phase:** Meningitis encephalitis, cerebellitis, or myelitis. Most patients recover but some have residual symptoms, the most common is a cognitive post-infectious symptoms. The Siberian subtype of TBE is associated with a higher risk of chronic neurologic symptoms.
The usual clinical course of TBE-Eu

This typical bi-phasic pattern is seen in 72-87%
The proportion of more severe clinical symptomatology of TBE increase with age (study from southern Germany year 1994-98 (n=656)

Kaiser R. Brain, 1999
Fatal cases of TBE-Eu is unusual

• In a European study (Euro Surveill. 2018 Nov 8; 23(45)) of 11 623 confirmed cases of TBE 2012-2016 (of which 95% were hospitalized) a case-fatality rate of 0,5% was seen and 2,5% had neurological sequelae.
  • None of the 20 fatal cases with know vaccination status were vaccinated except one that had received only one TBE-vaccine dose

• Of 2941 Swedish cases (Vernaité R et al Emerg Infect Dis 28(7), 2022) a mean death rate (year 2004-2017) of 0,75% was seen with an increasing fatality rate by age. The fatality rate 80-89 yrs of age was 3,45%. No fatal cases <40 yrs of age was seen in this summary.
Follow-up studies of adult patients with TBE in Sweden and Lithuania

• 1/3 have consisting symptoms of variable degree at follow up after 1-5 years

• Approximately 10% have signs of major neurological damage

• 1-2% are fatal

• 2-6% have a consisting paralysis
Risk factors for severe TBE with long lasting or permanent sequelae

- Severe disease on admission
- Age >50 years
- Slow development of neutralizing antibodies
- Monophasic disease
Study of 66 Swedish children with TBE – the proportion of children with mild, moderate or severe symptoms on admission

Mild = meningitis

Moderate = meningitis symptoms with seizures or focal neurology or a pathological EEG

Severe = encephalitis

Åsa Fawler, The journal of Pediatrics, Jan 17 2013
Number/percentage of TBE are a fairly low in children, and even more so below 7 years of age. Below, confirmed TBE cases in Stockholm county in different age groups 2006 - 2011

<table>
<thead>
<tr>
<th>Age</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 yrs</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>2 (2%)</td>
<td>6 (7%)</td>
<td>4 (5%)</td>
<td>5 (3.6%)</td>
</tr>
<tr>
<td>7-11 yrs</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>8 (5.8%)</td>
</tr>
<tr>
<td>12-18 yrs</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>6 (4.3%)</td>
</tr>
<tr>
<td>&gt;18 yrs</td>
<td>70</td>
<td>60</td>
<td>101</td>
<td>74</td>
<td>68</td>
<td>119 (86.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>78</td>
<td>119</td>
<td>89</td>
<td>78</td>
<td>138</td>
</tr>
</tbody>
</table>
Fatal cases in children are uncommon

I have found only 2 fatal cases in children reported up to 2010

- 11-year old child with brain stem encephalitis in connection with surgery due to suspected appendicitis (*Messner et al. 1981*)
- 12-year old boy under treatment with corticosteroids due to histiocytosis (*anectotal report*)
### Summary of 12 consecutive (prospective* or retrospective) studies of TBE in children up to 15 years of age

<table>
<thead>
<tr>
<th>Author/Country</th>
<th>Year of study</th>
<th>Severe disease</th>
<th>Age of severe disease</th>
<th>Sequalaes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harasek/Austria</td>
<td>1963-1973</td>
<td>2/38 (5,3%)</td>
<td>11 + 12 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Falk/Austria</td>
<td>1975-1979</td>
<td>5/80 (6,3%)</td>
<td>7-15 yrs</td>
<td>0</td>
</tr>
<tr>
<td>Helwig/Germany</td>
<td>1971-1983</td>
<td>3/13 (24%)</td>
<td>7-15 yrs</td>
<td>0</td>
</tr>
<tr>
<td>Messner/Austria</td>
<td>1974-1979</td>
<td>2/93 (2,2%)</td>
<td>2 of which 1 &lt;7 yrs</td>
<td>1 fatal (11 år)</td>
</tr>
<tr>
<td>Rakar/Slovenia</td>
<td>1978-1992</td>
<td>15/146 (10,3%)</td>
<td>7-15 yrs</td>
<td>6 (all ≥7 years)</td>
</tr>
<tr>
<td>Cizman/Slovenia</td>
<td>1993-1998</td>
<td>7/133 (5,2%)</td>
<td>7 of which 1 &lt;7 yrs</td>
<td>4 (all ≥7 years)</td>
</tr>
<tr>
<td>Kaiser/Germany*</td>
<td>1994-1998</td>
<td>14/77 (18,2%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Kaiser/Germany*</td>
<td>1994-2003</td>
<td>?/124</td>
<td>8 of which 1 severe</td>
<td>?</td>
</tr>
<tr>
<td>Tomazic/Slovenia*</td>
<td>1994</td>
<td>1/77 (1,3%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Lesnicar/Slovenia</td>
<td>1959-2000</td>
<td>14-25/371  (3,8 – 6,7%)</td>
<td>?</td>
<td>0</td>
</tr>
<tr>
<td>Fritsch/Austria</td>
<td>1981-2005</td>
<td>11/116 (9,5%)</td>
<td>?</td>
<td>2 of which 1 severe (5 yrs)</td>
</tr>
<tr>
<td>Stähelin-Massik/Switzerland</td>
<td>2000-2004</td>
<td>2/55 (3,6%)</td>
<td>6 weeks + 9 yrs</td>
<td>1 (9 yrs)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>Mean 8,0%</strong></td>
<td><strong>Of 8% &lt;15 yrs with severe disease only 1/10 was &lt;7 yrs</strong></td>
<td><strong>23/1246 (1,8%) of which 1 child &lt;7 år</strong></td>
</tr>
</tbody>
</table>
Even though children with TBE-Eu usually have a mild acute disease, follow-up of TBE cases in children (at Karolinska Hospital, Sweden) show a risk of remaining problems.

- Remaining problems were seen in approx. 70% of children (n=42) 3-17 years old (mean 10 years old) at follow-up after 2-6 years.
  - Headache approx. 60%
  - Cognitive problems approx. 60%
    - Memory
    - Concentration
  - 33% had problems with executive functions
  - Tiredness 45%
  - Irritability 42%

- Also, those children with a relative mild acute disease could show remaining problems at follow-up (Fowler et al, J Pediatr, 2013).
Conclusion of study in children with TBE at Karolinska Hospital Stockholm, Sweden was:

- Children often had a wage symptomatology (bad feeling in general, headache, fever, tiredness). Children also had more difficulties to explain their problems.

- TBE is probably an under diagnosed disease in children.

- Long-term symptoms, mostly cognitive disorder, was seen also in children, and the number of children with cognitive sequele was surprisingly high.

Sundin et al, 2011
Hansson et al, 2011
Thank you!