Chapter 6

TBE in children

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Key Points

- Most cases of TBE in childhood will present similarly as in adults. However, a more diffuse clinical picture is seen especially in preschool children.
- Laboratory evaluation may show elevated blood inflammatory indices, but cerebrospinal fluid analysis and anti-TBEV serology are needed for establishing the diagnosis.
- There is no specific treatment for TBE; supportive care needs to be provided based on the individual clinical course.
- The mortality in pediatric TBE is very low but severe courses have been reported in a fraction of the children.
- Long-term somatic residua exist, but are uncommon (2%) in childhood TBE. Yet, long-term symptoms and neurodevelopmental/cognitive deficits are seen in 10–40% of infected children.
- Protective immunity can be elicited in children by TBE vaccines as of 1 year of age.

Children, ticks, and TBE

Compared with tick-borne encephalitis (TBE) in adults, childhood TBE has been described as a rare disease, particularly in preschool children.[1–4] This is puzzling, as children appear to be perfect prey for ticks, primarily because of a high level of exposure and the short climbing distance to a proper bite site. The low incidence of pediatric TBE cases becomes even more puzzling as Borrelia infections are well documented in children.[5–7] Additionally, Borrelia infections have been reported to be up to 5 times more common in preschool children than in older children and adults.[5] The discrepancy between a high tick exposure and a low TBE incidence leads to the suspicion that childhood TBE is underdiagnosed.

Awareness of TBE varies greatly. In countries with a high TBE burden, such as Estonia, the pediatric cohort accounts for a large proportion of all cases, as was the case also in Austria in the pre-vaccination era.[8] The general TBE immunization policy in Austria has increased awareness of the disease.[9] The Baltic states have advocated for proper immunization strategies.[10] The general knowledge of TBE is likely higher in the high-endemic areas and as a consequence fewer cases are possibly eluded.

In addition, some childhood TBE cases are probably overlooked because of the non-specific clinical picture (discussed in more detail below).[5,6,11] Younger children also seem to be less frequently considered for TBE,[5] but the disease can be seen in children as young as only a few months of age.[12–15] The idea that pediatric TBE could be underdiagnosed was further substantiated by a high incidence, the highest in years, in a prospective study of neurologic complaints at an emergency ward in Stockholm, Sweden,[6] demonstrating the adage: “he who seeks will find.”

To summarize, children evidently get tick bites and they do contract TBE. The disease itself, the child’s attributes (e.g., age, physical activity level, etc.) and parental as well as medical community awareness may influence the number of children who are diagnosed.

Children’s clinical course of TBE

Acute phase or nonspecific phase

The onset and acute phases of TBE in children have been found similar in part to the clinical picture seen in adulthood, but there are also differences reported. Tick-bites have been recalled in 48–75% of childhood TBE cases.[3,5,16-18] Approximately 70% have had a biphasic clinical course, i.e., a flu-like prodrome followed by a short asymptomatic period and thereafter a varying degree of meningitis to meningoencephalomyelitis, as reported in prospective and retrospective studies,[1,3,16,17] others have reported considerably fewer biphasic courses, certainly among preschool-age children.[5,6] A large Polish retrospective study from 2020 compared 68 pediatric to 601 adult TBE cases, and concluded that the disease was milder in children.[19] However, the comparison was potentially biased as there were no standardized inclusion criteria.

That younger individuals may have a vague/nonspecific clinical presentation and a generally milder clinical course is

well established,[2,3,5,20] but this may also denote that childhood TBE manifests differently in children versus adults and that the condition may be underdiagnosed.[5,6] This notion was further emphasized by Meyer et al, who reported a case series of TBE appearing as fever without localized symptoms.[11]

In the majority of reports on pediatric TBE, fever is present in virtually all cases at diagnosis.[1,3,16,17] However, both retrospective data from a fairly large cohort[5] and prospective data from a study with broad inclusion criteria,[6] show that fever >38.5° C is not always observed in pediatric TBE. In addition to fever, headache and vomiting have been reported as central features of childhood TBE at rates of approximately 90–100% and 50–90%, respectively. Self-reported fatigue/malaise, behavioral changes, photophobia, muscle pain, etc. are commonly reported, but occur at varying frequencies.[1–3,5,6,16,17,21] Meningeal signs are prevalent findings, noted in >80% of infected children,[1,3,16-18] but here as well, young children have a less-pronounced clinical presentation.[5]The clinical picture of pediatric TBE is classified as meningitis in 63–79% of cases, meningoencephalitis in 21–38%, and meningoencephalo-myelitis in 0–4%.[1,16,21] Other findings in childhood TBE are tremor, impaired general appearance, somnolence, lymphadenopathy, apatheia, hyperesthesia, and confusion/ cognitive dysfunction.[1,3,5,6,16,17,21,22] Though uncommon, some children present with seizures and hemipareses.[1,5,17] A recent retrospective Lithuanian study on TBE in children noted a higher proportion of milder disease (i.e.) meningitis in children aged 1–8 years compared with those aged 9–17 years, who more often suffered from meningoencephalitis or meningoencephalomyelitis.[18] Again, the comparison was potentially biased as there were no standardized inclusion criteria.

Detection of specific anti-TBE virus (TBEV) antibodies, as described in other chapters, is required to establish a diagnosis. Some cases require testing of both acute and convalescent sera, as antibodies may be absent in the initial phase.[5,6] Although serologies are reported as diagnostic, they are of little help at the first clinical assessment in the acute phase. Instead, the clinical presentation corroborated with routine laboratory evaluation has to guide the clinician. Nonspecific inflammatory signs, i.e., leukocytosis, elevated C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR) are reported in many children with TBE.[1–3,5,16,17] Worth noting is that many adults with TBE present with less pronounced blood inflammatory indices.[3,5] Laboratory evaluation for children with suspected TBE should include lumbar puncture. The most common cerebrospinal fluid (CSF) finding is pleocytosis with a mononuclear preponderance.[1–3,5,16,17,22] Additionally, some children present with elevated CSF protein/albumin levels. However, this is more commonly observed in adults than in children,[3,5] suggesting a more restricted encephalitic presentation in childhood TBE. This can also be concluded from the lower proportions of meningoencephalitis and meningoencephalomyelitis observed in children compared with adults, as noted above.

Laboratory evaluation for children with suspected TBE should include lumbar puncture, as cerebrospinal fluid pleocytosis with a mononuclear preponderance has been described.[1–3,5,16,17,22] Additionally, some children have presented with elevated cerebrospinal fluid protein/ albumin levels. However, this has been more common in adults than in children,[3,5] suggesting a more restricted encephalitic presentation in childhood TBE. This can also be concluded from the lower frequencies of meningo-encephalitis and meningoencephalomyelitis observed in children than in adults, as noted above.

Electroencephalographic (EEG) examinations in the acute phase of childhood TBE can help confirm the diagnosis. The EEG abnormalities seen include mild to moderate, generalized, slowing background activity, but also sharp waves in contrast, though seldom generalized spike wave activity.[2,22] Magnetic resonance imaging (MRI) has been used infrequently in children with TBE. Similar to findings in adults, the most commonly reported finding is alterations in the thalami.[2,22-25] MRI changes have also been detected in cerebellar structures, putamen, and caudate nucleus, as well as the cortex. Of note, some children present with a normal MRI.[22,24] In a recent review of the spectrum of MRI findings in childhood TBE, von Stülpnagel et al reported poor outcomes, i.e., long-term neurologic disabilities and death, in children with MRI changes.[24] However, these data were retrospective and there might be a selection bias towards more severe cases undergoing MRI. Nonetheless, it can be concluded that pronounced CNS damage in pediatric TBE exists.

To conclude, the clinical picture of TBE in childhood bears similarity to the disease in adults. However, some pediatric patients, more likely the younger ones, may not present as ‘expected’. Fever, headache, and vomiting are common. Children tend to more commonly present with symptoms and findings of meningitis, with increased blood inflammatory indices. Anti-TBEV serology and cerebrospinal fluid analyses are essential in establishing the diagnosis. EEG and MRI can strengthen the diagnostics.

Short-term consequences

As in adults, most tick bites from TBEV-carrying ticks do not result in clinical cases. Nevertheless, childhood TBE is associated with severe disease in some of those with clinical infection, as described above. This was concluded by Fritsch et al., who demonstrated that children required a median of 18 days of care in pediatric hospital wards.[1] Others have reported median hospital stays ranging 5–13 days.[2,3,6,16,17]

A large proportion of children still have symptoms but do not require medical attention at discharge,[21,25] which contrasts with children with some other CNS infections.[26] Engman et al. reported significantly more days of acute illness in childhood TBE compared to children with neuroborreliosis or other infections with CNS symptoms. Additionally, they found a prolonged period of convalescence and more days of sick leave in the TBE cases.[27]

TBE in childhood naturally affects both boys and girls, but approximately twice as many cases are seen in boys. Boys also tend to have a more severe disease.[2,3,7,28,30]

That pediatric TBE has been associated with severe disease courses can be further supported by reported rates of admission into intensive care units, ranging from 5% to 22% of TBE cases.[1,17,28] Compared with adults, fatal cases of TBE are reported only infrequently.[5,28-31]

Long-term consequences

While the occurrence of long-term neurologic and neuropsychological sequelae in adults after TBE infection is well-established,[2,31] the literature is inconsistent when it comes to the risk for long-term residua of childhood TBE. For many years, but also recently, some studies have concluded that pediatric TBE has a more favorable outcome.[16,17,21]

However, defining the complications of TBE is important. Only determining the gross neurologic status and superficial assessment of health and cognitive functioning, leads to the conclusion that childhood TBE is not a long-term problem for most patients. But emerging data support the premise that pediatric TBE carries a risk of incomplete recovery, especially in terms of well-being and cognitive functions.

One of the first studies addressing the issue of incomplete neurocognitive recovery was published in 2005 by Schmolck et al. Over a mean of 3.2 years (range 6 months–11 years) after acute TBE illness, 19 pediatric subjects were evaluated in comparison with healthy controls. Children who had suffered from TBE displayed lower scores in a structured neurologic examination and had significantly impaired attention and psycho-motor speed. Additionally, only 1/14 children in the TBE group had a normal EEG during hospitalization, whereas the remaining children were found to display pathological symptoms (mainly background slowing) without clinical disease. At follow-up, 8/19 EEGs were normal.[22]

Later, in a Swiss study, researchers concluded that permanent residua (i.e., severe mental and physical handicap) after pediatric TBE were rare (1 child out of 55, approximately 2%), but no specific assessment of cognitive functions was performed.[21] By administering validated questionnaires, Fowler et al. showed that 4 out of 6 children had residual symptoms, not always obvious, several years after TBE was diagnosed.[32] The occurrence of residual symptoms was later confirmed by Engman et al. Pediatric TBE patients, recruited from a previous prospective study, followed-up 1 year after their acute disease, reported significantly more fatigue, headache, and irritability than did children after neuroborreliosis or control subjects. Additionally, the children were screened for neuro-developmental problems (e.g., executive functions, memory, motor skills, behavior, etc.) using a validated questionnaire. Children in the TBE group had significantly more difficulties (5 out of 7), mainly with memory, executive function, and perception.[27]

In a larger study by Fowler et al., the findings of residual symptoms and neurodevelopmental/cognitive problems in childhood TBE were consolidated. Of note, the severity of the acute phase of disease did not influence the risk of long-term disease burden. More than 3 residual symptoms (e.g., headache, fatigue, memory problems, irritability, concentration problems, etc.) were seen in approximately 70% of the children at follow-up on average 4.2 years after the acute disease. Clinically significant problems with executive functioning were noted in approximately 40% of the children. Additionally, a significant decrease in working memory index, but not global IQ, was seen using the Wechsler Intelligence Scale for Children-IV.[34] Prominent deficits in working memory capacity and increased task-related functional MRI signal in working memory-related cortical areas during working memory testing have been shown in pediatric patients after TBE. These functional MRI abnormalities suggest diffuse neuronal damage behind the development of neurodevelopmental/cognitive problems seen in childhood TBE.[35] Krbková et al. also described cognitive problems (memory problems and lowered school grades) at follow-up in a large study; however, they found such deficits to a somewhat lower extent (11%).[17]

Long-term sequelae of a somatic nature are less frequently reported in childhood TBE. However, such cases occur and should not be forgotten. Fritsch et al. reported severe neurologic residua (hemiparesis and epilepsia) at a rate of 1.7% in their large pediatric cohort.[1] Others have also reported on neurologic sequelae, mainly hemiparesis, in children with TBE.[13,17,23,28] However, the frequency of paralysis and paresis in pediatric TBE is only reported up to approximately 2%, which is lower than the rate seen in adults.[2,4,13,16,21,23,28] While rare, such neurologic residua constitute a significant handicap in those affected, disrupting quality of life for many years. That TBE in childhood can be associated with altered cerebral electrophysiologic processes, i.e., pathologic EEGs and development of epilepsia,[1,13,17,22,23] is further substantiated by a report by Mukhin et al. Rather treatment-resistant epilepsia partialis continua was seen in 10 Russian children (predominantly boys) days to years after TBE. This cohort

also suffered from oculomotor dysfunction, varying degree of paresis, dysarthria, cerebellar signs, and cognitive dysfunction.[29]

To conclude, pediatric TBE carries a high risk for subjective sequelae, which to some extent can be objectively assessed by using structured questionnaires and inter-views.[26,28,32] A Swiss review on sleep-related symptoms concluded that 73.9% of children suffer from fatigue at long-term follow up (≥12 months) after TBE.[36] The early findings by Schmolck et al.[22] that TBE in childhood can be associated with neurodevelopmental/cognitive difficulties have now been verified.[17,27,34] As summarized in a recent review by Dr. Steffen, although larger studies may be required to determine the incidence of these sequelae, the individual child's long-term disease burden cannot be neglected.[37]

In contrast to somatic residua and epilepsy, which of course are rare but more easily diagnosed, neurodevelopmental/ cognitive problems may elude diagnosis due to young children's difficulties in verbalizing their problems and for their parents to recognize them. Hence, an opportunity exists to advocate for structured follow-up of children diagnosed with TBE so that early actions can be taken (for example, to explain why the child may not function as usual, to initiate educational support, to start medication for attention deficits, etc.).

Immune response against TBE in children

Children, from the age of 1 year, as well as adults, can elicit protective immunity to TBEV (i.e., response to the viral E protein) by immunization with the two TBE vaccines available in the EU. These vaccines are based on the European TBEV strains Neudörfl (FSME-IMMUN® Junior) and K23 (Encepur® Children).[38] (For more details, see Chapter 14). The field effectiveness in children less than 15 years of age is reported to be 97% after immunization with either of the two vaccines; however, it should be noted that the vaccine based on the Neudörfl strain had a higher market share at the time of the study (>96%).[39] TBE vaccination effectiveness has also been demonstrated by the nearly complete disappearance of TBE in a highly endemic area with implementation of a general vaccination program.[4] Among the many publications on immunization in children, it is important to note that the vaccines marketed within the EU have been shown to be safe and effective in eliciting antibody titers, that the booster interval can be expanded, and that rapid immunization schedules have worked well.[40] However, primary TBE vaccination (i.e., the first 3 doses) preferably should be accomplished with the same vaccine because of differences in each vaccine's immunologic properties.[40,41,43]

Natural immunity to TBE seems to persist over time and as children age, according to Baldovin et al., but with the reservation that their cohort was small.[44] Truly long-term data on natural immunity (for example, follow-up of now-older adults after TBE in childhood years) have not yet been reported.

The differences in clinical appearance of TBE between children and adults could stem from the immune response to the TBEV. In adults, polymorphisms and alterations in immune receptor genes (such as *CCR5, TLR3*, and *CD209*) have been reported to play a role in predisposing individuals to infection and/or severity of TBE.[47-49] However, Engman et al. reported that the 32-basepair deletion in the chemokine receptor 5 gene (*CCR5*Δ32), which impacts adult TBE, was neither more frequent in children with TBE nor did it have any association with the clinical course.[27] The lack of an effect on clinical TBE course by *CCR5*Δ32 in children was later confirmed by Mickiene et al. Yet, the later and larger study by Mickiene et al. demonstrated that *CCR5*Δ32 predisposed children for TBE.[48]

Autoantibodies have been detected in children with TBE at a low frequency. The occurrence of these antibodies did not contrast to those with neuroborreliosis and had no association with the clinical course.[27] The first case of Anti-NMDAR antibodies in a child after TBE was recently published.[49] The role of autoantibodies in pediatric TBE pathogenesis needs to be further elucidated.

In a study of both children and adults, Palus et al. reported a significant global pro-inflammatory cytokine balance in patients with higher serum interleukin (IL)-12:IL-4 and IL-12:IL-10 ratios versus controls. Also, novel and mechanistically interesting biomarkers like hepatocyte growth factor and vascular endothelial growth factors were increased in patients with TBE.[50] The significance of immune reactions in pediatric TBE has also been reported by Fowler et al. They found that development of sequelae in pediatric TBE could be related to the grade of inflammation (i.e., cytokines) rather than direct neuronal damage. High concentrations of cytokines (interferon-γ, IL-6, and IL-8) in the CSF might be associated with a risk of incomplete recovery.[51] In a recent publication from the same group, the CSF IL-6:IL-10 ratio was found to be significantly higher in a cohort of 37 children with TBE, compared with pediatric neuroborreliosis cases and healthy controls.[52] Another recent study of children with TBE indicates a relative abundance of CD4+ T cells intrathecally.[53] But, as stated in Chapter 9, the complexity of the immune response to TBEV has not yet been fully understood.

To conclude, the available TBE vaccines based on the Neudörfl and K23 strains, respectively, are safe and provide a protective immunity in most children. The natural long-term immunity after childhood TBE must be further investigated. Evidence suggests that the immune reactions to the TBEV serve as a key player in the clinical course, including risk for residual symptoms and sequelae, in childhood TBE.

Concluding remarks

All children deserve the best chance to reach their full potential. Such a chance includes a life without TBE-related sequelae. Childhood TBE may be associated with death, with considerable acute disease severity, prolonged convalescence, and long-term residua. Hence, advocating for immunization against TBE in children, even for the smallest ones, and proper neurodevelopmental follow-up after cases of TBE infection cannot be regarded as controversial. Despite being infrequent, disabling neurologic injuries exist after pediatric TBE and, together with the emerging evidence of altered cognitive functioning, action clearly is required–both from the medical community and from the health authorities in TBE endemic regions.

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