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Tick-borne encephalitis in children

CLINICAL REVIEW

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The incidence of tick-borne encephalitis in Norway is increasing. The risk of infection shows considerable geographical variations, with clusters of cases in certain municipalities in the counties of Agder, and Vestfold and Telemark. There is also a major variation in clinical presentation. Only a small number of cases of tick-borne encephalitis in children have been reported in Norway, and the condition may be underdiagnosed. We present a clinical review, including two case studies, that focuses on the clinical presentation and diagnosis of tick-borne encephalitis in children.

Tick-borne infections are a public health issue in Europe. The incidence of tick-borne encephalitis (TBE) has large geographical variations, with the highest number of cases in the Baltic region and Central Europe (1). The TBE virus is categorised in three subtypes, named according to the geographical distribution (European, Far Eastern and Siberian) (2). The European variant is present in Norway, with ticks and small rodents constituting the main reservoir (3).

In endemic areas, 0.1–5 % of ticks are probably infected, but there are significant variations depending on the geographical location and the tick's stage of development (2, 3). The number of clinical cases is increasing in Europe despite the availability of effective vaccines (1).

In Norway, clinical cases are reportable to the Norwegian Surveillance System for Communicable Diseases (MSIS). According to MSIS, 2022 is tentatively a peak year, with 68 cases of domestic transmission, corresponding to a national incidence of 1.2 cases per 100,000 inhabitants. However, in endemic areas, the infection risk is significantly higher since all domestic cases have occurred after tick bites in the counties of Agder, Viken, and Vestfold and Telemark, with the highest number of cases in Arendal, Larvik and Porsgrunn municipalities. Children below the age of 18 represent only 9.5 % of cases, in contrast to Lyme borreliosis, where children constitute the group most frequently affected. In

2022, the TBE virus was the most common aetiology of viral infections in the central nervous system in children in Vestfold and Telemark, with six hospital admissions reported (Department of Microbiology, Vestfold Hospital Trust, unpublished data).

The purpose of this article is to raise awareness and the level of knowledge about TBE in children. The article is based on a selective review of the literature and the authors' experiences in clinical practice and microbiological diagnostics. The case studies involve two unvaccinated children with TBE.

Clinical presentation

Clinical cases occur during the period from April to November (1). The TBE virus is transmitted within minutes following an infected tick bite (2). Infection can progress asymptomatically, cause a transient febrile illness, or lead to infection in the central nervous system. The latter is most often characterised by a biphasic course (2). The median incubation period is eight days, and the initial phase of the disease is marked by fever and influenza-like symptoms (2). This is followed by a symptom-free interval of approximately one week, before a recurrence of fever and symptoms of central nervous system inflammation in the form of meningitis, meningoencephalitis or, more rarely, encephalomyelitis.

Children can develop an infection in the central nervous system even in infancy and generally have a milder course of illness than adults (4–6). The majority develop meningitis (58–97 %), characterised by non-specific symptoms such as high fever (93–100 %), headache (89–100 %) and nausea/vomiting (60–87 %) (4, 5, 7–9) . The proportion of children with a biphasic course varies considerably (20–90 %) across studies, and the first phase is often interpreted as an upper respiratory infection (5, 9, 10). Known tick bites are reported in 46–75 % of cases (4, 5, 7, 9, 10).

Neck stiffness is the most common clinical finding, but there may be no objective signs of infection in the central nervous system (4, 5, 7, 8, 11). Severe neurological findings such as reduced level of consciousness, ataxia, paresis and generalised seizures, can occur but are rare in children with meningoencephalitis (4, 5, 8).

Diagnostics

Recommended diagnostic criteria for a confirmed case of TBE are given in Box 1. In addition to clinical symptoms of infection in the central nervous system, inflammatory markers are usually present in the serum. Leucocytosis is common, while the CRP level tends to be normal or only slightly elevated (4, 5, 7, 10).

Box 1 Recommended diagnostic criteria for a confirmed case of TBE (12).

- Clinical symptoms of infection in the central nervous system
- Pleocytosis in spinal fluid (> 5×10^6 cells/L)
- At least one microbiological criterion:
- Presence of specific IgM and IgG antibodies in serum
- Presence of specific IgM antibodies in spinal fluid
- Significant increase in IgG antibodies in two consecutive serum samples
- Detection of TBE virus RNA

A lumbar puncture is needed to make the diagnosis. Moderate pleocytosis with lymphocytic predominance is classic, but early in the course, polymorphonuclear cells can be predominant (2). Albumin and protein levels are usually within the normal range, and elevated values correlate with the presence of encephalitis (4, 5, 7).

Detection of antibodies in the serum is the cornerstone of microbiological diagnostics (12). Specific antibodies are absent in the initial phase of the illness but are present when symptoms of central nervous system infection occur. Negative serology early in the course of the disease does not therefore rule out TBE. IgM antibodies have the highest sensitivity and can be detected in the majority of patients at the time of admission (7, 9). When only IgM antibodies are initially detected, a control sample should be taken after 10–14 days to confirm the development of IgG antibodies.

Antibody testing in spinal fluid is not routinely recommended, but the detection of intrathecally produced IgM antibodies is diagnostic in cases of suspected vaccine failure (12).

The TBE virus RNA can be detected by PCR examination in blood during the initial phase of the illness, but the test has low sensitivity and is not routinely performed in spinal fluid (12).

Microbiological diagnostics are indicated in order to rule out differential diagnoses requiring treatment, such as herpes virus and varicella encephalitis, neuroborreliosis and bacterial meningitis. Coinfection with Borrelia burgdorferi can occur (4, 9).

EEG usually supports the diagnosis in cases of meningoencephalitis (8, 13). An increased amount of slow background activity is the most common pathological finding, while other focal activity in the EEG is unusual (8, 13).

Diagnostic imaging such as MRI or CT scans are most beneficial in cases of acute and severe symptoms, primarily to rule out differential diagnoses that may require urgent treatment, for example intracranial bleeding, infarction or abscess. In TBE, any findings on a head MRI tend to be localised in the thalamus and basal ganglia, but these findings have low diagnostic specificity (12, 13).

Two examples of the aforementioned diagnostics and clinical presentations are presented in the case studies in Boxes 2 and 3.

Box 2

Patient 1

A boy of lower secondary school age developed a headache and a high fever in late summer. His condition deteriorated, with symptoms of unsteadiness, nausea, light sensitivity and impaired fine motor skills. Upon admission, he was clinically stable but had a stiff neck and exhibited noticeable behaviour changes. A head MRI was normal except for increased leptomeningeal enhancement, as seen in meningitis. A lumbar puncture revealed mononuclear pleocytosis as well as elevated levels of albumin and protein. Empiric therapy for acute encephalitis and neuroborreliosis was initiated. The boy developed spasticity, hyperreflexia and inverted plantar reflex. A standard panel for microbiological diagnostics in spinal fluid did not provide evidence of an etiological agent. An EEG performed on day three showed pathological findings with episodic slow activity. On the same day, IgM and IgG antibodies against the TBE virus were detected in the serum, consistent with TBE. The boy's travel history revealed that he had spent time in a known high-risk infection area prior to admission, but without a known tick bite. He was discharged after clinical improvement on day four. A three-week EEG still showed persistent abnormalities, while the neurological examination showed normal results after five weeks and EEG after eight weeks.

Box 3

Patient 2

In early autumn, an otherwise healthy boy of preschool age, living in a high-risk infection area, was admitted after a four-day medical history of reduced general condition, vomiting, low-grade fever, lethargy and headaches. A week earlier, he had experienced transient cold-like symptoms. Upon clinical examination, he appeared unwell and feverish, but without a rash, neck stiffness, light sensitivity or obvious focal neurological deficits. Initial blood tests showed only slightly elevated infection parameters. A lumbar puncture revealed mild pleocytosis with a predominance of mononuclear cells. He was initially treated with acyclovir and ceftriaxone for a suspected central nervous system infection. Microbiological diagnostics in spinal fluid, including PCR examination for neurotropic viruses, bacterial culture and Lyme serology were negative, but IgM and IgG antibodies against the TBE virus were detected in the serum. Family members had not observed a tick bite, but clinical and laboratory findings were consistent with TBE with meningitic presentation. Antimicrobial treatment was discontinued, and the boy was discharged after clinical improvement on day three after admission. Family members reported four months later that he had fully recovered.

Treatment

Treatment is symptomatic, for example antipyretics, analgesics, fluid therapy, antiemetics, anticonvulsants and, in the most severe cases, organ support. The proportion of children requiring intensive care varies considerably across studies (0–22 %) (6). Any empiric therapy initiated with acyclovir should be discontinued when the diagnosis is confirmed and herpes encephalitis has been ruled out (12).

Prognosis

Child deaths caused by the European subtype of the TBE virus are extremely rare, and severe neurological sequelae are less common in children than in adults (6). However, the risk of long-term cognitive dysfunction is a concern. In a Swedish follow-up study, half of the children experienced residual problems, including headaches, cognitive problems, irritability and fatigue four years after the illness (14). A German study observed persistent decreased background activity in EEG in children examined three years after they had encephalitis (13).

Follow-up

The need for outpatient follow-up will depend on the individual clinical presentation as well as any pathological findings in EEG or MRI scans. Healthcare personnel should be aware of the risk of cognitive sequelae, but there are currently no specific guidelines for how to carry out neuropsychological testing in children with TBE (12).

Vaccination

Vaccination provides effective protection against disease, and only sporadic cases of vaccine failure occur in children (6, 15). In high-endemic areas, i.e. with ≥ 5 cases/100,000 inhabitants per year, the WHO recommends vaccination for everyone from the age of one as part of a national or regional vaccination programme (15). In areas with a lower incidence, vaccination recommendations should be based on the local risk of infection (15). In Norway, the Norwegian Institute of Public Health recommends considering vaccination for children who are frequently exposed to tick bites in areas with clinical cases, including the coastline between Flekkefjord and Drammen and from Vestby southward (16). It is likely that a previous infection provides lasting immunity (12). It was not until January 2011 that vaccinations administered outside of the childhood vaccination programme were required to

be registered in the Norwegian Immunisation Registry, SYSVAK (17). The data on the number of children in Norway vaccinated against the TBE virus are therefore incomplete.

Summary

TBE should be suspected in exposed children who develop a high fever and headache in the period from April to November. Obtaining the child's travel history to endemic areas is important, and the absence of a known tick bite and neurological findings do not rule out the condition. TBE is diagnosed via a lumbar puncture and antibody testing in the serum. Vaccination can prevent new cases, and accurate epidemiological data are crucial for optimal vaccination guidelines.

The patients' parents/guardians have consented to publication of the case studies. Additionally, patient 1 has consented to publication of case study 1. The article has been peer-reviewed.

REFERENCES

1. ECDC. Tick-borne encephalitis Annual Epidemiological Report for 2020. https://www.ecdc.europa.eu/sites/default/files/documents/Tick-borne-encephalitis-annual-epidemiological-report-2022.pdf Accessed 20.6.2023.

2. Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet 2008; 371: 1861–71. [PubMed][CrossRef]

3. Vikse R, Paulsen KM, Edgar KS et al. Geographical distribution and prevalence of tick-borne encephalitis virus in questing Ixodes ricinus ticks and phylogeographic structure of the Ixodes ricinus vector in Norway. Zoonoses Public Health 2020; 67: 370–81. [PubMed][CrossRef]

4. Krawczuk K, Czupryna P, Pancewicz S et al. Comparison of tick-borne encephalitis between children and adults-analysis of 669 patients. J Neurovirol 2020; 26: 565–71. [PubMed][CrossRef]

5. Logar M, Arnez M, Kolbl J et al. Comparison of the epidemiological and clinical features of tick-borne encephalitis in children and adults. Infection 2000; 28: 74–7. [PubMed][CrossRef]

6. Steffen R. Tick-borne encephalitis (TBE) in children in Europe: Epidemiology, clinical outcome and comparison of vaccination recommendations. Ticks Tick Borne Dis 2019; 10: 100–10. [PubMed][CrossRef]

7. Bogdanavičienė K, Gudavičiūtė G, Šeškutė M. A Retrospective Analysis of Tick-borne Encephalitis in Children Treated in Kaunas Hospital During 2012 to 2019. Pediatr Infect Dis J 2022; 41: 702–5. [PubMed][CrossRef]

8. 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: 535–8. [PubMed][CrossRef]

9. Krbková L, Štroblová H, Bednářová J. Clinical course and sequelae for tick-borne encephalitis among children in South Moravia (Czech Republic). Eur J Pediatr 2015; 174: 449–58. [PubMed][CrossRef]

10. Sundin M, Hansson ME, Engman M-L 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 2012; 171: 347–52. [PubMed][CrossRef]

11. Meyer PM, Zimmermann H, Goetschel P. Tick-borne encephalitis presenting as fever without localising signs–a case series. Eur J Pediatr 2010; 169: 767–9. [PubMed][CrossRef]

12. Taba P, Schmutzhard E, Forsberg P et al. EAN consensus review on prevention, diagnosis and management of tick-borne encephalitis. Eur J Neurol 2017; 24: 1214–e61. [PubMed][CrossRef]

13. Schmolck H, Maritz E, Kletzin I et al. Neurologic, neuropsychologic, and electroencephalographic findings after European tick-borne encephalitis in children. J Child Neurol 2005; 20: 500–8. [PubMed][CrossRef]

14. Fowler Å, Forsman L, Eriksson M et al. Tick-borne encephalitis carries a high risk of incomplete recovery in children. J Pediatr 2013; 163: 555–60. [PubMed][CrossRef]

15. Organization WH. Vaccines against tick-borne encephalitis: WHO position paper. Wkly Epidemiol Rec 2011; 86: 241–56. [PubMed]

16. Skogflåttencefalittvaksine FHI. (TBE-vaksine) - veileder for helsepersonell. https://www.fhi.no/nettpub/vaksinasjonsveilederen-forhelsepersonell/vaksiner-mot-de-enkelte-sykdommene/skogflattencefalittvaksinasjon-tbe-/ Accessed 5.6.2023.

17. FHI. Nasjonalt vaksinasjonsregister SYSVAK. https://www.fhi.no/hn/helseregistre-og-registre/sysvak/om-sysvak/ Accessed 7.6.2023.

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