

Tick-borne encephalitis- clinical and virological aspects

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet, kommer att offentligen försvaras i Carl Kylberg, Medicinaregatan 9a, Göteborg, **fredagen den 5 februari 2021 kl 09.00**

av

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Avhandlingen baseras på följande delarbeten:

- I. Veje, M, Nolskog P, Petzold M, Bergström T, Lindén T, Peker Y, Studahl M. **Tick-borne encephalitis sequelae at long-term follow-up: a self-reported case-control study.** Acta Neurologica Scandinavica 2016; 134: 434-441.
- II. Veje M, Studahl M, Thunström E, Stentoft E, Nolskog P, Celik Y, Peker Y. **Sleep architecture, obstructive sleep apnea and functional outcomes in adults with a history of Tick-borne encephalitis.** *Submitted.*
- III. Veje M, Studahl M, Johansson M, Johansson P, Nolskog P, Bergström T. **Diagnosing Tick-borne encephalitis: a re-evaluation of notified cases.** European Journal of Clinical Microbiology & Infectious Diseases 2018; 37: 339-344
- IV. Veje M, Studahl M, Norberg P, Roth A, Möbius U, Brink M, Bergström T. **Detection of Tick-borne encephalitis virus RNA in urine.** Journal of Clinical Microbiology 2014; 52: 4111–4112
- V. Veje M, Studahl M, Bergström T. **Intrathecal complement activation by the classical pathway in tick-borne encephalitis.** Journal of NeuroVirology 2019; 25: 397–404

**SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



ABSTRACT

Tick-borne encephalitis (TBE), an important central nervous system infection in Europe and Asia, is caused by the TBE virus (TBEV), which is mainly transmitted to humans through tick bites. This thesis studied data from 201 of the 373 patients diagnosed in Region Västra Götaland between 1997 and 2017. The purpose was to investigate the burden of disease following TBEV infection. We also intended to evaluate existing diagnostic methods, and to expand knowledge concerning intrathecal immune defense mechanisms.

In **Paper I**, the medical records of 96 TBE patients were studied, and telephone interviews were held with 92 patients and 58 controls. After a median of 5.5 years post-infection, TBE patients reported significantly more complaints, compared with the control group, regarding memory, concentration, fatigue, headache, fine motor skills, initiative and motivation, as well as balance and coordination.

Paper II covered polysomnography investigations of sleep patterns in 22 patients (median two years post-TBE) and 20 matched controls. The former group significantly more often reported fatigue and negative impact on sleep related functional outcomes compared with controls, despite the observation of similar sleep patterns and frequency of obstructive sleep apnea.

Paper III evaluated the current methodology used in clinical practice to diagnose TBE by examining 248 stored serum and cerebrospinal fluid (CSF) samples from 129 notified TBE cases, 140 control sera, and ten CSF control samples. Diagnostic accuracy of serological testing (IgM and IgG) was considered high. Detection of TBEV-specific IgG in CSF and PCR for TBEV-RNA in serum samples provided additional diagnostic information.

Paper IV described PCR detection of TBEV-RNA in urine samples drawn from two TBE patients during the neurological disease phase.

In **Paper V**, complement activation in serum and CSF samples from 20 TBE patients and 32 controls was investigated, using commercially available ELISA kits. All of the examined complement factors C1q, C3a, C3b, and C5a were detected in the CSF at significantly higher concentrations among patients than in controls. Our findings indicate intrathecal activation of the classical pathway of the complement system in TBE.

Conclusions: TBE can lead to a number of long-term sequelae. Routine methodology currently used to diagnose TBE is accurate, however, and CSF-IgG and PCR provide additional value. The classical complement pathway is activated in the immune response to TBEV.

Keywords: Tick-borne encephalitis, TBE, zoonosis, sequelae, fatigue, polysomnography, sleep, functional outcome, serology, PCR, complement activation, classical pathway