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# Alphaherpesvirus infections of the central nervous system

## Biomarkers, diagnostics and antiviral therapy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal 2119, hus 2, Hälsovetarbacken, Arvid Wallgrens backe, fredagen den 18 juni, klockan 09.00

av **Johan Lindström**

Fakultetsopponent:

Professor **Pierre Tattevin**

Université Rennes 1, Frankrike

**Avhandlingen baseras på följande delarbeten**

I. Lindstrom J, Grahn A, Zetterberg H, Studahl M. **Cerebrospinal fluid viral load and biomarkers of neuronal and glial cells in Ramsay Hunt syndrome.** European Journal of Neuroscience. 2016 Dec;44(11):2944-9.

II. Lindstrom J, Bremell D, Grahn A, Blennow K, Zetterberg H, Studahl M. **CXCL13 in patients with facial palsy caused by varicella zoster virus and Borrelia burgdorferi: a comparative study.** Diagnostic Microbiology and Infectious Disease. 2020 Sep;98(1):115095.

III. Lindstrom J, Elfving K, Lindh M, Westin J, Studahl M. **Assessment of the FilmArray ME panel in 4199 consecutively tested cerebrospinal fluid samples.** Submitted manuscript.

IV. Lindstrom J, Hellden A, Lycke J, Grahn A, Studahl M. **An unexpectedly high occurrence of aciclovir-induced neuropsychiatric symptoms in patients treated for herpesvirus CNS infection: a prospective observational study.** Journal of Antimicrobial Chemotherapy. 2019 Dec;74(12):3565-72.

**SAHLGRENSKA AKADEMIN**
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# Alphaherpesvirus infections of the central nervous system

## Biomarkers, diagnostics and antiviral therapy

**Johan Lindström**

Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden 2021

### Abstract

Herpesviruses predate the evolution of humans and are globally ubiquitous. Herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and varicella-zoster virus (VZV) establish latency in neuronal tissue and may cause infections in the central nervous system (CNS). Despite advances in diagnostics and treatment, the disease burden remains high. The overall aims of this thesis were to explore and evaluate several aspects of HSV and VZV CNS infection, with the ultimate goal of improving clinical management, from diagnosis to treatment and prognostication.

**Paper I** explores cerebrospinal fluid (CSF) biomarkers in 28 patients with facial palsy caused by VZV. Biomarker expression was consistent with neurological damage and astrogliosis. This pattern was more pronounced in patients with concurrent mucocutaneous zoster rash than in those without rash, *zoster sine herpete*. Associations between biomarker concentrations and neurological outcomes could not be demonstrated.

**Paper II** evaluates the CXCL13 CSF biomarker as a means of discriminating between VZV and Lyme Neuroborreliosis (LNB) in cases of facial palsy. CXCL13 concentrations were significantly higher in patients with LNB facial palsy ($n = 21$), though there was some overlap with cases of VZV facial palsy ($n = 26$). Despite good performance measures, especially if analyzed early after onset of symptoms, careful interpretation is advised when concentrations are moderately increased.

**Paper III** assesses the performance of the FilmArray Meningitis/Encephalitis (ME) panel. The ME panel is a multiplex PCR panel for syndromic testing in CNS infections, able to detect 14 pathogens, including herpesviruses and bacteria. ME panel results were compared with routine diagnostic procedures in 4199 CSF samples from patients with suspected viral CNS infection. Discrepant results were thoroughly investigated to determine whether PCR detection was correct. A high performance level was demonstrated in calculations on individual pathogens, but 21 false negative and 20 false positive results were identified. If herpes simplex encephalitis is suspected, additional testing is warranted despite negative HSV-1 results from the ME panel. Interpretation concerning positive enterovirus, HHV-6, and *S. pneumoniae* results may also be complicated due to false positive or clinically insignificant results.

**Paper IV** is a pharmacokinetic study of acyclovir and its metabolite CMMG in 21 patients with acute CNS infection. Renal function, damage to the blood-brain barrier, dosage, and body weight all influenced CSF concentrations of both molecules. Acyclovir-induced neuropsychiatric symptoms (AINS) were unexpectedly identified in four patients, together with high CSF concentrations of CMMG, previously implicated in neurotoxicity. These results justify increased attention to suspected neuropsychiatric symptoms and careful consideration of dosages in acutely ill patients.

**Keywords**: herpesviruses, central nervous system, facial paralysis, cerebrospinal fluid, biomarkers, syndromic testing, acyclovir, neurotoxicity

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