Varicella-zoster virus infections of the central nervous system

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen, Infektionskliniken Sahlgrenska Universitetssjukhuset/Östra

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I. Persson A, Bergström T, Lindh M, Namvar L, Studahl M: **Varicella-zoster virus CNS disease--viral load, clinical manifestations and sequels**. *Journal of clinical virology* 2009, **46**(3):249-253

II. Thomsson E, Persson L, Grahn A, Snäll J, Ekblad M, Brunhage E, Svensson F, Jern C, Hansson GC, Bäckström M, Bergström T: **Recombinant glycoprotein E produced in mammalian cells in large-scale as an antigen for varicella-zoster-virus serology**. *Journal of virological methods* 2011, **175**(1):53-59.

III. Grahn A, Studahl M, Nilsson S, Thomsson E, Bäckström M, Bergström T: **Varicella-zoster virus (VZV) glycoprotein E is a serological antigen for detection of intrathecal antibodies to VZV in central nervous system infections, without cross-reaction to herpes simplex virus 1**. *Clinical and vaccine immunology : CVI* 2011, 18(8):1336-1342.

IV. Grahn A, Hagberg L, Nilsson S, Blennow K, Zetterberg H, Studahl M: **Cerebrospinal fluid biomarkers in patients with varicella-zoster virus CNS infections**. *Journal of neurology (Epub ahead of print)* 2013.

V. Grahn A, Nilsson S, Nordlund A, Lindén T, Studahl, M: **Cognitive impairment after neurological Varicella-zoster virus infection - a 3-year follow-up.** *Submitted*

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ABSTRACT

Both varicella (chickenpox), and the reactivated form of herpes zoster (shingles), may cause neurological complications with various central nervous system (CNS) manifestations. Following introduction of PCR as a diagnostic method, the possibilities to detect the virus in cerebrospinal fluid (CSF) and to explore this disease, have dramatically improved.

With the quantifiable properties of real-time PCR the question arose whether VZV viral load was correlated to the severity of neurological disease. In 97 patients, the medical records were retrospectively studied and the spectrum of clinical entities discerned. CSF VZV DNA was quantified in 66 of these cases. Baseline viral loads were higher in patients with meningitis and encephalitis as compared with those suffering from Ramsay Hunt syndrome. However, these differences did not reflect the severity of disease why this parameter was not a reliable predictor of outcome. Additionally, based on our data, VZV seems to be a more common aetiological agent of CNS infections than previously thought.

Despite the usefulness of PCR, this technique has its diagnostic limitations. In patients with late diagnosis, the VZV DNA may be absent at time of PCR analysis. Serological analysis for detection of intrathecal antibody production is then required. Using a crude VZV antigen does not properly discriminate between antibodies to VZV and HSV-1. We produced and evaluated a purified glycoprotein antigen, VZVgE. When 854 serum samples were analysed, VZVgE-ag showed equal sensitivity and at least as high specificity compared with VZVwhole-ag.

VZVgE was also evaluated as a serological antigen in CSF. Paired samples of CSF and serum from 29 patients with clinical diagnosis of VZV CNS infection (n=15) or herpes simplex encephalitis (HSE) (n=14), all confirmed by PCR were analysed. In ELISA, 11/14 HSE patients showed intrathecal antibody production with VZVwhole-ag compared with 4/14 using VZVgE-ag. In the patients with VZV CNS infection, the two antigens showed comparable results. When the CSF/serum samples pairs were diluted to identical IgG concentrations, higher CSF/serum optical density (OD) ratios were found in VZV patients using VZVgE-ag compared with VZVwhole-ag. These results show that VZVgE is a sensitive antigen for serological diagnosis of VZV CNS infection without cross-reactivity to HSV-1 IgG.

To evaluate the potential degree of brain damage in patients with VZV CNS infections, we prospectively studied the CSF concentrations of neuron-specific light chain neurofilament protein (NFL), glial fibrillary acidic protein (GFAp) and S-100β protein in 24 patients with VZV DNA positivity and acute neurological symptoms. Concentrations of CSF NFL and GFAp were moderately increased, while the S-100β levels were reduced. These results indicate that VZV might induce neuronal damage and astrogliosis, and this finding was most pronounced in the patients with VZV encephalitis.

The cognitive impairment in patients with VZV CNS infections is largely unknown. We investigated the cognitive impairment in 14 patients with predominant CNS infections caused by VZV in a 3-year follow-up. The VZV patients performed worse than controls (n=28) on 4 tests covering the domains of speed and attention, memory and learning and executive function. The VZV patients were also classified into the concept of mild cognitive impairment (MCI), which is associated with development of dementia. A greater proportion of VZV patients was classified with MCI compared with controls. These findings suggest that patients with previous VZV CNS infection might carry a risk of long-term cognitive impairment.

Keywords: Varicella-zoster virus infection, central nervous system, neurological sequelae, cerebrospinal fluid, viral load, intrathecal antibody production, glycoprotein E, biomarkers, cognitive impairment
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