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Letter to the Editor – Journal of Infection

Chronic-relapsing varicella zoster meningitis – successfully treated with varicella vaccine

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Dear Editor,

We note with interest recent reports on the problems of diagnosing central nervous system (CNS) infections,[1] particularly the study comparing the presence of varicella zoster virus (VZV) DNA in blood and cerebrospinal fluid (CSF) in patients with VZV-related neurological symptoms.[2] Here we report a case of chronic-relapsing VZV meningitis, where the episodes occurred with frequent and debilitating regularity.

A 62-year-old man, who worked as a General Practitioner at an asylum centre, presented with a 2-year history of headache, fatigue, diffuse myalgia, a low-grade fever, night sweats and mood disturbances. His symptoms waxed and waned every 1-3 weeks, without ever fully resolving, but never included seizures or focal neurological symptoms. He had lost 9 kg during this period. His work routinely exposed him to patients with various exotic and chronic infections, including a varicella outbreak 2 years previously.

General physical examination was unremarkable, apart from some limb myalgia. Specifically, neither neck stiffness nor any other focal neurological signs were detected. Other investigations (chest X-ray, echocardiography, abdominal ultrasound) were all normal. An MRI-brain showed some non-specific lesions in the deep white matter, compatible with Virchow-Robin spaces.

Full blood counts with differentiation, ferritin, lipid profile, thyroid stimulating hormone, CA19-9, liver function, serum glucose, urea and electrolytes and erythrocyte sedimentation rate were all normal, apart from a mild non-specific anaemia. Serological testing for HIV, cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex virus (HSV), *Brucella*, *Borrelia*, *Yersinia*, *Toxoplasma*, and *Mycoplasma pneumoniae* were either negative or just indicated past infection.

Cerebrospinal fluid examination revealed a slightly raised total protein (0.66 g/L) and a low glucose (1.9 mmol/L) with a glucose ratio of 0.44. No erythrocytes were seen, but 95 $x10^6$/L leucocytes were observed (primarily lymphocytes and monocytes). Polymerase chain reaction testing for CSF HSV and VZV was negative. Further CSF investigations using immuno-blotting showed intense IgG bands in the CSF, with fewer, weaker bands in a contemporaneous serum sample (**Figure 1**): CSF intrathecal VZV IgG titre was 2500, with a VZV-IgG index of 98.52, indicating intrathecal VZV-IgG synthesis.

A diagnosis of chronic-relapsing VZV meningitis was made, and a 2-week course of intravenous acyclovir (1000 mg TD) was given. The patient improved on treatment, but the meningitis symptoms recurred every 2 weeks once treatment had stopped.

Further, repeated CSF examinations, during symptomatic and asymptomatic periods, showed similar profiles to the above. Contemporaneous serum VZV DNA PCR was mostly negative except once when it was positive at a very low level (63 copies/ml of VZV DNA). Repeat isoelectric focusing and immune-blotting revealed an intrathecal oligoclonal IgG response, together with a VZV-specific monoclonal IgG response (**Figure 2**).

Further treatment with oral valacyclovir (1000 mg TDS for 7 days) followed by a suppressive dose (valacyclovir, 500 mg BD) for three months was then tried. However, the patient continued to experience meningitis symptoms on this medication. Treatment was continued with oral valacyclovir (1000 mg BD), but now in combination with monthly VZV hyper-immune globulin (VZIG, IM, 400 units). Although there was some improvement, the meningitis symptoms recurred every 3 weeks.

Several years later, we received an update from the patient. He had been on holiday in South Africa, during which he had mistakenly received 3 doses of the paediatric varicella vaccine instead of the regular VZIG. His symptoms improved for 4-5 weeks. On returning to The Netherlands, on this basis, his neurologist suggested zoster vaccine (which contains at least 19,400 PFU – plaque forming units - of VZV, per dose) for longer-term symptom relief. As this was not yet available, he was given 18 doses of paediatric varicella vaccine (which contains at least 1350 PFU, per dose) instead. This resolved his symptoms. He then received a depot corticosteroid injection for shoulder pain, after which his meningitis symptoms returned 3 weeks later. After a further 18-dose course of paediatric varicella vaccine, he has remained symptom-free.

Varicella-zoster virus remains latent in the neurons of cranial nerves and dorsal root ganglia for the entire life of the host after primary infection (chickenpox).[3] Herpes zoster or shingles is the most common form of VZV reactivation and is characterized by a dermatomal rash and radicular pain. Rarely, VZV spreads to the spinal cord and brain. When this occurs, CNS complications may develop without concomitant zoster rash.[4,5] Aseptic meningitis due to VZV is seen in both immunocompetent as well as immunocompromised patients.[6] The diagnosis is usually confirmed by a positive CSF VZV DNA PCR result, or less commonly, by the intrathecal detection of VZV-specific IgG.[7]

The repeated failure to detect CSF VZV DNA in this case during acute episodes may be due to the chronic course of the disease. A similar decrease in the percentage of CSF HSV PCR-positive cases can be seen within 2 weeks for HSV encephalitis,[8] which may also be true for VZV. The onset of symptoms in this patient was 2 years before the first CSF VZV PCR was performed. His symptoms were also limited to viral meningitis rather evolving into encephalitis, which may have also explained

the negative VZV PCR results.[9] However, the extensive intrathecal VZV IgG production confirmed the diagnosis of VZV aseptic viral meningitis.

The finding of a distinctly monoclonal intrathecal VZV-specific IgG is unusual and atypical (**Figure 2**). Normally, an oligoclonal response is required to clear the virus efficiently. Therefore, the patient may have a defect in his VZV-specific antibody affinity maturation, i.e. a partial 'immunological scotoma' to VZV, explaining his inability to clear (i.e. 'neutralise') the virus efficiently, allowing recurrent episodes of meningitis. Note that this case does not meet Bruyn's diagnostic criteria for Mollaret's meningitis,[10] as the patient was not completely symptom-free between episodes.

To our knowledge, such chronic-relapsing varicella zoster viral meningitis of such periodicity has not been previously described. The remarkable response to multiple doses of paediatric varicella vaccine was both fortunate and serendipitous. This patient likely suffers from a VZV-specific antibody maturation deficit that appears to have been overcome by the massive immune stimulation provided by multiple doses of paediatric varicella vaccine. Whilst such cases are rare, this report may assist in their management.

Acknowledgements

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Figure 1. Isoelectric focusing for VZV IgG. Isoelectric focusing of paired CSF and serum (**A** and **B**) stained for IgG in CSF, showing prominent oligoclonal bands in CSF, but absent from serum (consistent with local or intrathecal synthesis). The patterns have been aligned against the prominent band in the centre of the pattern on CSF to allow easy comparison. Although the distribution of bands appears slightly different between CSF samples this just reflects inter-assay variability in the analytical system (each sample pair was run on a different gel). The anode (+) electrode is on the left. The paired CSF and serum in images **A** and **B** are from samples taken approximately two months apart during acute illness episodes.

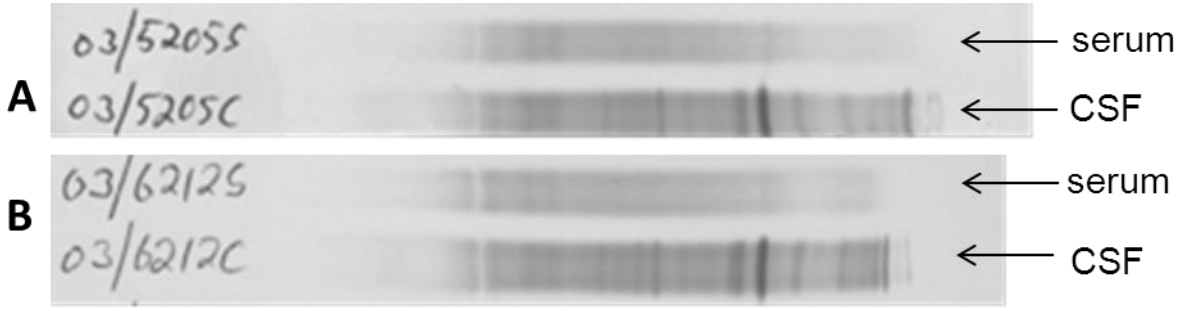

Figure 2. VZV-specific IgG. VZV-specific IgG showing a ladder-pattern of bands, predominantly in the CSF (**A**). This pattern is also just visible in the serum samples. The ladder-pattern is characteristic of a monoclonal antibody. Due to the strong staining, the anodic (left-most) bands have merged. The absence of any bands in the control immunoblot (using a cell-line without VZV, **B**) shows that the IgG in the patient's CSF and serum is highly VZV-specific.