
Case report

Prolonged detection of herpes simplex virus type 2 (HSV-2) DNA in cerebrospinal fluid despite antiviral therapy in a patient with HSV-2-associated radiculitis

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Introduction

Herpes simplex virus type 2 (HSV-2) belongs to Herpesviridae and causes most cases of genital herpes [1]. Its seroprevalence is 20–30% in developed countries and up to 80% worldwide [2]. Besides neonatal encephalitis and ‘aseptic’ meningitis, HSV-2 is associated with neurological manifestations such as radiculitis or myelitis. The symptoms of HSV-2 radiculo-myelitis may include pain, paresis, sphincter disturbances or sensory losses and are generally mild, but severe disease such as ascending necrotizing myelitis with fatal outcome has been observed [3–6]. Neurological HSV-2-associated disease may originate from primary infection or from reactivation of latent HSV-2 infection, for example, from the sacral ganglia. It can be diagnosed by testing CSF samples by PCR or the specific antibody index (AI) for HSV [4,7,8]. However, the clinical diagnosis might be complicated due to relatively unspecific symptoms and absence of muco-cutaneous HSV-2 manifestations.

The present case of a highly immunocompromised hematopoietic patient with HSV-2-associated radiculitis is particularly interesting, as high levels of HSV-2 DNA have been detected by real-time PCR in the CSF for a period of approximately 8 weeks despite intravenous acyclovir therapy. This gave rise to questions about the HSV-2 load kinetics in the CSF and the appropriate duration of antiviral therapy. To our
knowledge such prolonged HSV-2 DNA positivity in the CSF has not been reported previously.

Case report

We report a 69-year-old woman with an abdominal B-cell lymphoma first diagnosed 28 months ago and treated with chemotherapy (last cycle 20 months ago) to partial remission. Additionally, the patient presented with pancytopenia due to secondary, therapy-induced myelodysplastic syndrome. Moreover, she had a history of a follicular thyroid cancer (first diagnosis 14 years ago) with bone metastases including multiple metastases of the thoracic spine, which had been treated with multiple cycles of radio iodine therapies (last cycle three months before admission).

Upon admission the patient presented with urinary incontinence which had started two days ago, a moderate paresis of the right hip flexion and strong pain in the right groin. The Achilles tendon reflex was absent, but no sensory losses were noted. She had no history of herpes genitalis and typical skin lesions were absent. CSF taken three days after admission showed lymphocytic pleocytosis (178 cells/μl) with elevated glucose (5.0 mmol/l), lactate (3.96 mmol/l) and protein (0.97 g/l) levels. Although meningiosis carcinomatosa was initially suspected due to the pleocytosis, no cells indicative for meningiosis have been found upon repeated analyses. Magnetic resonance imaging (MRI) upon admission showed a significant enhancement of fibres belonging to the cauda equina, indicative of an inflammatory process (Figure 1A and 1C).

Quantitative HSV-2 PCR of the CSF (detection limit 500 copies/ml [9]) revealed 2.0 × 10^5 copies/ml at day 3 after admission. The HSV-2 serostatus (HerpeSelect 2 ELISA IgG; Focus Diagnostics, Cypress, CA, USA) was positive, while HSV-1/2 IgM (Enzygnost Anti-HSV/IgM ELISA, Eschborn, Germany) tested negative. Interestingly, HSV-2 immunoglobulin G was negative in serum obtained two years before, indicating seroconversion within the last two years. It remains unclear whether the radiculitis was result of a primary or a recurrent HSV-2 infection.

Therapy with acyclovir intravenously (750 mg three times daily) and low-dose prednisolone (70 mg/day by mouth) was started. Until discharge prednisolone was reduced to 10 mg/day. After discharge, acyclovir was orally administered for 4 weeks (2,000 mg/day) and prednisolone was tapered.

Further quantitative HSV-2 PCR testing at day 12, 19, 26, 33, 48 and 54 after admission showed ongoing positivity for HSV-2 DNA (Figure 2). The viral load in the CSF declined only slowly, showing the first significant drop (>0.5 log) at day 33 (6.5 × 10^4 copies/ml). At day 54, the HSV-2 load was still 1.6 × 10^4 copies/ml.

Although acyclovir resistance seemed unlikely, CSF samples from day 26 and 33, respectively, were assigned to HSV-2 thymidine kinase gene (UL23) sequencing. Genotypic resistance analysis was not completely interpretable, but the sequenced parts (nucleotides 1–367 and 836–1130 of the thymidine kinase gene) showed no mutations indicative for acyclovir resistance.

Additionally, intrathecal synthesis of HSV immunoglobulin G antibodies was measured quantitatively (Enzygnost Anti-HSV/IgG ELISA; Siemens Healthcare Diagnostics) by the specific antibody index (AI) [10]. The AI for HSV was only slightly elevated (1.8) upon admission, increased to up to 22.9 at day 19 and was still elevated at day 54 (13.5). Leukocyte counts in the CSF declined to 33 cells/μl at day 54 (Figure 2).

Symptoms showed a slow but continuous improvement so that upon discharge the paresis of the right hip flexion was absent. The urinary incontinence resolved after two weeks. The pain in the right groin regressed completely after 3 weeks.

At day 66 the patient was discharged. Therefore, monitoring of HSV-2 load was not continued. At day 138 after admission another CSF sample was collected during a routine follow-up. This sample was HSV-2 DNA negative, while the AI for HSV was still elevated.
HSV-2 load kinetics in the CSF

In conclusion, presence of HSV-2 DNA in the CSF for at least 8 weeks can be assumed.

A follow-up MRI (day 135) revealed a decreased enhancement in the cauda equina compared to the neuroimaging upon admission, supporting the diagnosis of HSV-2-associated radiculitis (Figure 1B and 1D).

**Discussion**

The described patient showed a very slow decline of HSV-2 loads in CSF over a period of at least 8 weeks after onset of symptoms, despite clinically effective antiviral therapy. Unfortunately, data about the HSV-2 load kinetics in the CSF and their diagnostic significance are scarce, especially in the context of HSV-associated radiculo-myelitis.

Previous studies about HSV-1/2 encephalitis showed that acyclovir treatment leads to a sharp reduction of the number of PCR-positive cases after two weeks and HSV DNA in the CSF is only rarely detectable after 30 days and may even be negative in case of a relapse [11–14]. In our case the patient’s immunocompromised status (pancytopenia and multiple neoplasms) might have promoted the prolonged presence of HSV-2 DNA in the CSF, similar to longer detectability reported for HIV patients [11].

The slow decline might be explained either by ongoing replication of the virus or by the protracted clearing of viral DNA from the CSF. The AI for HSV increased until day 19 after admission indicating the presence of an antigenic stimulus for antibody production such as HSV replication. Thereafter the AI declined continuously despite ongoing HSV-2 DNA detection, suggesting that HSV-2 replication was terminated by antiviral therapy and therefore an antigenic stimulus for further antibody production was lacking. Moreover, the major symptoms of the patient such as urinary incontinence and pain already improved after the first three weeks of antiviral treatment. Therefore, ongoing HSV-2 detectability might be rather explained by slow clearance of HSV-2 from the CSF. However, the patient was also treated with prednisolone which might have contributed to the fast resolution of symptoms by decreasing the inflammatory reaction, but on the other hand might have increased
the viral replication. The consequences of the viral load kinetics in the CSF can be discussed ambiguously: while ongoing replication of HSV-2 would have required extended antiviral treatment, protracted clearing of neutralized particles/DNA from the CSF would not necessarily have justified further antiviral medication.

Although prolonged detection of virus was reported as a marker for poor outcome of HSV encephalitis [12], its clinical significance in HSV-2 radiculo-myelitis is obscure. Even in the case of HSV encephalitis the duration of antiviral therapy in the context of prolonged HSV detection in the CSF is rather unclear: current guidelines recommend the treatment with acyclovir intravenously for 14–21 days and extention of the treatment has been proposed, if the CSF remains positive upon re-examination by PCR [15–17]. In our case the treatment of an immunocompromised patient with acyclovir for 66 days intravenously and for further 4 weeks as oral medication eventually led to the clearance of HSV-2 DNA from the CSF.

In addition to the described HSV-2 DNA kinetics, this report highlights the difficulty of diagnosing HSV-2-associated radiculitis or myelitis, due to the relatively unspecific clinical symptoms. Previous reports also described symptoms such as urinary retention, dull pain or sensory loss in the anogenital area, sciatalgia with leg weakness or missing deep tendon reflexes in patients with HSV-2 radiculo-myelitis [3,18,19]. Similar as here, CSF findings in HSV radiculo-myelitis usually show lymphocytic pleocytosis (up to 200 cells/µl) [20]. Moreover, a preceding anogenital rash or enlarged lymph nodes indicating primary or reactivated episode of herpes genitalis are not necessarily present [18]. Autopsy studies demonstrated that 40% of sacral dorsal root ganglia contain dormant HSV-2, but only 5% of these individuals had recognized genital herpes infection during life [4]. Thus, it can be suspected that several cases of neurological HSV-2 disease occur without typical muco-cutaneous lesions, as described for the present case. In our case the comorbidity of our patient with previously known bone metastases and multiple neoplasms in her medical history complicated the diagnosis, since, for example, meningitis carcinomatosa might have shown similar symptoms and CSF findings.

In summary, physicians should be aware of the symptoms of HSV-2 radiculo-myelitis to ensure an early diagnosis and antiviral treatment. The viral load kinetics of HSV DNA in the CSF and their impact on treatment and outcome deserve further investigation.

Disclosure statement

The authors declare no competing interests.

References

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