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CASE REPORT

Active intrathecal herpes simplex virus type 1 (HSV-1) and human herpesvirus-6 (HHV-6) infection at onset of multiple sclerosis

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Introduction

Several herpes viruses, including herpes simplex virus type 1 and 2 (HSV-1/2), varicella zoster virus (VZV), Epstein–Barr virus, and human herpesvirus-6 (HHV-6), have been suggested to be implicated in the pathogenesis of multiple sclerosis (MS) (Gilden 2005). We report a case of acute MS preceded by herpes zoster, temporarily associated with intrathecal reactivation of HSV-1 and HHV-6.

Case report

In October 2005, a 22-year-old immunocompetent male presented acute diplopia and paraparesis. Three weeks earlier, he had had fever and emithorax zoster, treated with famciclovir 500 mg tid for 7 days. Neurological examination showed right VI and central VII nerves palsy, lower extremities and left upper limb paresis, generalized hyperreflexia, right T6–T10 superficial hypoesthesia, and bilateral Babinski. Expanded Disability Status Scale (EDSS) score was 6.5. Magnetic resonance imaging (MRI) showed multiple brain and spinal cord lesions, some of which were gadolinium-enhancing (Fig. 1). Standard blood investigations were normal except ESR (31 mm/h) and fibrinogen (492 mg/dl). ANA titre was 1:160; ENA, ANCA, anti-dsDNA, lupus anticoagulant, anti-cardiolipin antibodies, C3, C4, thyroid function, vitamin B_{12}, and folate were normal. Anti-HIV-1/2 antibodies were negative, and CD4+ cell count was 2,724/μL. CSF examination revealed high HSV-1 and HHV-6 DNA copy numbers (Table 1). Electroencephalogram was normal; visual evoked potential (VEP) showed a prolonged left P100 latency.

Intravenous methylprednisolone 1 g/day was given for 10 days and intravenous aciclovir 10 mg/Kg tid for 3 weeks, with nerves palsy recovery and paraparesis improvement. After 12 days of aciclovir, HSV-1, but not HHV-6 DNA, was cleared from CSF (Table 1). In January 2006, the patient was asymptomatic except for post-herpetic neuralgia. Neurological examination showed superficial right T6–T10 hypoesthesia, hyperreflexia, right Babinski, and slight paraparesis. EDSS was 2. Brain and spinal MRI revealed disappearance of D5–D6 lesions and lack of enhancement of the other lesions. In March, HSV-1 DNA was undetectable in CSF, and HHV-6 DNA level had further decreased (Table 1).

In July 2006, brain MRI showed a new, non-enhancing, T2-hyperintense lesion, with the patient clinically stable. In November 2006, the patient presented paresthesia of the hands and cephalalgia. Brain MRI showed three new lesions, two of which were

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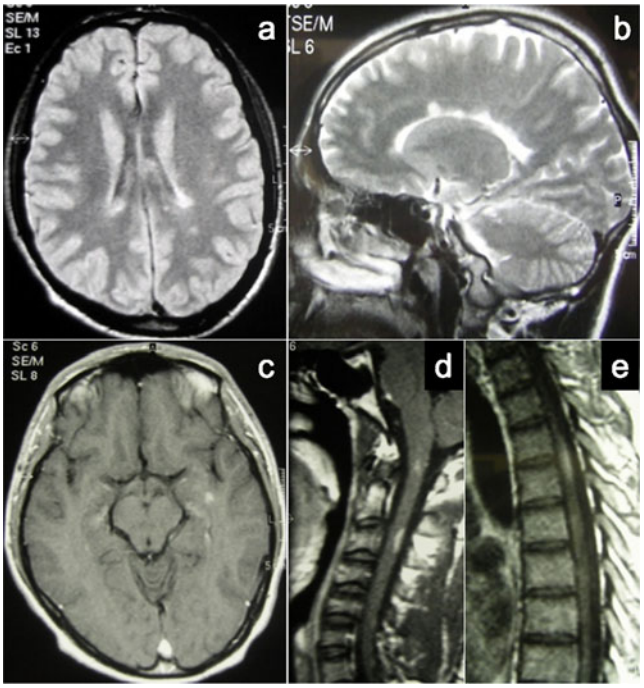

Fig. 1 Magnetic resonance imaging (MRI) at the onset of symptoms. **a** Brain axial proton density sequence showing hypointense lesions of the right periventricular region. **b** Brain sagittal T2-weighted sequence showing multiple hyperintense lesions involving periventricular white matter and corpus callosum. **c** Brain, **d** cervical, and **e** dorsal spinal cord T1-gadolinium-enhancing lesions

gadolinium-enhancing. Low level HHV-6, but not HSV-1 DNA, was detected in CSF (Table 1). Intravenous methylprednisolone 1 g/day was administered for 5 days, followed by clinical improvement and disappearance of MRI enhancement. At this time, the patient fulfilled McDonald's criteria for MS, and type b beta-interferon 250 mcg/tiw was started.

In July 2007, MRI showed a new, non-enhancing, T2-hyperintense lesion of the splenium of corpus callosum; EDSS was unchanged, HHV-6 but not HSV-1-DNA was found in CSF (Table 1). In the following months, neurological conditions and MRI remained stable. However, the patient experienced two new zoster episodes (May 2010 and February 2012; Fig. 2), both at the same localization of initial episode and successfully treated with famciclovir. At last visit (February 2012), EDSS was 1, and brain MRI was unchanged. Therapy with interferon-beta is ongoing.

Discussion

This report describes a case of acute MS onset that was preceded by zoster and temporarily coincided with high HSV-1 and HHV-6 DNA intrathecal levels. HSV-1 detection in CSF is diagnostic of HSV-1 encephalitis (HSE), resulting from virus replication in brain cells. Clinical, EEG, and MRI findings excluded classical HSE in our patient. Multiphasic acute disseminated encephalomyelitis (ADEM) was also considered unlikely because of lack of diagnostic criteria, i.e., encephalopathy, CSF pleocytosis, and absence or transitory presence of intrathecal oligoclonal bands (OCBs) (Tenembaum et al. 2007).

Several studies, including a survey of 54 cases from our Neurological Clinic, failed to identify HSV-1 DNA in the CSF of acute or stable MS patients (Martin et al. 1997; Alvarez-Lafuente et al. 2008; Franciotta et al. 2009; Mancuso et al. 2010). However, Bergstrom et al. reported a case similar to ours, with HSV-1 isolated from CSF and intrathecal anti-HSV-1 antibodies at onset of relapsing–remitting MS. As in our patient, HSV-1 was not isolated from CSF at follow-up (Bergström et al. 1989).

Higher detection rates of HHV-6 DNA in CSF, plasma, peripheral blood cells, or brain tissue of MS patients or of higher virus-specific IgG or IgM in CSF or serum suggested associations between HHV-6 and MS (Gilden 2005).

Table 1 Patient's CSF and plasma pattern at baseline and at follow-up

Date	CSF PCR (c/mL)		Plasma PCR (c/mL)		CSF cells/mm^3	CSF-serum albumin percentage transfer	Virus-specific IgG index			IgG oligoclonal bands [a]	
	HSV-1	HHV6	HSV-1	HHV-6			HSV-1	HSV-2	VZV	CSF	Serum
October 2005	26,790	58,500	n.d.	n.d.	4	0.6	3.8	<0.5	3.1	+	−
November 2005[b]	<200	10,900	<200	8,230	13	0.4	3.0	<0.5	2.9	+	−
March 2006	<200	676	<200	1,060	0	0.2	3.0	<0.5	2.5	+	−
November 2006	<200	1246	<200	3020	0	0.2	3.5	<0.5	3.0	+	−

OCTOBER 2005: Serum anti-HSV-1 and anti-VZV IgG: positive; serum anti-HSV-2 IgG, anti-HSV-1/2 and VZV IgM, HBsAb, anti-HCV and anti-borrelia IgG and IgM: negative, Herpes simplex virus type-2, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, and human herpesvirus 8 DNA were all undetectable at each time point. Normal values: PCR <200 c/mL; CSF-serum albumin percentage transfer <0.8; IgG index <0.5. PCR <200 c/mL; CSF-serum albumin percentage transfer; virus-specific IgG index <0.5.

n.d. not determined, + present, − absent

[a] Determined by isoelectrofocusing

[b] Following 12 days of intravenous aciclovir

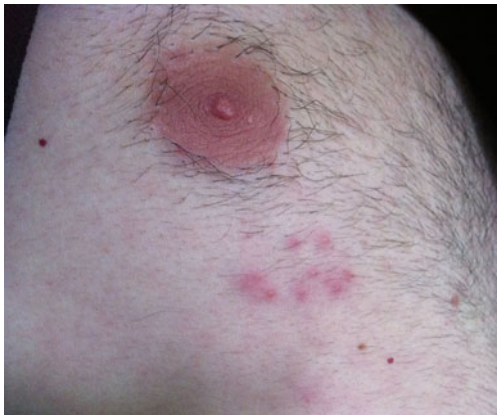

Fig. 2 Herpes zoster of the right emithorax in February 2012

However, these findings were inconsistent, and a causative relationship was not demonstrated. In our case, CSF HHV-6 might have either originated intrathecally or from the blood, as suggested by concomitant high level in plasma. In any event, clinical picture improved despite persistent HHV-6 replication in CSF and plasma, suggesting that HHV-6 infection was unlikely to sustain the disease.

In our case, the presence of OCBs and abnormal VEP at onset suggest that the underlying pathological process might have initiated before the clinical manifestations. Our patient had zoster 3 weeks before onset of symptoms, and thus a common, unknown stimulus might have triggered VZV, HSV-1, and HHV-6 from their sites of latency, leading to diseases distinct in time, localization, and clinical manifestations: herpes zoster resulting from reactivation and spread of VZV to the periphery, and neurological disease consequent to virus spread into CNS.

Although the role of these viruses in triggering MS in our patient remains speculative, there are observational and experimental clues supporting the hypothesis that viral infections might lead to brain damage, including demyelinating disease. Several human neurological diseases might originate from an immune-mediated reaction to HSV-1 antigens, including HSE relapse (Sköldenberg et al. 2006), ADEM (Kaji et al. 1996) and Bell's paralysis (Theil et al. 2003). In animals, peripheral HSV-1 inoculation causes multifocal CNS demyelination, resembling MS (Kastrukoff et al. 1987), and a novel gamma-2-herpesvirus has recently been isolated from brain lesions in primates with Japanese macaque encephalomyelitis, a spontaneous MS-like disease (Axthelm et al. 2011). Potential triggering mechanisms might involve the production of proinflammatory cytokines, e.g., interferon-gamma, which might activate "encephalitogenic" T cells (Panitch et al. 1987; Wekerle 1998).

Why, in our patient, HSV-1 did not cause the extensive tissue injury of HSE might have resulted from reduced neurovirulence of the HSV-1 strain. Indeed, the CSF strain of the case described by Bergström et al. (1990) replicated slowly in neuronal cell cultures and showed reduced neurovirulence in a mouse model compared with strains of patients with encephalitis or oral lesions.

In conclusion, our observation supports the hypothesis that an active viral infection of the CNS could trigger MS. The prompt use of antivirals and corticosteroids might have reduced viral burden and the extent of immunopathological injury.

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