Baló’s concentric sclerosis associated with primary human herpesvirus 6 infection

D Pohl, K Rostasy, B Krone, F Hanefeld

Background: Baló’s concentric sclerosis (BCS) is a demyelinating disorder believed to be a rare variant of multiple sclerosis (MS). Human herpesvirus 6 (HHV-6) is a highly neurotropic virus causing severe central nervous system (CNS) infections predominantly following reactivation of latent HHV-6 in immunocompromised individuals. Primary infection with HHV-6 usually occurs in early childhood manifesting as exanthema subitum. The clinical spectrum of primary infection in adolescents or adults has not yet been evaluated.

Case report: A previously healthy 13 year old girl developed acute hemianopsia and anoma 5 days after an episode of fever and malaise of unknown origin. Cerebral MRI revealed three white matter lesions, one with ring-like contrast enhancement. Lumbar puncture showed mononuclear pleocytosis of 30 cells/μl, oligoclonal IgG, and a normal protein level. Follow up cerebral MRI scans revealed lamellar concentric hemispheric lesions characteristic of BCS. The first neurological symptoms of the patient coincided with primary HHV-6 CNS infection, diagnosed by a positive PCR test of the CSF together with seroconversion. Response to antiviral and corticosteroid treatment was only temporary, but immunoglobulin treatment has so far been followed by clinical stability for 30 months.

Conclusions: To our knowledge, this is the first report both of an association between HHV-6 and BCS and of immunoglobulin treatment of BCS. A late primary infection with HHV-6 might be associated with BCS. Further studies in patients with this rare disease are needed to confirm this association and to evaluate the efficacy of antiviral and immunoglobulin treatment.

CASE REPORT

A 13 year old girl presented on 8 February 2001 with acute right sided hemianopsia and anoma 5 days after a 4 day episode of fever and malaise of unknown origin. Cerebral MRI revealed three white matter lesions, one with ring-like contrast enhancement. Lumbar puncture showed mononuclear pleocytosis of 30 cells/μl, oligoclonal IgG, and a normal protein level. Bacterial CSF cultures were negative. Under a presumptive diagnosis of encephalitis, treatment with acyclovir, ceftriaxone, and prednisolone was administered without benefit. Over the next 4 weeks, there was gradual clinical deterioration with severe headache, repetitive vomiting, and intermittently impaired consciousness. A repeat MRI showed a striking enlargement of the lesions with garland-like contrast enhancement (fig 1).

On 8 March 2001, when the patient presented at our clinic, she had marked alexia and dyscalculia in addition to the pre-existing symptoms. Screening for infectious diseases revealed HHV-6 positive IgM and negative IgG antibody titres and HHV-6 DNA in the serum. Concomitantly, HHV-6 DNA was detected in the CSF specimen obtained at the beginning of the disease. Table 1 provides a synopsis of the clinical and HHV-6 findings in the disease course.

Other serological and PCR findings were unremarkable, including serum antibodies to human immunodeficiency virus (HIV) type 1 and 2, herpes simplex virus (HSV) type 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), tick borne encephalitis (TBE) virus, measles, mumps, Borrelia burgdorferi, Treponema pallidum, Mycoplasma pneumoniae, and Toxoplasma gondii as well as PCRs for HSV and EBV in the CSF.

The patient was treated with methylprednisolone (1 g/day for 5 days with consecutive tapering) and, in view of the HHV-6 CNS infection, with foscarnet (Foscavir) for 3 weeks. Her anoma, alexia, and acalculia improved, but the hemianopsia remained unchanged. After 3 weeks of foscarnet treatment, no HHV-6 DNA was detectable in CSF or serum.

At the beginning of September 2001, after a clinically stable period of 6 months (attending school), the girl developed difficulties with spatial orientation, inappropriate smiling, and increased appetite. Cerebral MRI revealed three white matter lesions with concentric alternating rings of myelin preservation and loss. There is still controversy about whether BCS represents a variant of multiple sclerosis; TBE, tick borne encephalitis; VZV, varicella zoster virus; IFA, immune fluorescence assay; IVIG, iv immunoglobulins; MS, multiple sclerosis; TBE, tick borne encephalitis; VZV, varicella zoster virus

Abbreviations: BCS, Baló’s concentric sclerosis; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFA, immune fluorescence assay; IVIG, iv immunoglobulins; MS, multiple sclerosis; TBE, tick borne encephalitis; VZV, varicella zoster virus
the now garland-like contrast enhancing new lesion (fig 1). The patient received a second high dose methylprednisolone pulse (5 to 10 October 2001) without clinical benefit. On 12 October 2001, she experienced a first complex-partial seizure.

At that point treatment with immunoglobulins (monthly 2 g/kg iv over 4 days for 8 consecutive months) was started. Under this therapeutic regimen there was marked clinical improvement and even 30 months after the immunoglobulin treatment was discontinued, no new lesions were detected in regular follow up MRI scans (fig 1).

**Table 1 Clinical history of the patient and evidence for HHV-6 infection**

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical presentation</th>
<th>CSF PCR</th>
<th>Serum PCR</th>
<th>HHV-6 antibody titres</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/02/01</td>
<td>Hemianopsia, anomaia</td>
<td>Positive</td>
<td>ND</td>
<td>IgG negative, IgM 1:10</td>
</tr>
<tr>
<td>09/03/01</td>
<td>Alexia, dyscalculia</td>
<td>ND</td>
<td>Positive</td>
<td>IgG 1:40, IgM 1:40</td>
</tr>
<tr>
<td>20/03/01</td>
<td>Clinical improvement</td>
<td>Negative</td>
<td>Negative</td>
<td>IgG 1:80, IgM negative</td>
</tr>
<tr>
<td>12/04/01</td>
<td>Clinical stability</td>
<td>Negative</td>
<td>Negative</td>
<td>IgG 1:160, IgM negative</td>
</tr>
<tr>
<td>20/09/01</td>
<td>Impaired orientation, inappropriate smiling</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

Our patient with BCS had a concomitant CNS infection with HHV-6. While the viral association could be just coincidental, several arguments point to a possible role of HHV-6 in BCS: HHV-6, the causative agent of exanthem subitum, is a virus with great neuroinvasive potential. It has been shown to cause encephalitis and has been associated with other acute neurological processes such as febrile seizures, meningitis, Guillain-Barré syndrome, Bell’s palsy, transverse myelitis, acute disseminated encephalomyelitis, and fulminant demyelinating encephalomyelitis. Severe neurological symptoms predominantly occur following reactivation of latent HHV-6 in immunocompromised and, less often, in immunocompetent individuals. Several reports suggest HHV-6 is involved in the pathogenesis of MS, a chronic demyelinating disease with a clinical picture similar to BCS in some cases. Remarkably, a viral pathogenesis is suggested for the immunopathogenic subtype III in MS, and this subtype resembles the pathological appearance of BCS.

As almost all infections with HHV-6 occur in early childhood, primary infection with the virus in puberty or even later is an uncommon event and, apart from a severe infectious mononucleosis-like syndrome, the possible clinical variability of such a late primary infection has not yet been comprehensively described. To our knowledge, we present for the first time a patient with late primary HHV-6 infection associated with CNS demyelination. Possible mechanisms explaining virally induced myelin damage in our patient include autoimmunological processes such as molecular mimicry with activation of autoreactive T cells recognizing homologous amino acid sequences of the virus and myelin proteins. Remarkably, cross reactivity with HHV-6 and myelin basic protein was recently described.

BCS is being treated empirically with corticosteroids, but in our patient there was no obvious therapeutic effect with high dose methylprednisolone during the second attack of the disease. With reference to therapy for other immune mediated processes, we started treatment with pulsed iv immunoglobulins (IVIG), which led to long lasting remission even after termination of IVIG therapy. Whether this was due to treatment effect or natural disease course is difficult to assess. In any case, in view of the poor prognosis of BCS, we propose IVIG as another therapeutic option, especially in patients who do not respond to corticosteroids.

The present case indicates that a late primary infection with HHV-6 might be associated with BCS. Further studies in patients with this rare disease are needed to confirm this association and to evaluate the efficacy of antiviral and immunoglobulin treatment.

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Competing interests: none declared

Informed consent was obtained for the publication of details concerning the patient described in this study

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Received 30 December 2004
Revised version received 21 March 2004
Accepted 3 April 2005

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J Neurol Neurosurg Psychiatry 2005 76: 1723-1725
doi: 10.1136/jnnp.2004.062331

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