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 anosmia 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 anosmia 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 anosmia, 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 a new lesion without contrast enhancement. Lumbar puncture performed on 20 September 2001, again showed mononuclear pleocytosis of 26 cells/µl, oligoclonal IgG, and a normal protein level. DNA detection by PCR for HHV-6, HSV, and EBV was negative.

Despite high dose methylprednisolone and foscarnet treatment, there was further clinical deterioration. A control MRI 2 weeks later (1 October 2001) showed enlargement of existing lesions.

**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).

**Virolological and serological studies**

Antibodies against HHV-6 were detected in an indirect immune fluorescence assay (IFA) (Viramed, Planegg/Steinkirchen, Germany). Antibodies against other viruses and bacteria were analysed using standard technique IFA (EBV IgM-anti-VCA, IgG-anti-VCA, and IgG-anti-EA), anti-complementary immune fluorescence (EBV anti-EBNA), ELISA (HIV, HSV, VZV, CMV, TBE, measles, mumps, B burgdorferi, T gondii), complement fixation (M pneumoniae), and particle agglutination (T pallidum). Viral DNA for PCR amplification was extracted from CSF and serum with a QIAamp DNA blood kit (Qiagen, Hilden, Germany). DNA sequences of HHV-6, HSV, and EBV were amplified in PCR with Oligo Detect (Chemicon Light Diagnostics, Temecula, CA, USA).

**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 autoimmune immunological processes such as molecular mimicry with activation of autoreactive T cells recognising 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.

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

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

ND, not determined.

**Figure 1** Paired axial MRI images 4 weeks after disease onset (A), during the second attack 7 months later (B), and at remission 2 years later (C). Upper row: The FLAIR weighted images show typical large lesions with concentrically alternating hypo- and hyperintense lamellae during the two acute attacks (A, B) and a marked regression of the lesions 2 years later (C). Lower row: T1 weighted images after administration of gadolinium-DTPA show the characteristic garland-like lesion enhancement during the acute attacks, whereas there was no enhancement in the follow up scan (C).

**Authors’ affiliations**

D Pohl, K Rostasy, F Hanefeld, Department of Paediatrics and Paediatric Neurology, Georg August University, Robert-Koch-Str. 40, 37075 Goettingen, Germany

B Krone, Department of Virology, Georg August University, Kreuzbergring 57, 37075 Goettingen, Germany
Competing interests: none declared

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

Correspondence to: Daniela Pohl, Department of Paediatrics and Paediatric Neurology, Georg August University Goettingen, Robert-Koch-Str. 40, 37075 Goettingen, Germany; dpohl@med.uni-goettingen.de

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