Epstein-Barr Virus Infections of the Central Nervous System

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Abstract

Objective Epstein-Barr virus (EBV), a lymphotropic herpes virus causing infectious mononucleosis (IM), also causes various central nervous system (CNS) infections. In the present study, EBV CNS infections were investigated.

Patients and Methods For adult inpatients in our hospital and related hospitals between 1984–2002, CNS syndromes with IM symptoms were examined, and serologic positives were assessed according to established criteria. Polymerase chain reaction (PCR) was performed for cerebrospinal fluid (CSF) from seven patients.

Results Ten patients with EBV-related CNS infections were found; their mean age was 36 years (20–79 years). The neurologic forms were as follows: acute encephalitis (4 patients), acute cerebellar ataxia (1), acute disseminated encephalomyelitis (ADEM) (2), myelitis (1), and meningitis (2). The PCR from CSF was positive in two patients with meningitis, one patient with ADEM, and one patient with encephalitis-associated chronic EVB infection. One case of encephalitis and another of relapsing ADEM were attributed to chronic EVB infection.

Conclusion Our study identified a variety of EBV-related CNS infections. EBV CNS infections are divided into two groups: 1) CNS syndromes associated with primary EBV or reactivated infection, and 2) those associated with chronic EBV infection; it is notable that in the former, diverse CNS syndromes including ADEM can occur, whereas in the latter, chronic or recurrent CNS syndromes are produced.

Key words: encephalitis, acute disseminated encephalomyelitis, myelitis, meningitis, Epstein-Barr virus, chronic infection

Introduction

Infectious mononucleosis (IM) due to Epstein-Barr virus (EBV) is characterized by fever, eruption, atypical lymphocytes in the peripheral blood, tonsilar and lymph node swelling, and liver dysfunction (1). As the prevalence of serologic tests and PCR studies for EBV indicates, the clinical spectrum for EBV-related disorders is expanding to include chronic active EBV infection, Burkitt’s lymphoma, and central nervous system (CNS) lymphoma (2–4). Sometimes, EBV produces a broad range of CNS infections such as demyelinating disease, acute encephalitis, acute cerebellar ataxia, myelitis, or meningitis (5–13). Individual cases of these infections have been reported. Previously, we have also described cases of acute disseminated encephalomyelitis (ADEM) and meningitis (14, 15). However, to date, a large number of EBV CNS infections have not yet been analyzed. We investigated EBV CNS infections in our hospital and related hospitals.

Patients and Methods

CNS syndromes with IM symptoms consisting of fever, eruption, tonsillitis, lymphadenopathy, and/or hepatosplenomegaly were examined in adult inpatients between 1984–2002 in our department at Kurume University Hospital and in related hospitals. Clinical data including atypical lymphocytes and Paul-Bunnell test results were analyzed for each patient.

Diagnosis of acute encephalitis, ADEM, meningitis, myelitis, and cerebellitis (acute cerebellar ataxia) is based mainly on neurologic findings such as fever, meningeal signs, cerebral or spinal cord symptoms, and cerebrospinal (CSF) changes. Affected areas were evaluated by computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalogram (EEG). In particular, ADEM was diagnosed by multiple brain and/or spinal cord lesions on MRI.
and CSF findings (16, 17); for diagnosis, MRI T2, FLAIR signal hyperintensity had to be present in at least two locations with an elevated MBP level in CSF (normal level, <4.0 ng/ml).

A serologic positive when EBV-related antibodies were demonstrated was based on the following criteria (18, 19): 1) the presence of the EBV viral capsid antigen (VCA) IgM antibody, then negative; 2) a 4-fold or greater increase in the EBV VCA IgG during the disease course; 3) a transient elevation of the EBV early antigen (EA); or 4) \( \geq 1:320 \) of EBV VCA IgG levels without the EB nuclear antigen (NA) antibody, followed by an increase of EBNA. In addition, persisting \( \geq 1:1,280 \) of EBV VCA antibody with \( \geq 1:40 \) of EA diffuse or restricted (DR) over 3 months was regarded as indicative of a chronic active EBV infection (20, 21). The antibody assay of EBV was made by the indirect immunofluorescent method (Special Reference Laboratory, Tokyo).

Polymerase chain reaction (PCR) was performed for the CSF in seven patients. CSF was subjected to capillary PCR (22, 23). The PCR analysis was performed with 1 μl of extracted DNA from a 50 μl sample of CSF. The primers for the EBNA1 gene were those described by Telenti et al (23), using the sequences: 5'-GTGATCATCATCCGGGTCTC for the plus strand, and 5'-TTGCGGTGAACCTTCTTG for the minus strand. Products of the PCR were visualized with UV light by staining with ethidium bromide after gel electrophoresis, and EBV DNA was detected as a specific 220-bp band.

### Results (Table 1)

Ten patients with EBV-related CNS infections were found; their mean age was 36 years (20–79 years), with a 5:5 male:female ratio. The ten patients were observed for the past 18 years at facilities in Kurume City and surrounding areas, which encompass a population of approximately 1,000,000 people. The neurologic forms were as follows: acute encephalitis (cases 2, 3, 6, and 9), acute cerebellar ataxia (case 1), ADEM (cases 4 and 10), myelitis (case 5), and meningitis (cases 7 and 8). All patients presented with IM or IM-like syndromes such as eruption, tonsilitis, cervical lymphadenopathy, and so on. Atypical lymphocytes in blood were observed at a mean of 14.4% in the range of 3–47%, and were not observed in CSF. The Paul-Bunnell test results were primarily low values from 16x to 32x, except in case 3, which showed a value of 128x.

Serologic responses showed primary or reactivated infection with the presence of EBV VCA IgM or an elevation of

### Table 1. The 10 Cases of EBV-related Central Nervous System Infections, 1984–2002

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex (years)</th>
<th>Onset</th>
<th>Neuropsychic symptoms</th>
<th>Diagnosis</th>
<th>Days after onset</th>
<th>EBV VCA IgG, IgM (EA DR, EBNA)</th>
<th>CSF cells/mm³</th>
<th>serum ab/CSF ab</th>
<th>MBP ng/ml</th>
<th>PCR</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/M</td>
<td>1.‘84</td>
<td>l.t.ataxia</td>
<td>Acute cerebellar ataxia</td>
<td>10</td>
<td>160 (640)**, &lt;10&lt;10</td>
<td>3</td>
<td>320 &lt;4</td>
<td>n.d.</td>
<td>absent</td>
<td>(-) moderate</td>
</tr>
<tr>
<td>2</td>
<td>25/M</td>
<td>12.‘84</td>
<td>delirium</td>
<td>Encephalitis</td>
<td>12</td>
<td>320, 10</td>
<td>54</td>
<td>100 (160)**, &lt;10</td>
<td>n.d.</td>
<td>mild</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29/F</td>
<td>4.‘84</td>
<td>tremor</td>
<td>Encephalitis</td>
<td>20</td>
<td>640, 10</td>
<td>62</td>
<td>100 (160)**, &lt;10</td>
<td>n.d.</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25/F</td>
<td>6.‘87</td>
<td>somnolence</td>
<td>relapsing ADEM</td>
<td>20</td>
<td>1,280 (640)**, 10</td>
<td>20</td>
<td>320–160 8.3</td>
<td>n.d.</td>
<td>(-) moderate</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30/F</td>
<td>3.‘91</td>
<td>l.t. abducens palsy</td>
<td>Myelitis</td>
<td>12</td>
<td>20, 10 (80)**, &lt;10&lt;10</td>
<td>5</td>
<td>n.d. &lt;4</td>
<td>(-) severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>79/M</td>
<td>3.‘91</td>
<td>semicoma</td>
<td>Encephalitis</td>
<td>14</td>
<td>640, 10</td>
<td>72</td>
<td>160 (160)**, &lt;10</td>
<td>n.d.</td>
<td>(-) absent</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34/M</td>
<td>5.‘93</td>
<td>myoclonus signs</td>
<td>Meningitis</td>
<td>10</td>
<td>160, 10</td>
<td>66</td>
<td>100 (160)**, &lt;10</td>
<td>n.d.</td>
<td>(-) absent</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20/F</td>
<td>5.‘93</td>
<td>meningeal signs</td>
<td>Meningitis</td>
<td>10</td>
<td>320 (4), 10</td>
<td>102</td>
<td>80–40 &lt;4 (+)-(-) absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>54/F</td>
<td>6.‘97</td>
<td>somnolence</td>
<td>Encephalitis</td>
<td>20</td>
<td>1,280, &lt;10</td>
<td>80</td>
<td>80 &lt;4</td>
<td>(+) absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>42/M</td>
<td>2.‘02</td>
<td>semicoma bulbar sign</td>
<td>ADEM</td>
<td>10</td>
<td>640, &lt;10&lt;10</td>
<td>77</td>
<td>80 5.6</td>
<td>(+)-(-) moderate</td>
<td></td>
<td></td>
</tr>
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</table>

EBV VCA: Epstein-Barr virus viral capsid antigen, EA DR: early antigen diffuse or restricted, EBNA: EB nuclear antigen, CSF: cerebrospinal fluid, MBP: myelin basic protein, PCR: polymerase chain reaction, l.t.: left, n.d.: not done, ADEM: acute disseminated encephalomyelitis, days after onset: serum sample taken after onset of the illness, serum Ab/CSF Ab: serum EBV VCA IgG/CSF EBV VCA IgG ratio, (+): at recovery stage, (++)*: at relapsed time. Case 4 was reported in Neuroradiology 34: 340–342, 1992. Cases 7 and 8 were described in Journal of Neurology, Neurosurgery and Psychiatry 59: 99, 1995. Note: Cases 4 and 9 presented high titers of \( \geq 1:1,280 \) of EBV VCA IgG and \( \geq 1:40 \) of EA DR, respectively, persisting over 3 months.
EBV VCA IgG without EBNA, followed by an increase of EBNA (cases 1–3, 5–8, 10). Two cases revealed chronic EBV infection (cases 4 and 9), in which EBV VCA IgG from 1:1,280 to 1:2,560 persisted with an EBV EA DR over 1:40. However, systemic IM or IM-like symptoms such as atypical lymphocytes and lymphadenopathy did not differ between primary or reactivated EBV infection and chronic active EBV infection. PCR from the CSF was positive in two patients with EBV meningitis (cases 7 and 8), in one patient with ADEM (case 10), and in one patient with encephalitis-associated chronic active EBV infection (case 9). PCR results in cases 7 and 8 were previously described in the *Journal of Neurology, Neurosurgery and Psychiatry* (15).

Four patients with encephalitis (cases 2, 3, 6, and 9) showed consciousness impairment, tremor, myoclonus, and meningeal signs. Case 1 presented acute cerebellar ataxia with subacute necrotizing lymphadenitis, and histologic findings of the left cervical lymph node exhibited scattered necrotic foci. Case 5 showed myelitis consisting of tetraparesis and sensory impairment below the 3rd cervical spine with a significant increase of EBV VCA IgM. Based on the diagnostic criteria, case 4 was diagnosed as having an ADEM. This ADEM patient associated with chronic EBV infection did relapse after a year. The MRI findings were reported separately, in the journal, *Neuroradiology* (14). At relapse time, the EBV genome was negative in CSF by PCR, and MRI abnormalities appeared in the opposite basal ganglia and right white matter, in contrast with the locations in the first attack (Fig. 1). Based on the presence of extensive white matter lesions, and favorable corticosteroid response, the pathogenesis was presumed to be an autoimmune mechanism triggered by chronic EBV infection. Thus, we diagnosed case 4 as relapsing ADEM.

For the seven patients with encephalitis, ADEM, or myelitis, pulse-dose steroids were administered with or without acyclovir. Although all of the patients had a comparatively favorable outcome, one patient with ADEM relapsed after approximately a year. One patient with myelitis had a prolonged course, and three (cases 3, 4, and 9) improved with steroid therapy.

We present here the clinical data of two representative patients, one with encephalitis associated with a chronic EBV infection, the other with EBV-related ADEM.

Case 9 (Fig. 2): A healthy 54-year-old female complained of mild fever, headache, and altered consciousness in June 1997. Two weeks later, she was admitted to a related hospital. Mild consciousness disturbance (Japan Coma Scale 1–2) and meningeal signs were observed. Deep tendon reflexes in the four limbs were normal, and no cerebellar, sensory, or urinary disturbance was observed. Atypical lymphocytes were 7%. Blood chemistry showed normal values, except for a moderate elevation of AST and ALT. Chest, brain CT, and

![Figure 1. MRI of relapsing ADEM associated with chronic active EBV infection (Case 4). A, B. At the time of recurrence, T2-weighted axial MRIs reveal new lesions in the basal ganglia (arrow) opposite those of the initial lesions and in the right temporal and parietal white matter (arrow).](image-url)
MRI were normal. EEG revealed diffuse slow waves. CSF contained 30 cells/mm³, protein 60 mg/dl, and glucose 50 mg/dl. EBV PCR was positive in the CSF. The Paul-Bunnell test result was 16x. Serum EBV VCA IgG was 1:1,280, EBV VCA IgM <1:10, EA DR IgG 1:40, and EBNA 1:20. CSF EBV VCA IgG was 1:16, and EA DR IgG 1:1. Antibodies for herpes simplex virus (HSV) and Japanese encephalitis virus were negative. The patient rapidly recovered after treatment with acyclovir and steroid therapy, and the CSF findings were normalized. Three months later, serum EBV VCA IgG and EA DR IgG still showed high titers of 1:2,560 and 1:40, respectively. The patient was diagnosed as having acute encephalitis associated with chronic EBV infection. She was discharged with mild memory impairment on September 30. Three years later, she had had no sequelae.

Case 10 (Fig. 3): A healthy 42-year-old man complained of headache and common cold-like symptoms in the middle of February 2002, then ran a fever of 39°C and was admitted to a nearby hospital. On February 25, altered consciousness and conjugate deviation to the left side appeared. CSF contained 77 cells/mm³ (92% lymphocytes), protein 425 mg/dl, glucose 66 mg/dl. The patient was transferred to Kurume University Hospital. No lymphadenopathy or atypical lymphocytes in blood were observed. Neurologic examination revealed consciousness impairment (Japan coma scale 10), meningeal signs, facial diplegia, bulbar signs, myoclonus on left upper extremity, tetraparesis, and recto-urinary disturbance. Acyclovir (1,500 mg/day) and antibiotics (cefotaxime) were rapidly initiated. Ten days after admission, skin eruptions were observed on the torso and four limbs. EBV CSF PCR was positive; serum EBV VCA IgG was 1:640, EBNA 1:20 and EA DR <1:10, and Paul-Bunnell test was 32x; HSV complement fixation <1:4. EEG showed predominantly left-side slowness and spike discharges. MRI T2 and FLAIR exhibited multiple lesions at the basal ganglia, white matter, and brainstem (Fig. 4). In the middle of March, the patient’s condition was complicated by aspiration pneumonia; tracheotomy was performed and he was placed on a ventilator. Consciousness impairment was gradually improved, and he was transferred to our department on April 6. Neurologically he still revealed facial diplegia, bulbar signs, moderate weakness predominantly in the lower extremities, right Babinski sign, and recto-urinary disturbances. CSF findings showed 21 cells/mm³, protein 125 mg/dl, glucose 47 mg/dl, and myelin basic protein 5.6 ng/ml. Steroid pulse therapy was conducted. Neurologic symptoms and MRI lesions responded to the steroid therapy. The diagnosis of EBV-related ADEM was made based on EBV PCR positivity and multiple MRI lesions with increased MBP level. The patient was discharged in a wheelchair on May 10.
EBV CNS Infections

<table>
<thead>
<tr>
<th>2002 Feb</th>
<th>Admission</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td></td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

- Acyclovir 1,500 mg/day
- CTX
- CFPM
- CAZ
- mPSL 1,000 mg

Fever
Consciousness impairment
Left conjugate deviation
Bulbar symptoms
Tetraplegia
Sensory disturbance
Urinary disturbance

<table>
<thead>
<tr>
<th>CSF cells (/mm³)</th>
<th>77</th>
<th>167</th>
<th>98</th>
<th>37</th>
<th>23</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (mg/dl)</td>
<td>424</td>
<td>125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV PCR</td>
<td>(+)</td>
<td>(-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV VCA IgG</td>
<td>8</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum EBV VCA IgG</th>
<th>640</th>
<th>320</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>EA DR IgG</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>EBNA</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Figure 3. Clinical course of EBV-related ADEM (Case 10). CTX: cefotaxime, CFPM: cefepime, CAZ: ceftazidime, mPSL: methylprednisolone, CSF: cerebrospinal fluid, PCR: polymerase chain reaction, EBV VCA: Epstein-Barr virus viral capsid antigen, EA DR: early antigen diffuse or restricted, EBNA: EB nuclear antigen.

Discussion

In our study, ten patients with EBV-related CNS infections, including three previously reported patients (14, 15), were observed. In a nationwide survey during the period from 1989 to 1991 in Japan, EBV encephalitis was estimated to occur at a rate of 0.05 cases per year in a population of 1,000,000 (24). The present study for the past 18 years revealed rate of 0.56 cases per year in a population of 1,000,000 in Kurume City and the surrounding areas. However, the number of cases in our study was high in part because we included other neurologic forms such as myelitis and meningitis.

The EBV CNS infections were varied, and included acute encephalitis (4 patients), acute cerebellar ataxia (1), ADEM (2), myelitis (1), and meningitis (2). Serologic response was divided into two groups: one comprised of eight patients who revealed primary or reactivated infection based on the presence of EBV VCA IgM or ≥1:320 of EBV VCA IgG levels without the EB nuclear antigen (NA) antibody, followed by an increase of EBNA, and the other two patients who exhibited chronic active infection with persisting ≥1:1,280 of EBV VCA IgG and EBV EA DR at over 1:40. EBV-related CNS infections may be classified into two groups (Table 2): 1) CNS syndromes associated with primary EBV infection or reactivated infection, and 2) those associated with chronic active EBV infection.

In the literature, cases of EBV CNS syndromes associated with primary or reactivated infection, including the cases in our study, encephalitis and acute cerebellar ataxia are the most common (8–13, 25–29). With regard to the pathogenesis of EBV-related CNS infections, Imai et al (9) and Landgren et al (10) have suggested direct EBV infection as a cause based on the presence of the EBV genome, which was revealed by PCR in the CSF of the meningoencephalitis cases. In our two cases of meningitis, and in the case of ADEM associated with primary or reactivated EBV infection, EBV genome was detected in the CSF by PCR, and several other reports of PCR detection have appeared in the literature (28). Our acute encephalitis cases seem likely to belong to this group. On the other hand, Ito et al (12) demonstrated antineural antibodies in the sera of patient with acute...
cerebellar ataxia associated with EBV infection, which finding is suggestive of immunologic processes following EBV infection. Considering that our acute cerebellar ataxia and myelitis cases (cases 1 and 5) showed favorable response to corticosteroid treatment, lack of CSF pleocytosis and intrathecal antibody production, and so on, these two cases may be regarded as having similar postinfectious pathogenesis.

Recently, several cases of ADEM with or without radiculopathy have been reported (30–33). Tselis et al (30) reported a case of encephalomyelitis confirmed by serologic test and PCR, and Merelli et al (31) reported encephalomyelitis as a new syndrome with transverse myelitis and less severe encephalitis and radiculopathy. Although IM or IM-like symptoms in our ADEM case (case 10) were unclear, except for the presence of delayed rash, the lack of systemic IM symptoms in such patients should be noted. The pathogenesis may suggest more direct EBV infection, based on the findings of CSF PCR positivity and predominantly gray matter involvement in our case 10. At the same time, EBV serologic tests and PCR results should be checked to screen for patients with idiopathic ADEM.

It is especially noteworthy that two of our cases can be attributed to chronic active EBV infection. Although one of these cases was acute encephalitis, one patient showed relapsing ADEM with MRI abnormalities in the basal ganglia, midbrain, and extensive white matter. To the best of our knowledge, several EBV CNS syndromes associated with chronic active EBV infection have been reported. Neumann et al (34) reported three patients with chronic encephalitis associated with the laboratory findings of chronic EBV infection, although detailed data is not available. Adachi et al (35)
reported an adult case of chronic meningoencephalitis persisting over a period of several months, and Suzuki et al (unpublished data, June 2001) studied an adult case of recurrent neurologic deficits with chronic active EBV infection. An adult case of recurrent meningitis has been previously described (36). Frequent production of chronic or recurrent CNS syndromes may be characteristic of CNS infections associated with chronic active EBV infection.

Recently, Morita et al (37) reported three infantile cases of chronic active EBV infection with symmetrical calcification in the basal ganglia as well as hypersensitivity to mosquitoes and an increased number of NK cells. Caruso et al (38) reported a persisting, preceding focal neurologic defect that probably followed primary EBV infection. However, the former did not reveal any inflammatory findings such as CSF pleocytosis, and the latter did not show signs of chronic active EBV infection. Thus, further cases should be investigated to determine whether these forms of CNS syndrome belong to the same group associated with chronic EBV infection.

Regarding treatment, acyclovir and corticosteroids are recommended for EBV CNS infections, though the efficacy of acyclovir in EBV infections is not established. All of our patients, including those with chronic EBV infections, had comparatively favorable outcomes; one patient with ADEM did relapse after about a year, but this case and our case 9 have experienced no specific sequelae 3 years since onset. Generally, chronic active EBV infection has a poor prognosis; Yamashita et al (39) reported a fatal case of acute cerebellar ataxia and encephalitis accompanying chronic active EBV infection, and Kawa-Ha et al (40) reported the usefulness of interleukin 2 in the treatment of chronic EBV infection.

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References


