Epstein–Barr virus myeloradiculitis and encephalomyeloradiculitis

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Summary
We provide a comprehensive clinical, radiological and virological analysis of four patients with Epstein–Barr virus (EBV) infection of the nervous system. One patient developed acute myeloradiculitis, one had acute encephalomyeloradiculitis, one had acute meningoencephalomyeloradiculitis and one had a subacute meningo-myeloradiculitis. The ability of EBV to affect multiple parts of the entire neuraxis from meninges and brain to the spinal cord and peripheral nerves was evidenced by combinations of stiff neck and mental status changes, as well as patterns of weakness and sensory loss due to transverse myelitis or peripheral nerve disease. The CSF of all four patients contained a pleocytosis, predominantly mononuclear with elevated levels of protein, but a normal glucose level. In the two patients with acute myeloradiculitis and subacute meningo-myeloradiculitis, the MRI revealed an increased signal in the spinal cord and lumbosacral roots, but in the two patients with acute encephalomyeloradiculitis and acute meningoencephalomyeloradiculitis, the brain and spinal cord MRIs were normal. In all four patients, EBV DNA, but not cytomegalovirus (CMV), herpes simplex virus (HSV) or varicella-zoster virus (VZV) DNA, was found in the CSF. The antibody pattern in serum was consistent with recent infection, and both EBV immunoglobulin (Ig) M and IgG antibodies, but not antibodies to HSV, VZV or CMV, were found in the CSF. Finally, there were reduced serum/CSF ratios of antibody to EBV, but not to total IgG or albumin, consistent with intrathecal antibody synthesis. None of the four patients died and none had brain swelling or focal changes according to brain MRI. Residual neurological deficits were evident. The two patients with acute myeloradiculitis and acute meningo-myeloradiculitis had residual lower extremity weakness, and one of these patients later developed optic neuritis. The patient with acute encephalomyeloradiculitis had a moderate flaccid paraparesis, and the patient with subacute meningo-myeloradiculitis was left with sensory loss in the feet. Compared with neurological disease caused by other herpes viruses, the clinical features of acute EBV myeloradiculitis, encephalomyeloradiculitis, encephalomyeloradiculitis and subacute meningo-myeloradiculitis are distinctive. Of the eight human herpesviruses, EBV and VZV produce the most protean neurological syndromes. The mechanism by which EBV produces neurological disease is unknown. More correlative pathological, virological and immunological studies are needed in EBV-associated neurological disease.

Keywords: Epstein–Barr virus; encephalomyeloradiculitis; myeloradiculitis

Abbreviations: CMV = cytomegalovirus; EBNA = Epstein–Barr virus nuclear antigen; EBV = Epstein–Barr virus; ESR = estimated sedimentation rate; HSV = herpes simplex virus; Ig = immunoglobulin; MNC = mononuclear cells; PCR = polymerase chain reaction; PMN = polymorphonuclear cells; VCA = viral capsid antigen; VZV = varicella-zoster virus; WBC = white blood cells
Introduction
Primary Epstein–Barr virus (EBV) infection frequently results in infectious mononucleosis and, rarely, it produces a chronic active infection. EBV is also associated with nasopharyngeal carcinoma, Burkitt’s lymphoma, Hodgkin’s disease and lymphoproliferative disease in immunocompromised individuals. The wide range of clinical disorders produced by EBV, including molecular virological and immunological features of EBV, have recently been reviewed (Cohen, 2000).

The association of neurological disease with infectious mononucleosis was first documented 70 years ago (Epstein and Dameshek, 1931; Johansen, 1931) and has been extensively reviewed by Gautier-Smith et al. (1965). The exact incidence of neurological complications due to EBV is unknown, but has been estimated to occur in 1.0–5.0% of individuals with infectious mononucleosis. Despite the relatively low frequency of complications, CSF abnormalities have been found in >25% of cases (Silverstein et al., 1972). Given the widespread prevalence of human EBV infection throughout the world, the burden of neurological disease associated with EBV is probably underestimated. For example, virtually all CNS lymphomas in AIDS (acquired immune deficiency syndrome) patients contain EBV DNA (MacMahon et al., 1991).

EBV produces disease of both the CNS and peripheral nervous system. Most of the documentation has been provided by individual case reports of meningitis, encephalitis, myelitis or neuropathy, usually associated with a positive serum heterophil antibody titre. Some reports have also used the finding of EBV antibody in CSF to associate the virus with neuropathy (Bennett et al., 1996), myelitis (Feinberg et al., 1984) and encephalitis (Paskavitz et al., 1995). Most recently, polymerase chain reaction (PCR) technology has been used to help diagnose neurological disease produced by enteroviruses and herpesviruses (Casas et al., 1999). PCR has detected EBV DNA in the CSF of patients with encephalitis (Tsulis et al., 1997), myelitis (Merelli et al., 1997) and neuropathy (Bennett et al., 1996). However, because EBV encephalitis is usually not fatal, the putative site of virus-induced disease in the brain, spinal cord or meninges could not be confirmed until the advent of brain MRI. Herein, we provide a comprehensive analysis of four patients with myeloradiculitis and encephalomyeloradiculitis who were studied clinically and by MRI (Table 1), in conjunction with extensive virological analysis (both PCR and antibody testing) for EBV and other human herpesviruses capable of producing neurological disease.

Material and methods
PCR
Total DNA was extracted from CSF and from EBV-, herpes simplex virus (HSV)-, varicella-zoster virus (VZV)- and cytomegalovirus (CMV)-infected cells in tissue culture (Yamamoto et al., 1991). PCR was carried out using 1 ng of DNA from virus-infected cells and 40 μl samples in triplicate of DNA extracted from the CSF for amplification. DNA was amplified with EBV-, VZV-, HSV- and CMV-

| Table 1 Clinical features of patients with Epstein–Barr virus encephalomyeloradiculitis and myeloradiculitis |
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| Patient | Age | Gender | Diagnosis |
| 1 | 19 | F | Acute myeloradiculitis |
| 2 | 57 | F | Acute encephaloradiculitis |
| 3 | 38 | M | Acute meningoencephalomyeloradiculitis |
| 4 | 42 | F | Subacute meningomyeloradiculitis |

Fever, 2 weeks of progressive leg pain and weakness; hypotonic paraparesis, absent deep tendon reflexes but extensor plantar responses; fine touch, proprioception and pinprick sensation decreased in legs; EMG: normal nerve conduction, but decreased recruitment pattern distally in legs; spinal cord MRI: enhancement in lumbosacral spinal cord and nerve roots bilaterally

3-week history of headache, cough, malaise, fever, somnolence and a flaccid paraparesis with respiratory distress; hypotonic weakness and sensory loss to all modalities in the legs; brain and spinal cord MRI and EMG normal

Malaise, fever, headache, confusion, progressive bilateral leg numbness, weakness and urinary retention; stiff neck, somnolent, inattentive and poor recall; legs paralysed and sensory loss to T10; trace deep tendon reflexes in the legs; brain and spinal cord MRI normal

12-year history of intravenous Ig treatment-dependent common variable immunodeficiency syndrome; 6 weeks of progressive radioculard numbness in legs and perineum up to T8, difficulty walking, urinary urgency, frequency and incontinence; hypotonic legs; increased deep tendon reflexes; decreased sensation to all modalities up to T8 with ataxia secondary to sensory loss; cervical and lumbar spinal cord MRI revealed linear enhancement and multiple small enhancing nodules at C7–T1; brain MRI normal; CSF cytology revealed atypical lymphocytes; cervical leptomeningeal biopsy revealed chronic lymphocytic inflammation
specific primers, and hybridized with radiolabelled internal oligonucleotides as described previously (Devlin et al., 1992). A reaction tube with DNA omitted served as a negative control.

**Antiviral antibody**

**EBV**

Antibodies in CSF to EBV-specific antigens were identified by indirect immunofluorescence using commercial kits (Gull Laboratories, Salt Lake City, UT, USA). Immunoglobulin (IgM and IgG specific for the EBV viral capsid antigen (VCA), Epstein–Barr virus nuclear antigen (EBNA) and IgG to the diffuse and restricted forms of the early antigen were assessed. When both serum and CSF were available, titres were determined simultaneously. To identify IgM against EBV VCA, IgG was removed from serum and CSF by pretreatment with an IgG inactivation reagent (GullSorb, Gull Laboratories) according to the manufacturer’s instructions.

**HSV, VZV and CMV**

An established enzyme immunoassay performed without clinical information was used to identify antibody in serum and CSF to HSV, VZV and CMV (Forghani, 1986).

**Case reports**

**Patient 1 with acute myeloradiculitis**

A 19-year-old woman developed fever of 38.9°C followed by 2 weeks of progressive leg pain and weakness without sphincter problems. Neurological examination revealed a hypotonic paraparesis in the legs with absent deep tendon reflexes but with extensor plantar responses. Fine touch, proprioception and pinprick sensation were decreased in the legs. There were 23 000 peripheral white blood cells (WBCs)/µl, and the erythrocyte sedimentation rate (ESR) was 75 mm/h. The C-reactive protein was 20.7 (normal 0–1). Serum and CSF Lyme titre and serum angiotensin-converting enzyme were negative, and there were no antinuclear antibodies or anti-neutrophil cytoplasmic antibodies. MRI of the cervical and thoracic spine was normal; in the lumbosacral spine, increased signal was seen in the spinal cord and nerve roots bilaterally (Fig. 1). CSF contained 420 WBCs/µl [39% polymorphonuclear (PMN), 61% mononuclear (MNC)]; CSF protein was 204 mg%/ and glucose was 49 mg%. On EMG, the right median and tibial nerve F waves were normal, but there was a decreased recruitment pattern distally in the legs. She was treated empirically with ceftriaxone, 2 g/day, and acyclovir, 1200 mg/day for 14 days. A second CSF examination revealed 48 WBCs/µl (4% PMN, 96% MNC); CSF protein was 82 mg%, glucose was 48 mg% and cytology was normal. During the third week, her strength improved. Neurological examination revealed mild distal leg weakness with normal sensation and reflexes, but both plantar responses were still extensor. Repeat EMG and nerve conduction studies were normal. Fifteen months later, the right anterior tibial muscles were still weak, deep tendon reflexes were reduced in the arms and absent in the legs, but both plantar responses were flexor.

**Fig. 1** Lumbosacral spine MRI with gadolinium enhancement in Patient 1 (acute myeloradiculitis). Arrows denote increased signal in the spinal cord and lumbosacral roots on sagittal (A) and axial (B) views.
Virological studies

PCR showed that both blood MNCs and CSF contained amplifiable EBV DNA, but not HSV, VZV or CMV DNA. In serum, the EBV IgM titre was 1 : 10; EBV VCA IgG was 1 : 5120; EBV EBNA 1 : 640. In CSF, the EBV IgM titre was 1 : 10; IgG VCA 1 : 20; HSV, VZV and CMV IgG negative. Serum/CSF ratios: albumin 102; IgG 178; EBV 1.0; no oligoclonal bands. Serum EBV IgM 1 : 10; IgG VCA 1 : 20; IgG EBNA 1 : 20; HSV, VZV and CMV IgG negative.

Patient 2 with acute encephaloradiculitis

A 57-year-old woman developed headache, cough, malaise, fever, somnolence and mild lower limb numbness and weakness. Over the next 3 weeks, she developed urinary and faecal incontinence and her legs became paralysed. She was also hypothermic with a core temperature of 33°C. Respiratory distress developed necessitating intubation and ventilation. Neurological examination revealed a faccic paraplegia and sensory loss to all modalities in the legs. CSF contained 42 WBCs/µl (4% PMN, 96% MNC); CSF protein was 298 mg% and glucose was 84 mg%. Two brain MRIs, one cervical, thoracic and lumbosacral spinal cord MRI and two EMGs were normal. An EEG showed generalized bi-hemispheric slowing in the theta and delta range with occasional sharp waves in the frontotemporal regions. A second CSF examination revealed 19 WBCs/µl (65% PMN, 35% MNC); CSF protein was 254 mg% and glucose was 137 mg%. She was treated for 14 days with acyclovir and dexamethasone for presumed viral encephalitis. One month later, she was able to walk with the aid of a walking frame and sphincter function had returned to normal.

Patient 3 with acute meningoencephalomyeloradiculitis

A 38-year-old man developed malaise and fever, followed 2 days later by headache, confusion, progressive bilateral leg numbness, weakness and urinary retention. His legs were paralysed, and he had sensory loss up to T10. There were trace deep tendon reflexes in the legs with bilateral flexor plantar responses. CSF contained 68 WBCs/µl (2% PMN, 98% MNC); CSF protein was 77 mg% and glucose was 77 mg%, with no oligoclonal bands. A gadolinium-enhanced MRI of the brain and spinal cord was normal. He was treated empirically with acyclovir and steroids. On the third day, his mental status improved and he regained some leg movement. Two weeks later he was able to walk with assistance. Four months later he developed right optic neuritis. A brain MRI was normal, but an orbital MRI revealed an enhancing right optic nerve. He was treated with intravenous methylprednisolone for 3 days followed by an oral corticosteroid taper, and was placed on intramuscular interferon β-1a once weekly. One year later, he had a residual visual deficit.
right optic neuropathy and moderate loss of position and vibratory sensation in the legs, but was otherwise normal.

Virological studies
PCR showed that the CSF contained amplifiable EBV DNA, but not HSV or VZV DNA. In the CSF, both EBV IgM and IgG antibodies were present, there was no antibody to VZV and HSV IgG was weakly positive (Table 2).

Patient 4 with meningomyeloradiculitis
A 42-year-old woman with a 12-year history of intravenous Ig treatment-dependent common variable immunodeficiency syndrome presented with 6 weeks of progressive radicular numbness in her legs and perineum up to T8, difficulty walking, urinary urgency, frequency and incontinence. Mental status, cranial nerve and arm examination were normal. Her legs were strong, but hypotonic; deep tendon reflexes were increased and both plantar responses were flexor. There was mild decreased sensation to all modalities up to T8 with a mild appendicular ataxia secondary to sensory loss. The blood contained 6200 WBCs/μl, and the ESR was 12. Serum contained no Lyme, HIV or anti-nuclear anti-bodies. Serum IgM and IgG levels, including urine electrophoresis, were normal. Serum angiotensin converting enzyme and serological tests for syphilis were normal. The CSF contained 33 WBCs/μl (100% MNC); CSF glucose was 49 mg%, protein 49 mg%, with a normal IgG index and no oligoclonal bands. Repeat CSF revealed 27 WBCs/μl (98% MNC); CSF glucose was 50 mg% and protein was 41 mg%. CSF culture for aerobic and anaerobic bacteria, mycoplasma and fungi was normal. B- and T-cell flow cytometry and studies of CSF cells for T-cell receptor gene arrangement were normal. Gadolinium-enhanced MRI of the cervical and lumbar spinal cord revealed linear enhancement along its dorsal aspect, particularly in the conus and cauda equina, with prominent multiple small enhancing nodules at C7–T1 (Fig. 2). A gadolinium-enhanced brain MRI was normal. CSF cytology revealed atypical lymphocytes. A cervical leptomeningeal biopsy revealed chronic lymphocytic inflammation. During 3 weeks of hospitalization, her neurological examination was unchanged. She received a 10-day course of intravenous gancyclovir, 5 mg/kg twice daily. Before discharge, a gadolinium-enhanced cervical spine MRI revealed less leptomeningeal enhancement.

Virological studies
Serum EBV IgG antibody was 1 : 640, VCA IgM <1 : 10 and anti-EBNA 1 : 80 (all normal), but there was an elevated antibody titre (1 : 80) to the EBV EA. CSF EBV antibodies were all <1 : 10. PCR showed that both CSF samples contained EBV DNA, but not HSV, VZV or CMV DNA (Table 2).

Discussion
We describe the clinical, CSF, imaging and detailed virological analysis of four patients with combined central and peripheral nervous system disease produced by EBV. None of the patients died, but there were serious neurological deficits after resolution of acute disease.

In Patient 1, both the clinical and radiological findings were characteristic of myeloradiculopathy. The CSF abnormalities further indicated that disease was inflammatory. Extensive virological analysis of serum and CSF revealed the presence of EBV DNA in the CSF (as well as in blood MNC), but no CMV, HSV or VZV DNA in the CSF. Furthermore, the antibody pattern in serum was consistent with recent infection, and both EBV IgM and IgG antibodies, but not antibodies to HSV, VZV or CMV, were found in the CSF. Finally, there were reduced serum/CSF ratios of antibody to EBV, but not to total IgG or albumin, consistent with intrathecal synthesis. The clinical features of myelitis and MRI evidence of increased signal in the spinal cord and lumbosacral roots in this patient were similar to those described by Tselis et al. (1997) in which EBV DNA was found in the CSF. However, unlike our patient, the case in the study by Tselis et al. (1997) had clinical evidence of...
encephalitis and assessment was confounded by the presence of IgM antibody to *Mycoplasma pneumoniae* in the serum, although there was no *M. pneumoniae* DNA in the CSF. Extensive virological studies confirmed EBV-induced myeloradiculitis in our patient.

Patient 2 had an acute neurological disorder characterized by headache and mental status changes, flaccid paralysis, CSF pleocytosis and two very high CSF protein levels. Brain and spinal cord MRIs as well as EMG did not help to localize the neurological deficit. The combined clinical and CSF findings were most consistent with acute encephalitis and neuritis, although coexisting myelitis could not be ruled out. The CSF was weakly positive for HSV IgG, as found in other patients (Gilden et al., 1998). However, the presence of EBV DNA, but not HSV or VZV DNA, as well as EBV-specific IgM and IgG, but not VZV IgG, in the CSF indicated the EBV aetiology of the neurological disease. Unfortunately, serum was not obtained at the same time as the CSF, so serum/CSF ratios could not be calculated. Patient 2 resembles the recent description of two patients with acute encephalopathy and quadriaparesis, both of whom had CSF pleocytosis with abnormal F-wave latencies on EMG and normal distal nerve conductions early in the course of their disease, and a positive EBV serology (Morgenlander, 1996). However, unlike our study, no attempt was made to amplify EBV DNA in that analysis.

Patient 3 had an acute neurological disorder characterized by headache, stiff neck, transient mental status changes and paraparesis with sphincter impairment. The combined clinical and CSF findings were most consistent with acute meningoencephalitis and myelitis (urinary retention and a discrete T10 sensory level). Coexisting neuritis could not be excluded. Brain and spinal cord MRI were normal.

As in Patient 2, the CSF was weakly positive for HSV IgG. However, again, the presence of EBV DNA, but not HSV or VZV DNA, as well as EBV-specific IgM and IgG, but not VZV IgG, in the CSF indicated that EBV caused the neurological disease. Serum was not obtained at the same time as the CSF, so serum/CSF ratios were lacking. Patient 3 resembles the case of encephalomyeloradiculopathy described by Merelli et al. (1997), in which EBV DNA and antibody to EBV were found in CSF; their case was confounded by a rising serum antibody titre to CMV, although there was no CMV DNA or antibody in CSF. In both their case and Patient 3, residual paraparesis and sphincter impairment were observed.

Patient 4 developed a subacute myeloradiculitis involving the cervical and lumbosacral region corroborated by MRI (Fig. 2). No EBV antibody was detected in the CSF. However, EBV DNA, but not HSV, VZV or CMV DNA, was found in CSF on two occasions, along with elevated titres in serum to EBV early antigen (1 : 80). The MRI abnormalities, similar to those found in Patient 1 (Fig. 1), were supported by the leptomeningeal biopsy findings indicating chronic lymphocytic infiltration. Unfortunately, insufficient tissue was available for viral studies.

Of the eight human herpesviruses, EBV and VZV produce the most protean neurological syndromes. EBV may cause aseptic meningitis, encephalitis, myelitis, neuritis or overlapping myeloneuritis, encephalomyelitis or encephalomyeloneuritis. Even among the EBV neuropathies, there are numerous presentations characterized by ophthalmoplegia, lumbosacral plexopathy (Sharma et al., 1993; Steiner et al., 1999), sensory neuropathy (Rubin and Daube, 1999) or autonomic neuropathy (Bennett et al., 1996). In contrast, HSV-1 invasion of the brain produces a focal medial temporal lobe encephalitis. Similarly, HSV-2 usually causes aseptic meningitis (often recurrent) and only rarely causes encephalitis or neuropathy. The most common neurological complication of CMV is radiculoneuropathy, but this usually develops in immunocompromised patients and is often progressive, in contrast to the acute radiculoneuropathy produced by EBV in immunocompetent individuals. Like EBV, VZV produces a wide spectrum of neurological disease, causing encephalitis, myelitis or neuropathy (Gilden et al., 2000). Combined clinical and imaging features distinguish VZV- from EBV-induced disease. For example, VZV produces two forms of 'encephalitis' (Amlie-Lefond et al., 1995). The first is acute contralateral stroke (hemiparesis, aphasia) following trigeminal distribution zoster. The history of zoster and the focal lesion detected by MRI are characteristic of VZV, not EBV. The second form of VZV 'encephalitis' is diffuse small-vessel disease, which occurs mostly in immunocompromised individuals and reveals multifocal infarction on brain imaging. This differs from the normal or mildly swollen brain seen on MRI in immunocompetent patients with EBV encephalitis. Finally, the usual form of VZV neuropathy (zoster) is characterized by dermatomal distribution pain and rash. Even in a recent study that described unusual forms of acute, chronic and recurrent VZV neuropathy unassociated with pain and rash (Fox et al., 2001), only the case of acute neuropathy resembled some patients with EBV neuropathy.

Despite the lack of significant brain swelling or focal changes on MRI of most patients with EBV encephalomyeloradiculopathy, serious residual neurological deficit was present not only in our patients, but also in other patients with documented EBV encephalitis (Paskavitz et al., 1995) and encephalomyeloradiculitis (Merelli et al., 1997). Unfortunately, there is no definitive treatment for EBV infection of the nervous system. Steroids and immunoglobulins have been used, but their effects on disease progression are unknown (Bennett et al., 1996; Gavin et al., 1997). Antiviral agents have not been clinically useful. Lytic EBV infection *in vitro* is sensitive to acyclovir, but this reagent has only limited benefit in patients with acute EBV infection. Similarly, oral acyclovir, used to treat HSV and VZV infection, blocks EBV shedding in the pharynx of patients with infectious mononucleosis but has no effect on the course of disease (Andersson et al., 1985). Finally, the mechanism by which EBV produces neurological disease is unknown. In our patients, the development of neurological
deficit over weeks is consistent with either a subacute to chronic viral infection or a post-infectious process. More correlative pathological, virological and immunological studies are needed in EBV-associated neurological disease.

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References


