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Case Report

Enterovirus associated neurological disease in an HIV-1 infected man

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We report a case of relapsing multifocal neurological disease associated with CNS echovirus 6 infection in an HIV-1-infected individual with no evidence of immunoglobulin deficiency. The illness was initially characterized by optic and cranial neuropathies and myelopathy; concurrent granulomatous hepatitis suggested disseminated viral infection. Treatment with combination nucleoside analogues led to partial remission, but a demyelinating polyneuropathy subsequently developed. There was improvement and sustained remission in the polyneuropathy following treatment with intravenous immunoglobulin. Neurotropic enterovirus infection may be involved in the pathogenesis of certain HIV-associated neurological syndromes.

Keywords: human immunodeficiency virus; central nervous system; enterovirus; immunoglobulin therapy

Introduction

Persistent CNS enteroviral infection is well described in patients with severe immuoglobulin deficiencies (McKinney *et al*, 1987), but has not previously been associated with HIV-1 infection and other disorders of cellular immunity. A variety of neurological syndromes of uncertain etiology can occur early in the course of HIV-1 infection, prior to the onset of severe immunodeficiency, and have been presumed to result from HIV-induced immune dysregulation or auto-immunity (Berger *et al*, 1989; Price, 1996). We communicate here the first reported case of enterovirus-associated neurological disease in HIV infection.

Case Report

A 40-year-old man with previously uncomplicated HIV-1 infection diagnosed in 1990 was admitted to our hospital in October 1993 with a 6 week history of patchy numbness of face, limbs and trunk, headaches and diplopia associated with nausea, weight loss and fevers. He was poorly compliant with an antiretroviral regimen consisting of zidovudine (AZT) 250 mg twice daily. The patient had migrated to Australia from Chile in 1973. There was a past history of syphilis treated in the UK in 1977 with 2 weeks of intramuscular penicillin.

Physical examination revealed mild confusion, diplopia on lateral gaze, reduced left facial sensation, a right lower motor neurone facial palsy, mild right tongue deviation, decreased sensation to the mid forearms and calves, and depressed left biceps brachii and right ankle reflexes. Plantar responses were normal. On abdominal examination there was mild right upper quadrant abdominal tenderness. CD4+ T-cell count was 360 μL and CD8+ count 3402 μL. Contrast-enhanced computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the brain were normal. Cerebrospinal fluid (CSF) examination revealed eight mononuclear cells/μL, a protein concentration of 0.7 g/L, normal glucose, negative bacterial, mycobacterial, fungal and viral culture, no malignant cells, and negative syphilis serology. Blood treponema pallidum haemagglutination test (TPHA) was 3+ positive and Venereal Disease Research Laboratory test (VDRL) was negative. Blood film showed numerous atypical

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mononuclear cells, ESR was 42 mm/h and plasma alkaline phosphatase and aspartate aminotransferase were moderately elevated.

In the week following admission, bilateral VIIth, left VIth and right XIIth cranial nerve palsies, bilateral palatal weakness, left optic papillitis, focal weakness of the right hand and left foot, and generalized hyporeflexia developed. CSF examination on day 14 showed 46 mononuclear cells/μL and elevated protein concentration at 1.45 g/L. Viral culture of CSF was positive for echovirus serotype 6. IgG antibody to this echovirus isolate was detected in the patient's serum to a dilution of 1 : 1280, and was undetectable in serum stored from March 1993. Liver biopsy showed granulomatous inflammation, with negative fungal and mycobacterial stains. No definite viral particles were seen on electron microscopy. Liver function tests subsequently improved and remained normal for the duration of follow-up. With treatment consisting of didanosine (ddI), AZT and 14 days intravenous benzylpenicillin to cover neurosyphilis, there was gradual improvement in his clinical status and he was discharged home approximately 1 month after admission.

Two weeks later, having stopped taking antiretroviral drugs 10 days earlier, he presented with increasing lower limb weakness and urinary retention. There was bilateral leg weakness, increased knee reflexes and extensor plantars. CSF examination now revealed 63 mononuclear cells/μL, a protein concentration of 3.5 g/L and negative viral cultures. Polymerase chain reaction (PCR) of CSF for cytomegalovirus was negative. Serum echovirus 6 IgG antibody persisted at a titer of 2560. Electromyography (EMG) indicated upper motor neuron pattern denervation of leg muscles consistent with a low thoracic transverse myelitis, but MRI of thoracolumbar spine was normal. After reinstitution of combination antiretroviral therapy with ddI and AZT, neurological status improved and was stable over the next 12 months, with mild persistent spastic paraparesis and left optic atrophy.

Over the three months to March 1996, the patient developed progressive flaccid muscle weakness and hyporeflexia in all limbs and became bed-bound. EMG indicated a demyelinating polyneuropathy. CSF protein was 3.61 g/L; enterovirus RNA was undetectable by PCR of CSF. Since initiation of 3-weekly intravenous immunoglobulin infusions, there has been excellent and sustained recovery of neurological function. CD4+ count while on AZT and lamivudine in early 1998 was 600 μL and plasma HIV-1 RNA concentration remains less than 400 copies/mL using the Roche Monitor RT–PCR assay.

Discussion

Neurological disease due to opportunistic infections, non-Hodgkin's lymphoma and HIV-1 itself is a common feature of AIDS (Price, 1996). Our patient initially presented with cranial nerve and spinal cord lesions associated with CNS echovirus infection and greater than 2 years later with symmetric inflammatory demyelinating polyneuropathy. A multiple sclerosis like syndrome can occur in HIV-1 infected individuals (Berger *et al*, 1989), as can an inflammatory demyelinating polyneuropathy (Price, 1990), but the consecutive occurrence of these syndromes in the same individual has not previously been described. These neurologic disorders usually occur before severe CD4+ lymphocyte depletion and their specific aetiology and pathogenesis, although presumed to be mediated by autoreactive immune responses, are unknown (Price, 1990).

CNS inoculation of an enteroviral species in immunodeficient mice leads to a multiple sclerosis like syndrome, which may be mediated by autoreactive CD8+ and CD4+ T cells (Borrow *et al*, 1992; Pope *et al*, 1996). Neurotropic and neurovirulent enteroviral species are common human pathogens and, in patients with X-linked agammaglobulinaemia, can cause progressive neurological degenerative disease (McKinney *et al*, 1987). This may be accompanied by hepatitis, as seen in our patient.

Enteroviruses are the commonest identifiable cause of viral meningo-encephalitis in immunocompetent individuals (Jeffery *et al*, 1997). This report is the first of enterovirus associated central nervous system disease in an HIV-infected individual. It indicates a previously unappreciated role for enteroviruses in inflammatory neurological disease associated with HIV-1 infection and suggests that a careful search for CNS enteroviral infection may be warranted in patients with such disorders.

References

Berger JR, Sheremata WA, Resnick L, Atherton S, Fletcher MA, Norenberg M (1989). Multiple sclerosis-like illness occurring with human immunodeficiency virus infection. *Neurology* **39:** 324–329.

Borrow P, Tonks P, Welsh CJ, Nash AA (1992) The role of CD8+ T cells in the acute and chronic phases of Theiler's murine encephalomyelitis virus-induced disease in mice. *J Gen Virol* **73:** 1861–1865.

Jeffery KJM, Read SJ, Peto TEA, Mayon-White RT, Bangham CRm (1997). Diagnosis of viral infections of the central nervous system: clinical interpretation of PCR results. *Lancet* **349:** 313–317.

McKinney RE Jr, Katz SL, Wilfert CM (1987). Chronic enteroviral meningo-encephalitis in agammaglobulinemic patients. *Rev Infect Dis* **9:** 334–356.

Pope JG, Karpus WJ, Vanderlugt C, Miller SD (1996). Flow cytometric and functional analyses of CNS-infiltrating cells in SJL/J mice with Theiler's virus-induced demyelinating disease: evidence for a CD4+ T cell-mediated pathology. *J Immunol* **156:** 4050–4058.

Price RW (1996). Neurological complications of HIV infection. *Lancet* **348:** 445–452.