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JC virus associated meningoencephalitis in an immunocompetent girl

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Abstract

JC virus is most commonly acquired during childhood, and no clinical illness has been associated with primary infection, which is assumed to be asymptomatic. The only disease associated with JC virus to date is progressive multifocal leucoencephalopathy (PML), which is usually caused by viral reactivation in immunocompromised adults. A chronic meningoencephalitis associated with an active JC virus infection in an immunocompetent 13 year old girl is described.

JC and BK viruses are both members of the polyomavirus subfamily which infect humans. A high proportion of the population has serological evidence of infection, with the peak age of acquisition occurring during childhood. Primary JC virus infection is most common between the ages of 8 and 13 years. After infection, these viruses remain latent in the kidney and are subsequently reactivated during periods of immune dysfunction. It is under such circumstances that polyomavirus infection usually gives rise to symptoms. BK virus is associated with ureteric stenosis and haemorrhagic cystitis in transplant recipients and mild respiratory symptoms have been noted in immunocompetent children suffering primary infection. By contrast, JC virus has only been associated with progressive multifocal leucoencephalopathy (PML), usually among immunosuppressed individuals, particularly those suffering from AIDS.[1] No illness has been associated with primary JC virus infection in the normal host.

PML is characterised by the insidious onset of asymmetrical neurological impairment, due to multifocal demyelination in the brain, which is progressive and usually leads to death within months. The definitive diagnosis of PML is by immunocytochemical and histological examination of brain biopsy material.[1] Serological assessment of blood and cerebrospinal fluid (CSF) is only helpful in a minority of cases, possibly because of the suppressed immune system in these individuals, and also because PML probably represents reactivation rather than a primary JC virus infection.

We now present a case of active JC virus infection associated with an unusual neurological syndrome in a non-immunosuppressed 13 year old girl.

Methods

Total JC antibodies were detected by haemagglutination inhibition and are expressed as a titre. JC IgM was detected in an antibody capture radioimmunoassay similar to one described earlier for BK virus.[2] Full details of this assay are to be published shortly. Sera are deemed to contain significant IgM if the ratio of test sample result to negative control value (T:N) is >5.

Case report

A 13 year old girl presented to our casualty department in late October after tripping over her shoe lace and sustaining a head injury. This was associated with a brief episode of loss of consciousness. Initial examination and a skull *x* ray film were normal and she was discharged home well. She returned one week later with a history of headaches, vomiting, and aggressive behaviour. The behavioural changes had been developing over two to three weeks before the head injury. She had also lost 3·2 kg in weight over the same period.

On examination she had a flat affect but there were no abnormal neurological findings. Her tongue was fissured and her lips were cracked but the rest of the systemic examination was normal. She was observed on the ward where her illness progressed. Six days after her admission she suffered her first recorded pyrexia and this was associated with retention of urine which required urethral catheterisation. Investigations at this time showed her to have a neutrophil leucocytosis and a raised erythrocyte sedimentation rate (ESR) but her urine and blood cultures did not grow any micro-organisms. Other investigations included an abdominal ultrasound, a drug screen, and a pregnancy test, all of which were normal or negative. The patient continued to deteriorate with a flaccid paraplegia of the lower limbs, associated with extensor plantar responses. There was incontinence of urine and faeces and anaesthesia of saddle area distribution, as well as paraesthesia below the level of L2. In the upper limbs there was a mild bilateral lower motor neurone weakness with maintained palm reflexes and no sensory impairment.

A lumbar puncture was abnormal with a raised CSF pressure (300 mm H_2O), slightly high protein (0·5 g/l), and total white blood cell count of 75×10^6/l (70% mononuclear). CSF electrophoresis showed an inflammatory leak pattern with acute phase proteins but no oligoclonal bands. Electroencephalograms were abnormal on multiple occasions, showing bilateral delta waves and intermittent high amplitude slow waves of 3–4 cycles/second,

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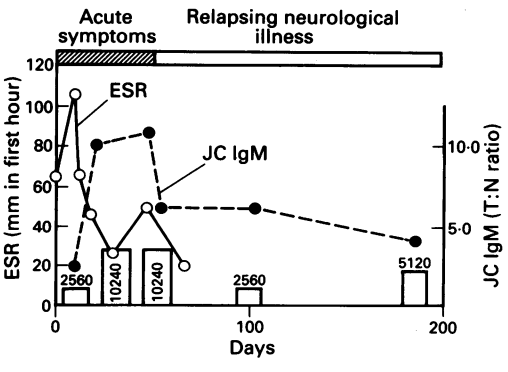
mainly right sided, but with no epileptic features. These appearances were compatible with an encephalopathic type illness. Computed tomography and magnetic resonance imaging scans of the brain and spine were normal. A clinical diagnosis of meningoencephalomyelitis was made.

Serological tests over this period showed the absence of serum IgG antibodies to cytomegalovirus, herpes simplex virus, and Epstein–Barr virus, and no change in titres of serum antibodies to influenza A and B, varicella zoster virus, and measles. Rubella IgG antibodies were present in her serum but were not detectable in CSF. A very low level of CSF measles antibodies was detected, but this was compatible with an inflammatory leak. No viruses were grown from successive cultures of saliva, stool, urine, and CSF, thereby excluding infection with mumps or an enterovirus. JC virus culture is a difficult procedure, requiring primary brain tissue, often taking up to one year, with a low pickup rate. It was therefore not undertaken. The JC virus serology is represented graphically (figure). The titre of total antibodies (haemagglutination inhibition antibodies) showed a fourfold rise, up to 1/10 240, and there was also a rise in the concentration of IgM, corresponding with the onset of febrile illness, which was preceded by a prodromal illness. A low titre of CSF JC virus antibody was detectable, but this can be attributed to a leak of protein from serum during the inflammatory process. The ESR mirrored the severity of symptoms.

The patient's acute symptoms resolved seven weeks after hospital admission and she was discharged. Her clinical course has fluctuated over the five month period since then with episodes of neurological relapse (see below). She showed some clinical features of PML, including persistent impairment of cognitive function, and disturbance of speech, vision, and movement. However, the typical rapid deterioration did not occur and she has made a neurological recovery, although some variable impairment of concentration and learning abilities persist. JCV IgM concentrations fell over time and, although there is a twofold increase in haemagglutination inhibition antibody titre with the most recent serum sample, this change is within the limits of assay variation.



The development of JC antibody responses in a girl with neurological symptoms. Total JC antibodies were measured by haemagglutination inhibition and expressed as a reciprocal of titre (shown in the baseline histogram). JC IgM antibodies were expressed as a T:N ratio.

Our patient had no impairment of cell mediated or humoral immunity as shown by normal serum immunoglobulins, T cell count, and subsets which were all measured at the recovery stage of her illness. She was also screened for evidence of sarcoid, human immunodeficiency virus, lymphoproliferative disease, tuberculosis, systemic lupus, and diabetes and all tests were reported as normal or negative.

Discussion

A brain biopsy for histological diagnosis was not undertaken but it is possible that this girl suffered a mild form of PML. Primary JC virus infection has been associated with PML, albeit in an immunosuppressed child,[2] and a non-progressive form of PML has been documented in adults.[3 4] On the other hand, a febrile illness, as observed in our patient, does not occur in PML, and computed tomography and magnetic resonance, both sensitive methods for detection of the demyelinating brain lesions,[5] were normal in this case. It is therefore likely that she suffered a chronic meningoencephalitis rather than classical PML. Of particular interest was the relapsing nature of her illness and the fact that behavioural problems remained, some seven months after onset, despite the resolution of all other neurological abnormalities. In fact her personality change predated other symptoms, leading to a major psychiatric input into her care during the initial stages of her illness.

This could be a primary JC infection, although no stored serum existed from before onset of symptoms so a seroconversion could not be documented. We have previously shown that of 46 children with rashes, none developed a serum concentration of JC IgM approaching that detected in this case (unpublished results). Further, a rising titre of IgG and IgM was observed over the period of this girl's illness. These two observations support our thesis that the serological findings we report are specific, and compatible with active JC virus infection. Interpretations other than a primary infection are that her illness is an atypical PML in a girl with a subtle lack of immunocompetence, or that the meningoencephalopathy is unrelated to JC virus infection and the immune response detected represents a reactivation of JC virus after the clinical illness. It is interesting to speculate that JC virus can cause forms of neurological illness other than PML. The availability of a JC IgM assay, utilised in this case, should help to investigate this possibility in children with otherwise unexplained neurological symptoms.

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