

for circulating plasminogen, is thought to minimise the systemic thrombolytic effects of tissue plasminogen activator.

Bleeding may be reduced by the regional application of tissue plasminogen activator directly onto the clot with the assumption that the thrombolytic effect will be entirely local. This is attractive for clots associated with indwelling intravascular catheters which may be used as the treatment route.

Our two patients received a low dose infusion of tissue plasminogen activator as a regional application to try to achieve clot lysis with minimal systemic effects.

A similar low dose (0.05 mg/kg/hour) regional infusion of tissue plasminogen activator has been used in four neonates with caval thrombosis secondary to indwelling intravascular catheters.<sup>2</sup> There was successful lysis of the clot in three of the patients. In one patient the infusion caused a decrease in fibrinogen concentrations and an increase in fibrin degradation products and this infant had an intraventricular haemorrhage.

When higher doses of tissue plasminogen activator (0.1–0.5 mg/kg/hour) were given to 12 children,<sup>3</sup> six had bleeding complications. In these six patients bleeding was associated with a tissue plasminogen activator dose of 0.46–0.50 mg/kg/hour).

The age of the clot to be lysed has an important effect on its susceptibility to thrombolysis. Most in vivo studies suggest that clots become more resistant to lysis as they age.<sup>4</sup>

Early initiation of treatment is important and this may have been a factor in the success of the low doses of tissue plasminogen activator reported here.

Although pharmacologically effective doses of tissue plasminogen activator appear to cause less of a systemic lytic effect than streptokinase,<sup>5</sup> there is a poor correlation between markers of systemic thrombolysis and bleeding complications.<sup>6</sup>

In view of the limited experience with the use of tissue plasminogen activator in children and the fact that these patients are likely to have a relatively high incidence of catheter associated thrombosis, our patients indicate that local application of low dose (0.01–0.05 mg/kg/hour) infusions may be a useful approach.

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## Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection

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### Abstract

**An encephalitic illness with a fatal outcome occurred in a 9 month old girl with virologically confirmed exanthem subitum. Human herpesvirus-6 (HHV-6) DNA was found in the cerebrospinal fluid at the acute stage of the disease by the polymerase chain reaction, but the virus antigen was not detected in her brain tissue. This suggests that HHV-6-induced encephalitis/encephalopathy may be due to a non-infectious process.**

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Central nervous system complications are well known during the course of exanthem subitum, which is caused by primary infection with human herpesvirus-6 (HHV-6). It has been strongly suggested that the virus invades the central nervous system and causes encephalitis or encephalopathy.<sup>1,2</sup> There is, however, little information on whether the virus invades the

brain tissue. We report a fatal case of exanthem subitum with encephalitic illness that occurred in the pre-eruptive stage of the disease. The virological and histopathological findings of the case are also presented.

### Case report

A 9 month old girl was admitted to the Kariya Sogo Hospital because of high fever and generalised clonic convulsions. She had been apparently well until the afternoon of the previous day (day 0) when her temperature had suddenly risen to 39.2°C. In the early hours of the next morning she had a generalised clonic convulsion that persisted for one minute; this occurred approximately 10 times during the next four hours. She vomited several times and became drowsy and was admitted to our hospital suffering from stupor that morning (day 1). On admission, physical examination revealed a well nourished, well developed infant with a normal anterior fontanelle. She had been born at full term after an uncomplicated pregnancy. Her

temperature was 38.6°C. A computed tomogram and electroencephalogram showed normal results. Her cerebrospinal fluid was examined; the concentrations of protein and glucose were normal and there was no pleocytosis. White cell count was  $2.5 \times 10^9/l$  with 19% lymphocytes. Other haematological and blood chemical analyses showed normal values except for a mild increase in her liver enzymes. She was treated conventionally for encephalitis and with acyclovir (30 mg/kg/day) because herpes simplex virus encephalitis was clinically suspected on her admission. Despite the treatment, her consciousness level worsened and she was assisted by mechanical ventilation. On day 3 of the illness her temperature returned to normal and a rubella-like skin rash appeared on her face and trunk. On the same day her brain function could not be detected by electroencephalography. Cranial computed tomography performed on day 8 of the illness demonstrated subarachnoidal bleeding, appreciable brain oedema, and diffuse hypodensities. On day 21 of the illness she did not respond to the usual cardiopulmonary resuscitative efforts. After parental permission was obtained, a piece of brain tissue was taken by needle biopsy.

#### Methods

HHV-6 was isolated by cocultivation of peripheral blood mononuclear cells (MNCs) from the patient with MNCs from cord blood, and antibody titres to HHV-6 were tested by the neutralisation test, as described previously.<sup>3</sup> Antibody titres to HSV types 1 and 2 were measured by the standard 50% plaque reduction neutralisation tests using the vero cell culture system.

HHV-6 and herpes simplex virus DNA were extracted from the cerebrospinal fluid and amplified by the nested polymerase chain reaction (PCR) using procedures reported elsewhere.<sup>4</sup>

HHV-6 antigen in the brain tissue was examined by enzyme immunoassay using monoclonal antibodies to HHV-6 as described elsewhere.<sup>5</sup>

#### Results

HHV-6 was isolated from blood obtained on day 1 of the illness, but not from blood on days 5 and 18. HHV-6 DNA sequences were detected in the cerebrospinal fluid obtained on day 1 of the illness by the PCR. There was a significant rise in the antibody titres to HHV-6 from day 1 (<4) to day 5 (128) and day 18 (>512) of the illness. On the other hand, there was no evidence of primary herpes simplex virus infection in blood and cerebrospinal fluid samples.

In the brain tissue obtained just after her

death there was no infiltration of inflammatory cells nor HHV-6 antigens.

#### Discussion

Several cases have been reported showing central nervous system complications in association with primary infection with HHV-6 in which it has been suggested that the central nervous system has been invaded by the virus.<sup>1,2</sup> Yamanishi *et al*, however, have reported that the virus DNA could have been amplified in seven (70%) of 10 samples of cerebrospinal fluid from patients with exanthem subitum who had convulsions or a bulging fontanelle, or both.<sup>6</sup>

It is important to note that in the present study the brain tissue obtained just after death did not have any inflammatory cells and there was no HHV-6 antigen despite the fact that HHV-6 DNA was clearly detected in her cerebrospinal fluid sample. Oedematous changes and the hypodense areas of the brain observed by computed tomography in our case and in other reported cases suggest encephalitic changes of the brain. However, the findings in the brain tissue of our case do not support this speculation. If enough (or the entire) brain sample had been available in our case we might have been able to ascertain the relationship between the histological findings and the distribution of HHV-6 antigen more precisely. Moreover, in order to confirm the encephalitogenic nature of the virus, localisation of HHV-6 antigen or the virus gene sequence in brain tissue would need to be shown by using sensitive and specific techniques.

It is generally believed that exanthem subitum is a common benign infectious disease and the prognosis is uniformly excellent even for cases complicated by convulsive seizures. However, although the case reported here is a rare complication of exanthem subitum, it is important for physicians who care for patients with exanthem subitum to be aware of the potential hazard of unexpected death.

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