**Herpes simplex serious neurological disease in young children: incidence and long-term outcome**

Katherine N Ward, Anu Ohrling, Naomi J Bryant, Jennifer S Bowley, Euan M Ross, Christopher M Verity

**ABSTRACT**

**Objective** To determine the contribution of herpes simplex virus (HSV) to serious neurological disease.

**Setting and patients** A 3-year prospective survey of children aged 2–23 months in Britain and Ireland.

**Results** 19 children had HSV central nervous system (CNS) infection; 13 aged 2–11 months had focal neuroimaging abnormalities and 11 long-term neurological sequelae. Of six aged 12–35 months, one had abnormal neuroimaging and three long-term neurological sequelae. 17 of the 19 had serious neurological disease. HSV CNS infection accounted for 23% of serious neurological disease in children aged 2–11 months and 4.5% in older children.

**Conclusions** The incidence of HSV-induced serious neurological disease in the UK was estimated at 1 in 64 000/year in younger children and 1 in 230 000 in older children. HSV CNS infection has clinical effects ranging from frank encephalitis to severe illness with fever and convulsions to milder disease lacking encephalopathy.

**INTRODUCTION**

Herpes simplex encephalitis (HSE) is the most common cause of sporadic encephalitis and without treatment 70% of patients die. Our knowledge of HSE relies on two clinical trials of antiviral drugs from the 1980s. Since then substantial changes in diagnostic methods, including PCR to test cerebrospinal fluid (CSF) for herpes simplex virus (HSV) DNA together with the use of aciclovir, have improved survival. However, the spectrum of clinical manifestations and long-term outcome need to be better defined so as to improve management and thereby decrease the still considerable morbidity and mortality associated with this devastating condition.

A prospective survey of children aged 2–23 months in Britain and Ireland with serious neurological disease showed for the first time that human herpesvirus-6 and -7 contributed significantly to this illness. Data collected included information on other pathogens, including HSV, and thus its contribution to the burden of disease could be assessed. The present paper reports the results obtained.

**METHODS**

**Patients**

**Case ascertainment**

Between October 1998 and September 2001 paediatricians were requested by the British Paediatric Surveillance Unit to report the cases of all children 2–35 months old with serious neurological disease. Neonates were excluded from the survey to avoid inclusion of inherited and mechanical neurological damage which often presents before 2 months of age. Details of each child’s neurological illness were collected using a short standard questionnaire. A further brief questionnaire was sent after at least a year to check long-term outcome, that is, whether the child had recovered or suffered developmental delay, persisting neurological deficit or convulsions. An additional questionnaire was sent to the referring hospital’s microbiology laboratory to confirm the microbiological results at the time of the child’s illness. Each questionnaire was scrutinised by a physician (KNW) to determine whether the details fitted the case definition (see below). Difficult cases were referred to one or more paediatricians (AO, CMV, EMR) for a final decision. The database of all reported disease episodes, regardless of whether or not they met the case definition, was re-examined by KNW for individuals with HSV central nervous system (CNS) infection.

**Definitions**

**Fever**

Fever was defined as a temperature ≥37.5°C.

**Serious neurological disease**

1. Severe illness with fever and convulsions
   i. with a total duration of ≥30 min
   ii. followed by encephalopathy for 2–23 h
   iii. followed by paralysis or other neurological signs not previously present for ≥24 h.

2. Encephalitis
   i. Encephalopathy for ≥24 h and two or more of the following:
      a. fever
      b. convulsions
      c. focal neurological findings (≥24 h)
      d. pleocytosis (>5 leucocytes/μl CSF)
      e. characteristic abnormal CT or MRI results.

3. Exclude
   i. viral (aseptic) meningitis without encephalopathy
   ii. the following confirmed causes: hypoxic/ischaemic, vascular, toxic, metabolic, neoplastic, traumatic and pyogenic infections
   iii. uncomplicated convulsions or a series of convulsions lasting <30 min
   iv. immunocompromised children.
HSV CNS infection
1. HSV DNA detected in CSF or an HSV-specific intrathecal antibody response, or
2. Evidence of primary HSV infection, that is, seroconversion to IgG or IgM, within 2 weeks of onset of serious neurological disease.

Ethics approval
Ethics approval was given by the Public Health Laboratory Service Ethics Committee, London.

RESULTS
Cases of serious neurological disease
Of the 267 episodes of disease reported, 19 cases of HSV CNS infection (table 1) and 163 cases of serious neurological disease were identified; 52 of the latter were in children aged 2–11 months and 111 in children aged 12–35 months.

The clinical features, neuroimaging results and long-term outcome of the 19 cases are given in table 2. Every case presented with convulsions (partial in 12/19) accompanied by fever in all but one instance. Focal neuroimaging abnormalities were noted in all children aged <11 months (temporal lobes in nine, frontal lobes in three and parietal lobes in seven) but in only one of the older children. There were no deaths, but 11 of the 13 children aged 2–11 months and three of the six older children had long-term neurological sequelae. The most common sequelae was developmental delay, but other persisting deficits included hemiparesis, quadriparesis and visual problems. Eight children had epilepsy.

Two patients (nos. 12 and 15) with HSV CNS infection did not meet our case definition of serious neurological disease.

The remaining 17 (11 encephalitis, six severe illness with fever and convulsions) accounted for 23% (12/52) of episodes of serious neurological disease in children <1 year old and 4.5% (5/111) in the older children. Because all 17 cases were in British children, we could estimate the incidence of serious neurological disease due to HSV CNS infection in the UK as 1 in 64 000/year in children aged 2–11 months and 1 in 230 000/year in children aged 12–35 months. In 1998–2001 there were 2.1 million children in the first year of life and 4.1 million in the second and third years (National Statistics Office website: http://www.statistics.gov.uk/popest).

DISCUSSION
This paper reports data on the incidence, spectrum of clinical presentation and long-term outcome of virologically confirmed HSV CNS infection in young children throughout the British Isles. So that milder cases would be included, the definition of HSV CNS infection covered more than just serious neurological disease, which in turn comprised not only encephalitis but also severe illness with fever and convulsions.

Thus only 58% of the children with HSV CNS infection in the survey had an illness that fitted our strict definition of encephalitis as the remainder did not fulfil the criterion of encephalopathy for ≥24 h. Such atypical forms of HSV CNS infection have been previously reported and together with our findings show that HSV is responsible for more than clear-cut encephalitis in young children.

Cases may have been missed in our survey because HSV DNA or pleocytosis may not be found in CSF soon after disease onset. Likewise, aciclovir treatment may result in the absence of CSF HSV DNA and delay antibody seroconversion.

Table 1 HSV CNS infection: results of laboratory investigations

| Patient no. | CSF WBC (lymphocytes)/RBC per µl | Protein (g/l) | Viral DNA* | Intrathecal antibody synthesis | Seroconversion to IgG or IgM† |
|-------------|----------------------------------|--------------|------------|-------------------------------|-----------------------------|
| 1           | 7 (NT)/1310                      | 0.8          | HSV‡       | NT                            | NT                          |
| 2           | 35 (35)/3500                     | 0.55         | HSV‡       | NT                            | NT                          |
| 3           | 25 (25)/3                        | 0.47         | HSV-1      | NT                            | NT                          |
| 4           | 23 (18)/<1                       | 0.6          | Negative   | NT                            | Yes                         |
| 5           | 93 (93)/285                      | 0.5          | HSV-1      | NT                            | NT                          |
| 6           | 2 (NT)/12                        | 0.68         | HSV‡       | NT                            | Yes                         |
| 7           | 560 (280)/900                    | 1.03         | HSV-1      | NT                            | NT                          |
| 8           | 7 (NT)/50                        | 0.34         | HSV-1      | NT                            | NT                          |
| 9           | 70 (70)/40                       | 0.32         | Negative   | Yes                           | NT                          |
| 10          | 21 (21)/115                      | 1.01         | HSV-1      | NT                            | NT                          |
| 11          | 97 (NK)/50                       | 1.0          | HSV-1      | NT                            | NT                          |
| 12          | 120 (85)/2510                    | NT           | HSV-1      | NT                            | NT                          |
| 13          | NT                               | NT           | NT         | NT                            | NT                          |
| 14          | <1 (<1)/50                       | 0.23         | HSV-1      | NT                            | NT                          |
| 15          | <1 (<1)/<1                       | NK           | HSV-1      | NT                            | NT                          |
| 16          | 1 (1)/10                         | 0.14         | HSV-1      | NT                            | NT                          |
| 17          | NK (NK)/NK                       | NK           | HSV‡       | NT                            | NT                          |
| 18          | NT                               | NT           | NT         | NT                            | Yes                         |
| 19          | 10 (10)/37**                     | 1.06         | HSV‡       | NT                            | NT                          |

*Tested for by PCR.
†Within 2 weeks of onset of serious neurological disease.
‡Virus not typed.
§First CSF nothing abnormal detected.
¶First CSF clotted.
**First sample WBC <1/RBC per µl 127.
CNS, central nervous system; CSF, cerebrospinal fluid; HSV, herpes simplex virus; NK, not known; NT, not tested; RBC, red blood cell; WBC, white blood cell.
| Patient (m|sex|age) | Fever (°C) | Encephalopathy | Convulsions (duration) | Lesions on CT | Lesions on MRI | Outcome (time after discharge) |
|----------|------|-------------|----------------|------------------------|---------------|----------------|-------------------------------|
| 1/F/3 months | Yes (39.2) | 2–23 h | Whole body (>30 min) | Haemorrhagic R and L hemispheres, oedema | ND | ND | Developmental delay (cognitive and motor) |
| 2/F/4 months | Yes1 (NK) | ≥24 h | Partial, L hemiclonic (>30 min) | Haemorrhagic R and L temporal and parietal | ND | ND | Developmental delay (cognitive) |
| 3/M/5 months | Yes (38.2) | ≥24 h | Partial (<15 min) | Haemorrhagic R and L parietal, low density R and L temporal and R parieto-occipital | ND | ND | Developmental delay (cognitive and motor) |
| 4/M/6 months | Yes (38.2) | ≥24 h | Partial (>30 min) and L hemiplegia ≥24 h | Low density bifrontal | ND | ND | Developmental delay (cognitive and motor), L hemiplegia, whole body convulsions (2 years) |
| 5/M/6 months | Yes (38) | ≥24 h | Partial L-sided (>30 min) and L hemiplegia ≥24 h | Haemorrhagic, low density L frontal, temporal and parietal | R cerebral hemisphere | ND | Developmental delay (cognitive and motor), L hemiplegia and convulsions (2 years) |
| 6/F/6 months | Yes (38.8) | ≥24 h | Partial motor (>30 min) and L hemiplegia ≥24 h | R parietal, occipital | ND | ND | Developmental delay (cognitive and motor), L homonymous hemianopia (1.5 years) |
| 7/F/6 months | Yes (38) | 2–23 h | Whole body (>30 min) | Low density frontal, temporal, parietal | R and L frontal and temporal, R parietal oedema and haemorrhage | ND | Developmental delay (cognitive and motor), quadriparesis, convulsions, atonic attacks (2.5 years) |
| 8/M/8 months | Yes (38.5) | ≥24 h | Partial, R-sided with ecologic crisis (>30 min) | Low density temporal lobe | ND | ND | Recovered (1 year) |
| 9/F/10 months | Yes (NK) | ≥24 h | Whole body (15–30 min) | Low density R temporal and parietal | R temporal – no normal parenchyma | ND | Developmental delay (cognitive and motor), autism, convulsions (4 years) |
| 10/F/10 months | Yes (38.5) | ≥24 h | Whole body (<15 min) | Low density R and L temporal lobe, serpiginous enhancement R sylvian fissure | ND | ND | Developmental delay (cognitive) (1 year) |
| 11/F/10 months | Yes (39) | ≥24 h | Partial (>30 min) | Low density L temporal lobe | R temporal haemorrhagic and L temporal, parietal and occipital | ND | Developmental delay (cognitive and motor), R hemiplegia, R homonymous hemianopia, convulsions (2 years) |
| 12/F/11 months | Yes (39.5) | <2 h | Partial (15–30 min) and Todd’s paresis5 | Low density L temporal | ND | ND | Recovered (2 years) |
| 13/F/11 months | Yes (38.6) | 2–23 h | Partial, R-sided (>30 min) and Todd’s paresis | Haemorrhagic R parietal lobe | R and L haemorrhagic parietal and paravagittal | ND | Needs speech therapy (2 years) |
| 14/F/14 months | Yes (37.8) | ≥24 h | Partial, clonic R arm (15–30 min) | Normal | Normal | ND | Recovered (NK) |
| 15/F/17 months | No | NK6 | Whole body (>30 min) | Normal | Normal | ND | Convolusions, absences but attends normal school (2.5 years) |
| 16/F/17 months | Yes (39.2) | <2 h | Whole body (>30 min) | Normal | Normal | ND | Recovered (1 year) |
| 17/F/18 months | Yes (39.0) | 2–23 h | Whole body (<15 min) and ataxia ≥24 h | Normal | Normal | ND | Hemiparesis (2.5 years) |
| 18/M/26 months | Yes (37.5) | ≥24 h | Partial (>30 min), ataxia ≥24 h | Normal | Normal | ND | Developmental delay (motor and cognitive) (4 years) |
| 19/M/35 months | Yes (38.5) | 2–23 h | Partial and whole body (15–30 min) and ataxia ≥24 h | Normal | Normal | ND | Recovered (3.5 years) |

*Depended on date child last seen and date of return of the questionnaire.

*Preceding admission.

†Preliminary admission.

‡Hemiplegia for <24 h.

§Ictal, given thiopentone and transferred to paediatric intensive care unit at another hospital. Patient described as encephalopathic but duration not given – not possible to differentiate drug-induced from virus-induced encephalopathy.

CNS, central nervous system; HSV, herpes simplex virus; ND, not done; NK, not known.

Indeed, nowadays CSF is rarely tested for intrathecal HSV antibody7 and this was certainly our experience. Finally, the declining use of HSV serum antibody tests together with a decrease in the use of lumbar puncture in paediatric practice may have affected detection.5 However, it seems that in fact few cases were missed. Analysis of Hospital Episode Statistics (HES) for England over 1998–2001 gives 52 cases of HSE in children <3 years old (data not shown). This figure is necessarily higher than ours since it includes neonates in whom HSE occurs in appreciable numbers (76 cases in 1986–1991, 83 cases in 2004–2006).8 Thus, although the HES data lack confirmatory virological evidence and a uniform case definition, they
fit well with our finding of postnatal HSV CNS infection if allowance is made for exclusion of neonates.

HSE classically presents as an acute illness characterised by fever and encephalopathy together with behavioural disturbances and/or motor deficits and/or convulsions. No sign is pathognomonic, but it is noteworthy that in our children <3 years old, convulsions (generalised or focal) were present in every case. Similarly, two studies of postnatal HSE report a predominance of convulsions in children aged <3 years as compared to older children who show a wider range of presentations.

Neuroradiology of postnatal HSE typically reveals focal haemorrhagic lesions localised to the medial temporal lobes, the insula and the orbital region of the frontal lobes of the brain. However, in our series the parietal lobes were frequently affected, confirming previous findings that in young children extra-temporal regions of the brain are often involved.

HSE outcome is difficult to predict early on and particularly in very young children in whom subtle defects may appear later; it is therefore important that almost all of our cases were followed up at least a year after presentation. Long-term sequelae were reported in many of the children. Adverse outcome was age-related and CT reflected this as abnormalities were described in all the younger children but in none aged >11 months. Likewise, high numbers of red cells in the CSF, reflecting haemorrhagic necrosis in the CNS, were confined to the younger age group. Of other recent studies of the long-term outcome of HSV CNS infection, that is, at least 6 months after onset, one reported that patients 3–35 months old were more likely to be severely disabled than older children. Our series further suggests that those <1 year old were at highest risk. Poor neurological outcome is associated with delayed initiation of aciclovir therapy and/or shorter courses of the drug but, although all children received aciclovir, the confounding effects of inadequate treatment could not be addressed as this information was not collected by us nor in the study of Ito et al. The influence of age of onset in relation to severity of long-term outcome requires prospective study taking into account the role of inadequate aciclovir therapy.

In conclusion, this survey documents the incidence of HSV-induced serious neurological disease in young children in Britain and emphasises that there are various presentations ranging from frank encephalitis to severe illness with fever and convulsions, and even a milder form lacking lengthy encephalopathy. Disease was commoner in children aged 2–11 months than in older children, and neurological sequelae and consequent severe disabilities showed the same trend. HSV CNS infection must always be considered in children presenting with convulsions even when apyrexial, without encephalopathy and with normal CT findings.

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Competing interests None.

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