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A major role of viruses in convulsive status epilepticus
in children: a prospective study of 22 children

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Abstract A group of 22 previously healthy children with their first convulsive status epilepticus (SE), treated at Kuopio University Hospital, Finland, were prospectively studied. Eleven children had febrile and 11 afebrile SE. Polymerase chain reaction was used to detect specific DNA from CSF, enzyme immunoassays and immunofluorescence assays to detect specific antibodies in serum and CSF, viral cultures were obtained from CSF, throat and stool and antigen detection from throat specimens. Viral infection was identified in 10 of 11 children with febrile SE (91%) and in 7 of 11 with afebrile SE (64%). Human herpes virus 6 infection was identified in 12 children (55%), and in at least six of them the infection was primary. Single cases of human herpes virus 7, parainfluenza 3, adenovirus 1, echovirus 22, rota, influenza A and Mycoplasma pneumoniae infection were diagnosed.

Conclusion Viruses, human herpes virus 6 in particular, seem to be major associated factors in convulsive status epilepticus, both febrile and afebrile. Human herpes virus 7 and Mycoplasma pneumoniae are novel agents associated with status epilepticus.

Key words Aetiology · Human herpes virus 6 · Prospective study · Status epilepticus · Viral infection

Abbreviations ASE febrile status epilepticus · CMV cytomegalovirus · FC febrile convulsion · FSE febrile status epilepticus · HHV human herpes virus · HSV herpes simplex virus · RSV respiratory syncytial virus · SE status epilepticus · VZV varicella zoster virus

Introduction

Convulsions comprise the majority of emergency cases in paediatric neurology. Status epilepticus (SE) is the most important of these. Owing to the life-threatening character and later morbidity risk of SE, effort has been put into developing prompt and efficient treatments [19].

While there is growing literature both on the basic mechanisms and different aspects of clinical features and prognosis in SE [1], its aetiology remains largely unknown.

Previous studies have suggested that aetiological factors determine the prognosis of SE, which emphasises the importance of good knowledge of the aetiopathology of SE [18]. Several studies on paediatric SE patients

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have elucidated gross correlations between patients’ demographic parameters, main aetiological groups, type of SE and/or prognosis [1, 16, 18].

The incidence of SE is highest in children under 2 years, and SE in younger children is commonly associated with high fever. Febrile convulsions (FC) have been reported to be associated with viral infections, especially enterov-, adeno- and parainfluenza viruses [21]. Studies by Suga et al. [24] and Hall et al. [8] suggest an important role for human herpes virus (HHV) 6 in febrile convulsions, including some cases of SE. Viral studies focusing on SE have not been reported. Our prospective, population-based study includes 22 previously healthy children with SE. The results indicate an obvious relationship between SE and viral infections.

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**Patients and methods**

**Patients**

The study was approved by the Research Ethics Committee of Kuopio University Hospital. Written informed consent was obtained from the parents of the children enrolled in this study. SE was defined as a seizure lasting for more than 30 min or recurrent seizures lasting altogether for more than 30 min with no recovery of consciousness between the seizures. SE was classified as febrile (FSE, rectal temperature ≥ 38.0 °C at the time of SE) or afebrile (ASE) idiopathic. Classification of seizures was based on the recommendation of the International League Against Epilepsy [4].

We studied 22 consecutive patients (13 boys and 9 girls) with their first convulsive SE and with no metabolic disorders or previous neurological problems or seizure history, admitted to the Department of Paediatrics, Kuopio University Hospital (taking care of all emergencies in an area with 45,000 children <16 years of age), from September 1995 to August 1998, indicating an incidence of 16.3/100,000 child years.

**Study programme**

The child’s history and the results of the physical and neurological examination were recorded on a detailed standard form by the investigators (AJ, EH) on admission, during hospitalisation and at the time of second CSF specimen collection. Paired serum and CSF samples were obtained on admission and at 9–27 days, and throat and stool samples on admission. An EEG was performed on all children on admission, CT of the brain on 12 of them, and MRI on all patients.

**Virological studies**

**Sero logical tests**

IgG and IgM antibodies to HHV-6 were measured by an indirect immunofluorescence test (in-house method) [15] and as a control by a commercial enzyme immunoassay kit (PanBio, Brisbane, Australia). Avidity of HHV-6 IgG antibodies (if reciprocal of IgG antibody titre was ≥40) was performed in serial dilutions using elution with urea in parallel as described [28]. The avidity was regarded low if the titre was reduced to ≥3 in logarithmic scale. HHV-7 IgG antibodies were measured by using a commercial kit (ABI Advanced Biotechnologies, Calne, Wiltshire, UK). IgG antibodies to herpes simplex virus (HSV)-1, HSV-2, varicella zoster (VZV), rota, Coxackie B5, non-tyred entero, respiratory syncytial (RS), adeno, influenza A and B, and parainfluenza 1 and 3 viruses and Mycoplasma pneumoniae were measured in serum and CSF using an enzyme immunoassay as described [13]. IgG and IgM antibodies to Chlamydia pneumoniae were measured using a micro-immunofluorescence test [27], and to cytomegalovirus (CMV) using commercial enzyme immunoassay kits (Labsystems, Helsinki, Finland). IgM antibodies specific to HSV and VZV were measured in serum and CSF using a commercial immunofluorescence antibody kit (Gull Laboratories, Salt Lake City, Utah).

**Nucleic acid detection**

PCR was used for detection of nucleic acids specific for HSV-1, HSV-2 and VZV using oligonucleotide primers derived from the DNA polymerase genes and luminometric microplate hybridisation for detection of the PCR product [26]. HHV-6 specific nucleic acid was amplified with H-6 and H-7 primers derived from the strain U1102 [8]. With annealing temperature of 51 °C the primers amplify efficiently and specifically both HHV-6-A and HHV-6-B types. The PCR product was detected with luminometric microplate hybridisation.

**Antigen detection**

From throat specimens, antigens specific to HSV, VZV, influenza A and B, parainfluenza 1 and 3, RS and adenoviruses were detected by conventional direct immunofluorescence techniques. From stool specimens, rotavirus and adenoviruses were detected by electron microscopy.

Viral cultures of CSF, throat and stool specimens obtained on admission were performed using four different cell types (human amniotic epithelial cells, African green monkey kidney cells, vero cells and human embryonic skin fibroblasts).

**Statistical analysis**

Fisher’s test was used for the comparison of parameters in FSE and ASE. Results were considered significant when $P \leq 0.05$.

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**Results**

**Clinical findings**

The mean age of the 11 FSE patients was 20 months and of the 11 ASE patients 81 months ($P < 0.001$). Respiratory symptoms were common in both (Table 1). All ASE patients had focal seizures compared with 4 of 11 of FSE ($P < 0.02$) (Table 2). Five children with FSE and one with ASE needed ventilatory support during SE. In the others respiration recovered between the recurrent seizures. At the time of the second CSF specimen collection, 9 to 27 days after admission, one child (Patient 12) had muscle hypotonies and tendency to opisthotonos and one (Patient 20) had left lower limb weakness.

**Virological findings**

HHV-6 specific DNA was detected in the CSF of two children (Table 1). Seroconversion to HHV-6 appeared