CAUSES OF FEVER IN CHILDREN WITH FIRST FEBRILE SEIZURES: HOW COMMON ARE HUMAN HERPESVIRUS-6 AND DENGUE VIRUS INFECTIONS?

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Abstract. This study was conducted to evaluate the etiologies of pyrexia in children with first febrile seizures using a prospectively recorded medical protocol, bacterial culture, and serologic tests for human herpesvirus-6 (HHV-6), dengue virus and Japanese B encephalitis (JE) virus. Of 82 children with first febrile seizures, who were between 3 months and 3 years old and had been admitted to Bhumibol Adulyadej Hospital between January 1997 and December 1998, 41 were boys and 41 were girls, with a mean age of 14.7 months. The average maximal body temperature was 39.7ºC. Approximately 70% of the children developed seizures on the first day of fever and the duration of the seizures varied from 1 to 30 minutes. In addition to fever and seizure, common symptoms and signs included coryza, diarrhea, vomiting, inflamed tympanic membranes and rash. The causes of fever documented upon discharge were, in order of frequency, upper respiratory tract infection, nonspecific febrile illness, diarrhea, urinary tract infection, viral infection, pneumonia, herpangina, measles, pneumococcal bacteremia and dengue fever. Serologic tests for HHV-6 IgM were positive in seven children (8.5%), and serologic tests for dengue and JE viruses were negative in all cases.

INTRODUCTION

Febrile seizures are the most common seizure disorder during childhood and the causes of fever most frequently reported are viral infections of the upper respiratory tract, roseola infantum and acute otitis media (Haslam, 1996). There is no well established documentation of possible causes of pyrexia in Thai children with first febrile seizures. Hence, we have conducted this research in order to evaluate the etiologies of fever in children with first febrile seizures.

MATERIALS AND METHODS

Children admitted between January 1997 and December 1998 in Bhumibol Adulyadej Hospital with first febrile seizures were eligible for enrollment. The inclusion criteria were (1) age between 3 months and 3 years, (2) temperature > 38.5ºC rectally, (3) no history of afebrile seizure, (4) no underlying neurologic and metabolic conditions, (5) no evidence of active central nervous system infection (*ie*, meningitis). Prospectively recorded medical protocols in terms of age, sex, maximal body temperature, characteristics and duration of seizures, symptoms and signs, laboratory findings and diagnosis upon discharge were reviewed. Two milliliters of blood were obtained before discharging the patients (day 2-6 of fever) and sera were kept frozen at -20ºC until tested. The sera were tested for human herpesvirus-6 (HHV-6) IgM and IgG antibodies by enzyme-linked immunosorbent assay (ELISA) (PanBio, Australia), at the Virology Unit, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, and the results were interpreted as positive, intermediate or negative according to the manufacturer's recommendation. The sera were also tested for dengue virus IgG and IgM, using the ELISA technique and the results were interpreted as positive (IgG or IgM ≥ 40 IU/ml) or negative (IgG and IgM < 40 IU/ml) at the Armed Forces Research Institute of Medical Sciences (AFRIMS). Moreover, the sera were tested for Japanese B encephalitis (JE) virus IgG and IgM antibodies due to the possible cross-reaction with dengue virus antibodies.

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RESULTS

A total of 82 children were enrolled. Their age ranged from 5-36 months, with a mean age of 14.7 months. Forty-one children were boys and 41 were girls. The average maximal body temperature during hospitalization was 39.7ºC. Seizures usually developed during the first two days of fever (92.7%) and were mostly of simple type (90.2%). The duration of seizures varied from 1 to 30 minutes. Presenting symptoms and signs were coryza (70.7%), diarrhea (24.4%), vomiting (19.5%), inflamed tympanic membranes (7.3%), exanthema (6.1%) and enanthema (2.4%).

Causes of fever documented upon discharge of the patients included upper respiratory tract infection (URTI) (53.7%), nonspecific febrile illness (15.9%), diarrhea (13.4%), urinary tract infection (UTI) (6.1%), viral infection (3.7%), pneumonia (2.4%), herpangina (1.1%), measles (1.1%), pneumococcal bacteremia (1.1%) and dengue fever (1.1%). Among 44 cases of URI, there were 31 cases of common cold, 6 cases of pharyngitis, 6 cases of otitis media and one case of sinusitis.

There was one blood culture positive for *Streptococcus pneumoniae*, five urine cultures were positive for *E. coli* (4) and mixed *Klebsiella / P. mirabilis* (1), and three stool cultures were positive for *Shigella* group D (1) and *Salmonella* spp (2). Serologic tests for HHV-6 IgM antibodies yielded positive results in 7 children (8.5%) and intermediate results in 35 children (42.7%). Of 7 documented cases of HHV-6 infection, the clinical diagnosis included otitis media (2), nonspecific febrile illness (2), UTI (1), diarrhea (1) and dengue fever (1). Serologic tests for HHV-6 IgG antibodies showed positive results in 57 children (69.5%) and intermediate results in 10 children (12.2%). Serologic tests for dengue and JE virus antibodies showed negative results in all sera.

DISCUSSION

Our study has shown that URTI was the most common cause of pyrexia in children with first febrile seizures. This was identical to the results obtained by a recent study which showed that URI and GI infection were the most two common causes of fever in this group of children (Hoonsawas *et al*, 1999). However, serologic tests for viral infection were not performed in their study. In comparison with the previous study (Barone *et al*, 1995), we found HHV-6 infection not to be a frequent cause of fever in our children (25.8% *vs* 8.5%), possibly due to the different methods of investigation and timing of blood collection. There were 35 children whose sera were interpreted as yielding intermediate results (possible HHV-6 infection). This might be due to early blood collection while the level of IgM antibody was rising. Unfortunately, we did not collect the convalescent sera to confirm the HHV-6 IgM or 4-fold rising of HHV-6 IgG tests. Additionally, at least 69.5% of the children had had previous HHV-6 infection.

A study of dengue infection during infancy has demonstrated that convulsions in dengue infants were more commonly found than in older children, probably due to febrile seizures (Pancharoen and Thisyakorn, 1998). However, we did not demonstrate dengue infection in our patients. Even though one of our children was clinically diagnosed as dengue fever, his serum was eventually tested and found positive for HHV-6 IgM and negative for dengue antibodies. In addition to these three viruses, several viruses can cause high fever in young children. Previous studies on the seroprevalence of cytomegalovirus and Epstein-Barr virus infections in Thai children have shown that these infections occur at a younger age (Pancharoen *et al*, 1998; Mekmullica *et al*, 1998). Serologic tests for other viruses including herpesviruses may help identify additional etiologies of fever.

In summary, URTI is the most common cause of fever in children aged between 3 months and 3 years with first febrile seizures. HHV-6 infection is not uncommon and serologic tests may be useful. To elucidate the causes of fever, both clinical and laboratory approaches, including bacteriologic and serologic methods, may be required.

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