

Clinical characteristics of febrile convulsions during primary HHV-6 infection

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Abstract

Objective—To clarify clinical characteristics of children with febrile convulsions during primary human herpesvirus 6 (HHV-6) infection.

Subjects and methods—The clinical characteristics of first febrile convulsion were compared between those with and without primary HHV-6 infection in 105 children. HHV-6 infection was verified by culture or acute/convalescent anti-HHV-6 antibody titres.

Results—Primary infection with HHV-6 was seen in 21 of 105 patients with febrile convulsions (3 upper respiratory infection, 1 lower respiratory infection, and 17 exanthem subitum). 13 of 23 patients < 1 year, 19 of 79 patients with first febrile convulsion, and 2 of 15 with second convulsion were infected with HHV-6. The median age of patients with first febrile convulsion and HHV-6 was significantly lower than those without infection. The frequency of clustering seizures, long lasting seizures, partial seizures, and post-ictal paralysis was significantly higher among those with primary HHV-6 infection than among those without. The frequency of atypical seizures in 19 patients with first febrile convulsion associated with primary infection was significantly higher than in 60 patients without primary infection. The frequency in infants younger than 1 year of age was also significantly higher than that in 10 age matched infants without primary infection.

Conclusions—These findings suggest that primary infection with HHV-6 is frequently associated with febrile convulsions in infants and young children and that it often results in the development of a more severe form of convulsions, such as partial seizures, prolonged seizures, and repeated seizures, and might be a risk factor for subsequent development of epilepsy.

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Keywords: febrile convulsion; human herpesvirus 6; risk factors; exanthem subitum; epilepsy

Exanthem subitum (roseola infantum) is a common infectious disease in infancy, which is characterised by fever persisting for three to five days and the appearance of a skin rash after subsidence of the fever. The disease is caused by primary infection with human herpesvirus 6 (HHV-6).^{1,2} It is well known that febrile

convulsions are common during the course of exanthem subitum.³ Several reports before the discovery of HHV-6 also indicated the occurrence of more serious central nervous system (CNS) complications or permanent sequelae.⁴⁻⁸ For many years, it was believed that febrile convulsions associated with exanthem subitum were the result of fever. However, recent reports suggest that the virus may invade the CNS during exanthem subitum and cause encephalitis, encephalopathy, or other CNS complications.⁹⁻¹²

Viral DNA is also frequently found in cerebrospinal fluid (CSF) samples from patients with exanthem subitum who have convulsions, bulging fontanelle, or both.¹³ However, current understanding of the clinical features of patients with primary HHV-6 infection and febrile convulsions is limited. In our study, we evaluated the involvement of primary HHV-6 infection in patients with febrile convulsions in childhood and compared the clinical features and backgrounds of these patients with those without evidence of primary HHV-6 infection to ascertain the clinical characteristics of children with febrile convulsions during primary HHV-6 infection.

Materials and methods

STUDY POPULATIONS

From February 1996 to July 1997, 105 infants and children who visited Fujita Health University Hospital and Showa Hospital as a result of febrile convulsions were enrolled. For the purposes of our study, the case definition of a febrile convulsion was a convulsive seizure in infants and children in association with a fever of 38.0°C or higher, but without evidence of any definitive causative disease, such as CNS infection, metabolic abnormality, or intoxication. Thus, both simple and complicated febrile convulsions were included. The age ranged from 1 to 77 months, with a median of 20.0 months (59 boys and 46 girls). All patients had no past history of afebrile seizure before the febrile convulsion. Blood samples were collected at least twice during the acute phase (within three days after rise of fever) and the convalescent phase (later than four days after rise of fever). Informed consent was obtained from parents of the subjects enrolled in our study after the project had been explained thoroughly. Our study was approved by the ethics committee of the university.

PRIMARY HHV-6 INFECTION

Antibody titres to HHV-6 were measured by an indirect immunofluorescence assay, as described previously.¹⁴ Isolation of HHV-6 was

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performed by co-cultivating peripheral blood mononuclear cells from patients with cord blood mononuclear cells, as described elsewhere.³ Primary HHV-6 infection was confirmed if the following criteria were met: (1) isolation of the virus from blood during the acute phase, and/or (2) seroconversion or a fourfold or greater increase in IgM or IgG antibody titres to the virus. Patients who did not meet these eligibility criteria were allocated to the no primary HHV-6 infection group.

DATA COLLECTION

We evaluated the clinical course, in particular, features of seizures, and complete physical and specific laboratory findings for CNS disorders. CSF samples were obtained at the onset of febrile convulsions in 20 patients. Electroencephalography (EEG) and cerebral computed tomography (CT) were performed within one to two weeks after the onset of febrile convulsions in 99 and 22 patients, respectively. We defined an EEG abnormality as the presence of paroxysmal discharges without high voltage slow waves in the background. We inquired about a previous history of convulsions and neurological abnormalities or developmental retardation and family history of febrile convulsions and epilepsy in parents/siblings in all cases.

For evaluation of factors related to recurrent febrile convulsions and the subsequent onset of epilepsy in patients with a first febrile convulsion, risk factors (warning factors) were used according to the criteria of Fukuyama *et al.*¹⁵ Risk factors were as follows:

- (1) Those related to the onset of epilepsy, namely: (i) apparent manifestations of neurological abnormalities or developmental retardation before the onset of febrile convulsions; (ii) atypical seizures (partial seizures, seizures lasting longer than 15–20 minutes (because parents often could not recall the precise duration), clustering (two or more) seizures within 24 hours); and (iii) family history of epilepsy in parents/siblings.
- (2) Those related to the recurrence of febrile convulsions: (i) febrile convulsion onset under

the age of 6 months; and (ii) a family history of febrile convulsions in one or both parents.

STATISTICAL ANALYSIS

The results obtained were analysed using the Mann-Whitney U test and χ^2 test. Values of $p < 0.05$ were considered to be significant.

Results

DIAGNOSIS

Primary HHV-6 infection was found in 21 (20%) of 105 patients with febrile convulsions. Acute infection with HHV-6 was verified by isolation of the virus in seven, virus isolation and serological response in five, and seroconversion or a significant increase in IgM or IgG antibody titres to the virus in nine. The other 84 patients (80%) were classified as having no primary HHV-6 infection. The clinical diagnosis of the 105 patients was as follows: upper respiratory infection in 52 (50%), lower respiratory infection in 24 (23%), exanthem subitum in 18 (17%), measles in four (4%), mumps in three (3%), enterocolitis in two (2%), and urinary tract infection in two (2%). Primary HHV-6 infection was found in three of 52 patients with upper respiratory infection, one of 24 with lower respiratory infection, and 17 of 18 with exanthem subitum.

AGE DISTRIBUTION

The age of patients with primary and no primary HHV-6 infection with febrile convulsions showed the following distribution: < 6 months, one *v* one; 6–11 months, 12 *v* nine; 1–2 years, eight *v* 43; 3–4 years, none *v* 25; and 5–6 years, none *v* six. Primary HHV-6 infection was found in 13 of 23 patients younger than 1 year of age.

FEBRILE CONVULSION EPISODE

Of the 105 patients, the febrile convulsion was the first episode in 79 (75%), the second in 15 (14%), third in five (5%), fourth in three (3%), fifth in two (2%), and eighth in one (1%). Primary HHV-6 infection was found in 19 of 79 patients having their first febrile convulsion episode and two of 15 with their second episode, but was not found in febrile convulsion episodes thereafter.

COMPARISON OF CLINICAL FEATURES AND BACKGROUNDS

The clinical features and backgrounds of patients having their first febrile convulsion with and without primary HHV-6 infection are shown in table 1. The first febrile convulsion episode was seen in 19 of 21 patients with primary HHV-6 infection and 60 of 84 with no primary HHV-6 infection. The median age of patients with primary HHV-6 infection was significantly lower than that of patients with no primary HHV-6 infection. There were no significant differences in sex, duration of fever, maximum body temperature, or day of febrile convulsion onset between those with and without primary HHV-6 infections. The frequency of mental retardation and family history of febrile convulsions and epilepsy was similar in both groups. The percentage of clustering

Table 1 Comparison of clinical features and backgrounds in patients with first febrile convulsion with and without primary human herpesvirus 6 (HHV-6) infection

	Primary HHV-6 infection (n = 19)	No primary HHV-6 infection (n = 60)
Age in months (median (range))	10.0** (5–26)	20.0** (1–74)
Number of girls	5	28
Mean duration of fever (days)	3.2	3.6
Mean maximum temperature (°C)	39.8	39.5
Mean onset of febrile convulsion (day)†	0.6	0.4
Mental retardation	0	1
Family history of febrile convulsions	6	10
Family history of epilepsy	0	0
Clustering seizures	7*	8*
Long lasting seizures	6*	6*
Partial seizures	4*	1*
Postictal paralysis	3*	0*
Prolonged disturbance of consciousness	0	0
Mechanical ventilation	0	0
Abnormal CSF findings	0/9	0/6
Abnormal EEG findings	0/18	2/55
Abnormal CT findings	1/10	0/6

* $p < 0.05$, ** $p < 0.01$ significant difference between both groups.

†The first day of fever was assigned as day 0.

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalograph.

Table 2 Risk factors for recurrent febrile convulsions and subsequent development of epilepsy in patients with or without primary human herpesvirus 6 (HHV-6) infection at the first febrile convulsive episode

	All infants with first febrile convulsions episode			Infants younger than 1 year with first febrile convulsions episode		
	Primary HHV-6 infection (n = 19)	No primary HHV-6 infection (n = 60)	p Value	Primary HHV-6 infection (n = 12)	No primary HHV-6 infection (n = 10)	p Value
Recurrent febrile convulsions						
Under 6 months	1	1	NS	1	1	NS
Family history of febrile convulsions	6	10	NS	4	1	NS
Epilepsy						
Mental retardation	0	1	NS	0	1	NS
Family history of epilepsy	0	0	NS	0	0	NS
Atypical seizures*	11	13	< 0.01	8	2	< 0.05

*Partial seizures and/or long lasting seizures more than 15–20 minutes in duration and/or clustering (two or more) seizures within 24 hours after onset. NS, not significant.

seizures ($p < 0.05$), long lasting seizures ($p < 0.05$), partial seizures ($p < 0.05$), and postictal paralysis ($p < 0.05$) was significantly higher in those with primary HHV-6 infection than in those without. CSF findings were all within normal ranges. EEGs were performed in 99 (94%) of the 105 patients. Of those, the test was performed at the first febrile convulsion episode in 73. Paroxysmal abnormalities were seen in two patients with no primary HHV-6 infection. Of the 16 patients with their first febrile convulsion episode evaluated by cerebral CT scanning, one patient with primary HHV-6 infection showed mild brain oedema at the onset of febrile convulsions. There were no significant differences in the frequency of abnormalities in CSF, EEG, or cerebral CT scanning findings between the two groups.

RISK FACTORS

Using practical guidelines for the management of febrile convulsions set by Fukuyama *et al.*,¹⁵ we examined the frequency of risk factors for recurrent febrile convulsions and the subsequent development of epilepsy between both patient groups with and without primary HHV-6 infection having their first febrile convulsion episode (table 2). Although a family history of febrile convulsions was found more frequently in those with primary HHV-6 infection than in those without, there was no significant difference between groups. Among the three risk factors for epilepsy, the frequency of atypical seizures was significantly higher ($p < 0.01$) in primary HHV-6 infection (11 of 19) than in no primary HHV-6 infection (13 of 60).

When the frequency was compared between infants younger than 1 year of age with (12 infants; median age, 9.5 months) and without (10 infants; median age, 8.5 months) primary HHV-6 infection, the atypical seizures were seen more frequently in infected patients (eight of 12) than non-infected patients (two of 10) ($p < 0.05$).

Discussion

Febrile convulsions are age dependent, with a peak age at 14–18 months, and are rare before 9 months and after 5 years of age. It is well known that viral infections of the upper respiratory tract, exanthem subitum, and acute otitis media are frequently associated with febrile convulsions.¹⁶ In our study, approximately 90% of patients with febrile convulsions

had upper and lower respiratory tract infections or exanthem subitum. The age distribution of febrile convulsions ranged from 1 month to 77 months and the peak age was 1–2 years. Primary HHV-6 infection was found in 20% of patients with febrile convulsions and more than half of these patients were younger than 1 year. The median age of patients with primary HHV-6 infection was significantly lower than those without primary HHV-6 infection, which can be easily understood in view of the fact that in Japan more than 90% of infants are infected with the virus by 1 year of age.^{14 17 18} Three quarters of our patients were experiencing a first febrile convulsion, in one quarter of whom it was caused by primary HHV-6 infection. Therefore, primary HHV-6 infection should be considered when encountering children under the age of 1 year with a first febrile convulsion. Recently, several papers have reported a high association between primary HHV-6 infection and occurrence of febrile convulsions. Hall *et al* reported HHV-6 complications in febrile children seen in an emergency department; they estimated that 31% of febrile convulsion cases were associated with acute HHV-6 infection.¹⁹ Other laboratories have reported a frequency of HHV-6 infection in 26–35% of children with febrile convulsions,^{20–22} which is compatible with our data.

This is the first report that the frequency of clustering seizures, long lasting seizures, partial seizures, and postictal paralysis in children having their first febrile convulsion episode is significantly higher in those with primary HHV-6 infections than those without. For the evaluation of factors predicting recurrent febrile convulsions and the subsequent onset of epilepsy in patients with or without primary HHV-6 infection in the first febrile convulsion episode, risk factors were used according to the criteria set by Fukuyama and colleagues,¹⁵ which are widely used as practical guidelines for physicians for the management of febrile convulsions in Japan. In our series, we studied the first febrile convulsion episode in 79 patients (19 with primary HHV-6 infection and 60 without primary infection). Although two categories (under 6 months of age and family history of febrile convulsions) that predict recurrent febrile convulsions were seen more frequently in primary HHV-6 infection than in controls, the difference was not significant. This is supported by a recent report²³ in which

it was shown that primary HHV-6 infection did not reveal an increased risk for recurrent febrile convulsions. On the other hand, the frequency of atypical seizures, one of the three categories that predict the subsequent development of epilepsy, was significantly higher among children with primary HHV-6 infection than in controls. In particular, atypical seizures were seen more frequently in patients with primary HHV-6 infection younger than 1 year compared with age matched patients without primary HHV-6 infection.

The association between febrile convulsions, HHV-6 infection, and atypical seizures is not understood, although it might be explained by the neurotropic nature of the virus, as supported by in vitro experimental data.²⁴ For example, it is well known that febrile convulsions occur early in the febrile course, when both peripheral blood mononuclear cell associated and cell free viraemia are frequently detected.²⁵ Viral DNA has frequently been detected by polymerase chain reaction (PCR) amplification in CSF obtained from infected children with or without CNS complications, and even in CSF samples without pleocytosis.^{10-13 26 27} It would be of particular interest to evaluate the relation between the density of HHV-6 in CSF and the development of atypical seizures. In addition, it is reported that localised inflammatory or oedematous changes occur temporarily in brain tissues in patients with encephalitis or encephalopathy, presumably in association with viral invasion.^{11 28 29}

Together, these results suggest that HHV-6 might invade the CNS during primary infection, infect neural and glial cells, and result in a more severe form of febrile convulsions. Alternatively, the impairment of cerebral blood flow for a short duration by virally induced vasculitis could explain the development of atypical seizures.³⁰⁻³² Recently, we reported that HHV-6 antigen could be detected in the endothelial cells of small vessels in the frontal lobe of brain from a fatal case of primary HHV-6 infection.²⁹ The possibility of viral invasion of the CNS during primary HHV-6 infection is supported by molecular and immunohistochemical studies showing wide distribution of HHV-6 in the brain tissues of a high proportion of subjects with both normal and altered immunity.³³⁻³⁹ Thus, febrile convulsions associated with HHV-6 infection might be the result of the direct invasion of the virus into the CNS and not simple fever. Because febrile convulsions associated with primary HHV-6 infection often develop into a more severe form, which might be a risk factor for subsequent epilepsy, a follow up study over a longer period is required to confirm this.

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FETAL AND NEONATAL EDITION

January 2000 issue

The following articles—being published in the January 2000 issue of the *Fetal and Neonatal* edition of the *Archives of Disease in Childhood*—may be of general interest to paediatricians.

International randomised controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome

J H Baumer

Randomised controlled trial of patient triggered and conventional fast rate ventilation in neonatal respiratory distress syndrome

M W Beresford, N J Shaw, D Manning

Premedication before intubation in UK neonatal units

S Whyte, G Birrell, J Wylie

Randomised controlled trial of thiopental for intubation in neonates

A Bhutada, R Sahni, S Rastogi, J-T Wung

Local anaesthetic effect of topical amethocaine gel in neonates: a randomised controlled trial

A Jain, N Rutter