ORIGINAL ARTICLE

Relationship between five common viruses and febrile seizure in children

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Objectives: To examine the role of viruses in febrile seizures (FS) by comparing the relative risk (RR) of developing FS with common viral infections and subsequent risk of recurrence.
Methods: We matched the medical records of all children admitted with FS over 5 years and the contemporary records for all admissions for febrile illnesses associated with influenza, adenovirus, parainfluenza, respiratory syncytial virus (RSV) and rotavirus to calculate the RR of FS following these viral infections. For patients admitted for a first FS, we carried multivariate analysis for type of viral infection, age of onset, family history, complex FS features and maximum temperature during the episode, to identify the risk factors for recurrence.
Results: There were 923 admissions for FS, of which 565 were for first seizures. The five most common viruses in FS were influenza (163/923, 17.6%), adenovirus (63/923, 6.8%), parainfluenza (55/923, 6%), RSV (25/923, 2.7%) and rotavirus (12/923, 1.3%). Incidences of FS in febrile illnesses due to these viruses were 20.8% (163/785) for influenza, 20.6% (55/267) for parainfluenza, 18.4% (63/343) for adenovirus, 5.3% (25/468) for RSV and 4.3% (12/280) for rotavirus. Complex FS occurred in 20.6% (n = 191) and the risk of developing complex FS was similar for the five viruses. Overall recurrence rate was 20.5% and was not predicted by type of viral infection.
Conclusion: The risk of developing FS is similar with influenza, adenovirus or parainfluenza and is higher than with RSV or rotavirus. Type of viral infection is not important in predicting complex features or future recurrences.

Febrile seizures (FS) are common causes of paediatric admission and parental concern.[1] The incidence of FS varies from 0.5–1.5% in China to 2.2–2.3% in North America and 8.8% in Japan.[2] Several long-term population-based studies have shown that the long-term outcome is benign[3 4] in terms of recurrence,[5–8] the development of unprovoked seizures[9 10] and neurodevelopment.[11–13]

On the other hand, studies on aetiology are less conclusive. Viral infection has been hypothesised to be one of the important causative factors. Different viral infections were shown to be present in at least 40% of children with FS in early clinical studies.[14–16] More recently, some viruses are postulated to be more "neurotropic" and more important in the causation of FS.

Human herpesvirus 6 (HHV-6) was found in one third of patients with FS by Hall *et al*[17] and was shown to be important in recurrence.[18] Chiu *et al* have shown that the risk of FS following influenza A infection was higher compared to other respiratory viruses and was associated with repeated seizures in the same febrile episode.[19] Van Zeijl *et al* suggested the importance of influenza A in recurrent FS by co-relating the seasonality of influenza A and FS.[20] Rotavirus-related gastro-enteritis was found to have twice the risk of seizure compared to other causes of gastroenteritis and also caused seizure without fever.[21–23] However, these studies all focused on a specific type of viral infection and did not compare different viral infections. Similarly, implicating causative association by correlation with seasons might have inappropriately neglected other confounders, including other co-circulating viruses in the same season.

We study the relationships of various viral infections in the clinical course of FS. A retrospective cohort study was conducted to examine whether some viruses might cause more FS (simple or complex types) and whether the type of viral infection predicts future recurrence of FS.

METHODS

In Hong Kong, the public hospitals provide more than 90% of in-patient and out-patient medical services. Our centre (Queen Mary Hospital) is a university-affiliated hospital and is the only public paediatric service provider (both ambulatory and in-hospital care) for the Western District of Hong Kong Island, with a population of 100 000 children aged 15 years or below. Our accident and emergency department provided 24 h free service until 2004. Also, as the attending physicians are non-paediatricians, all young children and infants with acute conditions including convulsion are routinely admitted to the paediatric wards. These special features in our health care system have enabled us to capture patients with FS without biasing towards the more severe spectrum and have allowed sophisticated clinical assessment and extensive investigations to confirm the diagnosis and causative agents.

Study population

A retrospective review on all children admitted to Queen Mary Hospital with FS was conducted for the 5 year period from March 1998 to February 2003, using the International Classification of Disease – 9th Edition, Clinical Modification (ICD-9-CM) discharge coding for FS (ICD-9-CM code 780.31).

We have avoided two recent important endemics in Hong Kong, namely the 1997 avian influenza endemic and the 2003 SARS endemic as they might affect the usual hospitalisation pattern. A relatively long study period (5 years) was selected in order to increase our sample size and to reduce the effect of temporal or seasonal variation commonly observed in viral infections.

Abbreviations: FS, febrile seizure; HHV-6, human herpesvirus 6; RR, relative risk; RSV, respiratory syncytial virus; UTI, urinary tract infection

Definition of FS, and inclusion and exclusion criteria

The computerised clinical records of children admitted for FS were reviewed. In our department, there is a standardised template for the computerised records of FS to facilitate data retrieval. The full clinical records were reviewed whenever the clinical information from the computerised records was inadequate or incomplete.

For FS, the definition by the National Institutes of Health Consensus Conference (1980)[1] was used to determine the inclusion criteria. This definition is often used as a practical definition for both management and research in children with FS. Children with history of afebrile seizure, evidence of central nervous infection and underlying neurological disorders were excluded. Simple FS was defined as primary generalised convulsion lasting less than 15 min and not recurring within 24 h, while complex FS was defined as focal or prolonged (>15 min) convulsion and/or more than one convulsion in 24 h.[1–4]

We defined maximum temperature as the highest rectal temperature recorded during the period of admission, and the duration of fever was the total duration of fever within the febrile episode. All children discharged when afebrile. The patient's characteristics (ie, gender, age at presentation of FS, simple/complex features, presence of family history of febrile/afebrile seizure, clinical diagnosis, duration of fever and maximum temperature during the illness) were reviewed.

Virological investigations

Since 1996, all children admitted with fever and/or symptoms of upper respiratory infections have had routine nasopharyngeal aspirate collected for rapid viral detection and culture, whether the child has had seizures or not. The antigen detection tests identified a panel of five respiratory viruses including influenza A and B, respiratory syncytial virus (RSV), parainfluenza and adenovirus using immunofluorescence techniques. The sensitivity and specificity were 85.9% and 87.1%, respectively, when compared to standard viral culture.[24] The results were available within 24 h of admission and have been proven to be cost-effective in the management of patients with upper respiratory tract infection.[25] At the same time, this practice also avoided the diagnostic bias caused by selective viral investigations for more seriously ill children or for children admitted with FS.

Stool enzyme immunoassays (for rotavirus) and cultures (for both bacteria and virus), and urine and blood cultures were performed whenever there was clinical suspicion of gastroenteritis, urinary tract infection (UTI) or bacteraemia. The sensitivity and specificity for enzyme immunoassays for rotavirus detection were 82–94% and 90–95%, respectively,[26] and the results were available within 2 days. However, HHV-6 serology and polymerase chain reaction were not routinely performed in our microbiology laboratory and a diagnosis of roseola infantum was based on clinical findings.

Recommendations from the evidence-based clinical guidelines on FS issued by the Hong Kong College of Pediatricians were followed in the investigation and management of children with FS.[27] Lumbar puncture was performed in most cases for the first ever FS in a young child, especially children aged <18 months. Those patients with abnormal lumbar puncture results were excluded from the present study.

Relative risk for developing FS and risk factors for FS recurrence

The data of all children with the discharge coding (primary and secondary) admitted with FS were analysed to identify the commonest infective agents isolated, which were influenza, parainfluenza, RSV, adenovirus and rotavirus.

The records of all paediatric patients admitted during the same study period, with a discharge coding for any of these five viruses, were retrieved by ICD-9 coding, regardless of whether the child had FS or not (487.1 for influenza, 079.89 for parainfluenza, 079.6 and 466.11 for RSV, 079.0 for adenovirus and 008.61 for rotavirus according to ICD-9-CM).

The temperature charts of these patients were retrieved and analysed, including the temperature taken at the accident and emergency department. Clinical diagnosis of the febrile episode was made according to history, physical examination and laboratory results. Those admitted without documented fever or with underlying neurodevelopmental disorders were excluded from the study.

The names and identity numbers of the patients in the two cohorts, that is, the patients admitted with FS and those admitted with febrile illness with any of the five viruses, were then matched. The RR (relative risk) of developing FS related to each of these five viral infections was defined as the number of patients developing FS divided by the total number of patients admitted with febrile illness related to that particular viral infection.

Patients admitted for their first FS were identified and all their subsequent in-patient and out-patient records were retrieved to identify any recurrences. Unpaired *t*-test and χ^2 test were used to compare continuous and categorical variables, respectively, between groups with and without recurrence of FS. Risk factors, including documented risk factors from previous studies[5–8] and the different types of viral infection, were examined by univariate analysis. Odd ratios were calculated for individual risk factors with 95% confidence intervals. Multivariate logistic regression analysis was used to examine the risk of recurrence after adjustment for individual risk factors. The Kaplan–Meier method was used to calculate the probability of recurrence with or without one or more risk factors and the overall recurrence risk during the follow-up period. A p-value <0.05 was taken as statistically significant.

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority (West Cluster) of Hong Kong.

RESULTS

Clinical features of children with FS

During the 5 year study period, there were 923 admissions for FS of which 565 were first FS. The male to female ratio was 1.4:1 and the mean age of onset was 2.1 ± 1.1 years.

A family history of FS or epilepsy was found in 17.5% and 2.7% of children, respectively. The seizures were simple in 732 (79.4%) and complex in 191 (20.6%). Of the 191 children with complex seizures, 24 had focal seizures, seizures were prolonged in 29 (duration >15 min) and 148 had repeated seizures within the same febrile episode.

The mean maximum temperature documented from admission in the accident and emergency department to discharge was 39.6 ± 0.61℃. The mean duration of fever was 2.46 ± 1.39 days.

Respiratory tract infection was the most common cause of fever and this was present in 79.5% of all admissions for FS. Gastroenteritis was second (5.5%) followed by roseola infantum (2.9%), UTI (1.1%) and bacteraemia (0.9%). Other causes of fever included post vaccination fever, Kawasaki disease, infectious mononucleosis, rubella, chickenpox and other non-specific viral illnesses.

Among all infectious agents identified, influenza (163/923, 17.6%) was the most common, followed by adenovirus (63/923, 6.8%), parainfluenza (55/923, 6.0%), RSV (25/923, 2.7%) and rotavirus (12/923, 1.3%). These five viral agents were present in

Table 1 Relative risk of developing febrile seizure following febrile illness associated with viral infections

Virus	Total number of febrile episodes	Number of episodes associated with FS (%)	Relative risk (95% CI)	p Value
Influenza	785	163 (20.8)	4.85 (2.74 to 8.57)	<0.001
Parainfluenza	267	55 (20.6)	4.81 (2.63 to 8.77)	<0.001
Adenovirus	343	63 (18.4)	4.29 (2.35 to 7.78)	<0.001
Respiratory syncytial virus	468	25 (5.3)	1.25 (0.64 to 2.44)	0.603
Rotavirus	280	12 (4.3)	Reference	

34.4% (318/923) of all admissions with FS in the 5 year study period.

Relative risks of developing FS due to influenza, parainfluenza, adenovirus, RSV or rotavirus

In the 5 year study period, there were 874 admissions for influenza, 333 for parainfluenza, 377 for adenovirus, 604 for RSV and 414 for rotavirus. Record review excluded 283 admissions without fever and 170 admissions of children with underlying neurological disorders or developmental delay. Six children were further excluded because their clinical histories were compatible with either acute viral encephalitis (n = 1, nasopharyngeal aspirate positive for parainfluenza virus) or acute encephalopathy of unknown aetiology (n = 5). Therefore, the total number of admissions was 785 for influenza, 267 for parainfluenza, 343 for adenovirus, 468 for RSV and 280 for rotavirus.

Matching these data showed that the incidence of FS in children hospitalised with influenza was 20.8% (163/785) for influenza, 20.6% (55/267) for parainfluenza, 18.4% (63/343) for adenovirus, 5.3% (25/468) for RSV and 4.3% (12/280) for rotavirus. The RRs of developing FS in a febrile illness caused by these five viruses are shown in table 1. The RRs of FS were similar for influenza, parainfluenza and adenovirus infection and were significantly higher than for RSV and rotavirus. The ratios of simple:complex FS were 42:121 for influenza, 12:43 for parainfluenza, 13:50 for adenovirus, 3:22 for RSV and 3:9 for rotavirus. Comparison showed that there was no significant difference (p = 0.612).

Recurrence of FS

A total of 565 children were admitted with first FS during the study period. The median follow-up was 3.08 ± 1.69 years. Of these 565 children, 82.5% were followed up for >1 year, 67.4% for >2 years and 51.8% for >3 years. Recurrence occurred in 18.2% (103/565) and the overall recurrence rate was 20.5%. Using the Kaplan–Meier method, the risk of recurrence was found to reach a plateau at the end of the second year of follow-up.[28] Univariate and multivariate analyses of the various risk factors showed that only three risk factors were significantly related to recurrence: (i) younger age (<1.5 years) of onset (OR 1.89, 95% CI 1.22 to 2.94), (ii) a family history of FS (OR 1.84, 95% CI 1.06 to 3.21) and (iii) complex FS at first presentation (OR 1.81, 95% CI 1.06 to 3.08). The type of viral infection in the first FS was not a significant risk factor (table 2).

DISCUSSION

We have found that influenza was the most commonly identified virus in children with FS. Using data by Chiu *et al*[29] on influenza-related paediatric hospitalisation in Hong Kong in 1998–1999, the population risk of FS for influenza would be about 40–43 per 10 000 under 5 years of age. This agrees with another study of 499 patients with FS conducted in our hospital over a 2 year period from 1996 to 1998.[19] In that study, it was also shown that there is an increased risk of FS with influenza compared to parainfluenza or adenovirus, and influenza-related FS was shown to have more complex features. These findings, however, could not be replicated in our present study with more patients and a longer study period. There was no difference in either the RR of developing FS or the tendency for complex features. Furthermore, the type of viral infection was not found to be associated with subsequent recurrence in our study. In fact, in contrast to observations in Asian countries such as Japan and Hong Kong, influenza infection is not as commonly associated with FS in Europe or the United States.[30] HHV-6 infection, on the other hand, is the most frequently associated virus and accounts for a third of all first FS in children <2 years of age in Europe and the USA.[30] It is possible that the apparent importance of influenza in previous studies might only reflect a higher incidence of influenza in the locality but not a genuine neurotropic property causing FS.

Our other findings on the risk factors for FS recurrence, however, were similar to many previous studies.[5–8] Young age at onset, complex features and a family history of FS were

Table 2 Univariate and multivariate regression analysis for recurrence of febrile seizure

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p Value	OR (95% CI)	Adjusted p value
Sex	1.16 (0.74 to 1.79)	0.577		
Age of onset <1.5 years	1.91 (1.24 to 2.95)	0.005	1.89 (1.22 to 2.94)	0.004
Family history of febrile seizures (first degree relatives)	1.85 (1.07 to 3.19)	0.036	1.84 (1.06 to 3.21)	0.028
Family history of epilepsy (first degree relatives)	1.65 (0.51 to 5.31)	0.604		
Complex seizure	1.79 (1.06 to 3.03)	0.041	1.81 (1.06 to 3.08)	0.028
Maximum temperature >40°C	0.71 (0.44 to 1.13)	0.424		
Maximum temperature >39°C	0.56 (0.32 to 0.96)	0.05		
Infections				
Influenza	0.66 (0.34 to 1.31)	0.31		
Adenovirus	1.22 (0.52 to 2.90)	0.55		
Parainfluenza	1.08 (0.43 to 2.71)	0.86		
Respiratory syncytial virus	1.52 (0.47 to 4.79)	0.7		
Rotavirus	1.12 (0.23 to 5.37)	0.88		

constant risk factors replicated by many large population-based cohort studies[28] and all suggested the important role of individual susceptibility in the pathogenesis of FS. Recent genetic association studies of polymorphisms in various cytokine/interleukin genes[31–34] also supports the importance of individual susceptibility. In a Danish population-based twin study, it was shown that heritability of FS was 70%, while individual-specific environmental factors, including different viral infections, could only account for the remaining 30% non-heritable variation.[35]

There are several limitations to our study. Firstly, despite our effort to identify an infectious cause in our patients admitted with fever or with FS, only about 40% of our cases of FS were found to have a definitive viral aetiology (for example, our microbiology laboratory does not routinely test for HHV-6). Previous findings in our department showed that 72% of children with laboratory evidence of primary HHV-6 infection had typical clinical features of roseola infantum infection.[36] With 2.9% of our children having clinical roseola infantum infection, we estimate that 35 cases of HHV-6 might be present in our cohort, making HHV-6 the fourth most common cause of fever in FS. As for the remaining patients with clinical viral syndromes but negative virological studies, the aetiology can be very heterogeneous and we have to exclude them from our analysis.

Secondly, our recurrence risk seems to be lower than that of previous studies.[5–8] Our centre is the only public hospital providing paediatric in-patient as well as out-patient services to all children in our catchment area. Therefore, all patients admitted to our centre for their first FS should have been readmitted to our centre in case of recurrence and followed up in our out-patient clinics. However, we believe that numbers may be underestimated as patients may attend private doctors or may move to another district after the first episode of FS, despite the fact that the most recent census suggests that our paediatric population has been relatively stable over the past 5–10 years.[37] Therefore, the estimated recurrence rate will represent the minimal figure.

Thirdly, in our study, the RRs of FS in febrile children admitted with rotavirus and RSV were found to be significantly lower. We do not have a definite explanation for this observation. One reason could be that seizures without fever were excluded even if a virus was identified. There is evidence that viral infection can lead to seizure without fever. Studies including ours have shown an association between afebrile seizures and gastroenteritis,[21–23] and we found that rotavirus-related seizures could occur in both febrile (41%) and afebrile (59%) children.[21] Studies in which HHV-6 or RSV caused afebrile seizures in children have also been reported.[38 39] These afebrile seizures are clinically similar to FS and their exclusion could have underestimated the tendency of developing seizures following rotavirus and RSV infection in our study. This group of children who developed seizures after viral infection without fever, whom we have excluded from this study, shall be our next target of investigation, which may pose a challenge to the traditional concept of ''febrile seizure''.

What is already known on the topic

- Febrile seizure (FS) is commonly associated with viral infection.
- Influenza is associated with a higher incidence of FS than other respiratory viruses, for example adenovirus or parainfluenza.

What this study adds

- Influenza infection is associated with a higher risk of FS than RSV or rotavirus, but not adenovirus or parainfluenza; however, the reason for this is unknown.
- The type of viral infection does not predict complex FS or recurrence risk.

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Severe enterovirus 71 infection

Hand, foot and mouth disease is usually caused by either coxsackievirus A16 or enterovirus 71 (EV71). Coxsackievirus A16 infection usually causes mild disease. Outbreaks of severe, and sometimes fatal, hand, foot and mouth disease with encephalitis and myocarditis have been reported from Bulgaria, Hungary, Malaysia, Singapore and Taiwan. These severe outbreaks have been related to EV71. A follow-up study in Taiwan (Luan-Yin Chang and colleagues. *New England Journal of Medicine* 2007;**356**:1226–34; see also Perspective, ibid: 1204–5) has shown that neurological development is particularly impaired in children who develop cardiopulmonary failure after CNS involvement in the acute phase of EV71 infection.

A severe EV71 epidemic occurred in Taiwan in 1998, and between 1998 and 2003 a total of 621 children were treated for EV71 infection at two major hospitals. They presented with hand, foot and mouth disease, herpangina or fever. A total of 232 of these patients had CNS involvement. Twenty five patients died in the acute phase and 14 died later. The follow-up cohort consisted of 142 patients with CNS involvement in the acute phase: 61 with mild CNS involvement (group 1), 53 with severe CNS involvement (group 2) and 28 with cardiopulmonary failure after CNS involvement (group 3). Median follow-up was 2.9 years (1.0–7.4 years). The children in group 3 were younger at disease onset (median age 0.7 years) than those in groups 1 and 2 (2.0 and 2.3 years). All patients in group 1 (usually with aseptic meningitis) recovered without neurological sequelae. In group 2, 32 patients had had encephalitis, all of whom made a good neurological recovery apart from one who was left with a mild facial palsy. Sixteen patients had had a poliomyelitis-like syndrome and nine of these had unilateral limb weakness and atrophy on follow-up. Five patients had had acute encephalomyelitis and one of these had unilateral limb weakness and atrophy. Of the 28 patients in group 3, 21 (75%) had neurological sequelae. Eighteen had unilateral limb weakness and atrophy, 17 had dysphagia and needed tube feeding, 16 needed ventilator support because of central hypoventilation, seven had facial palsy, five had seizures and psychomotor retardation secondary to hypoxia, and four had seizures alone. Delayed development on the Denver Developmental Screening Test (DDST II) and low full scale IQ (<85) on the Wechsler Intelligence Scale for Children (WISC-III) were much more common in group 3 than in group 2 (75% vs 5% and 50% vs 5% of those tested).

Among children with EV71 infection and severe acute neurological disease, those who went on to develop acute cardiopulmonary failure in the acute phase of the illness were much more likely to have neurological or cognitive impairment on follow-up.