Viruses and febrile convulsions

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SUMMARY In 276 children admitted to hospital with febrile convulsions a wide range of virus types was identified by means of nasopharyngeal secretions and cough/nasal swabs. The overall virus identification rate was 49%. Analysis of age, sex, family history, and past history showed no marked differences between the virus-positive and the virus-negative children. More than 80% had symptoms of respiratory infection in association with their convulsions, whether or not a virus was identified. Convulsions were not apparently more severe in the virus-positive group. Rapid virus diagnosis was found helpful in the management of children with febrile convulsions. The virus aetiology of many febrile convulsions has implications both for hospital cross-infection and for research into methods of prevention.

Febrile convulsions are a common childhood problem. Community studies suggest that more than 2 children in every 100 will experience one or more such seizures in the first 5 years of life (Van Den Berg and Yerushalmy, 1969; P. Harker, personal communication, 1975). Though the eventual prognosis is excellent for the great majority, each episode causes a definite small but unquantified risk of permanent brain damage (Ounsted, 1966/67), is intensely alarming for parents, and often involves admission to hospital at an age which is especially upsetting for the child. About one-quarter of the children who have a febrile convulsion will have a second, and one one-tenth will have further recurrences with an increasing risk of seizures being severe (Lennox-Buchthal, 1973).

The indications for prophylactic anticonvulsant therapy are not agreed (Asnes *et al.*, 1975). Doubts remain about the efficacy of the standard drugs (Melchior *et al.*, 1971; Faerø *et al.*, 1972), which may in any case produce troublesome side effects at this age (Thorn, 1975). These problems make the search for aetiological factors especially relevant. Considerable progress has been made towards the understanding of genetic and perinatal factors which may place a child at special risk of febrile convulsions (Lennox-Buchthal, 1973; Wallace, 1972). Relatively little, however, is known about the aetiology of the febrile illnesses provoking the fit. An association with the features of an upper respiratory tract infec-

tion in approximately two-thirds of cases has been reported (Millichap, 1968). Wallace and Zealley (1970) showed concurrent infection with a variety of viruses in 63% of a series of cases, but the sample studied was small and the method of selection not described.

A further difficulty in building up a balanced picture of both the aetiology and prognosis of febrile convulsions has been the failure by most authors to define adequately the clinical syndrome. Since 1970, routine virus surveillance of children admitted to Tyneside hospitals has shown a frequent association between viruses in the respiratory tract and febrile convulsions. Among children admitted to hospital with influenza A infection, 40% presented with febrile convulsions (Brocklebank *et al.*, 1972). The parainfluenza viruses have also been implicated (Downham *et al.*, 1974). We report the virus findings in a consecutive series of children admitted to hospital with febrile convulsions, and discuss the significance of the associations shown.

Methods

Patient selection and definition of clinical syndrome. The admission books for all children's wards in Newcastle and Gateshead were studied retrospectively, and all children admitted with a convulsion of any kind during a 2-year period from November 1971 to October 1973 were identified. The clinical notes for all these children were then examined.

A child was accepted as having had a febrile

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convulsion only if his records gave a clear history of a tonic or clonic seizure, associated either with a pyrexia of more than 38.0°C within 48 hours of admission, or with clear evidence from history or examination of a concurrent infective illness. Children were included on these criteria even if there was a history suggestive of epilepsy or of neurological deficit. Children whose cerebrospinal fluid showed inflammatory changes were excluded; in fact only a minority were investigated by lumbar puncture. The clinical records of the selected children were then analysed, and the virus laboratory records consulted.

Virology. Ward staff in Newcastle and Gateshead hospitals are encouraged to take nasopharyngeal secretions (NPS) and cough/nasal swabs (C/NS) routinely from children admitted with respiratory illness or febrile convulsions, and these were the specimens used for the current analysis. The methods in this laboratory for rapid diagnosis by the fluorescent antibody (FA) technique (Gardner and McQuillin 1974) and for isolation in tissue culture (Sturdy *et al.*, 1969), have been described previously.

Results

502 episodes which met our criteria defining a febrile convulsion were identified from the ward admission books during the 2 years from November 1971 to October 1973. Specimens for virus diagnosis (NPS and C/NS) were received from 276 of these. The 276 admissions involved 247 children, as some children were admitted more than once with febrile convulsions during the study period. The viruses identified, either by immunofluorescence or culture or both, are shown in Table 1. The overall virus identification rate was 49%. The two methods of

virus identification are compared in Table 2, showing that the diagnosis was made by the rapid fluorescent method in the majority of cases. Of the

Table 2 *Method of virus identification*

Fluorescent antibody technique	81
Tissue culture isolation only	55
Total	136

55 viruses which were identified by culture only, the great majority were virus types for which the FA technique was not available at the time.

More than 80% of the children had a respiratory illness at the time of their convulsion, and this preponderance of respiratory illness was similar in the virus-positive and virus-negative groups, and also in the group not investigated for viruses (Table 3). These respiratory illnesses included simple

Table 3 *Clinical illnesses associated with the febrile convulsions*

Patients	Respiratory	Other	Pyrexia alone	Total
Virus-positive	119 (87.5%)	4	13	136
Virus-negative	114 (81.5%)	10	16	140
Not investigated	197 (87.0%)	11	18	226

coryza, pharyngitis, tonsillitis, otitis media, and a small number with signs of lower respiratory tract infection.

The age and sex distribution, incidence of family history of fits in a first-degree relative, frequency of a previous history of fits or neurological abnormality, and the length of the seizure were all similar for the virus-positive and -negative children (Figs. 1 and 2, Tables 4-7). The month of admission of the

Table 1 *Viruses identified from 276 children admitted with febrile convulsions*

Influenza A	35
Influenza B	5
Parainfluenza 1	4
Parainfluenza 2	1
Parainfluenza 3	9
Parainfluenza 4A	4
Parainfluenza 4B	2
Respiratory syncytial virus	20
Rhinoviruses	3
Adenoviruses	26
Coxsackie B	14
Echoviruses	9
Measles	3
Mumps	2
Herpesvirus hominis	12
Total	149*

*The number of children in whom a virus was identified was 136 (49%); 13 children had two virus types identified simultaneously, one of which was usually herpesvirus or an adenovirus.

Fig. 1 *Age distribution of children admitted with febrile convulsions.*

Fig. 2 Sex distribution of children admitted with febrile convulsions.

Table 4 Family history of convulsions in a first-degree relative

Patients	Family history of convulsions	No family history of convulsions	Total
Virus-positive	38 (31%)	85 (69%)	123
Virus-negative	31 (25%)	93 (75%)	124
Total	69 (28%)	178 (72%)	247*

*Some children were admitted more than once with febrile convulsions during the study period, and therefore in Tables 4, 5, and 6, where each child rather than each admission is counted, the total is reduced to 247 (see text).

Table 5 Previous history of convulsions

Patients	Previous history of febrile convulsions	Previous history of other fits	No previous history of fits	Total
Virus-positive	32 (26%)	7 (6%)	84 (68%)	123
Virus-negative	29 (23%)	10 (8%)	85 (69%)	124
Total	61 (25%)	17 (7%)	169 (68%)	247

Table 6 History of previous neurological disorder (including epilepsy)

Patients	Previous neurological disorder	No previous neurological disorder	Total
Virus-positive	8 (7%)	115 (93%)	123
Virus-negative	8 (6%)	116 (94%)	124
Total	16 (7%)	231 (93%)	247

Table 7 Estimated duration of convulsions

Patients	Estimated duration of convulsions in minutes						Uncertain
	<1	1-4	5-9	10-19	20-29	≥30	
Virus-positive	6	32	24	28	2	14	30
Virus-negative	9	35	15	33	5	11	32
Total	15	67	39	61	7	25	62

virus-positive and -negative children is shown in Fig. 3. A biphasic curve of monthly incidence is seen for each year of the study, with peaks in January and the summer.

Fig. 3 Seasonal distribution of febrile convulsions.

Differential white cell counts. In the 121 children who had a leucocyte count, leucopenia (neutrophils <2000/ml) was rare, occurring in only 4 virus-positive and 5 virus-negative children.

Discussion

The findings indicate the importance of viruses in the aetiology of febrile convulsions. By means of respiratory specimens alone, a virus was shown in 49% of episodes investigated (Table 1). The similar

incidence of clinical respiratory illness among those not investigated (Table 3) argues against any selection in favour of respiratory viruses.

In 51% of the children no virus was shown. In this group, however, the predominance of associated respiratory illness (Table 3), the length of the convulsions (Table 7), and the age, sex, family history, and past history (Figs. 1 and 2, Tables 4-6) were all similar to those in the virus-positive group.

These similarities raise the possibility that many of the illnesses in the virus-negative group may also have had a virus aetiology which was not identified. As well as occasional technical failures in virus isolation, some viruses may have been types not amenable to routine methods of identification, such as the coronaviruses, while others might have been identified had faeces specimens been examined routinely. This last suggestion is one possible explanation for the increased proportion of virus-negative children through the summer months (Fig. 3), when enteroviruses might be expected to be more prevalent.

Febrile convulsions appear to be a nonspecific response, in a predisposed child, to any febrile illness, and not a specific manifestation of infection with certain agents. This is supported both by the multiplicity of virus types found, and by the similarity in clinical and epidemiological features between the virus-positive and -negative cases. Some viruses may be more likely to cause convulsions than others, but this possibility can be explored only by an investigation of the virus aetiology of febrile illness in the community as well as in hospital. The factors in the host which predispose to febrile convulsions have been reviewed by Lennox-Buchthal (1973); our findings for sex and age distribution, and for a family history of convulsions, agree broadly with those of other workers.

Lennox-Buchthal (1973) has argued that modified exanthem subitum, indicated by leucopenia, may be a common cause of febrile convulsions. This is not supported by our series in which only 9 out of 121 children had leucopenia, and no case of clinical exanthem subitum was seen.

Analysis of the seasonal distribution of admitted febrile convulsions (Fig. 3) shows peaks of virus-positive cases in January of each year of the study, and these coincided with simultaneous epidemics of influenza A and respiratory syncytial virus infection. The possible relationship of the summer month peaks to enteroviruses, which are not always identified in respiratory specimens, has already been mentioned.

Wallace and Zealley (1970) have suggested that a virus aetiology is more often associated with prolonged, focal, or multiple convulsions, and that identification of a virus infection might therefore imply a worse prognosis for recurrence of convulsions or other neurological residua. Our findings for the length of convulsions (Table 7) do not support this suggestion. It was not possible by retrospective analysis to establish reliably whether or not convulsions had been focal or multiple. The recurrence rate and subsequent neurological status of the children in this study will be determined by follow-up.

The majority of virus identifications were made by the fluorescent antibody technique, which gives a result within a few hours of admission. A positive virus identification was found to be a helpful aid to clinical assessment, and reduced the need for further investigations. It was also reassuring for the parents to learn that the causative agent had been identified.

The high rate of virus identification in children with febrile convulsions emphasizes the risk these children represent as sources of cross-infection in general paediatric wards. The majority are aged over 12 months, and therefore often not nursed in individual cubicles. Recovery is usually rapid, so that by the following day they are often mixing freely with other children on the ward, while still excreting virus. The problems of hospital cross-infection with respiratory viruses and the possibilities of prevention through rapid diagnosis and awareness of the risks have been discussed previously (Gardner *et al.*, 1973).

Prophylactic anticonvulsant therapy for febrile convulsions remains at best uncertain, and is in any case unlikely to be instituted until after the first convulsion has occurred. In the long run, a more hopeful approach to prevention may lie in the identification of the agents commonly responsible for these febrile illnesses, and the development and administration of virus vaccines to selected groups of children.

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