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Viral infections and recurrences of febrile convulsions

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To determine whether complicated febrile seizures occur more often in children with a proven viral infection, we performed viral examinations on 144 children with febrile convulsions, of whom 112 had simple and 32 had complicated seizures. A diagnosis of virus infection was verified in 46% of the former patients and 53% of the latter. Three adenoviruses, one parainfluenza virus type 2 and one type 3, one respiratory syncytial virus, one echovirus type 11, one herpes simplex virus type 2, and one influenza B virus were isolated from the cerebrospinal fluid. A simple febrile convulsion occurred in seven children with a positive cerebrospinal fluid viral isolation, and two had a complex febrile seizure. In a follow-up of 2 to 4 years (mean 3.3 years), 21 of the 107 children with simple seizures (19.6%) and 3 of the 32 children with complicated seizures (9.4%) had recurrent febrile seizures. The children with positive evidence for a viral infection, even with a virus isolated from the cerebrospinal fluid, had no more recurrences than those without any proven viral infection. We conclude that children with a proven viral infection have no worse prognosis than those without. (J PEDIATR 1990;116:195-9)

The diagnosis of febrile seizures is based on the presence of fever, age of the child, nature of the seizures, and exclusion of other causes such as central nervous system infections.[1-3] It hase been suggested that complicated febrile seizures occur more often in children with positive evidence of viral infection.[4] Some authors have postulated that febrile convulsions are, in fact, a manifestation of viral invasion of the brain tissue.[5,6] A virus has been found in the cerebrospinal fluid of some children with febrile convulsions, but the outcome for these children has not been reported.[6-8]

We performed a prospective study to evaluate further the role of viral infections in children with febrile convulsions.

METHODS

All children admitted to the University of Oulu Department of Pediatrics between Jan. 1, 1985, and Dec. 31, 1986, after their first febrile convulsion, irrespective of the age of the child, were included in the series, except for children with earlier nonfebrile seizures, bacterial or aseptic meningitis, encephalitis, or metabolic encephalopathies. Children with a stable neurologic deficit, such as cerebral palsy or mental retardation, were included. Sixty-eight boys and 76 girls fulfilled the inclusion criteria, their mean age being 1.9 years (range 0.3 to 8.2 years).

CSF	Cerebrospinal fluid
EEG	Electroencephalogram
EIA	Enzyme immunoassay
NPS	Nasopharyngeal secretions

A single seizure of less than 15 minutes' duration in the presence of a fever without focal features was defined as a simple febrile convulsion. Febrile seizures were defined as complicated if they lasted more than 15 minutes, had focal features, or occurred more than once in 24 hours. A similar classification has been used previously.[1-5]

Samples of CSF (143 children), stools (130 children), and nasopharyngeal aspirates (134 children) were collected

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Table I. Clinical diagnoses of infections in 144 children with febrile convulsions.

Clinical diagnosis	Seizure		
	Simple	Complicated	Total
Upper respiratory tract infection	58	20	78
Otitis media	7	1	8
Lymphadenitis colli	2	0	2
Pneumonia	5	1	6
Exanthem subitum	9	2	11
Gastroenteritis	10	5	15
Urinary tract infection	3	1	4
Meningococcal sepsis	1	0	1
Pneumococcal sepsis	2	1	3
Measles vaccination	5	0	5
Fever	10	1	11
TOTAL	112	32	144

Table II. Viral cause of infections in 144 children with febrile convulsions

Virus	Seizure		
	Simple	Complicated	Total
Adenovirus	10	8	18
RSV	6	3	9
Parainfluenza virus			
Type 1	2	1	3
Type 2	2	0	2
Type 3	3	3	6
Influenza A virus	6	0	6
Influenza B virus	2	0	2
Herpes simplex virus	2	1	3
Measles virus	5	0	5
Enteroviruses	11	0	11
Cytomegalovirus	1	0	1
Rotavirus	1	1	2
No virus	61	15	76
TOTAL	112	32	144

RSV, Respiratory syncytial virus.

for virologic examinations. Serum samples for serologic tests were taken on admission to the hospital and 1 and 2 months after the onset of the symptoms (114 children). The following laboratory tests were performed to exclude noninfectious causes of acute seizures: blood glucose; serum potassium, sodium, and calcium; serum creatinine; liver enzymes; and serum ammonia.

Electroencephalograms of 121 children (93 with simple and 28 with complicated seizures) were obtained within 4 days of the onset of symptoms. Repeat EEGs were obtained after 2 to 4 weeks in 89 cases and after 8 to 12 months in 86 cases. The differences in EEG findings between the children with simple and those with complicated seizures, and the virologic findings, were evaluated and then tested with a chi-square test.

The frequency of recurrences of febrile infections and febrile seizures and manifestations of nonfebrile seizures were evaluated with a mailed questionnaire 2 to 4 years (mean 3.3 years) after the first febrile seizure. The differences in these frequencies between the groups were tested with a chi-square test.

Virologic methods. The nasopharyngeal secretions for rapid diagnosis of respiratory virus antigens were tested by an enzyme immunoassay method capable of detecting adenovirus, respiratory syncytial virus, influenza A and B viruses, and parainfluenza 1, 2, and 3 viruses.[9]

The NPS, CSF, and stool specimens were inoculated onto monolayer cell cultures of human embryonic fibroblasts, Vero cells, Nbl cells (kidney cells of a spaniel), and LLC-MK_2 cells for virus isolation.[10] The respiratory viruses yielded by this isolation technique were demonstrated by means of the same EIA method as for virus antigens in the NPS. Herpes simplex viruses were detected with a fluorescent assay employing monoclonal type-specific antibodies (Microtrak, Syva Co., Palo Alto, Calif.). Enteroviruses were verified from their characteristic cytopathogenic effects or by neutralization, or both.[10] Rotaviruses were detected with a modified EIA.[11]

Complement fixation tests were carried out on paired sera. These tests consisted of panels for viruses (adenovirus; respiratory syncytial virus; influenza A and B viruses; parainfluenza 1, 2, and 3 viruses; cytomegalovirus; herpes simplex virus; varicella-zoster virus; measles virus; coxsackieviruses) and also for bacteria (*Mycoplasma pneumoniae* and *Chlamydia psittaci*).[12] Rubella antibodies were measured by means of the hemagglutination inhibition test and hemolysis in the gel test.[13, 14] Cytomegalovirus and rubella virus IgM antibodies were tested by a modified EIA method.[15] *Chlamydia trachomatis* IgG antibodies were demonstrated by means of a commercially available EIA kit (Labsystems Oy, Helsinki, Finland).

RESULTS

Of the 144 patients in our study, 112 had simple and 32 had complicated febrile seizures, their mean ages being 1.9 (range 0.3 to 7.0) and 2.2 (range 0.4 to 8.2) years, respectively. The most common clinical diagnosis was upper respiratory tract infection (Table I).

A viral cause was verified in 47% of the patients (Table II), a virus being detected by various methods in 101 samples from these 68 cases. In five patients, two different viruses were found, the illness being attributed to the virus to which the patient had a positive antibody response. If two

Table III. Clinical and virologic findings in nine children with a virus isolated from the CSF

Clinical diagnosis	Febrile seizure	Virus isolation from CSF	Antibody response	Virus isolation from stool
URI	Complicated	Adenovirus	Adenovirus	
URI	Complicated	Adenovirus		
URI	Simple	Herpes simplex virus type 2		
URI	Simple	Echovirus 11		Echovirus 11
URI	Simple	Parainfluenza 2 virus		
URI	Simple	Parainfluenza 3 virus		
Exanthem subitum	Simple	RSV		Poliovirus type 3
Diarrhea	Simple	Influenza B virus		
Fever	Simple	Adenovirus		

URI, Upper respiratory tract infection; *RSV*, respiratory syncytial virus.

different viruses were isolated from the NPS and stool in patients with respiratory symptoms, the disease was attributed to that from the NPS, because respiratory tract viruses usually relate to the illness in such patients.[16]

A virus was identified in the NPS from 30 of the 134 patients. Antigen detection and viral culture yielded the same virus in two patients, the viral culture alone was positive in 13, and the antigen alone was found in 14 patients. Echovirus 11 was isolated from the NPS of one child who also had a positive antigen for parainfluenza type 3 virus. Viral culture or antigen detection was positive in 19 fecal specimens. In one patient, both adenovirus and enterovirus were isolated from the stool.

There was a significant rise (fourfold or greater) in the antibody titer in 39 of 114 patients. In addition to viral antibodies, significant antibody responses were found to *M. pneumoniae* in two children and *C. trachomatis* in one. A virus of the same type as that found by the antibody tests was identified from 13 of the patients, either by isolation or by antigen determination. Two patients had a significant rise in two antibodies.

The viral cultures from the CSF samples of nine patients were positive (Table III); seven of these patients had had a simple and two a complicated febrile seizure. The CSF leukocyte counts (range 0 to 2 cells/mm^3) and the protein concentrations (range 14.3 to 27.5 mg/dl) and glucose concentrations (range 40 to 91 mg/dl) were within normal limits in all the patients.

Exanthem subitum occurred in nine children with simple and two with complicated febrile seizures. Bacterial infection was confirmed in 13 patients, four of whom had an intercurrent viral infection; 10 of these patients had had a simple and three a complicated febrile seizure.

The parents of 139 of the 144 children replied to the questionnaire; 102 of the 107 children with simple and 29 of the 32 with complicated febrile seizures had had further febrile infections. Febrile seizures had recurred in 21 of the 107 children with simple (19.6%) and 3 of the 32 with complicated febrile seizures (9.4%). The recurrences occurred in 11 of the 67 children with proven viral infection and 13 of the 72 with no viral infection. Of the nine children with a virus isolated from the CSF, one had a recurrent febrile seizure. All these differences between the groups were statistically insignificant. All the recurrent febrile seizures were simple ones. Only one child with an initial simple febrile seizure had had nonfebrile seizures during the follow-up period.

Of the 121 children, 40 (33%) had EEG abnormalities consisting of high-voltage focal slow waves, increased delta activity, irritative spikes with sharp waves, and paroxysmal discharges in the first EEG recording; 15 (17%) of 89 had these abnormalities in the second recording and 9 (10%) of 86 in the third recording. The differences in EEG findings between the children with simple and those with complicated febrile seizures were not statistically significant. The EEG abnormalities did not differ between the children with a virus isolated from the CSF and those without such viruses. All children were clinically healthy by the time of the third EEG recording.

DISCUSSION

Detection of a virus from a CSF sample provides the most convincing evidence of viral diseases of the central nervous system.[17] In our series, the nine patients with such an isolation had clinically typical febrile seizures. Familusi et al.[7] were able to isolate a virus from the CSF in 2 of 105 children with febrile convulsions and Lewis et al.[6] in 4 of 73 such children. In one report from Italy, an exceptionally high frequency of herpes viruses was found in the CSF (i.e., in 10% of patients with febrile convulsions[8]). In our series the nine children with a positive virus isolation from the CSF did not have any more severe EEG abnormalities than those without, and they were clinically healthy by the time of the third EEG recording. All these findings suggest that febrile

convulsions may be the sole manifestations of viral central nervous system infections.

The overall recurrence rate for febrile convulsions of 17% was relatively low compared with previously published figures of 33% to 47% recurrences, and was no higher after an initial complicated seizure.[1, 18] Moreover, the follow-up time for our patients was longer than in Wallace's series,[18] in which there were 47% recurrences. One explanation for the difference may be that our patients were enrolled in our study on a less selective basis, because nearly all children in Finland are admitted to the hospital after their first febrile seizure.

Febrile convulsions have been found to be the most common reason for hospitalization among children with influenza A virus infections.[19, 20] These findings support the view that influenza viruses are more neurovirulent than other viruses.[21] In one of our patients with simple febrile seizure, an influenza B virus was isolated from the CSF.

The proportion of patients with a verified viral cause (47%) was similar to that in earlier studies of febrile convulsions (18% to 63%).[5-7, 22] If one accepts a clinical diagnosis of exanthem subitum as a viral disease, then 55% of the children had a viral infection. In the series of Lewis et al.,[6] a viral cause was suggested in a further 21% of the children by the detection of interferon in their serum, increasing the proportion to 84%. It may be that viral invasion of the central nervous system is always present in patients with febrile convulsions, but because of the limitations in our diagnostic methods we are unable to identify it. Common respiratory viruses, such as rhinovirus and coronaviruses, were not included in our virologic battery of tests.[23, 24]

Bacterial infection as the sole cause was apparent in only nine of the 144 patients; in addition, there were two examples of pneumococcal and one of meningococcal sepsis, three patients with mycoplasma infection, and three with urinary tract infection. The other patients with bacteriologic findings also had an intercurrent viral infection. This supports the importance of viral infections as a cause of febrile convulsions.

There was no difference in the viruses found, nor in the frequency of recurrences, between the children with simple and those with complicated febrile seizures, nor did the EEG findings in the children with a proven viral infection differ from those in the cases without a viral infection. The changes in the first EEG recordings were similar to those in children with artificially induced hyperthermia.[25] This contradicts Wallace's suggestion[4] that complicated seizures occur more often in children with positive evidence of viral infection; even in that series, the difference was statistically insignificant. Our patients with a positive viral finding, even with a virus isolated from the CSF, had a good prognosis and had no more recurrences than those without any proven viral infection.

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REFERENCES

1. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics 1978;61:720-7.
2. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I. Prevalence and recurrence in the first five years of life. Br Med J 1985;290:1307-10.
3. Millichap JP. The definition of febrile seizures. In: Nelson KB, Ellenberg JH, eds. Febrile seizures. New York: Raven Press, 1981:1-3.
4. Wallace SJ. Factors predisposing to a complicated initial febrile convulsion. Arch Dis Child 1975;50:943-7.
5. Wallace SJ, Zealley H. Neurological, electroencephalographic, and virological findings in febrile children. Arch Dis Child 1970;45:611-23.
6. Lewis HM, Parry JV, Parry RP, et al. Role of viruses in febrile convulsions. Arch Dis Child 1979;54:869-76.
7. Familusi JM, Moore DL, Fomufod AK, et al. Virus isolates from children with febrile convulsions in Nigeria. Clin Pediatr 1972;11:272-6.
8. Squadrini F, Taparelli F, Nalin A, et al. Role of viruses in febrile convulsions [Letter]. Arch Dis Child 1980;55:828.
9. Sarkkinen HK, Halonen PE, Arstila PP, Salmi AA. Detection of respiratory syncytial, parainfluenza type 2 and adeno virus antigens by radioimmunoassay and enzyme immunoassay in nasopharyngeal specimens from children with acute respiratory disease. J Clin Microbiol 1981;13:258-65.
10. Schmidt NJ. Cell culture techniques for diagnostic virology. In: Lennette H, Schmidt NJ, eds. Diagnostic procedures for viral, rickettsial and chlamydial infections. Washington, D.C.: American Public Health Association, Inc., 1979:65-139.
11. Sarkkinen H, Tuokko H, Halonen P. Comparison of enzyme immunoassay and radioimmunoassay for the detection of human rotaviruses and adenoviruses from stool specimens. J Virol Methods 1980;1:331-41.
12. Hawkes RA. General principles underlying laboratory diagnosis of viral infections. In: Lennette H, Schmidt NJ, eds. Diagnostic procedures for viral, rickettsial and chlamydial infections. Washington, D.C.: American Public Health Association, Inc., 1979:3-48.
13. Steward GL, Parkman RD, Hopps HE, et al. Rubella virus hemagglutination-inhibition test. N Engl J Med 1967;276:554-7.
14. Väänänen P, Vaheri A. Hemolysis-in-gel test immunity surveys and diagnosis of rubella. J Med Virol 1979;3:245-52.
15. Tuokko H, Salmi A. Detection of IgM antibodies to measles virus by enzyme immunoassay. Med Microbiol Immunol 1983;171:187-98.
16. Cherry JD. Newer respiratory viruses: their role in respiratory illnesses of children. Adv Pediatr 1973;20:225-90.

17. Chun RWM. Viral diseases of the central nervous system. In: Swaiman KF, Wright FS, eds. The practice of pediatric neurology. St. Louis: CV Mosby, 1982:694-717.
18. Wallace SJ. Recurrence of febrile convulsions. Arch Dis Child 1974;49:763-5.
19. Brocklebank JT, Court SDM, McQuillin J, et al. Influenza-A virus infection in children. Lancet 1972;2:497-500.
20. Price DA, Postlethwaite RJ, Longson M. Influenzavirus A2 infections presenting with febrile convulsions and gastrointestinal symptoms in young children. Clin Pediatr 1976;15: 361-7.
21. Maurizi CP. Why was the 1918 influenza pandemic so lethal? the possible role of a neurovirulent neuraminidase. Med Hypotheses 1985;16:1-5.
22. Stokes MJ, Downham MAP, Webb JKG, et al. Viruses and febrile convulsions. Arch Dis Child 1977;52:129-33.
23. Fox JP, Cooney MK, Hall CE, et al. Rhinoviruses in Seattle families, 1975-1979. Am J Epidemiol 1985;122:830-46.
24. Schmidt OW, Allan ID, Cooney MK, et al. Rises in titers of antibody to human coronaviruses OC43 and 229E in Seattle families during 1975–1979. Am J Epidemiol 1986;123:862-8.
25. Baird HW, Garfunkel JM. Electroencephalographic changes in children with artificially induced hyperthermia. J PEDIATR 1956;48:28-33.