
Article abstract—A cohort of 666 children who had convulsions with fever were followed to determine the risks of subsequent epilepsy. High risks were found in children with preexisting cerebral palsy or mental retardation. Other major risk factors were atypical features of the febrile convulsions (such as focal seizures) and duration of febrile seizures for 10 minutes or more. The risk of developing epilepsy by age 20 was about 6 percent for all children who had experienced febrile convulsions. However, this risk figure consisted of a combination of 2.5 percent of children without prior neurologic disorder or atypical or prolonged seizures, and 17 percent of those with such complications.

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The risk of epilepsy following febrile convulsions

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The risk that epilepsy will develop in children who experience seizures with fever has been a controversial subject for some years. Studies have employed three designs: (1) comparison of the frequency of a history of febrile convulsions in patients with epilepsy with the frequency in controls; (2) comparison of the characteristics of febrile convulsions in patients who did and did not develop epilepsy; and (3) follow-up of children after febrile convulsions.

Most studies of the first type were done some time ago, and it appears that they included not only febrile convulsions but other symptomatic and idiopathic convulsions in young children. The results varied: Walton and Carter¹ found no greater frequency of prior childhood seizures among people with epilepsy, but Patrick and Levy² reported a fivefold increase in childhood convulsions among people with epilepsy.

Some investigators compared children who had febrile convulsions and subsequent epilepsy with those who had febrile convulsions without epilepsy.^{3,4} This type of study allows analysis of particular characteristics of the febrile convulsions. However, when the subjects include only patients admitted to specialty clinics, as in the study of Tsuboi and Endo,⁴ the results may not be applicable to febrile convulsions as they occur in the population at large.

A common method of studying the risk of epilepsy after febrile convulsions is to identify a cohort of individuals who have experienced febrile convulsions and follow them to determine the rates of subsequent epilepsy. Such studies have provided varied results: The reported frequencies

of epilepsy were 2 to 57 percent.^{5,6} This great variation appears to result from the methods of selecting the subjects with febrile convulsions, definitions of febrile convulsion and epilepsy, and the duration of follow-up of the cohort.

We utilized the resources of the Rochester, Minnesota, Epidemiologic Program Project, and the Comprehensive Epilepsy Program at the Mayo Clinic and the University of Minnesota to evaluate the risk of subsequent recurrent afebrile seizures in patients who have experienced febrile convulsions.

Methods. We reviewed the medical histories of residents of Rochester, Minnesota, who had a diagnosis of febrile convulsions, between 1935 and 1974. For those who were seen at the time of a febrile convulsion, follow-up information was obtained through the medical records, letters, and interviews with parents. Data were collected regarding the number of febrile convulsions, their unusual features, family history of convulsions of any type, presence or absence of other neurologic abnormalities, and anticonvulsant treatment. The occurrence of subsequent afebrile seizures in this cohort was compared to an expected rate based on the known average annual age-specific incidence rates for epilepsy in the Rochester population from 1935 to 1974.

The criterion for acceptance of a case was a record of a convulsive episode with a febrile illness in childhood. Patients who had had an afebrile seizure earlier than the febrile convulsion and those whose seizures occurred with cerebral infections were excluded. However, patients with postvacci-

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Table 1. Incidence of epilepsy subsequent to febrile convulsions in 666 residents of Rochester, Minnesota, 1935-1974

Age (years)	Follow-up: Person-years after febrile convulsion	Epilepsy, cases		RR	95% confidence interval
		Expected	Observed		
0-4	1900	1.30	15	11.5	6.4-19.0
5-9	2295	1.21	8	6.6	2.8-13.00
10+	4096	1.54	6	3.9	1.4-10.4
	8291	4.05	29	7.2	4.8-10.4

Table 2. Influence of age at first febrile convulsion on risk of subsequent epilepsy

Age (years)	Patients*	Expected	Observed	RR	95% confidence interval
Entire series					
<1	140	0.92	9	9.6	4.3-18.2
1-2	323	1.96	16	8.0	4.6-13.0
2-4	161	0.93	1	1.1	0.0-6.1
4+	41	0.24	3	12.5	2.6-36.5
Cases without neurologic deficit or exceptional features of convulsion					
<1	112	0.77	3	3.9	0.8-6.6
1-2	280	1.73	9	5.1	2.3-9.7
2-4	132	0.78	0	—	—
4+	37	0.22	2	9.1	1.1-33.9

*Age of one patient was unknown.

nation febrile convulsions were included. The criterion for a subsequent diagnosis of epilepsy was the occurrence of two or more seizures that were not associated with an obvious acute insult to the brain.

Findings. Incidence. Febrile convulsions. We identified 678 residents of Rochester who experienced febrile convulsions between 1935 and 1974. These cases were used in the computation of incidence rates of febrile convulsions. Over the 40-year period, the cumulative incidence rate of febrile seizures through age 5 was 2.3 percent. The frequency was slightly greater in males than in females, and the rates were consistent through the 40-year period.

Since 12 of the 678 cases were identified

retrospectively—as a result of diagnosis of epilepsy, or head trauma, or because a sibling had a febrile convulsion—only 666 were included in the follow-up study.

Epilepsy during follow-up. The 666 patients were followed for a total of 8291 person-years after the initial febrile convulsion. During this follow-up, 29 cases of epilepsy (two or more afebrile seizures) were observed.

In addition to the 29 patients who developed epilepsy, 5 others had seizures that did not meet the criteria for epilepsy (single idiopathic seizures in 4 and seizures associated with encephalitis in 1). The epileptic seizures were of various clinical types, in a distribution similar to that found in an extensive review of epilepsy in Rochester.⁷ The seizures were focal at onset in 16 cases, and of

Table 3. Influence of neurologic deficit and atypical character of febrile convulsions on risk of subsequent epilepsy

Subjects	Patients	Epilepsy, cases		RR	95% confidence interval	
		Observed	Expected			
Without neurologic deficit						
Atypical character of convulsion	No	569	14	3.50	3.9	2.1-6.4
	Yes	72	5	0.38	13.2	4.3-30.6
With neurologic deficit						
Atypical character of convulsion	No	15	6	0.10	60.0	22.0-130.8
	Yes	10	4	0.07	57.1	15.5-146.2

Table 4. Influence of duration of febrile convulsions on risk of subsequent epilepsy

Duration (minutes)	Patients	Epilepsy, cases		RR	95% confidence interval
		Expected	Observed		
Entire series					
Unknown	261	1.59	9	5.7	2.6-10.8
<5	211	1.28	6	4.7	1.7-10.2
5-9	79	0.44	3	6.8	1.4-19.9
10+	115	0.76	11	14.5	7.2-26.0
Cases without neurologic deficit or atypical features of convulsion					
Unknown	222	1.44	3	2.1	0.4-6.1
<5	188	1.17	5	4.3	1.4-10.0
5-9	66	0.37	1	2.7	0.1-15.0
10+	84	0.58	5	8.6	2.8-20.0

temporal origin in 10 of these. Generalized-onset tonic-clonic seizures occurred in 12 other patients, and 3 of these also had absence attacks. One case could not be classified.

Relative risk. The expected number of cases of epilepsy, derived by applying the Rochester age- and sex-specific incidence rates to the person-years of follow-up, was 4.05. The standardized morbidity ratio or relative risk (RR) is the observed number of cases divided by the number expected, or 7.2. Thus, during this follow-up period, the incidence of epilepsy was seven times greater in the febrile-convulsion cohort than in the Rochester population.

Age at onset of epilepsy. The RR of epilepsy subsequent to febrile convulsions declined with increasing age. It was 11.5 for ages of 4 years or less, 6.6 for ages 5 through 9 years, and 3.9 after age 9 years (table 1). The risk remained significantly increased during each age interval throughout the follow-up period.

Possible risk factors. Age at first febrile convul-

sion. Subjects less than 2 years old and those beyond 4 had high risks of subsequent epilepsy, whereas those aged 2 to 4 years had a lower risk (table 2).

Neurologic disorders. Neurologic abnormality was known or presumed to have existed in 25 of the 666 patients prior to the first febrile convulsion. Fourteen of these 25 had mental retardation (IQ less than 70), 7 had cerebral palsy, and 4 had both. These children had an especially high incidence of subsequent epilepsy, which developed in 10 (40 percent) of the 25 (table 3). The children with neurologic deficits tended to have their first febrile convulsion at earlier ages, and all who developed subsequent epilepsy had the first afebrile seizure prior to age 10 years.

Atypical character of febrile convulsions. Another risk factor for subsequent epilepsy was an atypical character of the febrile convulsions (table 3). In our study, this included unilateral or focal origin, repeated episodes the same day, and documented Todd (postictal) paralysis. Among patients

Table 5. Influence of low-risk and high-risk status* on risk of subsequent epilepsy

Patient group	Patients	Epilepsy, cases		RR	95% confidence interval
		Observed	Expected		
Low-risk	485	9	3.10	2.9	1.3-5.5
High-risk	181	20	0.95	21.1	12.9-32.5

*Low-risk: Without prior neurologic deficit or long duration (≥ 10 minutes) or other atypical features of febrile convulsion.
High-risk: With any of above.

Table 6. Influence of number of febrile convulsions on risk of subsequent epilepsy in high-risk and low-risk groups

No. febrile convulsions	Patients*	Epilepsy, cases		RR	95% confidence interval
		Expected	Observed		
Low-risk cases					
1	348	2.2	6	1.7	0.6-3.7
2	76	0.5	0	—	—
3	27	0.2	2	10.0	1.2-36.1
4	31	0.2	1	5.0	0.03-5.57
High-risk cases					
1	86	0.5	7	14.0	5.6-28.8
2	46	0.2	6	30.0	11.0-65.4
3	26	0.2	2	10.0	1.2-36.1
4	23	0.2	5	25.0	8.1-58.2

*In 3, number was unknown.

who did not have neurologic deficit, the RR was 13.2 in cases with exceptional features and 3.9 in those without.

Duration of febrile convulsion. Children whose febrile convulsions lasted less than about 10 minutes had a lower risk of subsequent epilepsy than those with one or more convulsions lasting longer (table 4). This was also true after exclusion of patients with prior neurologic deficits or seizures of atypical character.

If all patients with prior neurologic deficits or prolonged or otherwise exceptional febrile seizures were considered together as a high-risk group of 181 members, the RR was 21.1—contrasted with 2.9 in the low-risk group of 485 members without deficits or exceptional seizures (table 5).

Number of febrile convulsions. Overall, the incidence of subsequent epilepsy increased with the number of febrile seizures, but this association was not demonstrable in either the high-risk or the low-risk groups separately (table 6). The number

of subsequent afebrile seizures, however, was greater among the high-risk group.

Familial involvement. Of the 666 subjects with febrile convulsions, 12 were known to have a parent or sibling with epilepsy; and 3 of these 12 later developed epilepsy. A family history of febrile convulsions was considerably more common, for 23 percent of the probands were known to have a parent or sibling so affected. The RR of subsequent epilepsy was 11.6 among those known to have a parent or sibling with a history of febrile convulsions and 6.2 among the rest. Among the patients with an affected parent or sibling, males were at slightly higher risk than females, but among those without an affected relative, females were at higher risk than males.

Discussion. Incidence. Febrile convulsions. The 2.3 percent cumulative incidence of febrile seizures found in the Rochester population was similar to rates reported for two cohorts followed from

Table 7. Risk of epilepsy after febrile convulsion: Summary of reports

Report	No. cases of febrile convulsion	With subsequent epilepsy		Mean follow-up period, years*
		No.	%	
Herlitz, 1941 ¹²	424	14	3.2	7.8
Friderichsen and Melchior, 1954 ¹³	282	8	2.8	6
Frantzen and associates, 1968 ¹⁴	200	5	2.5	5
Van den Berg and Yerushalmy, 1969 ⁸	246	8	3.2	3.2
Nelson and Ellenberg, 1976 ⁵	1706	34	2.0	7
Present report	666	29	4.4	15

*The follow-up period at risk to subsequent epilepsy would be approximately 2 years (mean age at first febrile convulsion) less than mean age at last follow-up.

birth.^{5,8} Although our survey was population-based, we consider this estimate minimal and suspect that some milder cases were not identified. To be identified in our study, the child had to be seen by a physician and the physician had to enter the diagnosis. We know that some febrile seizures did not come to the attention of physicians, and that in other cases, although the occurrence of the seizures was known to physicians, the diagnosis was not entered at the Mayo Clinic or other local medical facility. As mentioned, 12 patients were excluded from follow-up because the history of febrile convulsion was obtained only in the course of later evaluation of some other problem. A special study in which inquiry was made of the parents of children born in Rochester in 1960 revealed a 3 percent cumulative incidence of febrile convulsions.⁷

Subsequent epilepsy. There have been several studies in which children who experienced seizures with fever were followed to ascertain how many subsequently developed epilepsy.

Studies of patients seen in specialty clinics or admitted to a hospital would include a greater proportion of individuals with complex or prolonged febrile seizures, who are at high risk. Among 105 febrile-convulsion cases observed by Zellweger,⁹ 15 patients developed epilepsy and 6 were suspected of having epilepsy. Peterman¹⁰ reported that 30 of 100 patients with febrile convulsions continued to have recurrent convulsions without fever. Of 498 children with febrile convulsions, Livingston⁶ stated that 282 (57 percent) developed epilepsy. High rates of subsequent seizures (17 percent) have been noted in patients admitted to a hospital or those attending a specialty clinic.^{4,11}

In cohort studies of unselected febrile-convulsion cases, 2 to 4 percent of the children developed epilepsy (table 7). There are several difficulties in interpreting and comparing these

studies. First, the follow-up period varied. Since seizures can begin at any time during life, the risk of epilepsy depends on the duration of follow-up. Second, the studies differed slightly in their definitions of febrile convulsions and of epilepsy. Friderichsen and Melchior¹³ considered certain febrile convulsions (i.e., those lasting more than 30 minutes) as epilepsy, and therefore omitted them from the study. Some studies, such as that of van den Berg and Yerushalmy,⁸ included as febrile convulsions those that occurred during cerebral infections. There were also differences in the definition of subsequent epilepsy. In the study of Nelson and Ellenberg,⁵ two or more afebrile seizures were necessary to satisfy the criteria for the diagnosis of epilepsy; but in other studies it appears that a single seizure was considered as epilepsy.

Of our 666 febrile-convulsion patients, 2.2 percent developed epilepsy by age 5, 3.5 percent by age 10, and 4.4 percent through the total follow-up. Overall, the RR of developing epilepsy after a febrile convulsion was 7.2. Our findings through the first few years were similar to those of other cohort studies. Although the risk of subsequent epilepsy was highest in the first few years after the febrile seizure, there was a significant increase during ages 5 through 9 and also later. The higher cumulative occurrence of epilepsy in our series, compared to other cohort studies, appears to be due to the longer follow-up.

The cumulative incidence rate of epilepsy by age 20 years in the Rochester population was 1.06 percent, and the expected occurrence between the mean age at onset of febrile convulsions (2 years) and age 20 was 0.87 percent. Hence the probability of developing epilepsy from the time of the first febrile convulsion to age 20 can be estimated as 0.87 times the RR.

The risk of subsequent epilepsy varied in our febrile-convulsion series. Patients in the high-risk group (with prior neurologic disorder or febrile

seizures that were exceptional or prolonged) had a 17 percent chance of developing epilepsy by age 20. The low-risk patients had only a 2.5 percent chance of developing epilepsy by age 20.

It is not possible to compare the risk of subsequent epilepsy in other reports, because the follow-up period varied. Most did not provide the incidence rate among the general population, so the relative risk is not known. Nelson and Ellenberg⁵ compared the 7-year cumulative incidence rates of epilepsy in groups with and without febrile convulsions. Since the cumulative incidence of epilepsy in the febrile-convulsion group was 20 per 1000, and that in the other group 5 per 1000, the RR should be 4. However, the febrile-convulsion group had lived the first 2 years of life (on the average) without epilepsy. Since these are high-incidence years for epilepsy, the cumulative incidence of afebrile seizures after febrile convulsion should be compared with the cumulative incidence from ages 2 through 7. This would be somewhat less than 5 per 1000, and therefore the relative risk of developing epilepsy after a febrile convulsion would be greater than 4. The data of van den Berg and Yerushalmy⁸ indicate that the relative risk during the limited follow-up period was probably very high, because the mean duration of follow-up after initial febrile convulsion would have been only 1 to 2 years, despite the fact that 3.2 percent of the subjects had already had at least one seizure.

Risk factors. Age. In several studies, patients at the extremes of age at their first febrile convulsion were at greater risk of subsequent epilepsy than others. Lennox³ and Tsuboi and Endo⁴ found that patients who had febrile convulsion and epilepsy were more likely to have had the initial febrile convulsion before age 1 year than those who had febrile convulsion only. In our series there was no definite relationship between the age at first febrile convulsion and the risk of subsequent epilepsy. Although the differences were not significant, the highest risks for subsequent epilepsy were found in those less than 2 years old or more than 4 at the first febrile convulsion. A very low risk of subsequent epilepsy was found in those aged 2 through 4 years at the first febrile convulsion.

Exceptional features of febrile convulsions. Like others who divided their febrile-convulsion series by special features (such as duration of seizure, focal features, or prior neurologic disorder), we found great differences in the risk of subsequent epilepsy. The differences in the reported risk of subsequent epilepsy (i.e., 2 to 57 percent) may be due, in large part, to the types of cases of febrile convulsions considered. In our study, as in that of Nelson and Ellenberg,⁵ patients whose febrile seizures had exceptional features were at high risk—although most will not develop epilepsy. Patients without such features were at much lower

risk, though still higher than the general population.

Number of febrile convulsions. Comparing patients with febrile convulsions who did and did not go on to have epilepsy, Patrick and Levy² found that 23.5 percent of those with epilepsy had had only one febrile convulsion, whereas 65.6 percent of those without epilepsy had had only one. Lennox³ found a slightly higher risk of subsequent epilepsy in those who had experienced three or more febrile convulsions. Tsuboi and Endo⁴ reported that an association with the number of febrile convulsions was demonstrable but was not pronounced until the number of febrile seizures reached 10. Nelson and Ellenberg⁵ found that in children whose prior neurologic status was normal, the risk of epilepsy was not affected by the number of febrile convulsions. However, those whose prior neurologic status was abnormal had considerably higher risk of epilepsy if they had had three or more febrile convulsions. In our series the risk of subsequent epilepsy was related to the number of febrile convulsions, but this relationship disappeared when the cases were stratified into high-risk and low-risk groups.

Familial involvement. Most investigators of the family history of patients with febrile convulsions found that epilepsy was rare among relatives, whereas a history of febrile convulsions was common. Our data were similar to those of Frantzen and associates,¹⁵ who found that the prevalence of epilepsy in relatives of patients with febrile convulsions was no higher than in the general population. The importance of a family history of febrile convulsions in prognosis of an individual's risk of subsequent epilepsy is unknown. Livingston, Bridge, and Kajdi¹⁶ found that the risk of subsequent epilepsy was highest in persons with a family history of epilepsy, intermediate in those with a negative family history, and lowest in those who had a family history of childhood, presumably febrile, convulsions. In our series, however, the risks of subsequent epilepsy were higher among those who had a parent or a sibling with a history of a febrile convulsion.

Sex. Lennox,³ in a case-control study, noted that females who had febrile convulsions had a rather high risk of going on to recurrent afebrile seizures. According to her data, the risk in females was 1.86 times that in males. In our series the difference was not significant, although females had 1.3 times the risk of males.

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