

LONG-TERM PROGNOSIS OF SEIZURES WITH ONSET IN CHILDHOOD

MATTI SILLANPÄÄ, M.D., PH.D., MERJA JALAVA, M.D., PH.D., OLLI KALEVA, B.Sc., AND SHLOMO SHINNAR, M.D., PH.D.

ABSTRACT

Background The long-term prognosis of seizures that begin in childhood is uncertain.

Methods We prospectively studied 245 children from the catchment area of Turku University Hospital in Turku, Finland, who had active epilepsy diagnosed between 1961 and 1964. Sixty-eight patients (28 percent) had idiopathic seizures (presumed to have a genetic origin), 54 (22 percent) had cryptogenic seizures (occurring in otherwise normal persons with no clear cause), and 123 (50 percent) had remote symptomatic seizures (with no immediate cause but occurring in persons with a prior brain injury or a static encephalopathy).

Results At the final follow-up in 1992, we had sufficient data on 220 patients (90 percent), 176 of whom were alive and 44 of whom had died; the remaining 25 had emigrated, could not be traced, or declined to participate. Thirty-nine patients who died were not free of seizures at the time of death, and 33 had remote symptomatic seizures. Among the surviving patients, 112 (64 percent) had been seizure-free for at least five years, including 83 (47 percent) who were not taking antiepileptic medications. The most important predictors of being seizure-free for at least five years were a rapid response to therapy (defined as a reduction in the frequency of seizures of 75 to 100 percent within three months of beginning treatment) and a diagnosis of idiopathic seizures. As compared with a matched control group, 99 patients with epilepsy but no other initial neurologic impairment were of similar socioeconomic status and had similar rates of passing an examination given after 12 years of school. Significantly more patients, however, had completed only six years of school (relative risk, 2.13), were unemployed (relative risk, 3.76), were not married (relative risk, 3.50), and did not have children (relative risk, 3.00).

Conclusions Although the majority of patients with epilepsy in childhood are free of seizures by the time they become adults, they are at increased risk for social and educational problems. Patients whose epilepsy does not remit also have an increased risk of death. (N Engl J Med 1998;338:1715-22.)

©1998, Massachusetts Medical Society.

MOST studies of the prognosis of epilepsy focus on short-term remission of seizures in patients with newly diagnosed epilepsy.¹⁻⁵ Outcomes after long-term remission of seizures have been reported in well-designed retrospective studies in Minnesota, Sweden, and Japan.⁵⁻⁷ With a few notable exceptions,^{7,8} data on mortality have been obtained from reviews of medical records and death certificates or

from studies of patients with refractory epilepsy.⁹⁻¹⁴ The long-term social, educational, and employment outcomes of people with childhood-onset epilepsy have not been a focus of study with the exception of a few reports of patients with refractory epilepsy who were seen in tertiary care centers.^{9,15} We report the long-term outcomes of a population-based cohort of 245 patients with epilepsy in childhood who were prospectively followed for several decades.

METHODS**Patients**

The study group included all children under 16 years of age who were living in the catchment area of University of Turku Hospital, Turku, Finland, at the end of 1964 who met the criteria for epilepsy (two or more unprovoked seizures).^{6,16-18} Patients were identified on the basis of hospital records and a review of the National Health Service records, a registry of all persons residing in Finland. Of the 245 patients identified, 223 (91 percent) were seen at University of Turku Hospital. The remaining 22 patients (9 percent) were seen at other hospitals and institutions in southern Finland. In Finland in the 1960s, all children with seizures were referred for evaluation. Ongoing surveillance of the national registry since that time has identified only three other patients who on review met the inclusion criteria and would have been included if identified at the proper time. Thus, the sample represents a population-based cohort of children under 16 years of age with epilepsy.

The 245 patients included 150 (61 percent) whose initial visit for evaluation of seizures occurred between January 1961 and December 1964 (incident cases). The remaining 95 (39 percent) were initially seen before 1961, but they were evaluated at least once during the study period of 1961 to 1964 and had had at least one seizure during the three years before that visit. All 245 were examined in 1972 by one pediatric neurologist,¹⁹ enrolled in a prospective, longitudinal study of outcomes, and followed for an additional 20 years. Follow-up included ongoing review of the medical records and a comprehensive reevaluation every five years. The final follow-up in 1992 consisted of a structured interview and a clinical examination. There were sufficient data for evaluation in the case of 176 patients who were alive in 1992 and 44 patients who had died (total, 90 percent). Of the remaining 25 (10 percent), 7 had emigrated, 10 could not be traced, and 8 declined to participate in the final follow-up.

Control Subjects

Of the 176 surviving patients with sufficient data for evaluation, 100 (57 percent) had uncomplicated epilepsy, which was defined as epilepsy without other initial neurologic impairment. For these 100 patients, a matched control group was selected from the nationwide population registry. We used stratified random

From the Departments of Pediatric Neurology (M.S., M.J.) and Biostatistics (O.K.), University of Turku, Turku, Finland; and the Departments of Neurology and Pediatrics and the Comprehensive Epilepsy Management Center, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, N.Y. (S.S.). Address reprint requests to Dr. Sillanpää at the Department of Child Neurology, University of Turku Hospital TYKS, 20520 Turku, Finland.

sampling to choose four potential control subjects for each patient, matched for sex, age, and place of birth. Of the first 100 potential control subjects, only 5 declined to participate, and the appropriate 5 from the second 100 potential controls were then substituted. One control subject who had erroneously been identified as male was subsequently excluded. The remaining 99 pairs of patients and control subjects were all given detailed questionnaires and interviewed.

The study design was approved by the joint ethics committee of the Turku University Medical School and the University of Turku Hospital. Oral informed consent was obtained from all subjects.

Definitions

For this report, the types of seizures, epileptic syndromes, and the causes of seizures were reclassified according to the current classification schemes and the guidelines for epidemiologic research of the International League against Epilepsy.¹⁶⁻¹⁸ These guidelines¹⁶ classify seizures as remote symptomatic, cryptogenic, or idiopathic. Remote symptomatic seizures are those without an immediate cause in a patient with either an identifiable prior brain injury such as major head trauma, meningitis, or stroke or a static encephalopathy, such as mental retardation or cerebral palsy, that is known to be associated with an increased risk of seizures. Cryptogenic seizures are those occurring in otherwise normal persons with no clear cause. Until recently, cryptogenic seizures were also called idiopathic seizures. In the new classification, the term "idiopathic" is reserved for seizures occurring in patients with epilepsy with a presumed genetic origin, such as benign rolandic epilepsy and childhood absence epilepsy.^{16,18}

A favorable early response to antiepileptic drugs was defined as a reduction of 75 to 100 percent in the frequency of seizures within three months after the initiation of treatment. Any patient who had been seizure-free for five years with or without medications was considered to be in remission.⁶ Patients were assessed to determine whether they had ever been in remission and whether they were in remission at the time of the last follow-up or death.

A patient with an IQ below 70 before the age of 18 years was considered to have mental retardation.²⁰ Cerebral palsy was defined as a chronic, nonprogressive cerebral disorder in young children that resulted in impaired motor function.²¹ The results of a neurologic examination were classified as abnormal if definite abnormalities such as hemiparesis, bilateral paresis, ataxia, or cognitive impairment were present. The presence of clumsiness, learning disabilities, or other "soft" neurologic signs was not sufficient to classify a patient as having neurologic abnormalities.

Socioeconomic status was defined according to the criteria of the Central Statistical Office of Finland.²² The classification is based, according to United Nations recommendations, on various criteria such as occupation and employment status and includes seven categories. Since the number of subjects in some categories was very small, the upper three categories were combined and considered to represent higher socioeconomic status, corresponding to an income level of approximately \$40,000 per year in the United States. The lower four categories were also combined and considered to represent lower socioeconomic status.

In the Finnish system of education, primary education is the equivalent of elementary-school education in the United States (kindergarten through sixth grade); a matriculation examination is taken after the completion of 12 years of schooling and is approximately equivalent to 1 year of college in the United States; and vocational training for specific occupations can begin after the ninth grade. The patients' levels of education were assessed with the use of these terms.

Statistical Analysis

We used statistical methods that take into account the time-dependent nature of the data²³⁻²⁶ using BMDP software.²⁷ The product-limit method was used to calculate the risk of death and

of remission at various times after the onset of the seizure disorder.^{23,26} Standard errors and 95 percent confidence intervals for the point estimates were calculated with a modification of Greenwood's formula.^{24,27} The results are displayed by means of Kaplan-Meier curves.^{23,24} Univariate and multivariable analyses were performed with the Cox proportional-hazards model.²⁴⁻²⁷ The rate ratio was used as a measure of the magnitude of the association between a variable and the risk of the measured outcome (death, remission, or remission in the absence of medications).²⁴⁻²⁷ For the comparison of social outcomes between subjects and controls, relative risks were used.^{26,27} The 95 percent confidence intervals were calculated from the logistic-regression models with a formula based on the normal approximation.^{26,27} In addition, Pearson's chi-square test, with Yates' correction when appropriate, and Fisher's exact test (two-tailed) were used. A P value of less than 0.05 was considered to indicate statistical significance. All P values are two-tailed.

RESULTS

Characteristics of the Subjects

The cohort included 134 male patients (55 percent) and 111 female patients (45 percent). The mean age at onset of epilepsy was 4.3 years (median, 3.0). At the time of the last follow-up, in 1992, the mean age was 32.5 years in the entire cohort and 35.6 years in the group of 176 surviving patients for whom data were available. During the period from January 1961 to December 1964, a total of 108,019 children under the age of 16 resided in the catchment area of University of Turku Hospital. The estimated annual incidence of epilepsy in this population was 0.35 per 1000 (95 percent confidence interval, 0.24 to 0.49), and the estimated prevalence of active epilepsy was 2.3 per 1000 (95 percent confidence interval, 1.46 to 3.45). The seizures were classified as idiopathic in 68 patients (28 percent), cryptogenic in 54 patients (22 percent), and remote symptomatic in 123 patients (50 percent). There were no significant differences between the 150 patients with incident cases and the other 95 patients with respect to cause or type of seizures and epilepsy syndrome.

Mortality

Data on mortality are summarized in Table 1. There were 44 documented deaths (18 percent), yielding a mortality rate of 6.23 per 1000 person-years (95 percent confidence interval, 5.72 to 6.71). The overall probability of survival was 0.94 (95 percent confidence interval, 0.91 to 0.97) 10 years after the onset of seizures, 0.88 (95 percent confidence interval, 0.84 to 0.92) 20 years after onset, and 0.75 (95 percent confidence interval, 0.64 to 0.86) 40 years after onset. The probability of survival as a function of age was 0.96 at 10 years of age (95 percent confidence interval, 0.94 to 0.99), 0.89 at 20 years of age (95 percent confidence interval, 0.85 to 0.93), and 0.80 at 40 years of age (95 percent confidence interval, 0.76 to 0.86).

The cause of the seizures strongly influenced mortality. The probability of survival to the age of

TABLE 1. RATES AND CAUSES OF DEATH AMONG A COHORT OF FINNISH PATIENTS WITH ONSET OF EPILEPSY IN CHILDHOOD.

VARIABLE	ALL PATIENTS (N=245)	PATIENTS WITH INCIDENT CASES* (N=150)	PATIENTS WITH IDIOPATHIC SEIZURES (N=68)	PATIENTS WITH CRYPTOGENIC SEIZURES (N=54)	PATIENTS WITH REMOTE SYMPTO- MATIC SEIZURES (N=123)
Outcome known — no.	220	137	56	48	116
No. of deaths	44	20	7	4	33
Deaths per 1000 patient-years — no. (95% CI)†	6.23 (5.72–6.71)	4.76 (4.38–5.25)	3.42 (3.05–3.78)	2.44 (2.10–2.72)	9.76 (9.19–10.43)
Age at death — yr					
Mean	18.6	20.6	23.3	19.3	17.5
Range	1–41	2–36	11–37	2–27	1–41
Remission status at time of death — no. (%)					
Not in remission	39 (89)	15 (75)	6 (86)	3 (75)	30 (91)
In remission	5 (11)	5 (25)	1 (14)	1 (25)	3 (9)
Medication	1	1	0	1	0
No medication	4	4	1	0	3
Death related to seizure — no. (%)‡	20 (45)	9 (45)	4 (57)	2 (50)	14 (42)
Witnessed seizure	9 (20)	4 (20)	1 (14)	2 (50)	6 (18)
Status epilepticus	3 (7)	2 (10)	0	1 (25)	2 (6)
Probable seizure	4 (9)	3 (15)	0	0	4 (12)
Drowning	4 (9)	1 (5)	0	0	4 (12)
Sudden unexplained death	3 (7)	1 (5)	3 (43)	0	0
Death not related to seizure — no. (%)	23 (52)	11 (55)	3 (43)	1 (25)	19 (58)
Pneumonia	12 (27)	4 (20)	0	0	12 (36)
Suicide	2 (4)	1 (5)	1 (14)	1 (25)	0
Other	9 (20)	6 (30)	2 (29)	0	7 (21)
Cause of death unknown — no. (%)	1 (3)	0	0	1 (25)	0

*An incident case was one in which the initial visit for the evaluation of seizures occurred between January 1961 and December 1964.

†CI denotes confidence interval.

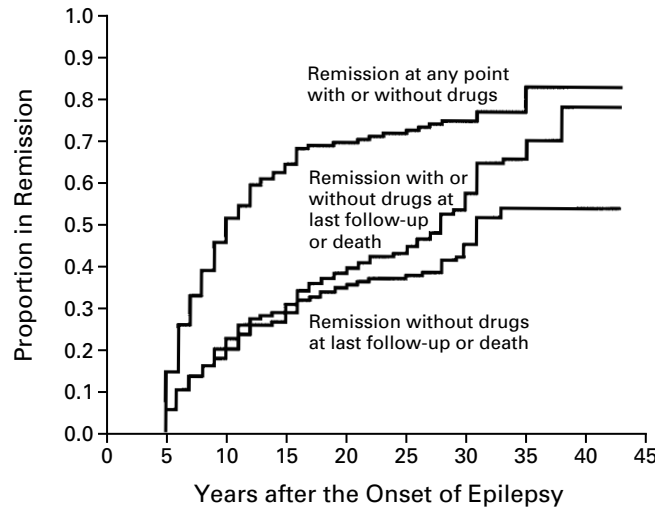
‡Death was definitely or probably related to a seizure.

40 was 0.87 among patients with idiopathic seizures (95 percent confidence interval, 0.77 to 0.96), 0.93 among those with cryptogenic seizures (95 percent confidence interval, 0.86 to 0.99), and 0.73 among those with remote symptomatic seizures (95 percent confidence interval, 0.65 to 0.81; $P < 0.001$ for the comparison with the other two groups). The mortality rate was also somewhat lower among patients with incident cases (4.76 per 1000 person-years; 95 percent confidence interval, 4.38 to 5.25) than among the other 95 patients (8.37 per 1000 person-years; 95 percent confidence interval, 7.84 to 8.99); the relative risk of death among those with incident cases was 0.53 (95 percent confidence interval, 0.31 to 0.90; $P = 0.03$). Thirty-nine of the 44 patients who died (89 percent) were not in remission at the time of death (relative risk of death among those not in remission as compared with those in remission, 9.26; 95 percent confidence interval, 3.78 to 22.70; $P < 0.001$). Death was definitely or probably related to a seizure in 20 cases. There were three cases of sudden unexplained death in patients with idiopathic epilepsy (at the ages of 13, 32, and 36) who were not in remission.

Remission

The data on remission are shown in Figure 1. The majority of patients who were alive at the time of the last follow-up had had a remission or were still in remission. Of 83 surviving patients who were in remission without medication at the last follow-up, 58 (70 percent) had been seizure-free for more than 20 years. Of the 176 surviving patients with sufficient data for analysis, 143 (81 percent) were in remission at some point. Of these 143, 67 (47 percent) subsequently relapsed, 49 while receiving antiepileptic medications. Thirty-six of the 67 who relapsed (54 percent) were in remission at the time of the last follow-up.

Multivariable analysis showed that the cause of the seizures, the response to anticonvulsant therapy, the initial frequency of seizures, and the type of seizures were all associated with a surviving patient's probability of being in remission at the time of the last follow-up (Table 2). The results were similar when the analysis was limited to patients with incident cases (Table 2). Patients with remote symptomatic seizures were significantly less likely to have a remission (Fig. 2) or to be in remission at the time



No. ALIVE AND IN FOLLOW-UP	245	227	206	179
No. OF EVENTS/NO. AT RISK				
Remission at any point with or without drugs	108/245	53/121	7/53	3/28
Remission with or without drugs at last follow-up or death	46/245	39/181	29/125	18/66
Remission without drugs at last follow-up or death	41/245	35/186	13/127	10/74

Figure 1. Kaplan–Meier Estimates of the Cumulative Probability of a Five-Year Remission in a Cohort of 245 Finnish Patients with Onset of Epilepsy in Childhood.

The cumulative probability of ever being in remission with or without antiepileptic drugs, of being in remission with or without antiepileptic drugs at the time of the last follow-up or death, and of being in remission without antiepileptic drugs at the time of the last follow-up or death is shown.

of the last follow-up, particularly in the absence of medications (Table 2), than patients with idiopathic or cryptogenic seizures ($P < 0.001$ for the comparison among groups). Patients with remote symptomatic epilepsy were also more likely to continue taking medication despite being in remission. An early response to drug therapy was the single best predictor of remission both in the overall cohort and in the three subgroups classified according to the cause of seizures (Table 2). An initial seizure frequency of less than once a month was also associated with a more favorable prognosis, but the number of seizures recorded before drug therapy was initiated was not related to the probability of remission. The type of seizure was also associated with the probability of remission (Table 2).

Social and Educational Outcomes

The relative risks of various social and educational outcomes among 99 patients with uncomplicated epilepsy, as compared with control subjects matched for age, sex, and place of birth, are shown in Table 3. The patients with uncomplicated epilepsy had significantly worse outcomes for all social and educational variables except the one related to passing the

matriculation examination. The results were similar when the analysis was limited to patients with incident cases. All children with uncomplicated epilepsy had at least a primary education. However, the patients were less likely than the control subjects to have continued their education. Despite these differences in the level of education, the socioeconomic status of the patients and the controls was similar. Not surprisingly, the 76 patients with epilepsy and other disabilities had poorer outcomes on each of these measures than the 99 patients with uncomplicated epilepsy (data not shown).

Similar proportions of patients with uncomplicated epilepsy in remission without medication at the time of the last follow-up and control subjects were of higher socioeconomic status and held a driver's license (Table 3). However, the patients were less likely to be married or living with someone or have children and had a marginally lower probability of being employed. The findings were similar when the analysis was limited to patients with incident cases or to those with idiopathic epilepsy. Of 66 patients with uncomplicated epilepsy in remission without medication at the time of the last follow-up, 47 (71 percent) had been in remission since the age of 20. Thus,

TABLE 2. MULTIVARIABLE ANALYSIS OF A SURVIVING PATIENT'S PROBABILITY OF BEING IN REMISSION AT THE TIME OF THE LAST FOLLOW-UP.*

VARIABLE	OVERALL COHORT				PATIENTS WITH INCIDENT CASES						
	TOTAL NO. OF PATIENTS	NO. IN REMISSION ON OR OFF MEDICATION (%)	RATE RATIO (95% CI)	P VALUE	NO. IN REMISSION OFF MEDICATION (%)	RATE RATIO (95% CI)	P VALUE	TOTAL NO. OF PATIENTS	NO. IN REMISSION OFF MEDICATION (%)	RATE RATIO (95% CI)	P VALUE
Overall cohort	176	112 (64)			83 (47)			117	66 (56)		
Early response to therapy	102	80 (78)	3.70 (2.04–6.68)	<0.001	64 (63)	10.43 (3.20–34.0)	<0.001	73	50 (68)	2.22 (1.24–3.96)	0.004
Complex partial seizures	74	35 (47)	0.30 (0.18–0.49)	<0.001	19 (26)	0.33 (0.15–0.71)	0.005	43	15 (35)	0.28 (0.13–0.59)	0.001
Atonic seizures†	14	3 (21)	0.22 (0.07–0.73)	0.002	2 (14)		0.46	11	2 (18)	0.26 (0.06–1.21)	0.05
Cause of epilepsy				0.31			<0.001				0.002
Remote symptomatic	83	37 (45)			16 (19)	1.00		46	11 (24)	1.00	
Cryptogenic	44	30 (68)			25 (57)	3.03 (1.41–6.54)		35	23 (66)	3.39 (1.57–7.31)	
Idiopathic	49	45 (92)			42 (86)	3.15 (1.54–6.43)		36	32 (89)	2.62 (1.21–5.66)	
Idiopathic epilepsy	49	45 (92)			42 (86)				32 (89)		
Early response to therapy	38	37 (97)	6.06 (1.42–25.8)	0.002	35 (92)	8.43 (1.09–64.9)	0.006	28	26 (93)	3.21 (1.01–10.7)	0.03
Initial seizure frequency <1/mo	24	21 (87)		0.06	18 (75)	2.04 (1.02–4.07)	0.04	18	14 (78)		0.57
Cryptogenic epilepsy	44	30 (68)			25 (57)				23 (66)		
Early response to therapy	27	21 (78)	3.32 (0.98–11.3)	0.03	18 (67)	7.55 (1.00–57.0)	0.008	23	17 (74)		0.11
Complex partial seizures	27	16 (59)	0.38 (0.16–0.88)	0.03	12 (44)	0.31 (0.12–0.79)	0.02	20	11 (55)	0.32 (0.13–0.80)	0.01
Remote symptomatic epilepsy	83	37 (45)			16 (19)			46	11 (24)		
Early response to therapy	37	22 (59)	3.21 (1.52–6.79)	0.001	11 (30)	7.61 (1.66–34.9)	0.002	22	7 (32)		0.09

*The variables entered into the multivariable analysis with the Cox proportional-hazards model included the age at onset of seizures, the cause of seizures, the type of seizures, the epilepsy syndrome, the initial frequency of seizures, early response to therapy, the number of seizures recorded before treatment was initiated, the occurrence of status epilepticus, the occurrence of seizures during both waking hours and sleep, neurologic status, and IQ. CI denotes confidence interval.

†Atonic seizures are most commonly seen in patients with remote symptomatic epilepsy.^{27,28,30}

adverse social effects persisted even in patients who entered adult life free of seizures and seizure medication.

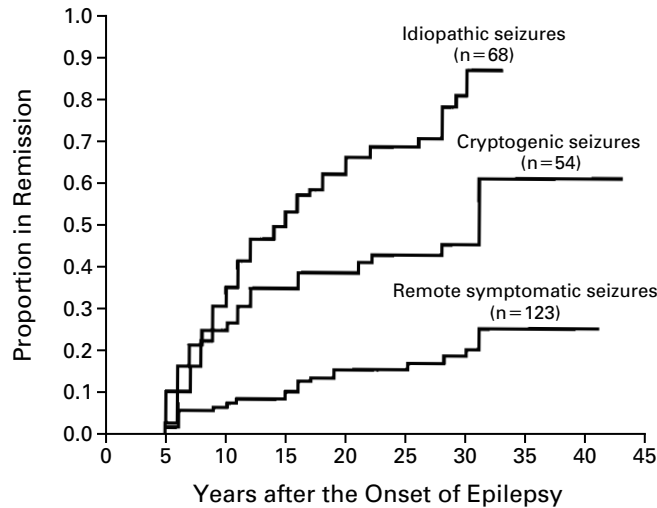
There were too few patients with uncomplicated epilepsy in remission who were taking medication (nine) for a comparison with those in remission without medication. However, 4 patients (44 percent) who were in remission with medication had a driver's license, as compared with 52 patients (79 percent) in remission without medication ($P=0.4$) and 88 control subjects (89 percent, $P=0.003$). In Finland, patients with well-controlled epilepsy may drive.

DISCUSSION

We assessed the long-term outcome of a population-based cohort with epilepsy of childhood onset that was prospectively followed for many years by a

single pediatric neurologist. The strengths of this study are the long-term follow-up with a high rate of retention of subjects, the availability of detailed information permitting accurate classification of the type of seizures, the epilepsy syndrome, and the cause of seizures, as well as an assessment of social and seizure-related outcomes.

The incidence and prevalence of epilepsy and seizures are consistent with those reported in other population-based studies.^{9,28-30} The proportion of patients with idiopathic seizures is also similar to that in other series.³¹ The higher proportion of patients with remote symptomatic epilepsy in our cohort than in other studies is due to the extensive analysis of the patients, which led to a reclassification of the cause in numerous patients and thus reduced the proportion of patients with cryptogenic epilepsy. Many patients initially considered to have crypto-



	NO. OF EVENTS/NO. AT RISK/NO. ALIVE AND IN FOLLOW-UP			
Idiopathic seizures	20/68/68	19/44/64	8/20/59	3/6/51
Cryptogenic seizures	13/54/54	7/39/51	3/30/49	4/22/44
Remote symptomatic seizures	8/123/123	9/103/112	2/77/98	3/46/84

Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of a Five-Year Remission without Antiepileptic Drugs in a Cohort of Finnish Patients with Onset of Epilepsy in Childhood, According to the Cause of Epilepsy.

genic epilepsy are subsequently found to have remote symptomatic epilepsy.³²

Mortality

Patients with epilepsy have an increased risk of death, including sudden death.⁷⁻¹⁴ The high death rate in our cohort may be partly accounted for by the higher proportion of patients with remote symptomatic epilepsy and by the fact that we counted all deaths in the cohort whether or not they were attributable to the seizure disorder. The lower mortality rate among our patients with incident cases was not accompanied by differences in other outcome measures in the surviving patients. In prior studies of children with seizures, the children were rarely followed into adulthood, when most of the deaths occur.^{5,7-9} The mortality rates in this cohort were similar to those reported in adults with refractory epilepsy, many of whom first began to have seizures in childhood.^{13,14}

Remission

The data on overall remission are consistent with those reported in Rochester, Minnesota,⁶ and the United Kingdom.³³ As in other studies, the cause of seizures was consistently associated with the probability of remission.^{5-7,33} The variable most strongly associated with remission was an early response to drug therapy. Other studies have reported that patients who have a response within the first year of

therapy have a better prognosis.^{1,2,6} These findings suggest that in selected situations, children and adolescents with persistent seizures may be candidates for surgery³⁴ after two years of appropriate medical therapy. However, although those with an early response did well, many of the children who did not have early responses eventually entered remission, a finding in agreement with a recent report on the prognosis of refractory childhood epilepsy.³⁵ These data on the early response to treatment are from an era that preceded the introduction of carbamazepine, valproate, and other, newer medications.³⁶ Although we believe that an early response to treatment is still valid as a predictor of favorable outcome, a higher proportion of patients without an early response than in our cohort may eventually enter remission with the use of these newer medications. The rate of remission without medication is less likely to be affected by the availability of new drugs, since it reflects the underlying course of the disorder.³⁷

Social and Educational Outcomes

The occurrence of seizures in childhood appears to have a long-term adverse impact on a patient's level of education and likelihood of employment, marriage, and having children. These adverse effects were found even in patients with idiopathic epilepsy in remission without medication, a group that would be expected to have the most favorable outcomes. This difference is not due simply to discrimination,

TABLE 3. RELATIVE RISKS OF VARIOUS SOCIAL AND EDUCATIONAL OUTCOMES AMONG 99 PATIENTS WITH UNCOMPLICATED EPILEPSY AS COMPARED WITH CONTROL SUBJECTS MATCHED FOR AGE, SEX, AND PLACE OF BIRTH.*

VARIABLE	CONTROL SUBJECTS (N=99)	ALL PATIENTS (N=99)			PATIENTS IN REMISSION WITHOUT MEDICATION (N=66)			PATIENTS WITH INCIDENT CASES IN REMISSION WITHOUT MEDICATION (N=54)			PATIENTS WITH IDIOPATHIC EPILEPSY IN REMISSION WITHOUT MEDICATION (N=42)		
		NO. (%)	NO. (%)	RELATIVE RISK (95% CI)	P VALUE	NO. (%)	RELATIVE RISK (95% CI)	P VALUE	NO. (%)	RELATIVE RISK (95% CI)	P VALUE	NO. (%)	RELATIVE RISK (95% CI)
Primary education only	23 (23)	47 (49)†	2.13 (1.41–3.21)	<0.001	29 (46)‡	1.98 (1.27–3.10)	0.004	22 (43)§	1.86 (1.15–2.99)	0.02	22 (56)¶	2.43 (1.55–3.82)	<0.001
Did not pass matriculation examination	74 (75)	76 (80)†	1.07 (0.92–1.25)	0.48	50 (79)‡	1.06 (0.90–1.26)	0.63	40 (78)§	1.05 (0.87–1.26)	0.77	34 (87)¶	1.17 (0.99–1.38)	0.17
No vocational training	51 (52)	66 (69)†	1.35 (1.07–1.70)	0.02	42 (66)‡	1.29 (0.99–1.68)	0.08	32 (63)§	1.21 (0.92–1.62)	0.26	29 (74)¶	1.44 (1.11–1.88)	0.02
Not married or cohabiting	10 (10)	35 (35)	3.50 (1.84–6.67)	<0.001	19 (29)	2.85 (1.42–5.74)	0.004	16 (30)	2.93 (1.43–6.01)	0.004	12 (29)	2.83 (1.33–6.03)	0.01
No children	16 (16)	50 (51)	3.00 (1.84–4.88)	<0.001	28 (42)	2.52 (1.49–4.27)	<0.001	22 (41)	2.92 (1.39–4.20)	0.003	16 (38)	2.26 (1.25–4.08)	0.01
No driver's license	11 (11)	39 (39)	3.55 (1.93–6.51)	<0.001	14 (21)	1.91 (0.92–3.94)	0.12	13 (24)	2.17 (1.04–4.50)	0.04	9 (21)	1.93 (0.83–4.31)	0.18
Not employed	8 (8)	31 (31)	3.76 (1.82–7.76)	<0.001	13 (20)	2.36 (1.04–5.38)	0.03	11 (20)	2.44 (1.05–5.70)	0.03	3 (7)	0.86 (0.24–3.07)	0.81
Lower socioeconomic status	51 (52)	64 (65)	1.25 (0.99–1.55)	0.08	40 (61)	1.18 (0.90–1.55)	0.32	34 (63)	1.22 (0.92–1.62)	0.23	28 (67)	1.29 (0.97–1.72)	0.14

*In the Finnish system of education, primary education is the equivalent of elementary-school education in the United States (kindergarten through sixth grade), a matriculation examination is taken after the completion of 12 years of schooling and is approximately equivalent to 1 year of college in the United States, and vocational training for specific occupations can begin after the ninth grade. CI denotes confidence interval.

†Data on education were available for 95 patients.

‡Data on education were available for 63 patients.

§Data on education were available for 51 patients.

¶Data on education were available for 39 patients.

since similar proportions of patients and control subjects had passed the matriculation examination and had higher socioeconomic status. Few data on educational outcomes in unselected groups of patients are available for purposes of comparison.³⁸ Studies of patients attending seizure clinics have reported academic underachievement in relation to IQ³⁹ and a higher proportion of unfavorable educational outcomes than in the general population.^{15,40-42}

Several studies of adults with active epilepsy have indicated they have lower rates of employment than similar control subjects from the general population.^{15,41,43,44} The differences were attributed to discrimination and to problems related to the active seizure disorder. Studies of patients who had refractory epilepsy in childhood also reported poor long-term employment outcomes even if the patients later became seizure-free.¹⁵ Our study demonstrates that even the mildest forms of childhood epilepsy can have a lifelong effect on employment status.

As compared with the general population, adults who had refractory temporal-lobe epilepsy as adolescents¹⁵ and adults with active epilepsy who were at-

tending a seizure clinic⁴¹ were less likely to be married. Decreased fertility has also been described in patients with refractory epilepsy^{15,45} and in men and women with active epilepsy.⁴⁵ A younger age at onset of epilepsy was associated with a decreased likelihood of having children, even after adjustment for the lower marriage rates.⁴⁵ The current data raise concern about the long-term adverse effects on marriage and fertility associated with the occurrence of even relatively mild seizure disorders in childhood. It is unlikely that more aggressive medical treatment would have altered the clinical course in the majority of the patients that we studied, since most had mild, self-limited epilepsy that responded readily to therapy.

Conclusions

The majority of patients with epilepsy that begins in childhood will become free of seizures by adulthood. Those who do not enter remission have an increased risk of death. Although patients with uncomplicated epilepsy have a favorable long-term medical prognosis, they are more likely to have lower levels of education and employment than the gener-

al population and less likely to marry or have children, even if they have been seizure-free without medication for many years. Future interventions will need to focus on the social aspects as well as the medical aspects of treating seizures.

Supported in part by grants from the Finnish Epilepsy Research Foundation and Turun Sanomat Group Printing House (to Dr. Jalava) and by a grant (NS26151) from the National Institute of Neurological Disorders and Stroke (to Dr. Shinnar).

REFERENCES

- Beghi E, Tognoni G. Prognosis of epilepsy in newly referred patients: a multicenter prospective study. *Epilepsia* 1988;29:236-43.
- Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. *N Engl J Med* 1984;311:944-7.
- Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. *J Pediatr* 1993;122:861-8.
- Sofijanov NG. Clinical evolution and prognosis of childhood epilepsies. *Epilepsia* 1982;23:61-9.
- Berg AT, Hauser WA, Shinnar S. The prognosis of childhood-onset epilepsy. In: Shinnar S, Amir N, Branski D, eds. *Childhood seizures*. Basel, Switzerland: S. Karger, 1995:93-9.
- Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729-37.
- Brorson LO, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987;28:324-30.
- Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. *Epilepsia* 1980;21:339-412.
- Hauser WA, Hesdorffer DC. *Epilepsy: frequency, causes and consequences*. New York: Demos, 1990.
- Lathers CM, Schraeder PL, eds. *Epilepsy and sudden death*. New York: Marcel Dekker, 1990.
- Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. *Ann Neurol* 1989;26:195-203.
- Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. *Epilepsia* 1995;36:29-36.
- Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 1995;36:1187-94.
- Derby LE, Tennis P, Jick H. Sudden unexplained death among subjects with refractory epilepsy. *Epilepsia* 1996;37:931-5.
- Ounsted C, Lindsay J, Richards P. *Temporal lobe epilepsy 1948-1986: a biographical study*. No. 103 of Clinics in developmental medicine. London: Mac Keith Press, 1987.
- Commission on Epidemiology and Prognosis, International League against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592-6.
- Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489-501.
- Idem*. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-99.
- Sillanpää M. Medico-social prognosis of children with epilepsy: epidemiological study and analysis of 245 patients. *Acta Paediatr Scand Suppl* 1973;237:1-104.
- International classification of impairments, disabilities, and handicaps: a manual of classification relating to consequences of disease. Geneva: World Health Organization, 1980.
- Bax MCO. Terminology and classification of cerebral palsy. *Dev Med Child Neurol* 1964;6:295-7.
- Classification of socio-economic groups. Helsinki, Finland: Central Statistical Office of Finland, 1989. (In Finnish.)
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Elandt-Johnson RC, Johnson NL. *Survival models and data analysis*. New York: John Wiley, 1980:150-80.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Kelsey JL, Thompson WD, Evans AS. *Methods in observational epidemiology*. New York: Oxford University Press, 1986.
- Dixon W. *BMDP statistical software*. Berkeley: University of California Press, 1990.
- Berg AT. The epidemiology of seizures and epilepsy in children. In: Shinnar S, Amir N, Branski D, eds. *Childhood seizures*. Basel, Switzerland: S. Karger, 1995:1-10.
- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993;34:453-68.
- Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley J. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia* 1996;37:19-23.
- Berg AT, Levy SR, Testa FM, Smith-Rapaport S, Shinnar S. Newly diagnosed epilepsy in children: the ILAE classification system applied in a community-based cohort. *Epilepsia* 1995;36:Suppl 4:29. abstract.
- Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case-control study. *Epilepsia* 1996;37:24-30.
- Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995;346:140-4.
- Engel J Jr. Surgery for seizures. *N Engl J Med* 1996;334:647-52.
- Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. *Ann Neurol* 1990;28:699-705.
- Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996;334:1583-90.
- Shinnar S, Berg AT. Does antiepileptic drug therapy prevent the development of "chronic" epilepsy? *Epilepsia* 1996;37:701-8.
- Camfield C, Camfield P, Smith B, Gordon K, Dooley J. Biologic factors as predictors of social outcome of epilepsy in intellectually normal children: a population-based study. *J Pediatr* 1993;122:869-73.
- Mitchell WG, Chavez JM, Lee H, Guzman BL. Academic underachievement in children with epilepsy. *J Child Neurol* 1991;6:65-72.
- Westbrook LE, Silver EJ, Coupey SM, Shinnar S. Social characteristics of adolescents with idiopathic epilepsy: a comparison to chronically ill and non chronically ill peers. *J Epilepsy* 1991;4:87-94.
- Callaghan N, Crowley M, Goggin T. Epilepsy and employment, marital, education and social status. *Ir Med J* 1992;85:17-9.
- Carlton-Ford S, Miller R, Brown M, Nealeigh N, Jennings P. Epilepsy and children's social and psychological adjustment. *J Health Soc Behav* 1995;36:285-301.
- Olsson I, Campenhausen G. Social adjustment in young adults with absence epilepsies. *Epilepsia* 1993;34:846-51.
- Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study. *Epilepsia* 1996;37:148-61.
- Schupf N, Ottman R. Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: social and biologic influences. *Epilepsia* 1994;35:750-6.