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Clinical Indicators of Genetic Susceptibility to Epilepsy

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Summary: We evaluated clinical indicators of genetic susceptibility to epilepsy in the families of 1,957 adults with epilepsy (probands) ascertained from voluntary organizations. Very few of the probands in this series had idiopathic epilepsy syndromes. Among relatives of probands with postnatal CNS insults, risks of epilepsy were no higher than in the general population. Risk was increased in relatives of probands without identified CNS insults (i.e., those with idiopathic/cryptogenic epilepsy) or with neurological deficit presumed present at birth, compared with relatives of probands with postnatal CNS insults. Among relatives of probands with idiopathic/cryptogenic epilepsy, risks were higher in parents and siblings, but not in offspring, of probands with generalized onset as compared with partial onset seizures. Risks in offspring were higher if the probands had onset of idiopathic/cryptogenic epilepsy before age 10 as compared with age ≥10 years, but risks in parents and siblings were not associated with the proband's age at onset. These results suggest that genetic susceptibility increases risk of some forms of cryptogenic epilepsy and of epilepsy associated with neurological deficit presumed present at birth, but not of postnatal symptomatic epilepsy. The influences on risk in offspring may differ from those in parents and siblings. **Key Words:** Epilepsy—Seizures—Epidemiology—Human genetics.

Despite strong evidence of a genetic contribution to epilepsy, little progress has been made in identifying specific genes that have a major effect on susceptibility. This slow progress is due in part to inherent complexity in the genetic contributions. One important source of this complexity is etiologic and genetic heterogeneity. Both genetic and nongenetic influences on susceptibility are likely to exist, and the important genetic influences are likely to differ across families or clinically defined subgroups. Discovery of clinical features that distinguish between genetic and nongenetic epilepsies is important for both research and clinical practice. This information is essential for the design of linkage studies because it can be used to decide which individuals should be assumed to be gene carriers; e.g., should subjects be classified as affected only if they have unknown etiology of epilepsy or should those with identified CNS lesions also be included?

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In previous family studies, two clinical features in probands, early age at onset and idiopathic/cryptogenic etiology, were shown to be associated with high risk in relatives (1–7). Risk is widely assumed to be higher in relatives of patients with generalized onset seizures than in relatives of those with partial onset seizures, but in most studies the difference between these two groups is small (8). In our analyses of offspring of epilepsy patients in Rochester, Minnesota (9), the higher risk in offspring of parents with generalized onset seizures was due entirely to very high risks in offspring of the subset with absence seizures. Thus, in offspring of most patients with generalized epilepsy, risk was no higher than in offspring of patients with partial epilepsy.

In this study, we evaluated potential clinical indicators of a genetic susceptibility to epilepsy by investigating the relations of etiology, seizure type, and age at onset of epilepsy in probands to risks of epilepsy in their first-degree relatives. The study population comprised families of 1,957 probands with epilepsy from the Epilepsy Family Study of Columbia University (EFSCU). The goals of this study, which was begun in 1985, were to evaluate the relations between clinical and genetic heteroge-

neity in the epilepsies and to test consistency of the familial distribution with various genetic and nongenetic models. In the present article, we describe the major results of the study with respect to clinical features in probands and their relations to familial risk of epilepsy.

Very few of the probands in the EFSCU series had idiopathic epilepsy syndromes. Therefore, the results pertain primarily to cryptogenic and symptomatic epilepsies, in which the role of genetic susceptibility is largely unknown.

METHODS

Study population

The methods for data collection in EFSCU were described in detail previously (10). Briefly, 1,957 adults with epilepsy (probands) were ascertained from voluntary organizations with 84% participation. We used semistructured telephone interviews with probands to obtain information on clinical characteristics of epilepsy and history of seizure disorders and related conditions in parents, full siblings, half-siblings, offspring, and spouses. Whenever possible (67% of families), we also interviewed an additional family informant (usually the mother of the proband) with regard to the same relatives reported on by the proband, to improve the sensitivity of the family history data. To confirm and augment the clinical detail on the family histories, we were also able to interview 51% of living adult relatives who were reported to have had seizures when they were aged ≥5 years. We obtained medical records for 60% of probands.

Eighty-seven percent of probands were white, 55% had ≥1 year of college education, and 60% were women. Subjects interviewed did not differ significantly in gender or ethnicity from those who refused, but were more educated than those who refused. Probands ranged in age from 18 to 82 years, (average 36 years).

Clinical diagnosis and classification

Diagnoses of seizure disorders were based on a review of all information collected on each proband or relative (proband interview, second informant interview, direct interview, and/or medical record). Epilepsy was defined as a lifetime history of two or more unprovoked seizures (11). The proband's family history report of epilepsy in parents and siblings had excellent validity (87% sensitivity, 99% specificity), using the mother's report as the gold standard (12).

We obtained data for classification of seizure type and etiology of epilepsy in the interviews with the probands and other family informants, supplemented by review of medical records whenever possible. Probands were asked about clinical manifestations and etiology of seizures with respect to themselves and any other relative they reported to have had seizures. The interviews with other family informants included the same questions about seizure type and etiology in the proband, the relative who was being interviewed, and any other relatives reported by the second informant to have had seizures. The final classification of seizure type and etiology was made on the basis of a case-by-case review of all of this information.

As previously described (13,14), the data for seizure classification included verbatim descriptions of seizures and closed-ended questions regarding relevant features (e.g., specific aura, unilateral signs, alteration in consciousness). We classified seizures according to the 1981 criteria of the International League Against Epilepsy (15). In the current classification of epileptic syndromes (16), patients with generalized onset seizures would be classified as having generalized epilepsies and those with partial onset seizures would be classified as having localization-related epilepsies. As we reported previously, the resulting seizure classifications were reliable (13) and valid as compared with diagnoses of physicians with expertise in epilepsy (14).

For classification of etiology, we asked specific questions about each of a series of factors demonstrated to be strongly associated with risk for epilepsy in previous epidemiologic studies. These factors included severe head injury (defined as injury associated with ≥30-min loss of consciousness or skull fracture) (17), stroke, brain tumor, brain surgery, and brain infection (specifically spinal meningitis or encephalitis). Whenever a history of one of these factors was reported, we inquired about the age at which it occurred, whether seizures had occurred in close temporal association, and how long after the event the seizures had occurred. Seizures occurring <7 days after the event were not considered to be epilepsy but were classified as acute symptomatic. We also asked about other factors potentially associated with seizures, including heavy alcohol drinking, diabetes, high blood pressure, paralysis, cerebral palsy, attendance at a special school because of a learning difficulty, and any other serious medical problem. This information was used to discriminate further between acute symptomatic and unprovoked seizures and to clarify the etiology of epilepsy.

We used three categories of etiology in probands: (a) idiopathic/cryptogenic, or epilepsy occurring in the absence of a history of an insult to the CNS demonstrated to increase greatly the risk of unpro-

voked seizures; (b) neurological deficit presumed present at birth (neurodeficit from birth), or epilepsy associated with a history of cerebral palsy (motor handicap or movement disorder) or mental retardation (I.Q. <70) presumed present at birth; and (c) postnatal symptomatic, or epilepsy associated with a history of a postnatal CNS insult that occurred ≥7 days before the first unprovoked seizure. We distinguished between neurological deficits and postnatal symptomatic epilepsies because previous studies have indicated a possible genetic relation between cerebral palsy and epilepsy (18–20).

Statistical analysis

We assumed that each relative was at risk of epilepsy from birth until current age or age at death (if unaffected) or age at first unprovoked seizure (if affected with epilepsy). We used actuarial life-table analysis (21) to estimate age-specific cumulative incidence of epilepsy in parents, siblings, and offspring within strata defined by the probands' etiology, seizure type, and age at onset of epilepsy. The resulting cumulative incidences may be interpreted as estimates of the risk that each family member will develop epilepsy by the time he or she reaches a specific age. We also used Cox proportional hazards analysis (22) to compute rate ratios (RRs) for epilepsy in relatives according to specific clinical features in probands. Among relatives of probands with idiopathic/cryptogenic epilepsy, we evaluated the independent effects of the proband's seizure type and age at onset on risk of epilepsy by performing multivariate Cox proportional hazards analysis (22) with both of these variables in the model. In a previous analysis of this dataset, we noted that the observed risks of epilepsy in relatives increased ~50% for each 20-year increase in birth year of the relatives, probably reflecting underreporting of epilepsy at young ages in older relatives (23). To adjust for this effect in the present analysis we added birth year of the relatives to the Cox models.

Among all 10,765 first-degree relatives of the 1,957 probands, 1,024 (10%) were excluded because of missing information on history of epilepsy or birth year (parents 14%, siblings 8%, offspring 6%). Thirty of the remaining 9,741 relatives were excluded from the analysis of proband etiology, and 25 were excluded from the analysis of proband age at onset because data on these proband diagnostic characteristics were missing. In addition, 426 relatives were excluded from the analysis of proband seizure type because the proband had both generalized onset and partial onset seizures (150 relatives) or unclassifiable seizures (276 relatives).

RESULTS

The distribution of seizure type in probands was 12% (N = 229) generalized onset, 84% (N = 1,652) partial onset, 1% (N = 26) both generalized and partial onset, and 3% (N = 50) unclassifiable. Age at onset of epilepsy ranged from birth to 69 years, with 28% aged <10 years, 39% aged 10–19 years, and 33% aged ≥20 years. Epilepsy was idiopathic/cryptogenic in 1,560 (80%), symptomatic in 391 (20%), and unclassifiable in 6 (0.3%) of the probands. Among the probands classified as having idiopathic/cryptogenic epilepsy, the distribution of seizure type was comparable to that in the total group of probands (13% generalized onset, 83% partial onset, 1% both generalized and partial onset, 3% unclassifiable). Although the information we collected did not permit definite assignment to epilepsy syndromes, none of the probands with partial onset seizures appeared to have idiopathic localization-related syndromes, and very few of the probands with generalized onset seizures appeared to have the idiopathic generalized syndromes as described in the current International Classification of Epileptic Syndromes (ICE) (16). Thus, most of those with idiopathic/cryptogenic epilepsy would have been classified as having cryptogenic epilepsy syndromes.

Among the 391 probands with symptomatic epilepsy, 29 were classified as having neurodeficit from birth (28 cerebral palsy, 1 mild intellectual impairment). All of the probands with neurodeficit had intelligence sufficiently high for them to understand and answer the interview questions, and none was severely retarded. The remaining 362 probands with symptomatic epilepsy were classified as postnatal symptomatic (vascular 36, posttraumatic 157, CNS infection 113, neoplastic 25, other 31).

In all three classes of relatives, cumulative incidence of epilepsy was higher if the proband's epilepsy was idiopathic/cryptogenic or associated with neurodeficit from birth than if associated with other factors (Fig. 1). Among relatives of probands with idiopathic/cryptogenic epilepsy, risks to age 40 years increased from 1.8% in parents to 3.2% in siblings and to 6.7% in offspring, whereas among relatives of probands with postnatal symptomatic epilepsy, risks to age 40 years were similar among parents (1.4%), siblings (1.3%), and offspring (1.5%) (Fig. 1). Among all relatives of probands with postnatal symptomatic epilepsy, cumulative incidence of epilepsy to age 40 was 1.5%, which is similar to the cumulative incidence in the general population of Rochester, Minnesota (1.6%) (22). Within the postnatal symptomatic category, the

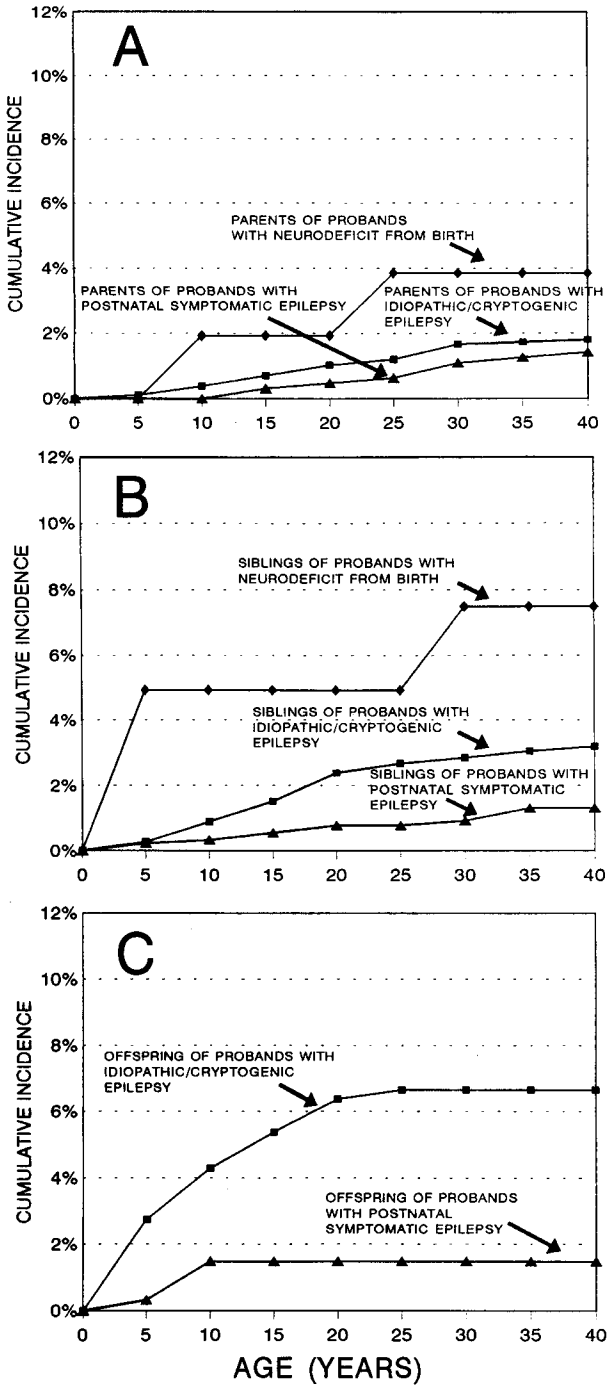

FIG. 1. Cumulative incidence of epilepsy in relatives of all probands by etiology of proband's epilepsy. Relatives of probands with idiopathic/cryptogenic epilepsy (squares), epilepsy associated with neurodeficit from birth (diamonds), and postnatal symptomatic epilepsy (triangles). Parents **(A)**, siblings **(B)**, offspring **(C)**.

risks to age 40 did not differ substantially among relatives of probands with different etiologies (vascular 1.2%, trauma 2.1%, CNS infection 2.2%, neoplastic 0, other 1.4%). With relatives of probands with postnatal symptomatic epilepsy used as the reference group, the RR for relatives of probands with idiopathic/cryptogenic epilepsy was 1.4 in parents, 2.6 in siblings, and 4.3 in offspring (Table 1). For relatives of probands with neurodeficit, the RR was 2.4 in parents and 5.9 in siblings. (Because there were too few offspring of probands with neurodeficit, we could not evaluate their risk.)

The remaining analyses were restricted to relatives of probands with idiopathic/cryptogenic epilepsy. Among relatives of probands with idiopathic/cryptogenic epilepsy with partial onset seizures, risks to age 40 increased in successive generations (parents 1.6%, siblings 3.0%, offspring 7.1%), whereas among relatives of probands with idiopathic/cryptogenic epilepsy with generalized onset seizures there was less increase in risk in successive generations (parents 3.2%, siblings 5.5%, offspring 4.3%) (Fig. 2). In parents and siblings, risks were higher in relatives of probands with generalized onset seizures than in relatives of those with partial onset seizures. This trend was reversed in offspring (Fig. 2), although the lower risk in offspring of probands with generalized onset seizures was not statistically significant. With relatives of probands with idiopathic/cryptogenic epilepsy with partial onset seizures used as the reference group, the multivariate RR in relatives of probands with idiopathic/cryptogenic epilepsy with generalized onset seizures was 1.8 in parents, 1.6 in siblings, and 0.5 in offspring (Table 2).

For comparison with previous findings in Rochester, Minnesota (9), we also examined occurrence of epilepsy in the relatives of probands with absence seizures specifically. In the present study, unlike in the Rochester study, prevalence of a history of epilepsy was not higher (and was actually slightly lower) if the proband had absence seizures

TABLE 1. *RR for epilepsy in relatives of probands with epilepsy by etiology of epilepsy in the probands*

Class of relatives/etiology of epilepsy in the proband	No. of Relatives		RR	(95% CI)
	Total	With epilepsy		
Parents				
Idiopathic/cryptogenic	2,717	65	1.4	(0.73–2.78)
Neurodeficit from birth	49	2	2.4	(0.54–11.18)
Postnatal symptomatic	606	10	1.0	(Reference)
Siblings				
Idiopathic/cryptogenic	3,681	108	2.6	(1.38–5.03)
Neurodeficit from birth	60	4	5.9	(1.86–18.94)
Postnatal symptomatic	892	10	1.0	(Reference)
Offspring				
Idiopathic/cryptogenic	1,365	67	4.3	(1.56–11.81)
Neurodeficit from birth	14	0	—	—
Postnatal symptomatic	327	4	1.0	(Reference)

RR, rate ratio; CI, confidence interval.
RR and 95% CI calculated from Cox proportional hazards model, with birth year of the relatives included as a covariate.

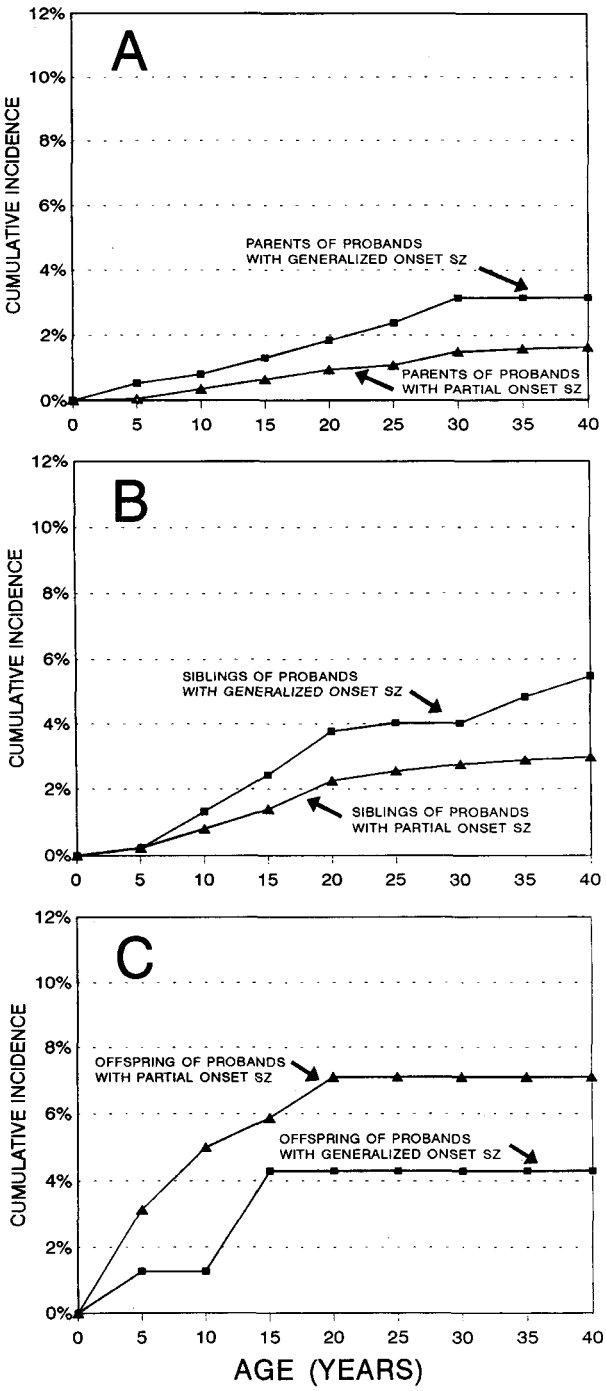

FIG. 2. Cumulative incidence of epilepsy in relatives of probands with idiopathic/cryptogenic epilepsy only, by seizure type of proband's epilepsy. Relatives of probands with generalized onset seizures (squares), partial onset seizures (triangles). Parents **(A)**, siblings **(B)**, offspring **(C)**.

than if the proband had other generalized onset seizures [relatives of probands with idiopathic/cryptogenic epilepsy: parents 4 of 159 (3%) vs. 10 of 222 (5%); siblings 7 of 189 (4%) vs. 14 of 273 (5%); offspring 0 of 70 (0%) vs. 5 of 105 (5%)].

Risk increased in successive generations in all three strata defined by the proband's age at onset (Fig. 3). Risk of epilepsy in parents was not associated with the proband's age at onset of idiopathic/cryptogenic epilepsy (Fig. 3 and Table 2). Risk was higher in siblings of probands with onset of idiopathic/cryptogenic epilepsy between the ages of 10 and 19 years than in those of probands with earlier or later ages at onset (Fig. 3 and Table 2). Risk was more than twice as high in offspring of probands with onset of idiopathic/cryptogenic epilepsy <10 years as in offspring of those with later ages at onset (Fig. 3 and Table 2).

DISCUSSION

The ICE established three etiologic categories, based on the presumed importance of genetic susceptibility (16). The term idiopathic is used for syndromes presumed to be of genetic origin; the term cryptogenic is reserved for those that are presumed to be symptomatic but that have no identified etiologic factors. The remaining cases, with identified CNS lesions, are classified as symptomatic. Our study population contains very few probands with idiopathic epilepsy syndromes. Hence, the present study was primarily a study of genetic contributions to epilepsies that would be classified as either cryptogenic or symptomatic in the syndrome classification.

Our findings suggest that the genetic influences on postnatal symptomatic epilepsy are minimal. In relatives of probands with identified postnatal CNS insults, the risk of epilepsy was similar to risk in the general population (24). Similarly, Schaumann et al. (25) recently reported that seizure risk was not increased in relatives of probands with posttraumatic epilepsy. In their study, relatives of probands who had seizures associated with alcohol had an increased risk, whether the seizures were unprovoked and associated with chronic alcohol abuse, or acute symptomatic and associated with alcohol intoxication. We did not have sufficient data to examine this subgroup separately.

As in previous studies (1–5), risk of epilepsy was higher in relatives of probands without identified CNS insults (i.e., those with idiopathic/cryptogenic epilepsies) than in relatives of those with symptomatic epilepsy. Because our idiopathic/cryptogenic subgroup was primarily cryptogenic, this higher risk suggests that genetic susceptibility contributes to some forms of cryptogenic epilepsy. Therefore, although cryptogenic epilepsy is defined in the syndrome classification as "presumed symptomatic but without identified etiologic factors," patients with cryptogenic epilepsy differ markedly from

TABLE 2. *RR for epilepsy in relatives of probands with idiopathic/cryptogenic epilepsy, by seizure type and age at onset of epilepsy in probands*

Class of relatives/seizure type and age at onset of epilepsy in the proband	No. of relatives		Univariate		Multivariate	
	Total	With epilepsy	RR	(95% CI)	RR	(95% CI)
Parents						
Generalized onset	362	14	1.8	(0.97–3.18)	1.8	(0.99–3.27)
Partial onset	2,252	50	1.0	(Reference)	1.0	(Reference)
Age (yr)						
<10	818	22	1.0	(0.52–1.83)	0.9	(0.48–1.75)
10–19	1,111	23	0.8	(0.41–1.40)	0.7	(0.39–1.33)
≥20	780	20	1.0	(Reference)	1.0	(Reference)
Siblings						
Generalized onset	457	21	1.7	(1.03–2.68)	1.6	(0.96–2.52)
Partial onset	3,063	85	1.0	(Reference)	1.0	(Reference)
Age (yr)						
<10	1,168	25	0.8	(0.44–1.35)	0.8	(0.43–1.33)
10–19	1,485	55	1.3	(0.84–2.15)	1.3	(0.80–2.06)
≥20	1,017	28	1.0	(Reference)	1.0	(Reference)
Offspring						
Generalized onset	171	5	0.5	(0.22–1.37)	0.5	(0.20–1.27)
Partial onset	1,122	61	1.0	(Reference)	1.0	(Reference)
Age (yr)						
<10	236	18	2.2	(1.23–4.07)	2.5	(1.37–4.68)
10–19	488	20	1.1	(0.63–2.01)	1.2	(0.65–2.10)
≥20	640	29	1.0	(Reference)	1.0	(Reference)

Abbreviations as in Table 1.

RR and 95% CI calculated from Cox proportional hazards model. Univariate analysis includes only birth year of the relatives as a covariate; multivariate analysis includes proband seizure type, proband age at onset, and birth year of the relatives.

those with symptomatic epilepsy in terms of the role of a genetic susceptibility. This implies that identification of a history of CNS injury provides important information about genetic risk.

In relatives of probands with neurodeficits presumed present at birth, risk of epilepsy was as high as in relatives of probands with idiopathic/cryptogenic epilepsy. The increased risk of epilepsy in relatives of probands with neurodeficit may reflect a shared genetic susceptibility to epilepsy and cerebral palsy. The findings of two previous studies provide support for this possibility. In the National Collaborative Perinatal Project, incidence of cerebral palsy in offspring was associated with the mother's history of epilepsy (18) and incidence of nonfebrile seizure disorders in offspring without cerebral palsy was associated with a history of motor deficits in siblings (19). Similarly, Rimoin and Metrakos reported an increased prevalence of convulsions and epileptiform EEG abnormalities in relatives of children with hemiplegia, a specific form of cerebral palsy (20).

Among relatives of probands without identified CNS insults, the relations of familial risk to proband age at onset and seizure type were similar in parents and siblings but differed in offspring. In parents and siblings, risks did not differ among the three strata of proband age at onset we examined (<10 years, 10–19 years, ≥20 years). In offspring, risks were twice as high if the proband had onset <10 years than if the proband had onset at older ages. These findings are difficult to compare with those of previous studies because of differences in the proband age-at-onset categories and the relative classes included. Lennox (1) reported a gradient of risk in first-degree relatives with proband age at onset, with risks highest in relatives of probands with onset before age 5 years, intermediate in those of probands with onset between the ages of 5 and 19 years, and lowest in those with older ages at onset. Eisner et al. (2) reported the highest risks to be in first-degree relatives of probands with onset before age 4. Annegers et al. (6) reported that the RR of unprovoked seizures was similar in relatives of probands with onset of idiopathic epilepsy <10 years and 10–16 years. In the Minnesota Clinical Epilepsy Research Program (5), epilepsy risks were higher for siblings of probands with onset <25 years than for siblings of those with later ages at onset. Ounsted (7) reported higher risks of epilepsy in siblings of probands with onset between 1 and 3.5 years than in siblings of those with either earlier or later age at onset. In that study, however, children with acute symptomatic seizures were included as probands; therefore, many probands with onset before age 1 may have had neonatal seizures rather

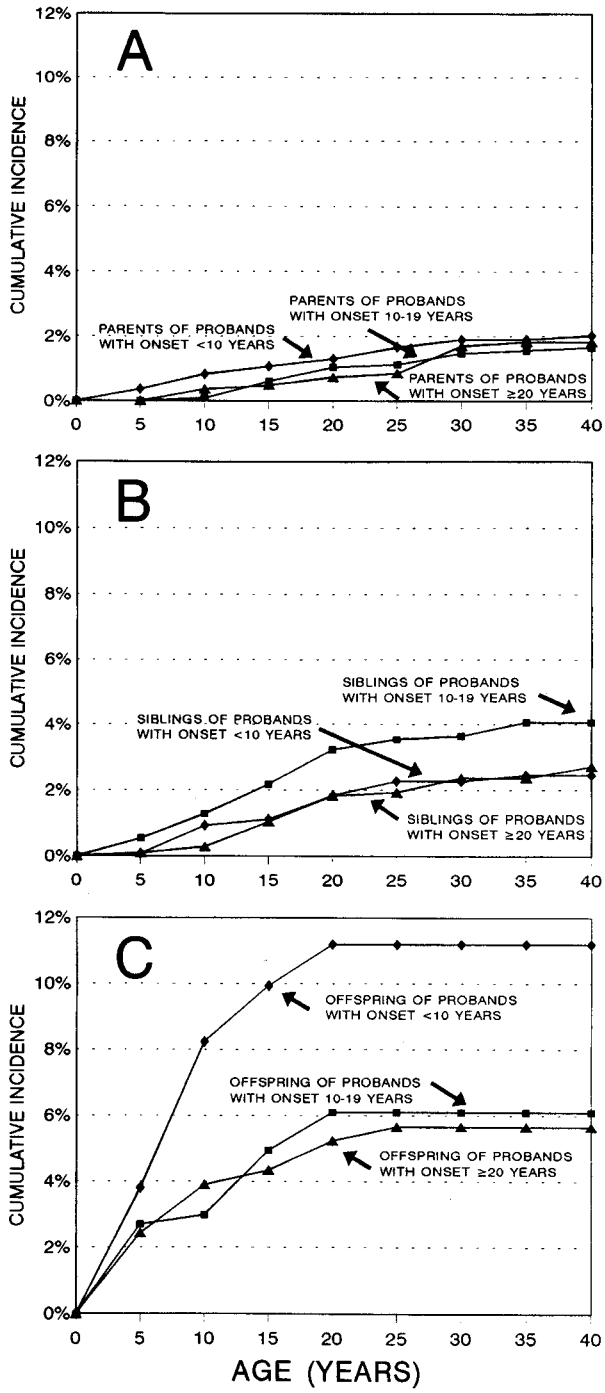

FIG. 3. Cumulative incidence of epilepsy in relatives of probands with idiopathic/cryptogenic epilepsy only, by age at onset of proband's epilepsy. Relatives of probands with onset at age <10 years (diamonds), age 10–19 years (squares), and age ≥20 years (triangles). Parents **(A)**, siblings **(B)**, offspring **(C)**.

than epilepsy. From the data reported by Tsuboi and Endo (3), we calculate that prevalence of a history of epilepsy was 3% in offspring of probands with onset <10 years and 2.7% in offspring of those with onset ≥20 years.

In parents and siblings, we confirmed the finding of previous studies that risks were higher if the proband had generalized onset seizures than if the proband had partial onset seizures (8). We did not observe this pattern in offspring, however. The results in offspring were similar to those in our previous analysis of risks in offspring of probands with epilepsy in Rochester (9). However, in that study, risks were higher in offspring of probands with absence seizures than in offspring of probands with other generalized or partial seizures, a finding not observed in the current study.

For many of the subgroups in this analysis, risks were lowest in parents, intermediate in siblings, and highest in offspring (Figs. 1–3). In a previous analysis, we showed that this apparent increase in risk in successive generations disappeared after we controlled for birth year of the relatives (23). Because incidence rates of epilepsy have not increased during the time periods we investigated among persons aged <40 years (24), we concluded that the apparent "cohort effect" was likely to be due to underreporting of epilepsy was present at young ages in older relatives. If the cohort effect were entirely due to underreporting, however, we would expect it to have a similar magnitude in different subgroups defined by clinical features in the probands. We noted instead that the apparent increase in incidence in successive generations was greater in some subgroups than in others. The greater increase in risk in some subgroups may reflect a true biological effect, possibly compatible with "anticipation" (26). The dramatic increase in risk in successive generations in relatives of probands with partial onset seizures makes this subgroup of interest for further investigation in this regard.

The differential cohort effect in families of probands with partial as compared with generalized onset seizures may explain the different relation of proband seizure type to epilepsy risk in offspring as compared with parents and siblings. On the other hand, the influences on risk in offspring may differ from those in parents and siblings. Risk of epilepsy is approximately twice as high in offspring of affected women as in offspring of affected men (27,28). This "maternal effect" is inconsistent with any conventional genetic model (25) and may reflect a maternally transmitted influence on susceptibility that affects risk in offspring but not in parents and siblings.

Members of the same family are expected to be correlated in terms of risk of epilepsy (whether due to shared genes or shared environment) and follow-up time. Because we treated each offspring or sibling as an independent observation, our analysis did not control for these intrafamilial correlations. This

lack of control would not be expected to bias our point estimates of the RR but would lead to some underestimation of the confidence intervals of the RR for siblings and offspring. This underestimation of the confidence intervals is probably not very great, however, because most sibships did not contain more than one affected sibling or offspring.

We ascertained our probands by sampling adults with epilepsy who had sought services from voluntary organizations. As a result of this ascertainment scheme, the probands in our study are unrepresentative of the general population of persons with epilepsy with respect to seizure type and duration of illness. The proportion with partial onset seizures (84%) is higher than that in prevalent cases of all ages in Rochester (59%) (11). However, the distribution of etiology and age at onset was similar to that of Rochester prevalent cases (Rochester vs. EFSCU: 24 vs. 20% symptomatic and age at onset <10 years 31 vs. 28%, 10–19 years 33 vs. 39%, and ≥20 years 36 vs. 33%) (11).

Among incident cases of epilepsy in Rochester, the probability of remission (≥5 consecutive years seizure-free) within 10 years after diagnosis was 65% overall, and was greater for patients with generalized onset as compared with those with partial onset seizures (~70 vs. ~60%), and for those with childhood onset epilepsy (age <10 years 75%, 10–19 years 68%, ≥20 years 63%) (29). Persons with childhood onset epilepsies that remit before adulthood were essentially excluded from the EFSCU sample of probands because they were unlikely, as adults, to have sought services from voluntary organizations. Therefore, probands with childhood onset epilepsies that were included in our series represent the relatively small proportion of such patients whose epilepsy fails to remit. Because many of the idiopathic generalized epilepsy syndromes have childhood onset and a benign course, our sample contains few probands with these syndromes. Underrepresentation of subjects with familial, early onset, remitting epilepsies may have led to a lower apparent effect of age at onset than would have been observed in a proband sample of incident cases. Selection of subjects with epilepsies of long duration may also have contributed to the lack of association between absence seizures and familial risk in our series; e.g., if the genetic contributions were smaller in absence epilepsies that fail to remit than in the more typical absence epilepsies that do remit, familial risks would be lower for probands with absence seizures in our series than in Rochester.

All but one of the probands in our study who were classified as having neurodeficit from birth had cerebral palsy. Furthermore, none of the probands in this subgroup had severe intellectual impairment, because participation required sufficiently high intelligence for the subjects to be able to answer the interview questions. This factor reduces comparability of our series with other series of patients with epilepsy associated with neurological deficit presumed present at birth.

Although our study population differs from the general population of epilepsy cases in terms of clinical characteristics, it is not seriously biased with respect to family history of epilepsy. Participation rates were high (84%), and we circumvented selection bias related to family history by avoiding mention of genetic factors when subjects were invited to participate (10). Furthermore, our estimates of epilepsy risks in siblings and offspring are similar to the findings of family studies in the population-based series of Rochester (12,30). The slightly lower risks in our series than in the Rochester series are probably primarily due to underreporting of epilepsy in relatives (23). This underreporting may be greater for some epilepsies (e.g., benign childhood epilepsies) than for others, especially in older relatives.

The EFSCU probands are likely to be similar to patients treated in adult epilepsy clinics in many respects (seizure type, etiology, age at onset, clinical course); e.g., the proportion of subjects with partial onset seizures in the EFSCU series is similar to that in other series of adults with epilepsy ascertained from clinical care settings (74–83%) (31–34). Because of this similarity, our results are likely to be generalizable to most adult clinical series. Therefore, the cumulative incidences shown in Figs. 1–3 have practical utility for estimation of the risks of epilepsy in relatives of patients being treated in adult epilepsy clinics.

Our results demonstrate that identification of CNS lesions provides important information about familial risk of epilepsy. Genetic susceptibility is likely to contribute to risk of some forms of cryptogenic epilepsy and of epilepsy associated with neurological deficit presumed present at birth, whereas it is unlikely to contribute to risk of epilepsy associated with postnatal CNS insults. Seizure type and age at onset of epilepsy were predictors of familial risk even in a study population that contained very few patients with idiopathic epilepsy syndromes. Among relatives of probands without identified CNS lesions, the influences on risk in offspring may differ from those in parents and siblings.

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