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Higher Risk of Seizures in Offspring of Mothers than of Fathers with Epilepsy

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Summary

Seizure risk has consistently been found to be higher in offspring of mothers than of fathers with epilepsy. This pattern cannot be explained by any simple genetic model. The present study examined the possibility that the pattern arises from differences between affected mothers and fathers in the characteristics of their epilepsy that influence offspring seizure risk. The study population comprised 687 offspring of parents with epilepsy from the Rochester–Olmsted County Record Linkage Project. Cumulative incidences of unprovoked seizures to age 25 were 8.7% and 2.4% in offspring of affected mothers and fathers, respectively. Cox proportional hazards analysis was used to calculate rate ratios (RRs) for unprovoked seizures in offspring. In the univariate analysis, risk of unprovoked seizures was higher if the affected parent was the mother (RR = 2.8, 95% confidence interval [ci] 1.1–7.2) or if the parent's onset was before age 20 (RR = 2.5, 95% ci 1.1–5.9), but there was no effect on offspring risk of either parent's etiology (idiopathic vs. remote symptomatic) or parent's seizure type (generalized vs. partial). These findings were not substantially changed in the multivariate analysis. Thus, differences between affected mothers and fathers in these characteristics did not account for the higher risk in offspring of affected mothers. Anticonvulsant use during pregnancy was not associated with increased offspring seizure risk. Seizure occurrence during pregnancy was associated with increased risk (multivariate RR = 2.4, 95% ci 0.8–6.9), but this effect did not account for a large part of the maternal excess. These findings provide evidence for a maternally transmitted influence on seizure susceptibility.

Introduction

We have previously reported a striking difference between men and women with epilepsy in the risks of seizure disorders in their offspring: offspring of affected women are more likely to have seizures than are those of affected men (Annegers et al. 1976, 1978). From a review and analysis of published data on the familial distribution of seizure disorders, we concluded that this finding had been very consistently observed and could not be explained by any conventional genetic model (Ottman et al. 1985).

In the present study, we have extended our investigations of seizure incidence in offspring of individuals with epilepsy by asking three specific questions. First, is the higher seizure incidence in offspring of affected women than in those of affected men, or *maternal excess*, still observed in an enlarged data set, with an increase in the years of follow-up of the offspring? Second, is the maternal excess explained by a higher proportion of affected mothers than affected fathers with "familial" types of epilepsy? Third, can the maternal excess be explained by either of two unique exposures to offspring of women with epilepsy, namely, seizure occurrence and anticonvulsant use during pregnancy?

In previous studies, three characteristics of epilepsy have been found to be associated with increased risk of seizures in relatives of affected individuals: early (vs. late) age at onset (Lennox 1947; Ounsted 1955; Gerken et al. 1977; Tsuboi and Endo 1977), idiopathic (vs. remote symptomatic) etiology (Lennox 1947; Harvald 1951; Tsuboi and Endo 1977), and generalized (vs. par-

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tial) seizure type (Beaussart and Loiseau 1969; Gerken et al. 1977; Tsuboi and Endo 1977). The maternal excess could therefore be explained by a higher proportion of affected mothers than affected fathers with these characteristics. For two of the three determinants of high familial risk, there is evidence of a higher prevalence among affected mothers than affected fathers. A higher proportion of affected mothers with early age at onset is expected because of *selective reproduction* (Ottman et al. 1985). Rates of reproduction have been found to be lower in individuals with epilepsy than in the general population, and lower in affected men than affected women (Harvard 1951; Tsuboi and Endo 1977; Annegers et al. 1978; Dansky et al. 1980; Webber et al. 1986). In one study (Dansky et al. 1980), rates of reproduction in affected men were lower in those with early than in those with late age at onset, whereas in affected women there were no differences according to age at onset. If generally observed, this pattern would lead to a higher proportion of affected mothers than affected fathers with early onset.

A higher proportion of affected mothers than affected fathers with idiopathic epilepsy might also be expected, because of sex differences in exposure to potential etiologic factors, such as head injury. Remote symptomatic etiologies have generally been found to be somewhat more common in males than in females—among incident cases in Rochester from 1935 to 1979, the proportion with remote symptomatic etiologies was 36% for males and 31% for females (J. F. Annegers, unpublished data).

Material and Methods

Rochester, MN, residents who were affected with epilepsy between January 1, 1935, and December 31, 1979, were ascertained from the Rochester–Olmsted County Record Linkage System (Hauser and Kurland 1975). These individuals included both incident cases diagnosed in Rochester during this period and prevalent cases who had been diagnosed elsewhere but who were Rochester residents during this period. Epilepsy was defined as recurrent unprovoked seizures, i.e., at least two seizures that were not precipitated by acute structural or metabolic insults to the central nervous system. Cases whose past medical histories indicated a presumed cause for these unprovoked seizures were classified as remote symptomatic, and those without such histories as idiopathic.

Offspring of these cases were identified by searching the records of female cases and wives of male cases for occurrence of pregnancies, and selecting live births resulting from these pregnancies. The records of the offspring were then reviewed for occurrence of seizures. To ensure complete ascertainment of seizures from birth, only offspring born in Rochester were included, and follow-up was truncated upon migration from southeast Minnesota, where medical records are included in the linkage system. The study population comprised 687 offspring born in Rochester between 1922 and 1985 and followed for occurrence of seizures through 1986.

The information included in the analysis was abstracted from three different sources. First, the record of the affected parent was the source of information on the characteristics of the parent's epilepsy (age at onset, seizure type, and etiology). Second, the record of the mother of the study offspring (whether or not she was the affected parent) was the source of information on pregnancy outcome, seizure occurrence during pregnancy, and anticonvulsant use during pregnancy. Third, the offspring's record was the source of data on his or her own medical history, including age at onset, etiology, and type of seizure disorder.

Standardized morbidity ratios for unprovoked seizures in offspring of affected individuals were calculated by comparing the observed number of affected offspring with expected numbers based on Rochester population age- and sex-specific incidence rates (Fleiss 1981). Cumulative incidence of unprovoked seizures in the offspring was computed using life table methods (Cutler and Ederer 1959). Univariate and multivariate Cox regression analyses (Dixon et al. 1985) were used to calculate rate ratios for seizure occurrence in offspring according to the affected parent's sex, age at onset, seizure type, etiology of epilepsy, and seizure occurrence and anticonvulsant use during pregnancy.

Results

Table 1 shows standardized morbidity ratios for unprovoked seizures in offspring of affected mothers and fathers. The number of offspring of affected mothers who had unprovoked seizures was 4.4 times that expected. In contrast, the number of offspring of affected fathers who had unprovoked seizures was only 1.6 times that expected. Thus, the degree to which unprovoked seizure incidence in offspring exceeded population incidence was much higher for offspring of affected mothers than for those of affected fathers.

Figure 1 illustrates cumulative incidence of unprovoked seizures in the general population and in offspring of parents with epilepsy, according to the affected par-

Table 1

Standardized Morbidity Ratios (SMRs) for Unprovoked Seizures in Offspring of Mothers and Fathers with Epilepsy

	No. of Offspring	No. Affected		SMR (95% Confidence Interval)
		Observed	Expected	
Offspring of affected mothers	369	17	3.8	4.4 (2.6–7.1)
Offspring of affected fathers	318	6	3.7	1.6 (.6–3.6)

ent's sex, age at onset, seizure type, etiology, seizure occurrence during pregnancy, and anticonvulsant use during pregnancy (figs. 1*A*–1*F*, respectively). Cumulative incidence to age 25 was much higher in offspring of affected women (8.7%) than in those of affected men (2.4%), but offspring of affected men did have higher risk than the general population (1.6%) (fig. 1*A*). Cumulative incidence was also much higher in offspring of parents with onset of epilepsy before age 20 (8.9%) than in those of parents with onset at age 20 or older (3.4%) (fig. 1*B*). There were no striking differences in risk between offspring of parents with different seizure types, when broadly categorized as generalized vs. partial seizures (5.8% vs. 5.3%; fig. 1*C*). However, risks were dramatically elevated for offspring of parents with absence seizures (cumulative incidence to age 25 = 26.8% ± 17.05 SE). There were no large differences in risk between offspring of parents with the other major seizure types (generalized tonic-clonic, myoclonic, simple partial, complex partial), but the number of offspring in each comparison group was small. Offspring of parents with idiopathic epilepsy had higher risks than offspring of those with remote symptomatic epilepsy (6.0% vs. 4.2%; fig. 1 *D*).

Among offspring of affected mothers, cumulative incidence to age 25 was much higher for offspring exposed to seizures during pregnancy (16.8%) than for unexposed offspring (7.3%) (fig. 1*E*). Risk of unprovoked seizures was also higher in offspring exposed in utero to anticonvulsants (13.0%) than in unexposed offspring of women with epilepsy (7.2%) (fig. 1*F*).

Univariate and multivariate rate ratios, estimated from Cox regression analysis, were used to quantify the effects of these parental attributes on offspring seizure incidence (table 2). The univariate rate ratio for sex of affected parent was 2.8, reflecting a nearly threefold increased rate of unprovoked seizures in offspring of affected mothers compared with those of affected fathers. A strong effect of parent's age at onset was also observed: the rate of unprovoked seizures in offspring of parents with onset before age 20 years was 2.5 times that in offspring of parents with later ages at onset. There was no evidence of an effect of generalized vs. partial seizure type on offspring risk (univariate rate ratio = 1.0). The univariate rate ratio for parent's etiology was only 1.3 and was not significant.

In univariate analyses of seizure occurrence and anticonvulsant use during pregnancy, only offspring of affected mothers were included. In multivariate analyses of these two variables, all offspring were included and offspring of affected fathers were classified as unexposed. The univariate rate ratio for seizures during pregnancy was 2.5, and that for anticonvulsant use during pregnancy was 1.6.

In the multivariate analysis, the rate ratio for parent's sex dropped from 2.8 to 2.1. Thus, a twofold maternal excess persisted after adjustment for confounding with other parental attributes that influence offspring seizure risk. The multivariate estimates of the rate ratios for parent's age at onset and seizure type were not substantially different from those in the univariate analysis. The rate ratio for parent's etiology dropped to 0.7.

We also repeated the analysis, using "absence vs. other" as the seizure type categories. The multivariate rate ratios were 2.0 (95% confidence interval 0.6–7.2) for seizure type and 2.0 (95% confidence interval 0.7–5.5) for parent sex. Thus, in our data the maternal excess could not be explained by a higher proportion of mothers than of fathers with absence seizures.

Both seizure occurrence and anticonvulsant use during pregnancy are strongly associated with age at onset of the parent's epilepsy, since offspring of cases with onset after the reproductive age period cannot be exposed. Control for confounding is therefore particularly important for these two variables. For prenatal

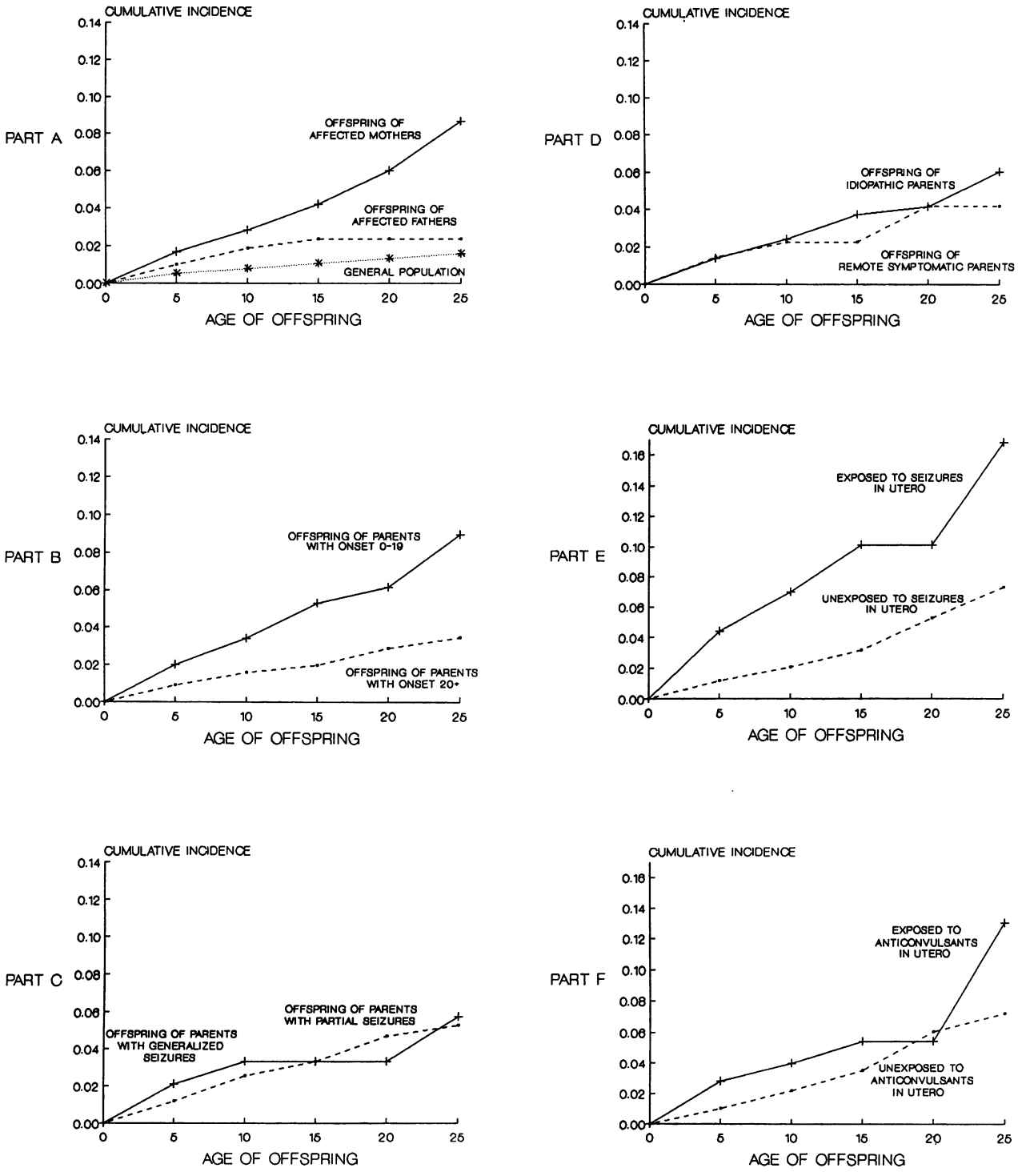

Figure 1 Cumulative incidence of unprovoked seizures in offspring of parents with epilepsy and in the Rochester, MN, general population. 1935–79 (*Y*-axis), by age of offspring (*X*-axis) and sex of affected parent (*A*), age at onset of parent's epilepsy (*B*), parent's seizure type (*C*), etiology of parent's epilepsy (*D*), in utero exposure to seizures (offspring of mothers with epilepsy only) (*E*), and in utero exposure to anticonvulsants (offspring of mothers with epilepsy only) (*F*).

Table 2

Univariate and Multivariate Rate Ratios (RRs) for Unprovoked Seizures in Offspring of Parents with Epilepsy, by Characteristics of Affected Parents

Characteristics of Affected Parents	No. of Offspring	No. Affected	Univariate RR (95% Confidence Interval)	Multivariate RR (95% Confidence Interval)
Sex:				
Female	369	17	2.8 (1.1–7.0)	2.1 (.7–6.0)
Male	318	6	1.0[a]	1.0
Age at onset:				
0–19	336	14	2.5 (1.1–5.9)	2.3 (.9–5.9)
20+	351	9	1.0	1.0
Seizure type:				
Generalized	393	14	1.0 (.4–2.3)	.9 (.4–2.2)
Partial	294	9	1.0	1.0
Etiology:				
Idiopathic	536	18	1.3 (.5–3.6)	.7 (.3–2.2)
Remote symptomatic	151	5	1.0	1.0
Seizures during pregnancy:[b]				
Yes	64	5	2.5 (.9–7.2)	2.4 (.8–6.9)
No	305	12	1.0	1.0
Anticonvulsants during pregnancy:[b]				
Yes	142	7	1.6 (.6–4.4)	1.0 (.4–2.9)
No	227	10	1.0	1.0

[a] Referent group.

[b] In univariate analysis, only offspring of affected mothers were included. In multivariate analysis, all offspring were included and offspring of affected fathers were classified as unexposed.

anticonvulsant exposure, the effect observed in the univariate analysis disappeared after adjustment for confounding. A 2.4-fold effect of seizures during pregnancy persisted in the multivariate analysis, however.

To examine further the possibility that intrauterine exposure to maternal seizures explained the higher seizure incidence in offspring of affected mothers than in those of affected fathers, we repeated the multivariate analysis after excluding offspring exposed to seizures during pregnancy. The rate of unprovoked seizures in unexposed offspring of affected women was still 2.1 times as high as in offspring of affected men (95% confidence interval 0.8–5.6).

None of the estimates in the multivariate analysis remained statistically significant, owing to reduced power for this type of analysis with our sample size.

Table 3 shows cumulative incidence of unprovoked seizures by sex in offspring of affected mothers and fathers. These sex-specific risks are informative for testing of genetic models that might explain the maternal

Table 3

Cumulative Incidence of Unprovoked Seizures to Age 25 in Offspring of Parents with Epilepsy, by Sex of Affected Parent and Offspring

	Male Offspring			Female Offspring		
	N	No. Affected	Cumulative Incidence ± SE	*N*	No. Affected	Cumulative Incidence ± SE
Offspring of affected mothers	204	10	.098 ± .032	165	7	.073 ± .029
Offspring of affected fathers	181	3	.020 ± .012	137	3	.028 ± .016

excess. A higher risk in offspring of affected mothers than in those of affected fathers was observed in both male and female offspring. In general, there was no substantial difference in risk between male and female offspring.

Discussion

The approach used in the present study is different from that of our previous studies of seizure risk in offspring of affected individuals (Annegers et al. 1976, 1978). In the earlier studies, offspring of affected parents were identified by searching the records of live births occurring in Rochester hospitals, to determine which births were to mothers or fathers with epilepsy. Unlike the present method, the parents with epilepsy were not restricted to be residents of Rochester or to have been incident or prevalent cases during a specified time period. This earlier approach was likely to lead to better ascertainment of offspring of affected mothers than of affected fathers because histories of epilepsy in mothers are routinely included in obstetrical records, while those of fathers are not. The method used to identify live births to affected fathers involved first identifying men with epilepsy, then identifying their wives, and determining which live births were to these women.

The present approach is an improvement over the previous method in two ways. First, ascertainment of offspring of affected parents is likely to be more complete for both affected mothers and fathers because the search began with identification of affected individuals and included all incidence and prevalence cases during a specified time period. Second, the data on the characteristics of the parents' epilepsy are likely to be more complete because the parents were restricted to include only Rochester residents. Compared with our most recent study of offspring, which included live births through 1976 (Annegers et al. 1978), this study includes 53 *fewer* offspring of affected women (because of the Rochester residency requirement) and, coincidentally, 53 *more* offspring of affected men.

Three methodologic problems of previous studies can be ruled out as explanations for our observation of a nearly threefold increased risk of unprovoked seizures in offspring of affected women compared with those of affected men. First, better reporting by mothers than by fathers of their children's seizure histories could have no effect on our findings, since information on seizure occurrence in offspring was collected by record linkage rather than by interviewing affected parents. Second, nonpaternity is an unlikely explanation because of the magnitude of the increased risk in offspring of affected women. To account for the threefold increased risk in offspring of affected women, two-thirds of the offspring of the affected fathers would have had to be biologically unrelated to them. Third, the maternal excess could not be explained by a higher proportion of affected mothers than affected fathers with three epilepsy characteristics that were previously reported to be associated with increased familial risk: early (vs. late) age at onset, generalized (vs. partial) seizure type, and idiopathic (vs. remote symptomatic) etiology.

Our data regarding the influence of age at onset on seizure risk in offspring confirm those of previous investigations (Lennox 1947; Ounsted 1955; Gerken et al. 1977; Tsuboi and Endo 1977). However, we were unable to confirm previous reports (Lennox 1947; Harvald 1951; Tsuboi and Endo 1977) of an effect of proband's etiology on seizure risk in relatives. The univariate rate ratio was only 1.3 (table 2), and it dropped to 0.7 after adjustment for confounding. We also failed to confirm previous reports (Beaussart and Loiseau 1969; Gerken et al. 1977; Tsuboi and Endo 1977) of a difference in risk between relatives of patients with different seizure types, when broadly categorized as generalized versus partial. However, we did confirm the dramatically increased risk that has been observed in relatives of patients with absence seizures (Metrakos and Metrakos 1961).

Beck-Mannagetta et al. (1986) recently reported that the higher risk in offspring of affected mothers was due to a higher proportion of mothers than of fathers with absence seizures. Our data do not support this explanation—the twofold rate ratio for parent's sex persisted in the multivariate analysis with "absence vs. other" as the seizure type categories. Doose and Baier (1987) have also provided evidence against this explanation. They found higher seizure risks in siblings of cases with absence epilepsy when the mother or her siblings were affected than when the father or his siblings were affected, suggesting that maternal factors are important *within* the absence seizure category.

The cause of the observed maternal excess remains to be resolved. The pattern may still arise from a higher proportion of affected mothers than fathers with epilepsy characteristics associated with increased risk in offspring, and not examined in this study. Severity of epilepsy, as manifested by either seizure frequency or disease duration, is one example of a characteristic that could be examined in future studies.

The maternal excess is inconsistent with conventional genetic models because of the sex-specific cumulative

incidences in the general population and the offspring (table 3). X-linked recessive inheritance predicts *higher* risk in sons but *equal* risk in daughters of affected females compared with those of affected males. X-linked dominant inheritance predicts *higher* risk in sons but *lower* risk in daughters of affected females than in those of affected males (Thompson and Thompson 1986). Our observation of a maternal excess for both sons and daughters is inconsistent with both of these predictions.

Single-locus or polygenic models that assume higher prevalence in males than in females predict higher risk in offspring (and other relatives) of affected females than in those of affected males (Ottman et al. 1985; Ottman 1987). These models, however, also predict much higher population incidence in males than in females, and much higher risk in male than in female offspring, regardless of the sex of the parent. Population incidence of epilepsy is only slightly higher in males than in females (Ottman et al. 1985). In addition, risk was only slightly higher in sons than in daughters of affected females and was slightly *lower* in sons than in daughters of affected males. These models, too, are therefore inconsistent with the sex-specific incidence rates.

The most parsimonious explanation for the maternal excess is that there is a *maternally transmitted* influence on seizure susceptibility (Fine 1977). This type of inheritance could result from cytoplasmic inheritance or from the intrauterine, neonatal, or early childhood environment provided by the mother. The familial distribution could be produced either by the mother's nuclear or mitochondrial genotype or by environmental factors.

The observation of higher risk in offspring of affected fathers than in the general population (fig. 1*A*) suggests that maternal transmission cannot entirely account for the familial distribution of epilepsy. A maternally transmitted influence on seizure susceptibility may be important in only some families and may in some families interact with conventional genetic susceptibility.

Two types of etiologic factors that would be expected to result in maternal transmission may be relevant for epilepsy. First, women with epilepsy have increased risk of complications of pregnancy and delivery (Teramo and Hiilesmaa 1982); if these complications raised the risk of epilepsy in offspring, a pattern of maternal transmission would be observed. Recent evidence places the association of perinatal complications with epilepsy in doubt (Susser et al. 1985). In the present study we examined two special perinatal complications for offspring of women with epilepsy: seizure occurrence and anticonvulsant use during pregnancy. Anticonvulsant use during pregnancy was not associated with increased seizure risk in offspring. Seizure occurrence during pregnancy was associated with increased risk, but this effect did not account for a large part of the maternal excess—a twofold increased rate of seizures in offspring of affected females was observed after adjustment for this variable in the multivariate analysis, and this effect persisted even after excluding offspring exposed in utero to seizures. A similar effect of noneclamptic seizures during pregnancy was observed in the National Collaborative Perinatal Project (Nelson and Ellenberg 1982). This relationship might reflect differences in severity of epilepsy, rather than an effect of seizures per se, because women who have seizures during pregnancy might have a higher seizure frequency than those who do not.

Second, seizure susceptibility may be influenced by a defect in the mitochondrial genome. Data on the mitochondrial myopathies, a group of disorders of mitochondrial function (DiMauro et al. 1986), support the plausibility of this hypothesis. In some families, the disorder appears to be maternally transmitted and may be caused by a mitochondrial gene (Egger and Wilson 1983). In one such family, the clinical manifestation of the disorder includes myoclonic seizures (Rosing et al. 1985).

Testing of the hypothesis of maternal transmission of seizure susceptibility should be one of the highest priorities for research on the genetic epidemiology of seizure disorders. Future studies should examine the distribution of epilepsy in relatives other than offspring, to evaluate consistency with the maternal transmission model, either alone or in combination with conventional genetic models. If maternal transmission is confirmed, molecular studies might be used to evaluate the role of specific etiologic factors such as mitochondrial genes.

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