

Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study

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Abstract

Objectives To investigate whether age at onset of epilepsy, type of epilepsy, family history of psychosis, or family history of epilepsy affect the risk of schizophrenia or schizophrenia-like psychosis among patients with epilepsy.

Design Comparison of population based data.

Setting Danish longitudinal registers.

Subjects The cohort comprised 2.27 million people.

Main outcome measures Epilepsy, psychosis, personal birth data.

Results We found an increased risk of schizophrenia (relative risk 2.48, 95% confidence interval 2.20 to 2.80) and schizophrenia-like psychosis (2.93, 2.69 to 3.20) in people with a history of epilepsy. The effect of epilepsy was the same in men and in women and increased with age. Family history of psychosis and a family history of epilepsy were significant risk factors for schizophrenia and schizophrenia-like psychosis, and the effect of epilepsy, both in cases and families, was greater among people with no family history of psychosis. In addition, the increased risk for schizophrenia or schizophrenia-like psychosis did not differ by type of epilepsy but increased with increasing number of admissions to hospital and, particularly, was significantly greater for people first admitted for epilepsy at later ages.

Conclusions There is a strong association between epilepsy and schizophrenia or schizophrenia-like psychosis. The two conditions may share common genetic or environmental causes.

Introduction

Several studies, but not all, have found a higher prevalence of schizophrenia-like psychosis in patients with epilepsy compared with the general population. The underlying causal mechanism is unclear. Seizures may damage the brain, which may in turn increase the risk of schizophrenia-like psychosis, or the two conditions may share common aetiological factors. Genetic vulnerability to psychosis may facilitate the development of psychosis in the patients with epilepsy.^{1 2} However, there have been no published family history studies with appropriate methods.³ In addition, differences in risk of developing psychosis remain poorly understood.

In this population based cohort study we examined the risk of schizophrenia or schizophrenia-like psychosis associated with a history of epilepsy using data from Danish longitudinal registers. We also investigated how and to what extent this risk is influenced by family histories of psychosis and of epilepsy.

Methods

Subjects and data assessment

All data in this study were retrieved from Danish longitudinal registers and merged by means of the unique personal identification number given to all Danes at birth and to new residents in Denmark.

We identified virtually all of 2 315 857 people who were born in Denmark from 1 January 1950 to 31 December 1987 and could be linked to their mother. We excluded individuals who were not alive at the 15th birthday, who died or emigrated before the year 1977, and who had been admitted to a psychiatric hospital before the onset of epilepsy or who had been admitted with a schizophrenia-like psychosis before the age of 15. We thus included 2 270 372 people and followed this cohort from their 15th birthday or 1 January 1977 (whichever came later) until the date of onset of schizophrenia or schizophrenia-like psychosis, the date of death, the date of emigration, or 31 December 2002 (whichever came first).

Treatment in Danish hospitals is free for all residents. Admissions to general hospitals have been recorded in the national hospital register since 1977 and to psychiatric hospitals in the Danish psychiatric central register since 1967. Data on outpatient contacts became available in the registers after 1995.

We retrieved personal data on epilepsy from 1 January 1977 to 31 December 2002 from the Danish national hospital register. Examination of inpatient and outpatient data from 1995 to 2002 showed that the annual incidence of epilepsy was about 65 per 100 000 population, and about 80% of all incident cases were admitted to hospital. Because of this and because these data have been available since 1977 we considered only inpatients. We categorised epilepsy according to the diagnosis at each admission: complex partial seizures, other partial seizures, generalised epilepsy, and other or unspecified epilepsy. We grouped the age at onset (first record in the register) into eight categories. We also constructed a variable indicating the total number of hospital admissions for epilepsy until the onset of schizophrenia or schizophrenia-like psychosis.

We obtained psychiatric information from the Danish psychiatric central register. Our diagnoses of interest were schizophrenia and the broad category of schizophrenia-like psychosis. The date of onset referred to the date of first admission to a psychiatric hospital for schizophrenia or schizophrenia-like psychosis that was recorded on the register.

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Family history of psychosis and epilepsy was obtained using the civil registration system to link the identification numbers of parents and siblings to the psychiatric central register and the national hospital register. Of all cohort members for whom we could identify a mother, 97.3% also had registered links to a father and 84.5% had links to at least one sibling. We defined psychosis in family members hierarchically: schizophrenia, schizophrenia-like psychosis, or affective psychosis. A family history of psychosis or epilepsy means that at least one parent or sibling had been admitted to hospital for psychosis or epilepsy before the index case was admitted for schizophrenia or schizophrenia-like psychosis.

Statistical analysis

We assessed the relative risk of schizophrenia or schizophrenia-like psychosis through log-linear Poisson regression. We tested for interactions between variables and for linear trend. We controlled for possible confounding and treated age, calendar year of diagnosis, epilepsy status, type of epilepsy, and schizophrenia or schizophrenia-like psychosis status as well as the family historical data as time dependent variables. See bmj.com.

Results

In our cohort, 34 494 (1.5%) had a history of epilepsy, with a median age of 14.7 at the first admission. During follow-up, 276 (0.8%) of them were later admitted to hospital for schizophrenia and 519 (1.5%) for schizophrenia-like psychosis. The median duration between the first admission for epilepsy and the first admission of schizophrenia or of schizophrenia-like psychosis was 8.2 years or 8.0 years, respectively. See bmj.com for person years at risk.

Main effect of epilepsy

A history of epilepsy was associated with an increased risk of schizophrenia or schizophrenia-like psychosis; and the effect remained virtually unchanged when we controlled for various potential confounders (table). People with epilepsy had nearly 2.5 times the risk of schizophrenia and nearly three times the risk of schizophrenia-like psychosis compared with the general population.

The impact of epilepsy on the risk of schizophrenia or schizophrenia-like psychosis was not statistically different by sex (test of sex interaction: $P=0.31$ for schizophrenia, $P=0.51$ for schizophrenia-like psychosis) but differed significantly by age ($P=0.01$ for schizophrenia, $P=0.04$ for schizophrenia-like psychosis). See bmj.com for stratified analyses by age.

Family history of psychosis and epilepsy

A family history of psychosis and a family history of epilepsy were significant risk factors for schizophrenia and schizophrenia-like psychosis after we adjusted for personal history of epilepsy.

We found that the effect of both personal and familial history of epilepsy interacted with the effect of a family history of psychosis (test of interaction: $P=0.0081$ and $P=0.0732$, respectively, for schizophrenia-like psychosis). A personal history of epilepsy had a stronger effect on the risk for schizophrenia or schizophrenia-like psychosis in people without a family history of psychosis than for people with it. At the same time, a family history of epilepsy significantly increased the risk only for people with no family history of psychosis. See bmj.com.

Type of epilepsy, age at admission, and number of admissions

All types of epilepsy significantly increased the risk of developing schizophrenia or schizophrenia-like psychosis (see bmj.com). The relative risk associated with complex partial epilepsy was slightly higher than the others, but the differences were not significant.

The effect of epilepsy differed significantly according to age at first admission for epilepsy and number of admissions. The relative risk increased consistently with increasing age at onset (see bmj.com). For every five year increase in age at diagnosis the increase was linear, resulting in an analogous relative risk of 1.20 (1.12 to 1.28, $P<0.0001$) for schizophrenia of 1.20 (1.14 to 1.26, $P<0.0001$) for schizophrenia-like psychosis. This effect was also evident when we stratified analyses by age. The relative risk for schizophrenia or schizophrenia-like psychosis also tended to be higher for people with multiple admissions for epilepsy.

Relative risk (95% confidence interval) of schizophrenia and schizophrenia-like psychosis associated with epilepsy and family history of psychosis and epilepsy

Variable	Schizophrenia		Schizophrenia-like psychoses	
	Crude	Adjusted*	Crude	Adjusted*
Personal history of epilepsy:				
No (reference)	1	1	1	1
Yes	2.60 (2.31 to 2.93)†	2.48 (2.20 to 2.80)†	2.98 (2.73 to 3.25)†	2.93 (2.69 to 3.20)†
Family history of psychosis:				
No (reference)	1	1	1	1
Schizophrenia	8.43 (7.78 to 9.13)†	7.57 (6.98 to 8.20)†	6.77 (6.32 to 7.25)†	6.24 (5.83 to 6.69)†
Schizophrenia-like psychosis	4.63 (4.22 to 5.09)†	4.28 (3.89 to 4.70)†	4.29 (3.97 to 4.62)†	4.03 (3.73 to 4.35)†
Affective psychosis	2.33 (2.17 to 2.50)†	2.25 (2.10 to 2.42)†	2.34 (2.22 to 2.47)†	2.27 (2.15 to 2.40)†
Family history of epilepsy:				
No (reference)	1	1	1	1
Yes	1.28 (1.16 to 1.41)†	1.11 (1.01 to 1.22)‡	1.34 (1.25 to 1.44)†	1.20 (1.11 to 1.29)†

*Adjusted for age, sex, calendar year of diagnosis, place of birth, paternal and maternal age at birth, and birth order as well all variables in table. Test of interaction, based on the adjusted analyses—sex and epilepsy: $P=0.31$ for schizophrenia, $P=0.51$ for schizophrenia-like psychosis; age and epilepsy: $P=0.01$ for schizophrenia, $P=0.04$ for schizophrenia-like psychosis.

† $P<0.01$.
‡ $P<0.05$.

Discussion

People with a history of epilepsy have nearly 2.5 times the risk of developing schizophrenia and nearly three times the risk of developing a schizophrenia-like psychosis compared with the general population. The risk increases with age. Both a family history of psychosis and a family history of epilepsy increase the risk for schizophrenia or schizophrenia-like psychosis in the general population. The effect of epilepsy, both in cases and in families, is modified by the effect of a family history of psychosis; the increase in risk is more pronounced for people with no family history of psychosis. The increased risk associated with epilepsy is similar in patients with various types of epilepsy, but it increases with increasing number of hospital admissions for epilepsy, and, in particular, it was significantly greater with increasing age of people who had their first admission for epilepsy.

Strengths and weaknesses

Linking personal information from various Danish longitudinal registers allowed us to follow a large population based cohort for a long period yielding high statistical power and enabling the assessment of interactions between variables. The data are collected systematically, which may reduce the risk of differential misclassification bias. Although we included only inpatients in the analyses, we believe this selection bias is limited because the annual incidence of registered epilepsy in Denmark is comparable with that found in, for example, the US. Also, nearly 80% of all incident cases are admitted to hospital and, as the Danish health system is free, our study is probably not subject to selection bias due to socioeconomic differences in access to care.

Comparison with other studies

To our knowledge this is the first population based study on epilepsy and schizophrenia-like psychosis that has taken the family history of psychosis and epilepsy into consideration and examined the interactions between these factors. Our results corroborate results of previous clinical studies,⁴ suggesting a strong association between epilepsy and schizophrenia-like psychosis. Our findings are in line with the literature reporting aggregation of psychoses in families due to shared genetic or environmental factors, or both.⁵⁻⁸ We think that this study is the first to show that a family history of epilepsy increases the risk of schizophrenia or schizophrenia-like psychosis even after adjustment for the effects of personal history of epilepsy and other factors. This finding suggests that genetic or environmental factors shared by family members may have an important role. Moreover, our findings underlie the suggestion that epilepsy and schizophrenia or schizophrenia-like psychosis—may share common genetic or environmental causes, or both.

Previous reports are inconsistent on the role of age at onset of epilepsy in the risk for schizophrenia-like psychosis. However, these previous studies were based on small clinical samples with large variations in the inclusion criteria for participants as well as in the measurement of psychosis. Our study, which followed a large cohort for a long period, shows that the relative risk for schizophrenia or schizophrenia-like psychosis

What is already known on this topic

Several studies, but not all, have found a higher prevalence of schizophrenia-like psychosis in patients with epilepsy compared with the general population

What this study adds

People with a history of epilepsy are at increased risk for schizophrenia and schizophrenia-like psychosis

Both a family history of epilepsy and a family history of psychosis are significant risk factors for schizophrenia and schizophrenia-like psychosis

The increased risk associated with both personal and familial history of epilepsy is stronger among people with no family history of psychosis

The increased risk for schizophrenia or schizophrenia-like psychosis does not differ by type of epilepsy, but it increases with increasing number of admissions to hospital and particularly with increasing age at the first admission for epilepsy

is greater for people first admitted for epilepsy at later ages.

Evidence from experiments has suggested that deficits in behaviour and cognition caused by seizures probably depend on the age at which seizures occur (less severe deficits at younger ages) and frequency and severity of seizures, and may not become obvious until long after the onset of the epilepsy.⁹ These theories seem to explain our findings regarding the greater risk associated with, for example, increasing age, age at onset of epilepsy, and number of admissions for epilepsy.

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