Epilepsy and non-organic non-affective psychosis
National epidemiologic study

SØREN RASK BREDKJÆR, PREBEN BO MORTENSEN and JOSEF PARNAS

Background This study tests the hypothesis that epilepsy increases the risk of developing schizophrenia and other non-affective functional psychoses using a nationwide sample of people with epilepsy.

Method A record linkage study between a sample from the National Patient Register, consisting of 67,116 people with epilepsy, and the Danish Psychiatric Register identified all people with non-affective psychoses with onset after the first epilepsy diagnosis. The relation between risk of psychiatric disorder in people with epilepsy and the general Danish population was estimated.

Results The incidences of the spectrum of non-organic non-affective psychosis, non-affective psychosis and schizophrenia were significantly increased both for men and women, even after exclusion of people diagnosed as suffering from a learning disability or substance misuse.

Conclusion This study supports the notion of an association between epilepsy and the risk of subsequent non-affective psychosis.

It is commonly accepted that people with epilepsy have more psychiatric problems than normal individuals (Trimble, 1991). The pathogenetic hypothesis of a relationship between epilepsy and chronic 'schizophrenia-like' psychosis was introduced on the basis of uncontrolled, highly selected case series (Slater et al., 1963). Slater et al.'s study had a profound impact, stimulating research on the association between limbic system pathology and psychotic phenomena (Stevens, 1988). Following Slater's study, schizophrenia-like psychosis in epilepsy became rapidly accepted as a nosographic concept, with implicit assumptions of causality from epilepsy to psychosis (Parnas & Korsgaard, 1982). These pathogenetic assumptions materialised in the ICD-8 (World Health Organization, 1967) diagnostic category of 'psychosis due to epilepsy' (psychosis ex epilepsia). In the current diagnostic systems, however, such as ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994), the presence of epilepsy automatically leads to a diagnosis of 'organic mental syndromes and disorders' and does not allow the diagnosis of functional psychoses such as schizophrenia, even if all required criteria are met (Trimble, 1991). Some investigators have interpreted the association between epilepsy and psychosis as spurious (Parnas & Korsgaard, 1982; Schmitz & Wolff, 1991; Stevens, 1991; Mace, 1993). In the absence of suitable long-term prospective data, the existence of nationwide population registers, of both psychiatric and general hospital admissions, offers unique opportunities to study the question of whether epilepsy predisposes to psychosis.

METHODS

Sample
The present study population represents a total national sample consisting of 67,116 persons (35,897 males and 31,219 females) who, on one or more occasion, had been admitted to a Danish general hospital with a diagnosis of epilepsy (ICD-8: 345) during the period 1 January 1977 to 31 December 1992 (see Table 1). This sample was identified in the National Patient Register in which all admissions to general hospitals since 1977 (when the register was established) are recorded. Data from a recent Danish population study, which examined validity of the hospital diagnosis of epilepsy, indicate that 74% of hospital cases with a diagnosis of epilepsy at discharge also fulfil the International League Against Epilepsy (1989) criteria for epilepsy (Skaup, 1996). In people with more than one admission, we selected the diagnosis of epilepsy from the latest admission and if that diagnosis of epilepsy was unspecified (ICD-8: 345.99), we used the specified one from the next latest admission, whenever possible.

Register merging
Through linkage into the Danish Psychiatric Register, using the unique person identifier, all the people ever admitted for the first time to a psychiatric hospital department, after their first recorded epilepsy admission, were identified. A total of 89 people with schizophrenia, (ICD-8: 295), 151 people with non-affective psychosis (ICD-8: 295, 297 or 298.39), excluding confusional psychotic episodes (ICD-8: 298.29) and 361 people diagnosed as having suffered from a spectrum of non-organic non-affective psychotic disorders (ICD-8: 295, 297, 298.39, 301.09, 301.29 or 301.83) were identified after their first epilepsy diagnosis (see Table 1). This spectrum concept was originally used in the Danish adoption studies, and includes personality disorders with a putative link to schizophrenia (that is, paranoid, schizoid personality disorder and borderline schizophrenia) (Kety et al., 1978).

These two national registers cover the total Danish population, which, combined with limited emigration and ascertainment of all death records, assures a complete follow-up. These two registers cover all inpatient facilities for psychiatric treatment and treatment of epilepsy, respectively. Seven thousand seven hundred people were excluded from the analysis because they had been admitted to psychiatric hospitals and psychiatric wards in general hospitals in Denmark prior to their first epilepsy diagnosis. Since both alcohol and drug misuse...
and organic disorders associated with learning disabilities can increase the risk for convulsive disorders (Hauser & Annegers, 1993), all the individuals ever diagnosed with such disorders (ICD-8: 291, 294.3, 303, 304 or 310–315) were excluded from some of the analyses presented, in order to give conservative risk estimates.

**Risk calculation**

The relation between risk of a given psychiatric disorder in people with epilepsy and the general Danish population was estimated by calculating the indirectly standardized incidence ratio (SIR). This ratio is obtained by dividing the observed number of psychiatric cases by the expected number of cases, the latter being national incidence rates as recorded in the Danish Psychiatric Register. This calculation is adjusted by gender, one year calendar periods and age groups, yielding the specific number of person-years in the study population. The denominator and numerator rates were obtained in exactly the same manner. This calculation is analogous to the calculation of a standardised mortality ratio (SMR; Breslow & Day, 1987). All observation periods were defined as starting on the first day of first admission recorded with an epilepsy diagnosis and finishing with the date of the psychiatric admission, the date of death or by censoring on 31 December 1992. The P values were calculated as the exact one-tailed probability of the observed number of schizophrenia cases, multiplied by two, assuming that the observed number of cases observed a Poisson distribution (Ipsen & Feigl, 1970).

**RESULTS**

The incidence of the spectrum of non-organic non-affective psychosis, which includes personality disorders of broadly defined schizophrenia spectrum disorders, was significantly increased both for men and women in the study population (SIR=3.00, P<10^{-8}; see Table 1) and the results remained significant after exclusion of all the people ever diagnosed as suffering from learning disabilities, alcohol misuse or drug misuse (see Table 2).

Restricting analyses to non-affective psychosis only (schizophrenia, paranoid psychoses and 'reactive psychosis') the incidence was significantly increased (SIR=2.74, P<10^{-8}) both for men and women in the study population (see Table 1), and also remained significant after exclusion of people with a learning disability and substance misuse (see Table 3).

The incidence of schizophrenia alone (SIR=2.15, P<0.001) was significantly increased both for men and women in the study population (see Table 1) and remained significant after exclusion of people diagnosed as suffering from a learning disability or substance misuse (see Table 4).

Tables 2–4 present SIRs by diagnostic group, gender and type of epilepsy. As a general finding, the SIR is elevated for both men and women, and for both psychomotor and grand mal epilepsy. The only exception is schizophrenia, where SIR is significantly elevated only for women with epilepsy in general and significantly increased only for men with psychomotor epilepsy.

**DISCUSSION**

Although a pathogenetic association between epilepsy and schizophrenia-like psychosis has frequently been proposed on the basis of studies of selected in-patient populations, so far no epidemiological

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**Table 1** Material and standardised incidence ratios (SIR) of the spectrum of non-organic non-affective psychosis, non-affective psychosis and schizophrenia in Danish in-patients with epilepsy 1977–1992

<table>
<thead>
<tr>
<th>National epilepsy sample</th>
<th>n=67,116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorder (ICD–8: 290–309), prevalence</td>
<td>n=11,287</td>
</tr>
<tr>
<td>National epilepsy sample excluding people with a psychiatric diagnosis prior to their first epilepsy diagnosis</td>
<td>n=59,416</td>
</tr>
<tr>
<td>Psychiatric disorder (ICD–8: 290–309), incidence</td>
<td>n=3587</td>
</tr>
<tr>
<td>SIR of the spectrum of non-organic non-affective psychosis (ICD–8: 295, 297, 298.39, 301.09, 301.29 or 301.83)</td>
<td>SIR=3.00</td>
</tr>
<tr>
<td>SIR of non-affective psychosis (ICD–8: 295, 297 or 298.39)</td>
<td>SIR=2.74</td>
</tr>
<tr>
<td>SIR of schizophrenia (ICD–8: 295)</td>
<td>SIR=2.15</td>
</tr>
</tbody>
</table>

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**Table 2** Incidence of the spectrum of non-organic non-affective psychosis (ICD–8: 295, 297, 298.39, 301.09, 301.29 or 301.83), excluding concomitant learning disabilities or substance misuse in 59,416 people with epilepsy 1977–1992; main groups

<table>
<thead>
<tr>
<th>Epilepsy groups (ICD–8)</th>
<th>Males</th>
<th>95% CI</th>
<th>Females</th>
<th>95% CI</th>
<th>Males and Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>All epilepsy (345)</td>
<td>125</td>
<td>2.33***</td>
<td>(1.94–2.78)</td>
<td>131</td>
<td>2.26***</td>
</tr>
<tr>
<td>Grand mal epilepsy (345.10)</td>
<td>42</td>
<td>2.20***</td>
<td>(1.59–2.97)</td>
<td>44</td>
<td>2.29***</td>
</tr>
<tr>
<td>Psychomotor epilepsy (345.31)</td>
<td>30</td>
<td>5.07***</td>
<td>(3.42–7.24)</td>
<td>18</td>
<td>2.39**</td>
</tr>
<tr>
<td>Non-specified epilepsy (345.99)</td>
<td>43</td>
<td>2.15***</td>
<td>(1.56–2.90)</td>
<td>47</td>
<td>2.13***</td>
</tr>
<tr>
<td>Petit mal epilepsy (345.09)</td>
<td>1</td>
<td>0.58</td>
<td>(0.01–3.22)</td>
<td>9</td>
<td>3.43**</td>
</tr>
<tr>
<td>General convulsions (345.19)</td>
<td>4</td>
<td>1.65</td>
<td>(0.45–4.22)</td>
<td>7</td>
<td>3.94**</td>
</tr>
<tr>
<td>Focal epilepsy (345.30)</td>
<td>3</td>
<td>1.25</td>
<td>(0.26–3.66)</td>
<td>5</td>
<td>1.83</td>
</tr>
</tbody>
</table>

In the other groups of epilepsy both the observed and the expected number of non-organic non-affective psychosis were small, leaving the results of the analysis inconclusive. SIR, standardised incidence ratio. *P<0.05, **P<0.005, ***P<0.00001.
study with an adequate sample size has been published to support such a hypothesis (Mace, 1993). The present study supports this notion of an association between epilepsy and the risk of non-affective psychotic spectrum disorders, no matter how narrowly defined. There is a trend for decreasing risk with narrowing of the criteria for psychosis, which may reflect non-specific pathogenetic effects of epilepsy or differential effects for different subgroups of psychopathology.

Possible bias

The possibility of Berkson’s fallacy cannot be entirely ruled out in the present study (Berkson, 1946). Berkson observed that hospitalised people with a given illness are more frequently comorbid with another illness than comparable individuals in the general population. People with epilepsy who never seek medical treatment or are treated on outpatient basis might have a lower incidence of psychoses than inpatients (Zielinski, 1974). In the present context, we have no information on the risk of psychiatric hospitalisation in Denmark among people with epilepsy treated in outpatient facilities. However, one Danish study demonstrated that people with epilepsy treated in hospitals did not differ significantly from those treated in private practice on a variety of psychometric measures (Naylor, 1996). Danish epidemiological data show that people with schizophrenia are not admitted significantly more often to general hospitals than people among the general population are (Fink, 1990).

Conversely, the observed risk levels, at least for broadly defined psychosis spectrum, may be attenuated by the fact that psychopathology is detected only on the basis of hospitalisation.

Since the health system in Denmark is public and free of charge, this study has no apparent selection bias caused by socioeconomic factors.

Type of epilepsy and the risk of psychosis

Several investigators have found an excess of temporal lobe epilepsy among people with psychosis and epilepsy (Slater et al, 1963; Perez & Trimble 1980). The present study is equivocal in this respect, because the increased risk was found for both psychomotor and grand mal epilepsy, with the exception of schizophrenia alone, which was selectively associated with the diagnosis of temporal lobe epilepsy. In these comparisons, however, the sample sizes were very small (see Table 4).

Diagnostic issues

A study based solely on register data confronts the problem of validity of diagnoses. Here, a compromise must be found between accuracy of diagnosis and the need for a sufficiently large sample size, allowing epidemiological estimations. In Danish psychiatry, where ICD-8 was in use until 1994, there was a tradition of a very narrow, conservative, Kraepelinian notion of schizophrenia (Jørgensen et al, 1987).

The diagnosis of ‘psychosis due to epilepsy’ was not included in our analyses, although we identified 79 people with this diagnosis. In the ICD-8 used in Denmark, there were no specific rules for making such a diagnosis, but the custom was, under the impact of Slater et al’s (1963) influential publication, to make this diagnosis in individuals suffering from and presenting with a schizophrenia-like picture. Consequently, the observed SIR regarding non-affective psychosis among people with...
epilepsy must be considered as strongly attenuated and conservative. Inclusion in the analysis of those people diagnosed as having psychosis due to epilepsy would have dramatically increased the apparent risk of psychosis, no matter how narrowly defined.

**Relationship between epilepsy and psychosis**

The present study supports an association of epilepsy with schizophrenia and other non-affective functional psychoses, but this is not necessarily a causal relationship. A hypothesis has been proposed suggesting that physiologically enhanced neuronal activity in the limbic structures during the reproductive period may predispose to schizophrenic psychosis through several different processes (Stevens, 1991).

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**REFERENCES**


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