Chronic alcohol use and first symptomatic epileptic seizures

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Objective: To establish whether chronic alcoholism and alcohol consumption are risk factors for developing a first symptomatic epileptic seizure.

Methods: Multicentre case-control study of 293 patients (160 men, 133 women) with a first seizure symptomatic (either acute or remote) of head trauma, stroke, or brain tumour, matched to 444 hospital controls for centre, sex, age (±5 years), and underlying pathology.

Results: The risk of first seizure in alcoholics was no higher than in non-alcoholics for men (odds ratio 1.2, 95% confidence interval 0.4 to 3.2) or women (1.5, 0.1 to 54.4). The odds ratio (both sexes) was 1.2 (0.8 to 1.7) for an average intake of absolute alcohol of 1–25 g/day, 0.9 (0.5 to 1.5) for 26–50 g/day, 1.6 (0.8 to 3.0) for 51–100 g/day, and 1.4 (0.5 to 3.5) for >100 g/day.

Conclusions: We found no evidence of an association between alcohol use or alcoholism and a first symptomatic seizure.

Symptomatic epileptic seizures, according to the guidelines for epidemiological studies on epilepsy, are classified as provoked or unprovoked, depending on the time between the insult to the central nervous system (CNS) and the seizure. Provoked is equivalent to acute symptomatic, and unprovoked symptomatic includes seizures with a presumed remote cause, or owing to progressive CNS disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders. Three aetiological factors (stroke, head trauma, and brain tumours) account for half to two thirds of symptomatic disorders.
were excluded because they presented a dual aetiology (for example, stroke and brain tumour). The other aetiologies of symptomatic seizures were: cerebral atrophy (n = 22), multi-infarct dementia (n = 8), CNS infection (n = 8), blood electrolyte disorder (n = 3), perinatal encephalopathy (n = 4), multiple sclerosis (n = 2), and other CNS disorder (n = 9).

Controls
We found two controls for each case from the list of patients admitted to the emergency room, with a negative history of epileptic seizures (excluding febrile seizures). We excluded five possible controls who did not drink alcohol for religious reasons or lifestyle rules (no case was forbidden to drink for these reasons). The first two controls that matched the case were interviewed. Controls were matched to cases according to centre, age (+5 years), sex, and timing and type of the CNS insult. For example, we matched acute symptomatic seizures after stroke and head trauma (that is, occurring within seven days) to controls with stroke or head trauma in the seven days preceding the interview. Remote symptomatic seizures from stroke and head trauma were matched to controls with the same conditions occurring more than seven days before interview. Seizures occurring as the presenting symptom of a brain tumour (acute symptomatic) were matched to controls with a brain tumour diagnosed within one week; other seizures in patients with a brain tumour (remote symptomatic) were matched to controls with a brain tumour diagnosed more than a week before the interview. Controls of patients with remote symptomatic seizures had to have an interval between CNS insult and study entry at least equal to that of the matched case.

Definition of the case
A case was defined according to the WHO criteria, as the acute onset of neurological symptoms of presumed vascular origin and >24 hours duration. Head trauma and brain tumours were accepted when diagnosed by the attending neurologist. Brain tumours included primary and secondary tumours, and arteriovenous malformations.

Design of the questionnaire and data quality
The questionnaire collected information on demographic data (sex, level of education, marital status, residence, place of birth and occupational); family history of seizures, prenatal, perinatal, and postnatal risk factors; and problems related to alcoholism (family history of alcoholism and use of illicit drugs; number of road accidents, jail convictions, dismissals from work, and hospital admissions for alcohol abuse). Specific information on the preparation and validation of the questionnaire and the definitions of the risk factors are reported elsewhere. Subjects were classified according to their current drinking status as: non-drinkers if they drank less than once a year; ex-drinkers if they had abstained from drinking for at least one year and had previously drunk at least once a month; occasional drinkers if they drank at least once a year, but less than once a month; or current drinkers if they did not fit into any of the previous categories. Current drinkers were classified according to their drinking habits during the week (continuous versus binge drinkers) and during the day (at-meal versus between-meals drinkers). Continuous drinkers were persons who drank every day of the week, binge drinkers those who drank only, or considerably more, at the weekend in terms of quantity and frequency. At-meal drinkers were those who drank only during meals, between-meals drinkers those who drank at meals and between meals. Subjects were asked about the age at starting and, for ex-drinkers, at stopping drinking, and their patterns of drinking.

The average daily intake of absolute alcohol (ADAA) in the six months before inclusion in the study, or before stopping drinking for ex-drinkers, was calculated for each person, asking separately about white and red wine, beer, aperitifs, “bitters”, spirits, and laced coffee to obtain the number of servings drunk per occasion, the number of occasions per day, and the number of days per week. We multiplied the number of servings per drinking occasion by the number of occasions per day by the number of days per week to calculate the number of servings per week for each beverage. This number was multiplied by the average alcohol content (grams) of each beverage, and the total of all beverages was divided by seven to calculate the ADAA in grams per day. The diagnosis of chronic alcoholism was based on the Münchner Alkoholismustest (MALT). A MALT score under 6 is normal, between 6 and 10 is borderline, and above 10 is diagnostic for alcoholism. Instructions were given on how to standardise use of the MALT. Mean corpuscular volume (MCV) and gamma-glutamyl-transpeptidase (γ-GT) were considered altered when >98.0 fl and >45 U/l.

Conduct of the study
Cases and controls were interviewed by a neurologist who was blind to the classification of cases. Interviews were done within 48 hours of the seizure (cases) or admission (controls), after informed consent. When the interview was impossible (patient unable to cooperate), the next-of-kin was interviewed (proxy respondent). Proxy respondents were necessary for 67 cases (23%) and 75 controls (17%) (p < 0.05). When neither the case nor the proxy was available or able to respond, the case was considered lost. When neither the control nor a proxy was available, the control was replaced.

MCV was not recorded for 14% and γ-GT for 19% of subjects. A CT scan was done in all cases and an EEG in all but 19. Other examinations (for example, magnetic resonance imaging) were scheduled according to the clinical decisions in each centre, but the results were not used to classify patients.

Statistical analysis
The role of the risk factors was estimated by calculating the odds ratios (OR), with 95% confidence intervals (CI) determined according to Cornfield. The χ² test and Student’s two tailed t test were used where appropriate. The percentage of non-respondes was less than 2% for quantification of alcohol use, less than 5% for demographic data, and less than 10% for the MALT, problems related to alcoholism, and drinking patterns. The percentages of missing data were similar for cases and controls, except that MCV and γ-GT were missing more frequently among controls, and problems with alcoholism were missing more often among cases.

Assuming a prevalence of exposure of 5%, the sample needed to detect a risk of 2.5 with an alpha error of 0.05 and a beta error of 0.20 was 215 cases with two controls per case, and 301 cases with one control per case.

Table 1 Cases and controls according to time and type of symptomatic seizure

<table>
<thead>
<tr>
<th>Type of Symptomatic Seizure</th>
<th>No.</th>
<th>%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute symptomatic controls/cases</td>
<td>Stroke</td>
<td>193/105</td>
<td>44/36</td>
</tr>
<tr>
<td></td>
<td>Head trauma</td>
<td>13/10</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>Brain tumour</td>
<td>121/102</td>
<td>27/35</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>327/217</td>
<td>74/74</td>
</tr>
<tr>
<td>Remote symptomatic controls/cases</td>
<td>Stroke</td>
<td>86/56</td>
<td>19/19</td>
</tr>
<tr>
<td></td>
<td>Head trauma</td>
<td>18/13</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>Brain tumour</td>
<td>13/7</td>
<td>3/2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>117/76</td>
<td>26/26</td>
</tr>
</tbody>
</table>
RESULTS

We included 324 patients, 303 with a first ever seizure and 21 with a first medically evaluated seizure. The two groups were similar with respect to the main demographic characteristics. Thirty one cases (10%) were excluded: four were discharged or transferred to other hospitals before interview, three refused, seven died before the interview, and 17 had no surrogate responders. Thus we ended up with 293 cases (160 men, 133 women). There was no significant difference between included and excluded cases in age, sex, schooling, marital status, occupation, place of birth, MCV, γ-GT, medical part of the MALT, time and type of underlying aetiology, and type of seizure. In the cases, partial seizures with or without secondary generalisation were the predominant pattern (151 patients, 52%) followed by generalised tonic-clonic seizures (95, 32%) and by complex partial seizures with without secondary generalisation (47, 16%). The leading cause of seizures was stroke (161, 55%), followed by brain tumour (109, 37%) and head trauma (23, 8%). We collected 444 of the 586 expected controls (76%), giving a ratio of 1.5 controls per case, 1.2–1.9 in each aetiological category (table 1).

Cases and controls were similar with respect to mean age, schooling, marital status, residency, place of birth, road accidents, problems with the law, and dismissals from work. Cases were more frequently employed (42% v 34%, p < 0.05) than controls.

The risk of first seizure in alcoholics (MALT >10) was not significantly higher than for non-alcoholics, for men (OR 1.2, 95% CI 0.4 to 3.2) or women (1.5, 0.1 to 54.1). It was also not higher for men (1.2, 0.5 to 2.8) and women (1.5, 0.2 to 9.2) with borderline values (MALT 6–10). Altered biological markers of alcoholism were similarly distributed in cases and controls (men: MCV 10% v 8%, γ-GT 29% v 25%; women: MCV 3% v 2%, γ-GT 21% v 14%; NS).

Current drinkers did not have a higher risk of first seizure than non-drinkers for men (OR 1.0, 95% CI 0.5 to 1.9) or women (1.4, 0.8 to 2.3). The mean age at starting for current drinkers was similar in cases and controls, both for men (17.7 v 19.0 years, NS) and women (20.0 v 19.0 years, NS). Ex-drinkers had a risk of first seizure lower than 1 for both sexes (men 0.7, 0.3 to 2.0; women 0.7, 0.3 to 2.1).

The mean ADAA was similar for current drinker cases and controls of both sexes: men 39.5 v 37.2 g/day; women 19.2 v 18.5 g/day; NS). The average amount of each beverage drunk (table 2) was similar for seizure patients and controls, for both sexes. No difference was found in drinking patterns between cases and controls for men and women separately (data not shown) and for both sexes combined (table 3). As the risk was not higher for occasional drinkers than non-drinkers, we pooled the two categories for further analysis. The risk was not significant in all categories of alcohol consumption (table 4).

Considering the timing of seizures (all aetiologies combined), the mean ADAA for current drinkers was not different for cases and controls, either acute (34.2 v 32.1 g/day, NS) or remote (27.6 v 30.7 g/day, NS). After combining patients with acute and remote symptomatic seizures, the mean ADAA was significantly higher for cases with head trauma (52.1 v 25.8 g/day, p < 0.05), slightly higher for stroke (34.2 v 30.5, NS), and lower for brain tumour (26.1 v 36.2, NS). Tables 5 and 6 show the risk of first seizures in relation to seizure timing and aetiology.
tumour account for the majority of symptomatic seizures in
the consequence of a known or suspected cerebral dysfunction
such as head injury, cerebrovascular accident, brain tumour,
and others. However, the identification of an epileptogenic
lesion in a patient’s history does not exclude the role of other
factors. For example, why do some patients with vascular
lesions in similar brain areas develop seizures while others do
not? Does the factor considered as “aetiological” explain the
risk of having a seizure, or are other factors needed? From an
epidemiological point of view each risk factor should be
evaluated as one of several that dictates the higher or lower
probability of a first seizure.

Alcohol use is a powerful risk factor for a first seizure for
adults of both sexes; its strength is high for idiopathic/
cryptogenic seizures with a dose-response effect, while its role
in symptomatic seizures is more controversial. Acute sympto-
matic seizures were only slightly related to alcohol in our pre-
vious study, while the New York study showed a two- to ten-
fold risk for alcohol users (although significant only above 200
g/day). Furthermore, in our previous study we did not find any
relation between alcohol and remote symptomatic seizures. Clinical series have reported a high frequency of
symptomatic or partial seizures in alcoholics. These
differences may depend on various factors, including different
populations, ascertainment methods, levels of exposure, and
drinking habits. Confounding could also play a role: as heavy
alcohol use is a risk factor for stroke and head trauma, any
change in risk could be erroneously attributed to alcohol. To
control for confounding we matched our cases to controls
having the same underlying pathology, to eliminate its effect
on the risk of seizures. Since stroke, head trauma, and brain
tumour account for the majority of symptomatic seizures in
population studies, we limited our sample to these three
categories.

The main finding is that alcohol use did not increase the
risk of a first symptomatic seizure in both sexes. Current
drinkers were similarly represented among patients with sei-
zures and non-epileptic controls, and the mean quantity of
alcohol consumed, in total and for each beverage, was similar
for cases and controls of both sexes. The risk did not increase
significantly, even with ADAA higher than 100 g/day. No dose-
response pattern was detected. Ng and colleagues found a
high risk for those drinking more than 200 g/day, but we had
only one person (a control) who drank this much. Thus, we
cannot rule out that there may be an association for very heavy
alcohol consumption, as our sample was not large enough to
draw conclusions for such high levels.

The mean ages for starting drinking and drinking patterns
were similar for cases and controls; biological markers and the
alcoholism test were also similarly distributed. All these
observations point in the same direction and seem to exclude
any association between alcohol use and a first symptomatic
seizure. One possible explanation of the difference between
this and other studies is that the associations observed were a
result of confounding.

No substantial difference was evident between acute and
remote symptomatic seizures, although acute seizures had a
slightly higher risk in all alcohol consumption categories. Considering each putative cause, we found a minimal (not
statistically significant) effect of alcohol for stroke and head
trauma patients, but only for high doses in the latter.

Some possible flaws of our study need to be discussed. The
identification of alcoholics and the measures of alcohol intake
were based on a questionnaire and self reporting; this could
lead to under-reporting of an undesirable social behaviour,
such as heavy alcohol use. However, self reporting is tradition-
ally considered superior to biochemical markers, and questionnaires have greater sensitivity and positive predictive
value than blood chemistry tests in the identification of alco-
holics; in addition, there is no reason to think of a different
recall between cases and controls. On the other hand, alcohol
exposure could have been overestimated in hospital controls,
though this seems improbable as the ADAA in controls was
similar to that in our other study with different controls, and
in a survey on the general population in the same study area.

Some problems arise from the larger proportion of proxies
interviewed among cases than controls, and the incompleteness
of control recruitment. In a previous reliability analysis,
proxies gave a slightly higher ADAA, which was not statistically significant; for this reason a bias caused by the larger number of proxies would have increased the ADAA of cases, with consequent higher risk estimates. We were able to recruit less than two controls per case, because of the difficulty of matching for the underlying pathology. If the control:case ratio were higher for the aetiology thought to be less frequently associated with alcohol use (brain tumour), this could have lowered the risk estimates; however, this was not the case as brain tumours had the lowest ratio (134:109, that is 1.2). Finally, compared to incidence studies,7 8 we had a lower percentage of head trauma and a higher percentage of brain tumour, given the type of participating centres (mostly neurology departments).

In conclusion, this study provides no evidence of any association between alcohol use and a first symptomatic seizure, either acute or remote, and gives some clues to explain better the relation between alcohol and seizures. When another powerful aetiological factor, such as stroke, brain tumour, or head trauma is identified, alcohol use no longer has any influence. Furthermore, if alcohol causes a generic lowering of the seizure threshold, its effect should be similar in idiopathic and symptomatic seizures, which is not the case. In fact the effect of alcohol seems specific only for idiopathic/cryptogenic seizures, although its mechanism is not yet understood.

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REFERENCES

1 Commission on Epidemiology and Prognosis, International League against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34:592–6.