Geir Bråthen

THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES

CONTENTS

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LIST OF PAPERS

PAPER I.

Bråthen G, Brodtkorb E, Helde G, Sand T, and Bovim G:
The diversity of seizures related to alcohol use. A study of consecutive patients. European Journal of Neurology 1999; 6:697-703.

PAPER II.

Bråthen G, Brodtkorb E, Sand T, Helde G, and Bovim G. Weekday distribution of alcohol consumption in Norway: Influence on the occurrence of epileptic seizures and stroke. European Journal of Neurology 2000; 7:413-421.

PAPER III.

Bråthen G, Bjerve K, Brodtkorb E, and Bovim G. Validity of carbohydrate-deficient transferrin and other markers as diagnostic aids in the detection of alcohol-related seizures. Journal of Neurology, Neurosurgery, and Psychiatry, 2000; 68:342-348.

PAPER IV.

Bråthen G, Bjerve KS, Brodtkorb E, Helde G, Bovim, G. Detection of alcohol abuse in neurological patients: Variables of clinical relevance to the accuracy of the %CDT-TIA and CDTect methods. Alcoholism: Clinical and Experimental Research. 2001; 25:46-53.

PAPER V.

Sand T, Bråthen G, Brodtkorb E, Michler RP, Helde G, Bovim, G. Clinical utility of EEG in alcohol-related seizures. Submitted.

SUMMARY

The aims of this dissertation were to investigate alcohol-related seizures in clinical neurological practice. We wanted to assess the extent of this problem, to classify the seizures, and to investigate methods to improve the clinical diagnosis of such seizures. We propose an arbitrary but simple and reproducible way of diagnosing alcohol-related seizures and alcohol withdrawal seizures. Papers I and II relate to seizure classification and the extent of the problem in relation to the level and weekly pattern of alcohol use. Paper III investigates the performance of various biological markers as aids in the diagnosis of alcohol-related seizures. Paper IV explores pitfalls in the result interpretation for two methods for detection of CDT in patients with neurological disorders. Paper V investigates the utility of standard EEG for the identification of alcohol-related seizures.

Even though the general alcohol consumption in our region is low, every third patient with an epileptic seizure leading to hospitalisation had hazardous alcohol consumption.
Evidence of focal lesions or focal seizure start was found in a high proportion of alcohol-related seizures. All such seizures were secondarily generalized and thus, we challenge the established impression that the vast majority of alcohol-related seizures are primarily generalized. Binge drinking (more than six drinks for men or four drinks for women, in a single drinking occasion) was common, but had little influence on seizure susceptibility or timing of seizures. In contrast to prior knowledge, we found that in some patients there was no time lag from cessation of drinking to the occurrence of a seizure, but falling intake levels prior to withdrawal seizures were demonstrated. This indicates that a state of relative withdrawal while still drinking may be sufficient to induce a seizure. Carbohydrate-deficient transferrin (CDT) is the most accurate biomarker for alcohol use and a good adjunct to the diagnosis of alcohol-related seizures, but its accuracy does not compete with a good clinical investigation. Generally poor accuracy should be expected for fertile women. Women on enzyme-inducing antiepileptic drugs who drink no or little alcohol seem to be at risk of having false positive CDT. Other variables associated with increased CDT were low body mass index, or having total transferrin levels outside normal range. A definitely abnormal EEG suggests epilepsy or symptomatic seizures unrelated to alcohol use. The predictive value of a normal EEG is limited, bur the typical post-ictal finding in alcohol-related seizures is nevertheless a normal low-amplitude EEG record.
The best method for identification of alcohol-related seizures is a clinical work-up based on a thorough medical history. The Alcohol Use Disorders Identification Test (AUDIT) provides a reliable measure of drinking habits. CDT is a good supplement to the clinical diagnosis when there is doubt, if factors associated with false-positive values are appreciated. The diagnostic value of EEG is limited.

ABBREVIATIONS AND CORRECTIONS

List of abbreviations

AED	Antiepileptic drug
ALAT	Alanin aminotransferase
ANOVA	Analysis of variance
ARS	Alcohol-related seizures
ASAT	Aspartate aminotransferase
AUC	Area Under the Curve
AUDIT	Alcohol Use Disorders Identification Test
AWS	Alcohol withdrawal seizures
CAGE	A 4-item questionnaire for alcohol abuse, see explanation in text.
CDT	Carbohydrate-deficient transferrin
%CDT	CDT method provided by Axis Biochemicals ASA
CDTect	CDT method until recently provided by Pharmacia-Upjohn, Uppsala, Sweden; now marketed by Axis Biochemicals ASA.
CNS	The central nervous system
GT	Gamma-glutamyltransferase.
GTC	Generalised tonic-clonic seizure
HPLC	High Performance Liquid Chromatography
HUNT	The Nord-Trøndelag Health Survey
ILAE	International League Against Epilepsy
MCV	Mean Corpuscular Volume
QEEG	Quantitative electroencephalography
ROC curve	Receiver Operating Characteristics Curve
TIA	Turbidimetric Immuno-Assay

Corrections

Two errors occur in Paper I:

1.
Throughout the paper, AUDIT > 8 should read AUDIT ≥8.

2.
185 sciatica patients were reported. Four patients, who were admitted to hospital twice during the study period, were included into the study with separate case numbers and remained undetected until the article was printed. For the other articles, the correct n=181 sciatica patients have been included.

INTRODUCTION

Historical notes

For millennia, harmful effects of alcohol drinking on the body have been appreciated. Wine was used in Mesopotamia, as early as 3000 B. C., and early Greek and Egyptian writings discussed the effects of alcohol in moderation as well as the problem of drunkenness. The relation of alcohol to seizures was appreciated by Hippocrates [1], as well as by the Romans, who even put a name to it; Morbus Convivialis, or "Disorder related to partying" [2].

Although the connection of alcohol to seizures was recognized [3], minimal progress was made to knowledge in this field until modern times. As early as 1851, Magnus Huss showed that after prolonged intoxication, alcoholics might have seizures[4]. He also established that epilepsy patients who drink must be differentiated from alcohol abusing patients suffering from epileptic seizures during withdrawal [5]. Echeverria [6] described in 1881 an alcoholic population of which 45% had seizures at some stage. The pharmacologist Schmiedelberg (1883) was the first to recognise that ethanol is a depressant of the central nervous system [7]. Sir William Gowers [8] noted that seizures were associated with "alcoholic excess" and were normally "excited by a bout of drinking", and in 1899 Bratz [9] noted that epilepsy could be induced by alcohol abuse. Kraepelin (1916) [10] described the increased sensitivity to alcohol in case of epilepsy. In the last two centuries, theories on the nature of the connection of alcohol use to seizures have flourished, e.g. that epilepsy and alcoholism might be related genetically [11], and that parental alcohol abuse might favour development of seizures in the child. While Lennox [2] found that alcohol abuse was not more prevalent among epilepsy patients than others, Bowman and Jellinek [12] came to the opposite conclusion. Prior to the 1950s, the literature contained mostly case reports. Then came the landmark studies of Maurice Victor and co-workers, first with the 1953 article describing the alcohol withdrawal syndrome [7], and later (1967) an article exploring the nature of alcohol withdrawal seizures [13]. These two articles formed a basis for our current knowledge and are both still frequently cited. Although ethically more than questionable, the experimental study of Isbell *et al.* [14] documented in detail the clinical features of alcohol intoxication and subsequent withdrawal symptoms in imprisoned drug addicts. Even though many of the older hypotheses can be rejected today, the connection between epileptic seizures and alcohol use is still obscure, and a variety of theories, terms, and definitions are still matters of debate.

Terminology

A major problem in reviewing publications concerning the relation between alcohol and epileptic seizures emerges from the confusion of terms. Many materials, even the frequently cited ones, provide widely different and vague definitions of the connection between alcohol use and seizures. Although several

studies have addressed this specific problem, little unanimity has been accomplished. Some terms that have been used in previous publications are discussed below.

Alcoholic epilepsy

Early reports dealing with "alcoholic epilepsy" included individuals with unprovoked seizures as well as seizures associated with alcohol abuse [6, 9]. Victor and his co-workers used this term for the occurrence of seizures, primarily GTCs, in persons following a period of chronic daily abuse of alcohol [7, 13]. These and some other authors used "alcoholic epilepsy" interchangeably and synonymously with the term "Rum fits". By their definition, they included the alcohol withdrawal seizures and, mainly for that reason, some authors have suggested that the term should not contain the word "epilepsy" [15, 16]. Other authors, perhaps more fruitfully, reserved the term "alcoholic epilepsy" for recurrent seizures in alcohol-abusing subjects who were not previously suffering from epilepsy or other diseases with potential to cause seizures, and did not have alcohol withdrawal seizures [17, 18]. By that definition, the term was mainly applied to epilepsy caused by alcohol abuse, regardless of whether the cause was metabolic or post-traumatic. Tartara *et al.* stressed that the term should not be applied if alcohol was still being consumed at seizure onset [19]. To complete the confusion, some authors have also used "alcoholic epilepsy" for seizures directly triggered by alcohol ingestion [15].

Rum fits

"Rum fits", as stated above, has been used interchangeably with "alcoholic epilepsy" by some authors. However, most authors seem to regard rum fits as synonym for alcohol withdrawal seizures [20]. Some authors reserved the term for a subtype of alcohol withdrawal seizures that occur in short series [21].

Alcohol-provoked seizures

Hillbom and his group consequently have used the term "alcohol-provoked seizures" [22]. He defines such seizures as seizures occurring as a symptom of the alcohol withdrawal syndrome (in patients with symptomatic alcohol withdrawal), or seizures in patients who have been intoxicated by ethanol within 12 hours prior to the seizure. By that definition, a direct relation to either intoxication or withdrawal is ensured, which is useful for research on the direct connection of alcohol use to seizures, although other seizure types are probably missed, such as for example cases of epilepsy secondary to alcohol abuse. A narrower definition of alcohol-provoked seizures was offered by Bartolomei *et al.* who reserved the term for seizures occurring immediately (within one hour) after ingestion of alcohol [23]. In my opinion such seizures constitute a special group, as discussed later under the heading "alcohol-induced seizures".

Other terms

Alcohol epilepsy [24] and *Alcohol-induced epilepsy* [9] have rather vaguely been used for the appearance of attacks due to alcohol abuse. There seems to be a general consensus that *Alcohol-related seizures* simply states a relation of a given seizure to alcohol use.

WHAT IS AN ALCOHOL-RELATED SEIZURE?

Even the question itself can be questioned, as it suggests that "alcohol-related seizure" is a distinct entity, which it clearly is not. Many authors have attempted to sort out the complex connections between alcohol abuse and seizures, and in particular to define alcohol-related seizures nosologically. Several proposals for classification of alcohol-related seizures have previously been published. For example, Deisenhammer separated seizures occurring only during alcohol withdrawal (group I) from seizures occurring spontaneously as well as in withdrawal (group II) [25]. The classification proposed by Mattson [26] is possibly the most comprehensive one (Table 1).

Table 1. Alcohol-related seizures (From Mattson, 1990).

I. ALCOHOLISM

A. Acute cerebral or medical disorders
   1. Metabolic
   2. Toxic
   3. Infection
   4. Trauma
   5. Coincidental disorders

B. Withdrawal syndrome

C. Epilepsy
   1. Symptomatic of long-term effects of disorders not noted in 1A
   2. Coincidental symptomatic epilepsy
   3. Latent epilepsy unmasked by alcoholism
   4. Epilepsy due to neuronal damage caused by alcohol?
   5. Epilepsy due to kindled effect of repeated withdrawal seizures?

II. EPILEPSY

A. Alcoholism developing in patients with epilepsy

B. Seizures precipitated by alcohol use in non-alcoholic patients with epilepsy

C. Latent epilepsy unmasked by alcohol use

D. Seizures induced by direct effect of alcohol?

The many possible connections between alcohol use and seizures listed in table 1 demonstrate the complex nature of the relationship. The problems that face the

researcher trying to find inclusion criteria for a study on patients fulfilling one or more of the categories become obvious. The list of possibilities does not link well to the terminology used in previous works (as discussed above). Also, some of the listed connections carry question marks, as their pathophysiology is poorly settled. Others are indirect, such as cerebral infections in alcohol abusing individuals leading to seizures. Although infections are more prevalent with alcohol abuse than in the general population, it can be discussed whether seizures occurring during the course of an infectious disorder affecting the CNS deserve their place as an alcohol-related seizure entity. This and other examples draw the picture of how very heterogeneous the group of patients with alcohol-related seizures is. The most distinct entities are discussed below.

ALCOHOL WITHDRAWAL SEIZURES

The alcohol withdrawal seizure is a symptom in the early withdrawal syndrome [7, 14], mainly occurring within 48 hours of cessation of drinking [13], during which the seizure threshold is reduced [27]. The seizure has been reported to be predominantly generalised tonic-clonic, occurring as a single seizure in 50% of cases or as a series of up to six seizures within a 6-hour period [13, 14]. The occurrence of withdrawal seizures is a strong risk factor for progression into a severe withdrawal state, with following development of delirium tremens in up to 30% of cases [13].

This is the clearest entity among the alcohol-related seizures. Nevertheless, even this well-described connection has been challenged by an epidemiological study which suggested that seizures in alcoholic persons are due to the direct toxic effect of alcohol on the brain, and that withdrawal is not a significant mechanism [28]. A correlation of total alcohol consumption to seizure susceptibility has been confirmed in two other epidemiological studies [29, 30]. However, one can not from that conclude that the mechanism is toxic, and not related to withdrawal. Such a hypothesis contradicts virtually all the pharmacological, clinical and experimental evidence that has accumulated in the past 50 years [31], that indicates a key role for cessation of drinking, with subsequent zero or falling blood and brain alcohol levels.

POST-TRAUMATIC EPILEPSY SECONDARY TO ALCOHOL ABUSE

Partial onset seizures with or without secondary generalisation prevail when epilepsy develops in an alcohol-abusing subject with a history of traumatic brain injury. In the Victor and Brausch material (1967), 7% of cases were thought to have epilepsy that began after the alcohol abuse. Verma *et al.*, on the other hand, found that prior head injury accounted for the majority of seizures not related to alcohol withdrawal [32]. Post-traumatic seizures reportedly occur mainly outside the timeframe of the early withdrawal state. Prior head trauma have often been significant so that they are reported by patient or proxies, or noted in hospital records. The onset of post-traumatic alcohol-related seizures may occur earlier than what is the case for withdrawal seizures, often before age 30 [33]. For the Nordic population, this type of alcohol-related seizure, it may be postulated, are

more prevalent than in other countries, as binge drinking is a risk factor for head trauma (see discussion on binge drinking below).

ALCOHOL-INDUCED SEIZURES

The occurrence of seizures directly precipitated by ingestion of alcohol is well documented, but their characteristics have never been well described [34]. Bartolomei *et al.* [35] reported three women presenting with complex partial seizures provoked by alcohol ingestion, in which no focal abnormality was seen on CT or MR images. One was a known alcohol abuser, the others were not. All three patients were still intoxicated at time of the seizure with blood ethanol levels of 1.5-5.0 g/l. Marinacci [36] proposed that psychomotor temporal lobe seizures directly triggered by alcohol ingestion explained unmotivated violence ("blackouts") in some individuals. These and other reports [15] suggest that ethanol itself in rare situations may have the potential to trigger seizures directly. As proposed by Tartara and co-workers [19] one hypothesis may be that alcohol-induced seizures are symptoms of a relative withdrawal state, during which there are temporarily falling serum ethanol concentrations and/or increased concentrations of alcohol metabolites during an ongoing drinking period. That is not compatible with case reports of seizures occurring less than one hour after a single ethanol intake.

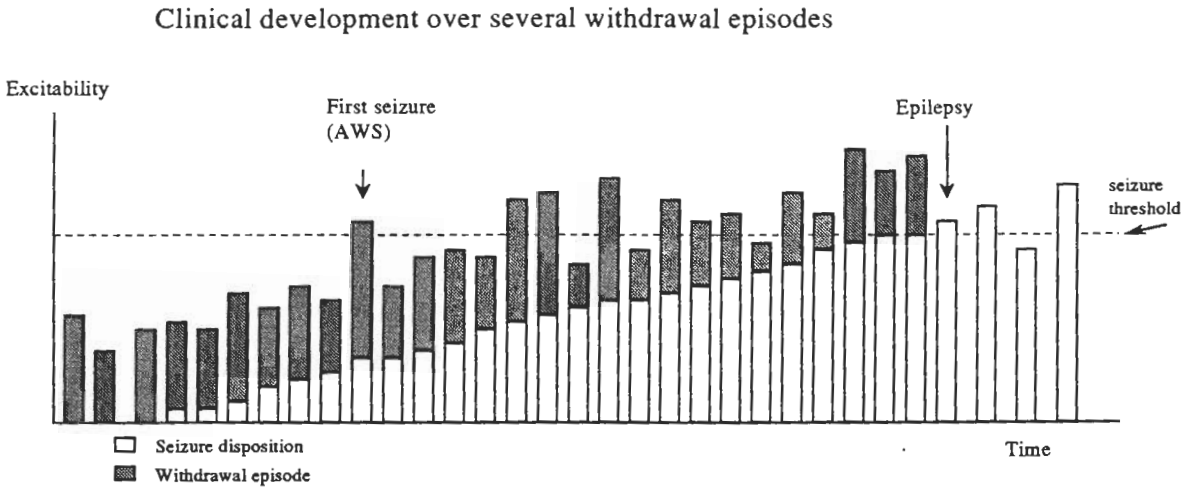
Yamane and Katoh [15] stated that the term "alcoholic epilepsy" should be restricted to those in whom repeated seizures were provoked directly by alcohol intake and in whom there were no other predisposing factors. That definition of alcoholic epilepsy differs substantially from the definition used by other authors. A more appropriate term for this entity might be "alcohol-induced seizures" as discussed above.

ALCOHOL-INDUCED EPILEPSY (ALCOHOLIC EPILEPSY)

Alcohol-induced epilepsy should in my opinion be the preferred term for the situation when epilepsy develops as result of (long-term) alcohol abuse. As there have been several interpretations of the term "alcoholic epilepsy", it should be entirely avoided. However, the probably best definition of the latter term would be "epilepsy developing as result of alcohol abuse", with the exclusion of both post-traumatic and withdrawal seizures.

Epilepsy may result from neuronal damage caused by alcohol. An intriguing hypothesis is that repeated alcohol withdrawal seizures may render the brain increasingly more excitable, leading to an epileptogenic state reminiscent of the "kindling" model [23, 37]. Figure 1 is a model for such a development. This model is complicated by the fact that many alcohol-abusing patients tend to have significant head trauma during the course of their alcohol career. It can be discussed if focal onset seizures in such a patient should be classified as post-traumatic seizures due to alcohol abuse, particularly when CT or MR images show a focal lesion.

Figure 1.
A model for development of spontaneous seizures (alcohol-induced epilepsy) as result of repeated withdrawal episodes (kindling).



LATENT OR PRE-EXISTING EPILEPSY UNMASKED BY ALCOHOL USE

In many cases, alcohol use is closely connected to the occurrence of seizures although there is no indication of alcohol abuse. This is the case for seizures occurring after alcohol intake in a young patient suffering from an alcohol-sensitive epilepsy syndrome, such as Juvenile Myoclonic Epilepsy [38], or the epilepsy syndrome with GTCs on awakening. Such a seizure, one might argue, is alcohol-related, as it is directly connected to the alcohol intake. However, the occasional alcohol intake may be connected to one or several other factors likely to increase seizure susceptibility [39], sleep deprivation being probably the most important single factor. Mattson (table 1) differentiates latent epilepsy unmasked by alcohol intake from seizures precipitated by alcohol use in patients with epilepsy. Although describing two different clinical situations, the pathophysiology of the two categories is probably similar.

(PRE-EXISTING) EPILEPSY COMPLICATED BY ALCOHOL ABUSE

Alcohol abuse developing in a subject with known, pre-existing epilepsy is a challenging situation in which difficult treatment choices have to be made. Deisenhammer *et al.* [25] considered that alcohol abusing individuals with risk factors for epilepsy, e.g. cerebral lesions, a history of epilepsy prior to the onset of alcohol abuse, or a history of seizures in the family, should be offered AED treatment. Others [40] have pointed out that such treatment might, due to poor compliance, be futile or even increase the tendency to seizures, due to ethanol-drug interaction and variable serum concentrations. Thus, the need for AED treatment for this group should be considered carefully, on an individual basis.

HOW MUCH ALCOHOL IS TOO MUCH?

Not all alcohol-abusing individuals develop seizures, and not all epilepsy patients get seizures when they drink alcohol. Furthermore, alcohol-related seizures occur as result of a number of different mechanisms. Thus, attempts to decide what amount might generally be needed to induce a seizure may seem impossible. However, this is an important consideration in the daily life of many epilepsy patients. In a study by Mattson *et al.* [41], seizure exacerbation was reported by 5% of individuals after 1-2 drinks, but by 85% of individuals after consuming 5-6 drinks. In a study by Rodin *et al.* [42] 25 epilepsy patients were intoxicated with alcohol on a single occasion. EEG activity slowed, but no epileptiform activity was seen, and none had subsequent seizures. A survey of 112 non-alcoholic epileptic patients indicated that moderate to heavy quantities of alcohol exacerbated seizure occurrence [43]. This view was supported by a study showing that among outpatients with known epilepsy who attended a specialised epilepsy clinic in London, regular alcohol use seemed to be an important factor in patients with poor seizure control [44]. The double-blinded experimental work of René Höppener [24] provided the probably best basis for some guidelines. He concluded that in patients with epilepsy, the seizure risk did not increase from consumption of 1-3 drinks, twice a week. Furthermore, he found that this level of ethanol use had no influence of the serum concentrations of carbamazepine, phenobarbital, or phenytoin, although a trend towards increased valproate concentrations was demonstrated. However, the severity of the epilepsy was not accounted for.

ALCOHOL CONSUMPTION IN NORWAY

The amounts of alcohol consumed in Norway are generally considered modest. From official sales figures [45], alcohol sales in Norway constitute approximately 45% of the mean sales in the EU countries. As the price policy is strict in Norway as well as in the other Nordic countries (except Denmark), unregistered alcohol consumption (legal and illegal private import, illegally home made liquor, smuggled spirits, home-made wine, etc) is thought to be significant. This proportion of the total consumption has rather consistently been estimated to 23-30% in various studies originating from Finland [46], Sweden [47], Iceland [48], and Norway [49]. Thus, an additional 25% can safely be added to the Norwegian sales figures. This does not, even if there were no unregistered alcohol consumption in the EU countries, bring the general consumption in Norway above 60% of the mean ethanol consumption in EU. Consequently, severe alcohol abuse, alcohol-related organ damage, as well as alcohol-related seizures can be postulated to be less prevalent in Norway than in continental Europe.

CHRONIC VERSUS BINGE DRINKING

The term "binge drinking" describes drinking a large amount of ethanol in a limited period of time. Some authors have used the term for periodical alcohol abuse rather than single drinking occasions [50]. However, most authors more fruitfully reserve the term for a situation in which the ethanol intake on one drinking occasion, normally limited to one or a few days, exceeds a certain amount [51], normally above the threshold of inebriation or intoxication. Different amounts of alcohol have been used as criteria for a significant "binge", but there is unanimity that it implies drinking to intoxication, and most authors have used threshold intakes of 5 or 6 standard alcohol units on one drinking occasion as definition requirement. A gender-specific threshold for men and women has been proposed, as use of the same threshold may underestimate the negative health consequences of binge drinking for women [52].

Whereas chronic alcohol abuse is associated with a broad range of neurological and medical disorders [53], binge drinking has been associated with a high risk for all types of injuries due to accidents or violence, physical or sexual assault [54]. Thus, in a population with a high incidence of binge drinking, alcohol-related injuries may be prevalent, even though the general alcohol consumption level is comparably low.

WEEKDAY VARIATION OF ALCOHOL INTAKE, BINGE DRINKING, AND SEIZURES

Binge drinking in weekends has been thought to be a predominant feature of alcohol consumption of the general population in the Nordic countries. In contrast, binge drinking in other countries, such as in the USA, is a feature of drinking among students and other young population groups [55]. Although a well-known cultural feature [56], this drinking pattern has been poorly documented in Norway. The relation of weekend binges to the occurrence of epileptic seizures has been addressed in a few reports [22, 57]. Hillbom [22] reported that alcohol-provoked seizures occurred more frequently on Mondays, related to cessation of drinking at the end of weekends. He also found that binge drinking for only a couple of days seemed to be sufficient to precipitate seizures, a finding in contrast to the generally accepted requirement of longer drinking periods to produce withdrawal seizures. Although demonstrating a mechanism similar to that of alcohol withdrawal seizures, Hillbom was reluctant to classify Monday seizures occurring after few days' drinking as withdrawal seizures.

BINGE DRINKING AND STROKE

An association of heavy alcohol consumption to stroke, particularly in young patients, seems theoretically plausible [58]. In a study from Finland, brain infarction was closely related to binge drinking, and increased in frequency on Saturdays and Sundays [59]. A more recent study showed an association between alcohol intake and brain infarction during weekends and holidays for young women in particular [60]. The alcohol sales in Finland are nearly twice as high as in Norway [45], and in

prominent in Finland than in our society. However, we defined this an area for the present research, as even in Norway, reports indicate that binge drinking should be a significant risk factor for stroke among young patients.

The need for diagnostic aids

Whereas studies have shown high prevalence of alcohol-related seizures in hospital materials [22, 61], only a little proportion seems to be recognised by clinicians [62]. The diagnosis of alcohol-related seizures is difficult, and patients probably often conceal alcohol as seizure aetiology while in hospital. Obtaining an adequate drinking history is the key to the diagnosis of alcohol-related seizures, but this may prove difficult. For these reasons, the use of biological markers for alcohol abuse in patients with acute seizures are often necessary. Detection of alcohol-related seizures is important for specific reasons: This seizure aetiology is associated with elevated crude mortality [62, 63], and the treatment of alcohol-related seizures differs from the treatment of seizures with other aetiologies. Although the alcohol withdrawal seizure is a rather late symptom of alcohol abuse, other types of alcohol-related seizures are not. Early information about alcohol as a possible reason for seizures is important, as brief (minimal) intervention, which simply implies telling the patient that his or her alcohol consumption might be too high and a cause for the seizure, leads to reduced drinking [64].

Biochemical markers for alcohol-related seizures

Traditional tests for determination of alcohol abuse or ethanol ingestion are inexpensive, but suffer from poor accuracy. The number of novel tests is increasing, and the field is rapidly moving beyond ethanol alone as marker of ethanol intake. Determination of ethanol concentration in blood is accurate and relatively inexpensive. Measurement of ethanol metabolites, such as acetaldehyde, acetaldehyde-protein adducts, or acetate are in part expensive procedures and their usefulness largely remain to be proven [65]. A recently developed laboratory test involves determination in urine of 5-OH-tryptophol, which is expressed as a ratio to the concentration of 5-hydroxyindol-3-ylacetic acid (5HTOL/5HIAA). This ratio is very sensitive to ethanol intake and can be observed for many hours after ethanol is no longer detectable. The clinical use of these tests for investigation of alcohol-related seizures is limited. The complex method precludes performance of the test in most clinical laboratories [65]. If the alcohol withdrawal state is not clinically obvious, 5-OH-tryptophol might be detectable as indication of recent ethanol intake. For patients with alcohol-induced seizures, one would expect ethanol to be present in the blood at the time of seizure onset. It might even be argued that this should be a definition requirement for the alcohol-induced seizures.

Several blood tests can be utilised as biological markers for long-term alcohol intake, or alcohol abuse. Mean Corpuscular Volume (MCV) is known to increase in response to alcohol ingestion, and as the half-life of red cells is approximately

120 days, this marker has the potential of disclosing a long-term abusive pattern. However, its sensitivity and specificity is not impressive. Liver enzymes (ASAT, ALAT) may be increased in response to the inducing effects of ethanol or as result of liver damage. Gamma-glutamyl transferase (GT) is a sensitive marker for alcohol abuse, but lacks specificity, as several factors other than ethanol intake may lead to elevated GT.

CARBOHYDRATE-DEFICIENT TRANSFERRIN

Carbohydrate-Deficient Transferrin (CDT) has been established as the most specific biomarker of sustained alcohol abuse [66, 67]. In well-contrasted populations of middle-aged male alcohol abusers versus control subjects, sensitivity and specificity have been reported as high as >80% and >90%, respectively [68]. However, several studies of unselected patients have shown poor accuracy of CDT, in the range of 22-69% [68-73, 74].

Several methods for determination of CDT in serum exist [75]. Two main methods have been marketed. CDTect was developed and until recently marketed by Pharmacia-Upjohn's laboratories in Uppsala, Sweden. The assay measures the absolute concentration of three carbohydrate-deficient isoforms, namely asialo-, monosialo-, and disialo-transferrin (≤ pI 5.7). As of October 1998, Axis Biochemicals, Oslo, Norway acquired the alcohol-related business from Pharmacia&Upjohn, including the CDTect kit. %CDT-TIA (Turbidimetric Immuno Assay) is the currently marketed version of the CDT test kit from Axis Biochemicals,. Two differences separate the two tests: Firstly, %CDT measures, in addition to the isoforms measured by CDTect, also trisialo-transferrin, which is included in the result by 50% of its value. Secondly, %CDT expresses a ratio of absolute CDT to total serum transferrin. Many studies have compared the two tests, and although there are studies in favour of both variants, most authors have found minor differences [76]. The accuracy of both tests is optimal when they are used to assess whether middle-aged male alcoholics are currently drinking, or not. In mixed materials containing men and women, subjects of all ages, and all grades of alcohol use, test accuracy is low, and differences between the two tests become clinically interesting. One focus of Paper IV was to compare the two tests in this context, in order to evaluate whether one or the other should be recommended for neurological patients.

Serum CDT has a half-life of approximately 15 days [66]. Manufacturers of CDT tests state that a daily ethanol intake exceeding 60g for more than two weeks will normally produce a positive CDT value. Thus, CDT is a measure of hazardous drinking lasting for weeks. If sustained, 60g ethanol daily is a rather high drinking level and this threshold requirement is probably an important reason why the accuracy of CDT is reported to be low in unselected patient materials, that may contain a low proportion of abusers. The quantity, frequency, and duration of the alcohol consumption needed to cause elevated CDT may vary individually, and is probably in most cases higher than what most clinicians would consider a hazardous or harmful drinking level. As CDT is the hitherto most accurate marker

for alcohol abuse available, we chose to assess the accuracy of CDT as a tool for the diagnosis of alcohol-related seizures.

Utility of EEG techniques to detect alcohol use or abuse

One possible way of differentiating epilepsy patients who abuse alcohol from alcohol abusing individuals with withdrawal seizures (but not epilepsy) is through recording of interictal EEG [25, 77]. The standard EEG recording has generally been considered of little help in the diagnosis of alcohol-related seizures [78]. Among 130 EEG recordings from patients with "alcoholic epilepsy" reported by Victor and Brausch [13], EEG was normal in 109, and the predominant abnormality in the remaining 21 was generalised slowing. In a study of 117 patients with alcohol withdrawal seizures, Hauser *et al.* (1982) found that 97% of EEGs were normal or showed non-specific abnormalities [79]. However, certain features of standard and quantitative EEG are typical for alcohol influence, some of which may prove sufficiently accurate to be utilised for diagnostic purposes.

EEG CHANGES DURING ALCOHOL INTOXICATION

Acute alcohol ingestion causes slowing of alpha frequency, and increased alpha power, both in controls and alcohol abusers [80]. Variable results from alcohol exposition in high-risk individuals have been reported; e.g. less alpha frequency slowing [81] or more (slow) alpha power increase [82] compared to low-risk individuals. It may be difficult to separate the effect of alcohol abuse per se from the effects of associated morbidity, such as cerebral trauma [83]. Ethanol in low dosages causes a general stimulating effect, leading to desynchronization of EEG and increased beta activity. In higher dosages, there is a general slowing of cerebral activity, expressed by depressed frequency and increased amplitude. Twin studies indicate that a strong genetic influence on the EEG response to ethanol is present [84].

RESTING EEG IN SUBJECTS WITH HAZARDOUS DRINKING LEVELS

Resting EEG recorded from patients with hazardous drinking levels is predominantly normal [85]. Quantitative analyses have shown that alcohol abusing individuals have less alpha (8-13 Hz) than controls [86]. Subjects at risk for alcohol abuse may have less (slow) alpha and more beta activity in their resting EEGs compared to low-risk control subjects [87], but baseline EEG differences have not always been found [82]. It has been speculated if low alpha may be associated with a higher arousal in alcoholics who are not under the influence of alcohol, and if so, that alcoholics may drink to "normalise" arousal [86].

EEG CHANGES ASSOCIATED WITH ALCOHOL WITHDRAWAL

The EEG in patients with withdrawal seizures has been reported normal [13, 86]. EEGs recorded within a few days after adult first generalised seizures (of all

aetiologies) were normal in 44%, showed focal abnormalities in 24%, and diffuse abnormality in 32% of cases [88]. Thus, the significance of a normal post-seizure EEG may be a potentially useful factor, indicating an alcohol-related seizure.

PHOTIC RESPONSES

A strong reaction to photic stimulation was observed by Giove [89]. This reaction, called the photomyoclonic response, is associated with increased muscle tone (Bickford *et al.*, 1952). Victor and Brausch [13] found unique photomyoclonic and photoconvulsive responses that were most prominent during the first and second day after the last drink, after which they disappeared completely. More recent reports have been unable to reproduce such a high occurrence of photic responses, however [90]. Hauser *et al.* [79] recorded EEGs in 117 patients during the time interval that Victor and Brausch (1967) found abnormal EEG responses to photic stimulation, but found only one case that demonstrated a photoparoxysmal pattern.

AIMS OF THE STUDY

The main aim of the present study was to improve the clinical diagnosis of alcohol-related seizures.

PAPER I

1. We wanted to determine to what extent seizures leading to hospital admission were related to alcohol use.
2. We wanted to study whether the seizure and syndrome classification of alcohol-related seizures according to the ILAE classifications [91, 92], differed from that of seizures not related to alcohol use.

PAPER II

3. We wanted to relate the occurrence of alcohol-related seizures to the weekly pattern of alcohol consumption, with an emphasis on binge drinking in weekends.
4. We also wanted to assess the potential influence of binge drinking on the occurrence of ischemic stroke.

PAPER III

5. We wanted to assess the utility of various biological markers as aids to the diagnostic work-up of alcohol-related seizures. The utility of the Axis %CDT test was investigated in comparison with other markers
6. We wanted to relate the potential of biological markers to the clinicians' opinions on to what extent each seizure was alcohol-related

PAPER IV

7. We wanted to compare the utility of two commercially available methods for determination of carbohydrate-deficient transferrin (CDT) in neurological patients.
8. We wanted to identify reasons for the reported poor accuracy for this type of patient materials.

9. We wanted to bring further documentation for a coincidental finding in Paper III indicating that enzyme-inducing antiepileptic drugs might influence CDT and cause false-positive results.
10. We aimed at determining whether there were other and unknown pitfalls to the interpretation of CDT results.

PAPER V

11. We investigated neurophysiological features (standard EEG, and photic EEG responses) with the potential to be of help to the clinical diagnosis of alcohol-related seizures.
12. We wanted to identify discriminant features of EEG that might be clinically useful in making a diagnosis of alcohol-related or alcohol withdrawal seizures, or in excluding such a diagnosis.

METHODOLOGICAL CONSIDERATIONS

Recruitment of patients and control subjects

Patients for the present study were recruited from the Department of Neurology, Trondheim University Hospital, from January 1995 through October 1996. In that period of time, all patients who were admitted to the department for either acute seizures, strokes, or radiating leg pain (sciatica) were informed about the study, invited to participate, and eventually signed their informed consent.

Table 2. Study population reported in each paper.

	Seizure patients	*Stroke patients*	*Sciatica patients*	*Epilepsy outpatients*	*Healthy subjects*
Paper I	142		185*		254
Paper II	142	91	181	91	254
Paper III	158				
Paper IV	150	81	166	87	
Paper V	73		79	37	

*See correction on page 5

Several seizure patients were unable to participate for some reason (For details, see Paper 1, Figure 1). This was also the case for stroke patients, although their numbers have not been summarised as detailed. Very few sciatica patients refused or were unable to participate. In the seizure group, seizure classification revealed that there were 142 epileptic seizures and 16 non-epileptic seizures (8 convulsive syncopes and 8 pseudo-epileptic seizures). As Papers I and II explored the nature of epileptic seizures, we included only the 142 epileptic seizure patients. For Paper III, which related to detection of alcohol abuse among seizure admissions, all the 158 patients who were admitted for acute seizures were considered eligible for inclusion, although CDT data was available for only 150. Paper IV includes all patients with CDT results. Table 2 gives an overview of the study population that was included in each paper. For further details on the material, please refer to materials section of each paper.

Measuring alcohol consumption and abuse

There are two principally different ways of retrospectively asking how much alcohol a given person has consumed in a given period of time. One is to use questions that indirectly assess the general level of alcohol use (questionnaires), the

other is to try to obtain as certain information as possible on the exact alcohol intake during the time-span of interest. Validated methods have been developed for both alternatives.

QUESTIONNAIRES FOR DETECTION OF ALCOHOL ABUSE

A number of questionnaires have proven useful for identification of patients with alcohol abuse. CAGE is an acronym for a) Have you ever felt you should Cut down on drinking? b) Have people Annoyed you by criticising your drinking? c) Have you ever felt bad or Guilty about drinking? and d) Have your ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye-opener). The questions are simple and the sensitivity and specificity have been reported above 80% [93]. The brief Michigan Alcoholism Screening Test (BRIEF MAST) is regarded insensitive to milder levels of alcohol abuse. The Munich Alcoholism Test (MALT) is a composite test, which scores consumption, physical signs and symptoms and biological abnormalities [94]. It is an effective and useful instrument for identifying alcohol-abusing subjects in patient populations, but as the test combines data from clinical examination and a self-administered questionnaire, its daily use in a clinical setting is rather demanding. Also, the test aims at identifying alcoholism rather than moderate-level alcohol abuse.

As all drinking levels were represented in our study population, use of questionnaires designed to detect chronic alcohol abuse would have identified a narrow group of subjects with clearly abusive patterns, whereas many cases with intermediate degrees of abuse (hazardous consumption) would have been "lost", e.g. coded as alcohol-negative.
The Alcohol Use Disorders Identification Test (AUDIT) was developed to detect hazardous or harmful drinking. In contrast to most of the previous questionnaires, AUDIT is composed of questions related both to recent drinking levels, attitudes to drinking as well as the harmful effects of drinking (Table 3). Its range of scores from 0 to 40 gives the researcher the opportunity to define an appropriate cut-off score from the desired sensitivity and specificity for any given study. Division of the population into more than two groups by using two cut-offs is also possible [95]. The most commonly applied cut-off points have ranged between 8 and 11. We defined AUDIT scores >= 8 as cut-off, as previous papers have shown >90% sensitivity at >80% specificity for detection of hazardous alcohol consumption [96-98].

REPORTING RECENT DRINKING

Validity studies on self-reported alcohol consumption have generally concluded that such reports are reliable [99]. Diary gives more accurate information on alcohol consumption than questionnaires do [100], but require a prospective study design, which was not the case in the present study. For registration of alcohol consumption, Sobell and Sobell proposed the timeline follow-back method [101]. The method is calendar-aided and in essence, the subject is asked about his or her alcohol intake in relation to events that can be retrospectively determined from the

calendar. Some authors have stated that alcohol intakes for up to a year backward in time can be measured reliably by this method. In the present study, we applied a modified timeline follow-back technique, asking about the alcohol consumption only during the last eight days. In retrospect, as we have performed studies on CDT, which has a half-life of approximately 15 days [66], we could have registered a longer time-span, preferably a month. However, even from as short a period as 8 days, the study subjects reported significantly lower alcohol consumption on the same weekday one week prior to the interview, as "yesterday". We interpreted that finding as result of recall bias (see Paper II). If we were to register a month's alcohol intake, an even stronger recall bias would probably have occurred. As a result of that, we believe that the mean daily consumption during the last eight days is the best estimate for the recent alcohol intake.

METHODS FOR DETERMINATION OF CARBOHYDRATE-DEFICIENT TRANSFERRIN

We used two commercially established methods for detection of CDT. CDTect is the name of the method that was produced and marketed by Pharmacia-Upjohn, Uppsala, Sweden. The test measures the absolute quantity of the transferrin isoforms a-, mono-, and disialo-transferrin (pI $\geq$ 5.7). The other test, %CDT by Axis Biochemicals ASA, Oslo, Norway is principally different as it relates the quantity of the carbohydrate-deficient isoforms to the total transferrin concentration. This has been done mainly in order to adjust for total transferrin alterations that may occur in some patients. Another difference is that %CDT includes approximately 50% of the isoform trisialo-transferrin. Many studies have compared the accuracy of the two methods, and in general there are minor differences.

STATISTICAL COMPARISON OF LABORATORY TESTS

Although they might be clinically useless, the correlation between two tests may be excellent, provided that the tests perform equally poorly. A difference plot (Bland-Altman plot) provides a better comparison between two such tests [102]. However, a requirement of the difference plot is that the two tests measure exactly the same phenomenon, and use the same scale for the results. That is not the case for the two tests %CDT-TIA and CDTect. Another way of comparing two different tests for the same phenomenon is by use of Receiver Operating Characteristics (ROC) curves [103, 104]. ROC curves, as shown in Papers III and IV, are plots of the sensitivity and specificity of each test in relation to a "gold standard", in quadratic graphs. From such graphs, the sensitivity at any given specificity of the test can be read directly. Also, the area under the ROC curve (AUC) is a measure of the overall test performance (accuracy) at all possible values for sensitivity and specificity. In this respect the method is impressive, but for clinical purposes it should be acknowledged that only a part of the ROC curve is of actual interest, as specificity above a certain level is normally wanted. The most "fair" comparison of two diagnostic tests would, consequently, be measurement of AUC for the part of the ROC curve that is of clinical interest. Definition of such an area would have to

Table 3. The Alcohol Use Disorders Identification Test (AUDIT)

1. How often do you have a drink containing alcohol?

	(Score)
[ ] Never	(0)
[ ] Monthly or less	(1)
[ ] Two to four times a month	(2)
[ ] Two to three times a week	(3)
[ ] Four or more times a week	(4)

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

[ ] 1 or 2	(0)
[ ] 3 or 4	(1)
[ ] 5 or 6	(2)
[ ] 7 to 9	(3)
[ ] 10 or more	(4)

3. How often do you have six or more drinks on one occasion?

[ ] Never	(0)
[ ] Less than monthly	(1)
[ ] Monthly	(2)
[ ] Weekly	(3)
[ ] Daily or almost daily	(4)

4. How often during the last year have you found that you were not able to stop drinking once you had started?

[ ] Never	(0)
[ ] Less than monthly	(1)
[ ] Monthly	(2)
[ ] Weekly	(3)
[ ] Daily or almost daily	(4)

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

[ ] Never	(0)
[ ] Less than monthly	(1)
[ ] Monthly	(2)
[ ] Weekly	(3)
[ ] Daily or almost daily	(4)

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

[ ] Never	(0)
[ ] Less than monthly	(1)
[ ] Monthly	(2)
[ ] Weekly	(3)
[ ] Daily or almost daily	(4)

7. How often during the last year have you had a feeling of guilt or remorse after drink?

[ ] Never (0)
[ ] Less than monthly (1)
[ ] Monthly (2)
[ ] Weekly (3)
[ ] Daily or almost daily (4)

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

[ ] Never (0)
[ ] Less than monthly (1)
[ ] Monthly (2)
[ ] Weekly (3)
[ ] Daily or almost daily (4)

9. Have you or someone else been injured as a result of your drinking?

[ ] No (0)
[ ] Yes, but not in the last year (2)
[ ] Yes, during the last year (4)

10. Has a relative or friend, or a doctor of other health worker been concerned about your drinking or suggested you cut down?

[ ] No (0)
[ ] Yes, but not in the last year (2)
[ ] Yes, during the last year (4)

SCORING:
Questions 1-8 are scored 0,1, 2, 3, or 4.
Questions 9 and 10 are scored 0, 2, or 4 only.
The minimum score (for non-drinkers) is 0 and the maximum possible score is 40.
A score of 8 or more indicates a strong likelihood of hazardous or harmful alcohol consumption.

FROM: Saunders JB; Aasland OG; Babor TF; de la Fuente JR; Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption. II. *Addiction* 88(6): 791-804, 1993.

be arbitrary, as it is not easy to define the limits of clinical interest in this respect. In addition, such a measurement requires mathematics that is not normally supported by ROC curve software programs. Consequently, we compared the whole AUCs as indicators for overall test accuracies. In Paper IV, the situation emerged in which it was of interest to measure the areas under two curves occurring from analysis of two mutually exclusive populations, namely women and men. There do exist methods for doing that [105], but they are methodologically complex. However, by comparison of 95% confidence intervals, it could be determined whether the differences were statistical significant or not (at the $p<0.05$ level). No further attempt was done to assess the exact p value for these comparisons.

Proposal for a simplified classification

"Alcohol-related seizures" is no entity, but merely a collection of seizures that are connected to alcohol use in different ways. In order to detect patients with alcohol-related seizures for the present study, we applied simple and reproducible operational definitions for seizures related to alcohol use (AUDIT $\geq$8), and for the subgroup of withdrawal seizures (AUDIT $\geq$8 and recent (<72 hours)) alcohol consumption, with the specific aim to avoid definition problems. This way of defining seizures related to alcohol use has, in our opinion, the advantage of being reproducible, which may enable comparison of materials from different centres, focusing on various medical problems. By these definitions, we report frequencies of alcohol-related seizures and withdrawal seizures well in accordance with the literature [22, 61, 106], especially when taking into consideration the relatively low alcohol intake in the Norwegian population [45].

Papers are not included due to copyright restrictions

GENERAL DISCUSSION

Seizure types related to alcohol use

GENERALISED TONIC-CLONIC SEIZURES

Out of the adult onset generalised seizures in the present material, almost two thirds occurred in AUDIT positive patients. Adult onset generalised seizures rarely are symptoms of an idiopathic epilepsy syndrome, as such seizures predominantly start in childhood or adolescence. In a large consecutive study of first-ever seizures, alcohol abuse was the most prevalent aetiology of first-ever generalised seizures in adults, comprising 30% of the patients between 30 and 60 years of age [88]. We conclude that a high suspicion of alcohol abuse is justified when investigating such a patient.

Among the 33 patients who were classified as having alcohol withdrawal seizures in Paper I, we found that only 17 had generalised onset seizures. The remaining 16 seizures, having features consistent with partial onset, were all secondarily generalised. Secondarily and primarily generalised seizures are clinically indistinguishable when the patient is brought to the emergency room and seen by the clinician. Therefore, we propose that the high proportion of primary GTCs reported in several previous studies, may be an overestimation. These data do not contradict the interpretations of several authors that "pure" alcohol withdrawal seizures are primarily generalised tonic-clonic seizures. In their landmark article from 1967, Victor and Brausch [13] reported 95% of seizures to be GTCs. They included 241 patients who all had a known history of alcohol abuse as well as a history of seizures. These criteria probably led to recruitment predominantly of patients with alcohol withdrawal seizures, which is probably why the seizures nearly exclusively were classified as primary GTCs with normal interictal EEGs. Other studies that have used wider criteria for alcohol-related seizures have reported a higher proportion of focal onset seizures, as shown in table 4.

PARTIAL ONSET SEIZURES

As shown in Table 4, the proportion of partial seizures in our material was higher than that of comparable studies. Some of the previous studies were performed in populations characterised by considerably higher alcohol consumption, and thus, a higher proportion of seizures related to the alcohol withdrawal syndrome could be expected among acutely admitted seizure patients. In some studies, seizures occurring in patients with known focal brain lesions were excluded from the definition of alcohol-related seizures. It should also be born in mind that the availability of neuroimaging techniques was different from today in most of these

studies. Schwartz *et al.* [107] reported in 1974 that out of 26 alcohol abusing patients with focal (onset) seizures, 22 (86%) had their seizures within 48 hours after cessation of alcohol intake. They hypothesised that these were alcohol withdrawal seizures with a focal start due to pre-existing, mainly post-traumatic, brain lesions. In a series of patients with known epilepsy attending an epilepsy clinic for poor seizure control, 56% of alcohol-related seizures were focal [44]. When withdrawal seizures were excluded from a group of Danish patients with late-onset epilepsy (>25 years of age), 23% of seizures occurred in alcohol abusing individuals, and as much as 73% of those were secondarily generalized complex partial seizures [108]. These findings support our results suggesting that focal onset seizures related to alcohol abuse are more prevalent than hitherto appreciated.

Table 4. Seizure types related to alcohol use, compared to unprovoked seizures

	Generalised	Partial	Unknown
Victor & Brausch 1967	95%	5%	0%
Earnest & Yarnell 1976	65%	24%	11%
Krauss & Niedermeyer, 1991	86%	7%	7%
Hillbom, 1980	83%	13%	8%
Paper I	49%	51%	0%
Unprovoked seizures:			
Forsgren et al., 1996	16%	68%	13%
Hauser et al., 1993	48%	48%	3%

Our criteria for identification of partial onset seizures were rather liberal, as focal lesions on CT or MR images ("white spots" in MR images excluded) as well as focal EEG abnormalities were taken as evidence for focal seizure onsets, rendering the identification of primary GTC seizures an exclusion diagnosis. This way of identifying partial seizure onsets was adopted from recent epidemiological studies [109, 110]. Using these criteria, Forsgren *et al.* (1996) reported a 68% proportion of unprovoked seizures as having partial onset (Table 4). Hauser *et al.* [111] classified partial onset seizures by the post-hoc diagnostic impression from reading available histories and did not use interictal EEG to modify the seizure classification. They found that 48% of unprovoked seizures had partial onset, less than the findings of Forsgren *et al.* More surprising was their 48% proportion of generalised seizures, however. While Forsgren *et al.* scored seizures without an observed seizure start as "unknown", Hauser *et al.* did not. One might suspect that a high proportion of the generalised seizures reported by Hauser *et al.* had partial onsets or focal abnormality on interictal EEG. On the other hand, there is a possibility that the criteria used by Forsgren *et al.* as well as in Paper I, might over-estimate the proportion of partial onset seizures. Nevertheless, it reflects common

clinical practice that GTCs in patients with cerebral lesions are considered secondarily generalised. Although the clinical classification of secondarily generalised seizures rests on observation of the seizure onsets, a recent study showed that seizures in patients with generalised epilepsy may have intermittent focal features [112]. It may seem that alcohol-related seizures include less partial onset seizures than unprovoked seizures of all causes or seizures due to epilepsy, but the proportion of partial onset alcohol-related seizures is still probably higher than previously presumed.

STATUS EPILEPTICUS

Out of the 49 AUDIT positive seizure patients, two (4%) presented with status epilepticus (seizure duration more than 30 minutes). Both had consumed alcohol in excess during the last week, and had positive CDT. One had normal interictal EEG; the other had focal EEG abnormality. Only 3-8% of withdrawal seizures go on to status [13, 22], but on the other hand, alcohol abuse is probably the commonest cause for status epilepticus [113, 114]. A third of patients who present with alcohol-related status epilepticus are thought to develop delirium tremens. Complex partial status epilepticus confirmed by ictal EEG has been reported in a patient whose seizures repeatedly were provoked by ingestion of alcohol [115], thus probably representing an alcohol-induced seizure.

THE CONCEPT OF ALCOHOL WITHDRAWAL SEIZURES

Although the best-described entity of the alcohol-related seizures and supported by considerable pathophysiological and clinical evidence for its existence, alcohol withdrawal as a cause for seizures was challenged by an epidemiological study indicating that seizures were due to a dose-dependent toxic effect of alcohol [28]. Similar findings of dose-dependent connections between alcohol and seizures have been the results of two other epidemiological studies [29, 116]. In Paper II, we demonstrate that before the onset of an alcohol withdrawal seizure, the alcohol intake seems to drop, probably inducing a state of "relative withdrawal" in which serum ethanol concentrations are falling. Also, we found symptoms of an early withdrawal state, such as elevated pulse rate, in the withdrawal group. These findings provide, together with a high number of previous studies, a strong case in favour of the existence of the alcohol withdrawal seizure.

The findings of Ng *et al.*, showing a dose-dependent connection of alcohol to seizures, may not contradict the concept of alcohol withdrawal, but rather indicate that additional mechanisms are at play. It is not surprising that the incidence of seizures was higher among those who had the highest lifetime alcohol intake. That is in fact supportive of the withdrawal syndrome, as it is well known that alcohol withdrawal seizures predominantly develop from long-term alcohol abuse. Consequently, from epidemiological studies assessing odds-ratios for seizures, a dose-dependent relation of alcohol consumption to withdrawal seizures might be expected. Ng *et al.* reported that 45% of their patients had their seizure within the generally accepted timeframe for withdrawal seizures, but stated that they were not

necessarily AWS [28]. From their epidemiological approach they concluded that the direct (toxic) effect of alcohol was more important than the withdrawal effects. That seems an inappropriate conclusion to reach from their study design.

Given the general agreement that prophylactic treatment for withdrawal seizures is at most a short-term antiepileptic regimen [40] as opposed to the more rigorous treatment of epilepsies, the clinical importance of a correct categorisation of alcohol-related seizures is obvious. Although weekend binges have been shown sufficient to cause seizures [22], in most cases, considerably more than a weekend binge would be necessary in order to produce withdrawal seizures. If a high degree of weekend drinking were a predominant feature of patients with abusive patterns, one might expect to see a clustering of seizures on Sundays and Mondays. Furthermore, a selection bias towards withdrawal seizures in the first days of the week might be the result of our definition requirement of an alcohol intake within the last 72 hours, as alcohol consumption peaked on Saturdays. However, in this material, we found no weekday variations of admissions for withdrawal seizures. In the withdrawal subgroup, many were unemployed, on sick leave, or on disability pension. To these subjects, it may be argued, weekdays did not matter as much as to those who were working and consequently, an even distribution of their seizures through the week might be anticipated.

Demographic aspects

GENDER

There is a general agreement that more men than women develop alcohol-related seizures. Women accounted for only 10 and 18% of the patients in the studies of Devetag [18] and Hillbom [22], respectively. Although patients with post-traumatic epilepsy are known to include more males [117], as shown in table 5, the preponderance of men among patients admitted for acute seizures, is almost fully accounted for by alcohol-related seizures.

Table 5. Male to female ratio in studies of consecutively hospitalised patients with alcohol-related seizures, and seizures unrelated to alcohol.

	Earnest & Yarnell, 1976	Hillbom, 1980	Paper I
Alcohol-related	4.1 to 1	4.8 to 1	2.1 to 1
Other aetiologies	1 to 1	1.1 to 1	1 to 1
Total	1.7 to 1	2 to 1	1.3 to 1

There may be two possible causes for this difference. The male brain might be more susceptible to developing seizures in response to alcohol intake than the female brain is. No data seems to support such a theory. More likely, different drinking levels may account for the gender difference. Table 6 shows that men

generally drink more ethanol than women do, and the difference is similar to the gender differences of admissions for alcohol-related seizures. A complicating factor is that the first-pass metabolism of ethanol is somewhat higher in men, leading to lower s-ethanol concentrations than in women, in response to an identical intake.

Table 6. Male to female ratios of reported recent alcohol intake prior to seizures (g per day).

	Men	Women	Ratios and p values
Lechtenberg and Worner, 1992 [37]	303±226 g	238±327 g	1.3 / p=0.028
Leone et al 1997, cases [30]	59 g	32 g	1.9 / p not available
Leone et al 1997, controls	36 g	14 g	2.6 / p not available
Paper IV	21±87 g	6±14 g	3.4 / p=0.001

AGE

We found that AUDIT positive seizure patients were younger than AUDIT negative (Paper II), seemingly due to a distinct reduction in the occurrence of alcohol-related seizures above age 50 years. In some contrast to previous studies showing younger age at admission for AWS than other ARS [23], AWS patients in our material did not differ from the remaining AUDIT positives in this respect. This is in consistency with previous studies that generally have reported patients with alcohol-related seizures to be 30-60 years [22, 118]. In our material, alcohol consumption peaked in 40-49 year old subjects, in consistency with the peak occurrence of alcohol-related seizures.

HOSPITAL ADMISSIONS FOR ACUTE SEIZURES RELATED TO ALCOHOL USE

We found that 49 out of 142 patients with acute epileptic seizures were AUDIT positive, fulfilling our main criteria for having alcohol-related seizures. In the AUDIT negative group, only one seizure patient was found to have consumed an excessive amount of alcohol last week, indicating that AUDIT served its purpose for group separation well in this respect. Few previous studies have assessed the prevalence of ARS among consecutively hospitalised seizure patients, and comparison of such studies is difficult due to variable criteria. Rather different criteria have been applied, explaining the variation of the proportions of alcohol-related acute seizures (Table 7).

Table 7. Alcohol abuse among patients with acute seizures

Study	n	Proportion of Patients	Criteria for alcohol abuse
Earnest and Yarnell, 1976 [61]	472	41%*	"History of alcohol abuse"
Gottstein, 1977 [120]	153	26%	"Symptomatische Krampfanfälle: alkoholtoxisch"
Hillbom, 1980 [22]	560	49%*	Alcohol intoxication <12hrs, or withdrawal symptoms
Krumholz et al., 1989 [121]	200	41%*	(Currently) alcohol abusing individuals
Brinar et al., 1991 [122]	194§	42%*	Alcoholism, or suspected alcoholism.
Jallon, 1997 [123]	273	30%	Provoked by alcohol intoxication or withdrawal, or unprovoked in alcoholism. [124]
Jallon, 1999 [125]	309	30%	Provoked by alcohol intoxication or withdrawal, or unprovoked in alcoholism. [124]
Paper I	142	35%*	AUDIT scores >=8

* Consecutive materials. § First-ever seizures

INCIDENCE AND PREVALENCE OF EPILEPSY AND UNPROVOKED SEIZURES

The prevalence of epilepsy has been estimated in a study from Northern Sweden to 553 per 100.000, with a ratio of men to women of 1.1 to 1, and a 68% proportion of partial seizures [109]. The age-adjusted incidence of unprovoked seizures is 56-61 per 100.000 person years [110, 111], whereas the age-adjusted incidence of epilepsy in Rochester, Minnesota was 44 per 100.000 person-years, with a sixty-percent proportion of partial seizures [111]. The two populations are similar to ours, both genetically and with respect to culture and living standards. No population-based study of seizures in alcohol abusing individuals exists, but the prevalence of epilepsy in alcohol abusers has been stated to be at least triple that of the general population [119].

PREVALENCE OF ALCOHOL ABUSE

The prevalence of alcohol abuse is not easily determined as, in contrast to epilepsy, there is a continuum from no alcohol consumption to severe abuse, and consumption levels vary in time. A very broad estimate for the incidence of alcohol dependent persons in Norway is from 20.000 to 300.000 persons (Fekjær HO. Personal communication). Better estimates exist for the population drinking levels in a given period of time [45]. The terms "alcoholism" and "alcoholics" are still commonly used in daily life although replaced in DSM-III and IV with "Alcohol dependency syndrome", and "Alcohol abuse". In the ICD-10 disease classification, criteria are given for acute alcohol intoxication, hazardous alcohol

intake and harmful alcohol use, alcohol dependence, alcohol withdrawal with or without delirium, and various alcohol-related psychiatric or organic syndromes. Noteworthy, the ICD-10 threshold for hazardous alcohol consumption is probably higher than normally applied in Norway, as mental or physical health damage is a diagnostic requirement.

THE PREVALENCE OF SEIZURES IN PATIENTS WITH ALCOHOL ABUSE

As the prevalence of alcohol abuse is virtually impossible to determine, it follows that no good estimate exists for the prevalence of seizures in patients with alcohol abuse. Reports range from 0.6% to 15% [126]. Somewhat surprisingly, even broader estimates have been published for the incidence of seizures during detoxification, ranging from 0% to 24% of patients [126].

ALCOHOL ABUSE AMONG EPILEPSY PATIENTS

Patients with known epilepsy are routinely warned against excessive alcohol use, and indeed, in our material, 27% of both acute seizure patients and epilepsy outpatients were abstainers, a much higher proportion than expected from the general population. It is well known that alcohol is a seizure-provoking factor in the general population of epilepsy sufferers, however. In support of that, we found a higher proportion of AUDIT positive subjects among epilepsy patients who were hospitalised for acute seizures (18%), than for epilepsy outpatients (10%). In the large questionnaire-based study by Lennox [2], 26% out of 1254 epilepsy patients above age 15 reported a "moderate" alcohol consumption and 6% reported that their consumption was "in excess". Among those who used alcohol "infrequently", 15% reported that their seizures were sometimes or frequently influenced by alcohol use, whereas this proportion was 57% among "frequent" alcohol users.

Binge drinking, seizures, and strokes

The notion that binge drinking is a common feature of alcohol consumption in our area was confirmed by our finding that approximately 10% of the study population had been binge drinking within the last week. As expected, alcohol consumption peaked on Saturdays and the weekly variation of alcohol intake was greater in subjects with low consumption levels. Among the seizure patients, the proportion of binge drinkers was higher (23%), but we were unable to link binge drinking as such to the weekly variation of seizure admissions. The Monday peak of seizure admissions was due to AUDIT negative patients who had not been binge drinking (Paper II). Unfortunately, these analyses suffered from a rather sparse material.

Brain infarcts due to alcohol abuse or binge drinking have been reported for young stroke patients [127]. Few young stroke patients were included in our material. Out of the 11 stroke patients below age 45, three were AUDIT positive and only

one admitted to drinking alcohol immediately prior to the stroke onset. None of the three were CDT positive, indicating that they were not heavy drinkers. Thus, although this study failed to demonstrate any relation between alcohol use and stroke, or weekday variation of stroke admissions, the result is not valid as a negative finding.

Pathophysiology of alcohol-related seizures

The present thesis was not designed to shed light to pathophysiological mechanisms for alcohol-related seizures. However, a short review seems appropriate.

ETHANOL: A TOXIC SEDATIVE

Ethanol is a sedative and CNS-depressant compound, and as such it has anticonvulsive properties. Both single ethanol doses and chronic ethanol administration have increased seizure thresholds in animal studies. Anti-myoclonic effect of ethanol intake has been demonstrated for subjects with progressive myoclonic epilepsy [128]. Murphree proposed that ethanol might have a biphasic stimulant or depressant effect [129], which is probably not the case. Ethanol's actions on particular neurotransmitter systems are remarkably selective. Ethanol suppresses CNS activity by altering membrane properties and functions, and by enhancing the inhibitory effects of GABA. Benzodiazepines and barbiturates 130 enhance these effects. Ethanol's gabaergic properties probably explain the efficacy of benzodiazepines in treating alcohol withdrawal symptoms.

THE ALCOHOL WITHDRAWAL STATE AND THE KINDLING MECHANISM

In a study on mice, the seizure threshold was raised with alcohol ingestion, and reduced on cessation of drinking, and the reduction of seizure threshold during withdrawal was correlated to number of days on fixed high daily alcohol intake [131]. Similar experiments have been repeated in several species. Very few human studies on intoxication and withdrawal have been performed, and for ethical reasons similar studies as that of Isbell *et al.* [14] should never be carried out. However, these studies provided good evidence for seizures occurring as symptoms of alcohol withdrawal. Alcohol dependence and subsequent withdrawal in humans has been thought to require years of alcohol abuse [7], but in many animal experiments withdrawal symptoms, including seizures, could be established within few days [131, 132]. Hillbom (1980) showed that seizures occurred after short drinking periods, even after weekend binges, but he did not conclude that those seizures were withdrawal seizures. However, these and other reports suggest that the withdrawal state may be induced by considerably shorter drinking periods than proposed by Adams and Victor (1953).

The kindling model of AWS suggests that repeated episodes of alcohol withdrawal may lead to increased severity of the withdrawal state with a greater likelihood of

seizures [133, 134]. Individuals who have had five or more withdrawal episodes seem to have greater risk for AWS. Drug treatment of withdrawal symptoms seems to reduce the susceptibility to kindled seizures. Theoretically, there seems to be some rationale for prevention of withdrawal seizures with carbamazepine, which has known anti-kindling effects. However, benzodiazepines are sufficient to prevent seizures [135].

STRUCTURAL BRAIN ABNORMALITY

Alcohol abusing individuals are more susceptible to a number of disorders that predispose to seizures. The role of ischemic stroke is previously discussed. Alcohol abuse is associated with a high incidence of cerebral trauma, leading to diffuse axonal damage (concussion and contusion), or subdural, epidural, or traumatic subarachnoidal haemorrhages. Higher incidences of infectious diseases (brain abscess, neurosyphilis, AIDS, etc.) have been reported, but probably play a minor role for patients in our region. Noteworthy, all the above mentioned conditions have the potential to cause focal brain damage, and probably are important causes for partial alcohol-related seizures.

Chronic alcohol abuse causes both general and specific brain pathology, such as atrophy of the frontal, cortical, and subcortical structures, hippocampal sclerosis, and atrophy of the vermis cerebelli and the mammillary bodies. The relation of these and other lesions to the occurrence of seizures is obscure, though, and for that reason no further elaboration seems appropriate.

METABOLIC DISTURBANCES RELATED TO ALCOHOL USE

In alcohol-abusing individuals who are investigated for acute seizures, concomitant withdrawal of benzodiazepines, illegal drugs, or legally prescribed medication (analgesics) should be considered. Combined benzodiazepine and alcohol abuse may cause a delayed development of withdrawal symptoms, and the risk for seizures is elevated for a longer time-span [136]. Alcohol inhibits gluconeogenesis and can lead to hypoglycaemia, which is reported to be a common finding in patients with alcohol-related seizures. Devetag reported faulty carbohydrate metabolism with a "peculiar" glucose tolerance test [18]. The role of magnesium in the genesis of seizures is controversial. Magnesium excretion is promoted by alcohol [137]. Although magnesium depletion may cause withdrawal-like symptoms, magnesium therapy has failed to relieve symptoms of alcohol withdrawal.

PATHOPHYSIOLOGY OF ALCOHOL-RELATED STROKE

The pathophysiology of alcohol-related brain infarction is complex and will not be reviewed fully in this thesis. Several mechanisms have been proposed, such as dehydration, changed cerebral blood flow, or impaired platelet function leading to altered haemostasis [138]. Transient atrial fibrillation leading to thrombus formation (Holiday Heart) may result from alcohol abuse [139]. Risk factors for alcohol-related brain infarction include hypertension, history of migraine, use of oral

contraceptives, and smoking [140]. Smoking and hypertension, two very prominent risk factors for stroke, are correlated to alcohol abuse. Hypertension is probably induced by the pressor effect of ethanol abuse, which induces elevated cortisol, catecholamine, and insulin levels [141]. The interested reader should refer to Hillbom [58] and Camargo [142] for reviews. In recent years, a protective effect against cardiovascular diseases has been proposed for moderate alcohol use [143], with an U- or J- shaped relation between consumption levels and risk for ischemic stroke [142]. Recent epidemiological studies suggest that red wine may have an additive effect to that of ethanol, probably due to the antioxidant properties of flavonoids [144]. The level of alcohol consumption that offers optimal cardiovascular protection is high, and has the potential to cause other alcohol-related conditions in some individuals. Devastating medical and social consequences may result from public advise based on results on cardiovascular morbidity only.

Laboratory markers for alcohol-related seizures

ACCURACY

We found that for detection of alcohol-related seizures (Paper 3) the accuracy of %CDT was moderate, with a sensitivity of 41% and a specificity of 84%. Thus, if no clinical information were available, %CDT would rightfully identify only one in three seizure patients with probable alcohol abuses. Even for AWS, the sensitivity barely exceeded 50%. The alcohol consumption level required to produce %CDT above 6.0% is reported to be at least 60g ethanol daily for at least two weeks. Our results may indicate that in order to produce alcohol withdrawal seizures, a daily consumption lower than that may be sufficient. However, as discussed below, there are several factors besides recent alcohol use that may contribute to reduce test sensitivity.

At 80% specificity, direct comparison of %CDT and GT showed superiority of %CDT with sensitivity of 43%, compared to the 26% sensitivity of GT, a significant difference. Previous studies comparing CDT to GT have shown variable results and some have reported equal or even better performance for GT.

GENDER DIFFERENCES

Both CDT tests performed better for men than for women (Papers III and IV), in consistence with previous studies. In Paper IV we found that total transferrin alterations were seen predominantly in women. In addition, we confirmed recent findings of reduced total transferrin levels in post-menopausal women, leading to increased %CDT and reduced CDTect levels for this subgroup. These findings seem to account at least in part for the gender differences.

CDT AS A MARKER FOR ALCOHOL ABUSE IN NEUROLOGICAL PATIENTS

In Paper IV, we performed multiple regression analyses with CDT as the dependent variable in order to identify variables that were correlated to CDT, and thus confounding factors to alcohol use or abuse. Predictors for the variation of CDT was investigated separately for those who reported no ethanol intake during the last eight days in order to minimalise the effect of ethanol intake, and for the whole study population. Multiple regression was preferred to logistic regression in order to assess variations in absolute CDT levels, not only over/under pre-determined cut-off levels. The findings of the resulting regression analyses were interesting, and clinically important. Use of anti-epileptic drugs, low body mass index, or being a female in fertile age, were factors associated with higher CDT levels. The significance of these variables is thoroughly discussed in Paper IV.

Also involved in producing false positive and false negative cases were alterations of total transferrin (TF). As expected, transferrin above reference caused false positive CDTect (Paper IV, Table 6). Transferrin below reference was seen in five cases with false positive %CDT, which is not surprising as the %CDT value is expressed as a percentage of total transferrin. One reason for dividing absolute CDT with the total transferrin concentration as is done in %CDT, was to avoid false positive cases in patients with elevated transferrin. As shown in Paper IV, that objective is obtained, but at the cost of false-positives among those with low transferrin. In a patient group with abnormal serum transferrin concentrations, the CDTect assay gave 18% false positive values whereas the %CDT-TIA showed 100% specificity [145].

COMBINATION OF CDT AND OTHER MARKERS

Many papers have tried to assess the accuracy of various combinations of biomarkers for alcohol use, as no single marker has shown acceptable accuracy [66]. Various formulas and combination methods to combine CDT and GT have been tried, but results are not convincing. As demonstrated in Paper IV, no particular method for combination of CDT and GT seems to provide any advantage to each of the variables. MCV is of little use as alcohol marker due to poor sensitivity, although recent data suggest that combination with MCV improve sensitivity of both GT and CDT [146].

CLINICAL RELEVANCE OF THE INFLUENCE OF AED ON CDT

Patients using enzyme-inducing AEDs had elevated CDT levels. In total abstaining individuals (n=89), %CDT was significantly elevated in both genders, whereas no effect was seen for CDTect. In a larger subgroup including patients who had not been drinking during the last week (n=259), a difference emerged also for CDTect in women, whereas there was no difference for men (Paper IV). Thus, women seemed to be particularly vulnerable to the effects of enzyme-inducing AEDs. False-positive CDT was seen mainly in patients with very little or no recent alcohol consumption. With increasing ethanol use, the effect of AED

seemed to be "overwhelmed" by the influence of ethanol. Several patients were probably hiding their drinking, but in others, AED use was the only explanation for false-positive CDT. Thus, false allegations of alcohol abuse may occur, probably not in those who consume some alcohol weekly, but rather among those who rarely drink at all. That is clinically highly relevant.

COMPARISON OF BIOMARKERS TO CLINICAL EVALUATION

As shown in Paper I, the accuracy of the clinicians' evaluation of a relation of alcohol to a given seizure was better than that of CDT. Clinician's scores yielded a sensitivity of 62% at a specificity of 89% for some suspicion that alcohol might be related to the seizure. A direct comparison is unfair to the biomarker. By the cut-off that was applied to %CDT we "asked" CDT to find patients with "hazardous" drinking levels, whereas clinicians were asked to point at patients in whom alcohol use was in any way a factor related to the seizure. We then related the scores of the clinicians, and CDT, respectively to whether the patient was AUDIT positive or not, which is a questionnaire-based score, and as such based on clinical data. Naturally, the clinicians also had a much broader basis for their decisions, than the single biochemical factor measured by CDT. Thus it is not very surprising that the clinicians performed better than CDT.

However, it should be added that for this study, the clinicians were specifically asked to evaluate the role of alcohol for each case. Only in a minor proportion of these cases, the role of alcohol use was discussed in patient records. Previous studies have shown that many cases of alcohol-related seizures are missed by clinicians while in hospital. In an unknown proportion of cases the reason is that the patient does not want to focus on his or her alcohol use. It may be suspected though, that many patients are missed simply because the doctor does not ask about alcohol use, or asks single routine questions only. Reviews on hospital records on this matter show that alcohol use information is lacking in many cases, and in most cases, there is only a note stating "little" or "moderate" alcohol use, which is rather useless information. Routine use of structured questions would probably lead to improved data. The CAGE questionnaire is simple, but somewhat insensitive to hazardous drinking levels. The AUDIT questionnaire, although consisting of 10 questions, is easily administrated in 2-3 minutes, and provides valid data for all drinking levels.

Although the alcohol consumption in general is rather low in Norway, it seems that alcohol abuse among seizure patients is equally frequent in our sample (i.e. 35%) as in the population studied by Tardy et al (alcoholism in 20%, alcohol as cofactor in 17%) [88]. This may suggest that a specific focus on the alcohol history can increase the fraction of identified subjects.

The utility of EEG as diagnostic aid

In Paper V, standard EEG was investigated as a possible marker for alcohol-related seizures. We found that if a patient admitted for acute seizures had an

abnormal EEG, there was an 83-90% probability that the seizure was not related to alcohol use, dependent of the criteria applied for "abnormal EEG". Conversely, the predictive value of a normal EEG for the diagnosis of an alcohol-related seizure was not that impressive (38-52% probability of ARS). Thus, a definitely abnormal EEG suggests epilepsy or symptomatic seizures unrelated to alcohol, whereas a normal EEG is not a particularly useful predictor for ARS.

Some clinical features of the seizure may be utilised to discriminate between alcohol-related and other seizures. Seizure duration was markedly longer in patients with epileptic seizures, and although we suspected this variable to explain some of the EEG slowing, this notion was not confirmed by our correlation analysis. It is possible that the information about actual seizure duration is prone to errors, however, because relatives and others who witness the seizure seldom measure the elapsed time accurately. The seizure duration difference between groups may be a referral bias. Patients with known epilepsy tend to be admitted to hospital only when their seizures are more severe or longer lasting than usual.

Early reports of a high incidence of photomyoclonal (PMR) and photoparoxysmal (PPR) response in alcoholics [13] have been disputed [86, 147]. The present results confirm the notion that photomyoclonic and photoparoxysmal responses are not common features of the early phase after an alcohol-related seizure early in the withdrawal phase.

Both definite EEG slowing and epileptiform EEG activity suggests that the seizure is not purely alcohol-related. EEG-photosensitivity can not be used as a clinical marker of alcohol related seizures. Different stimulus-light intensities and serial recordings during the first few days should be used in future photic stimulation studies before a conclusion can be reached regarding photosensitivity in the withdrawal phase.

Limitations of the study

The healthy controls that were collected for this study were not optimal representatives of the population of our region. 82 of the healthy controls were employees at the local newspaper. It is a general notion that journalists may have higher ethanol consumption than the general population, but there were few journalists among the controls. As it turned out, the newspaper control subjects included more men than the study groups did, and the proportion of abstainers was smaller then presumed in the population. This led to the inclusion of an additional control group of 172 subjects who were invited to a follow-up interview for a large regional health survey, the Nord-Trøndelag Health Survey (HUNT). For the present study, they contributed only by reporting their actual alcohol intake during the last eight days. The resulting control group of 254 individuals had a proportion of abstainers, consumption levels, and gender and age distributions that were similar to the findings for the sciatica group (inpatient controls).

When trying to calculate the actual alcohol consumption of a study population, over-estimation of alcohol intake is rarely considered an option, as it is easy to assume that all misreporting is underreporting. That is also the case for this study. We have, for instance, not considered false-positive AUDIT scores a realistic option, and false-negative CDT results have not been very well explored. Deliberate over-reporting of alcohol intakes aside, questionnaire-based intake estimates may be biased by the way questions are perceived by certain study groups [148]. Thus, validation of such instruments is important. As Norway participated in the original development of AUDIT, we consider that questionnaire to be well validated for a Norwegian study group [149].

EEG was not recorded in all the study patients. For some groups there were few patients. In particular, the group of patients with known epilepsy and alcohol abuse consisted of only 5 individuals. This combination is a particular challenge as AED use is indicated, but often complicated by extremely poor compliance and alcohol-drug interaction problems.

WHAT DID WE LEARN?

The definition of ARS

"Alcohol-related seizures" should be used as a broad term describing seizures that occur in concordance with alcohol intake levels or patterns that may be harmful. In many cases, alcohol use is an etiological factor, but probably more frequently it is a seizure-triggering factor in patients with seizures of other aetiologies. Several seizure types may be related to alcohol use. The clinical significance of these observations is that alcohol use should be regarded as a possible contributing factor in the clinical work-up of all patients with seizures.

Diagnosing alcohol-related seizures in individual patients

In order to be able to diagnose alcohol-related seizures, the single most important step in the clinical investigation, is to obtain a thorough alcohol history. As easy as it seems, doctors seem to fail to a great extent in recognising the symptoms and signs of alcohol abuse during a normal consultation [150]. Patients must be asked frankly about alcohol use. The AUDIT questions constitute a simple and sensitive aid to this work-up, and routine use of AUDIT should be considered. AUDIT and CDT are complementary instruments for alcohol screening [151], with the potential to identify different segments of patients at risk of developing alcohol-related neurological disorders.

A partial onset seizure does not rule out the possibility of an alcohol-related seizure. Many clinicians suffer the general misunderstanding that alcohol-related

seizures exclusively are primarily GTCs. Although this is generally the case for the alcohol withdrawal seizure, many other alcohol-related seizures are partial in onset (post-traumatic seizures, epilepsy complicated by alcohol abuse, etc.) In our material 51% of the alcohol-related seizures had partial onset, all of which were secondarily generalised.

Biological markers

Whenever hazardous alcohol consumption is suspected in a seizure patient, biological alcohol markers may be used to support the clinical diagnosis. GT is a sensitive, but not specific marker. CDT is the best available marker today. Its accuracy is rather good but some factors should be acknowledged by the clinician in order to ensure sufficient accuracy for seizure patients of both genders, with unknown alcohol consumption. The most important factors that seem to be associated with reduced CDT accuracy, are use of enzyme-inducing antiepileptic drugs, alterations of total transferrin, and low body mass index. Poor accuracy should be expected particularly for females of fertile age.

EEG

We found that the negative predictive value of a normal EEG was good (77 - 83%) for the detection of an alcohol-related seizure in a patient with no known epilepsy. The positive predictive value of a normal EEG for ARS was much lower, ranging from 42 to 55 percent depending on the definition of abnormality. Thus, the normal (low-amplitude) post-ictal EEG, although being suggestive of an alcohol-related seizure, provides limited support to the clinical work-up. It is important to realise that these figures apply to an unselected population of seizure inpatients. EEG of patients with co-existing epilepsy and alcohol abuse could not be analysed statistically due to small numbers (n=5). However, if these five patients were excluded the estimated predictive value did not change much.

AIMS FOR FUTURE STUDIES

Alcohol and epilepsy

Despite being the focus of several investigations during the last decades, the relationship between alcohol use, epilepsy, and seizures is still not sufficiently elucidated. More detailed population-based epidemiological studies are needed [119]. One angle of attack is to estimate the occurrence of alcohol-related seizures in a large subgroup with pre-existing epilepsy. This could be done by prospectively following a large cohort of epilepsy outpatients, taking into account their drinking patterns. Such a study would need to be performed in more than one centre in order to obtain a sufficient sample size.

In terms of classification, some of the clinical entities described in the introduction may be fruitful tools for further investigation. As stated previously, this research field has long suffered from lack of consensus. International consensus work towards definitions for at least some of the entities seems appropriate. Members of the Alcohol and Epilepsy panels of the European Federation of Neurological Societies (EFNS) have recently started a Task Force with the aim to produce guidelines for the investigation and treatment of alcohol abuse in epilepsy, and epileptic seizures in alcohol abusing individuals. I will participate to that work.

An epidemiological epilepsy study based on data from The Nord-Trøndelag Health Survey (HUNT) is under planning. As part of HUNT, the CAGE questionnaire was presented to all inhabitants of Nord-Trøndelag aged 20-69 years. A comparison of self-reported epilepsy with the CAGE scores would provide interesting epidemiological data.

There is a strong concern that poor medication compliance and potential pharmacological interactions between AEDs, alcohol, and other legal or illegal drugs may complicate the seizure situation, and that patients might be better off without AEDs, as suggested by, among others, Hillbom and Hjelm-Jaeger [40]. From the present project we were hoping to have material for a study on medication compliance. However, data was not of a sufficient quality, or quantity, for that purpose. A designed study in order to shed light to this issue is among our plans.

Biological markers

The finding that enzyme-inducing antiepileptic drugs seem to have the potential to elevate CDT, in some cases to false-positive levels (Papers III and IV) has clinical implications to the use of CDT for neurological patients. As stated in Paper III, confirmation of the findings in a designed study on a different population is needed. In co-operation with pharmacologists at the University of Umeå, we are currently investigating the effects of short-term enzyme induction with carbamazepine, on CDT among other biochemical variables.

The bias caused by enzyme-inducing properties of particular drugs is probably not restricted to epilepsy patients. Patients who use any sort of therapy that induces enzymes belonging to the microsomal cytochrome P-450 group, may be at risk of being positive if tested for CDT. The probably strongest enzyme inducing drug in common use is rifampicin (Rimactan®). Use of this particular drug is strictly controlled and restricted to treatment for tuberculosis. In Middle Norway few patients suffer from tuberculosis, but the prevalence of this disease is rapidly increasing worldwide. To this patient group, knowledge of a high probability of false-positive test for alcohol abuse is of clinical importance. As result of these considerations, in collaboration with the outpatient clinic for lung diseases, we are currently running a controlled study with the aim to assess the influence of rifampicin on CDT levels.

Further exploration of the influence of AED on CDT is possible, as HPLC has been performed for a large proportion of the material and is stored at the

laboratories of Axis Biochemicals ASA in Oslo. For selected subgroups on monotherapy with particular AEDs, investigation of the CDT isoforms might not only show why the test is elevated and provide data that might be useful to develop an improved test, but also give some clues as to the biochemical pathways involved.

The findings in Paper IV, suggesting that enzyme-inducing AEDs may cause false-positive CDT in as much as 20% of non-drinking women needs confirmation. We want to perform a case-control study on female outpatients on monotherapy with enzyme-inducing AEDs and age- and consumption- matched controls.

Further investigation of EEG

Quantitative EEG data is available for the material presented in Paper V. Preliminary results suggest that some parameters differ between particular seizure groups. The clinical utility of QEEG is uncertain due to the complexity of data analysis and interpretation. However, these analyses might provide new data on the detailed features of post-ictal EEG in patients with and without alcohol abuse.

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