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Epilepsy and alcohol

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ABSTRACT – While the links between alcoholism and epilepsy are well demonstrated, the classification of alcohol related seizures is still controversial. The best recognized seizures are the "alcohol withdrawal seizures" (AWS). However, experimental and clinical data strongly suggest that withdrawal is not the only mechanism by which the chronic absorption of alcohol may act. Specific epileptogenesis may underlie seizures unrelated to withdrawal (SUW). Epileptogenesis in this context involves several mechanisms including alterations of excitation/inhibition systems and a kindling-like effect. A classification scheme was proposed in which patients presenting with seizures unrelated to any cause other than alcohol are classified in several successive stages of "alcoholic epilepsy", the first being characterized by AWS, the second by SUW and the last by persistent chronic seizures.

Keywords: alcohol, epilepsy, generalized seizures, partial seizures, alcohol withdrawal seizures (AWS)

Alcohol abuse and its consequences have been known since ancient times; Egyptian texts over 8000 years old make reference to them. Later, Hippocrates described seizures related to alcohol abuse, and the Romans used the term *morbius convivialis* to describe alcohol related seizures (Hauser 1990).

Subsequently, the relation between the two pathologies became the object of various interpretations (for example, genetic links between criminality, epilepsy and alcoholism have been proposed) (Hauser 1990).

Although these ideas are now outdated, the fact remains that the relationship between the two pathologies is complex. The existence of chronic epilepsy related to alcohol is generally accepted in France and in some European countries, but has been given little or no recognition by the international community (Gordon and Devinsky 2001). This is perhaps due to the manner of alcohol intake and, therefore, to the clinical presentation of alcohol related seizures. In addition, experimental data are often difficult to interpret, and human studies are ethically difficult to conduct.

This contribution discusses the notion of "alcoholic epilepsy" (AE), a very old term in neurological culture, going back to the 19th century (Giove and Gastaut 1965). Alcoholic epilepsy can be defined as repeated seizures in alcoholics having no previous history of epilepsy, or other potentially epileptogenic diseases; the epilepsy being unrelated to acute alcohol intake or to withdrawal (Devetag *et al*. 1983). We will come back to the notion of withdrawal because we consider important to not completely dissociate withdrawal-related seizures from seizures unrelated to withdrawal (Bartolomei *et al*. 1997).

From this perspective, alcoholic epilepsy is considered as a separate entity, with a specific pathogenesis different from the pure pharmacological effect observed in cases of "alcohol withdrawal" seizures. In the latter case, the brain is considered as a victim of the pharmacological effect of withdrawal. Withdrawal related seizures are already mentioned in the

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classification of epileptic syndromes, in which alcohol related epilepsy is listed under the subgroup of seizures caused by pharmacological or toxic agents (Commission on Epilepsy 1989).

Epidemiology

At present, we can refer to two controlled studies that demonstrate the relationship between alcohol consumption and epileptic seizures (Ng *et al*. 1988, Leone *et al*. 1997). We will examine them briefly after a review of certain more general epidemiologic concepts.
Several studies conducted in emergency or neurological departments have shown that with 40 to 50% of seizures observed in adult patients were alcohol related, a finding that would make alcohol as one of the major risk factors for seizures in adults (Hillbom 1980, Lennox 1941).
Overall, it has been estimated that epileptic seizures are 3 times more frequent in chronic ethylics (Hauser *et al*., 1988, Chan 1985). Incidence of epilepsy in chronic alcoholics is more difficult to establish.
It is estimated that 4 to 7% of chronic alcoholics have seizures (Giove and Gastaut 1965). Moreover, a longitudinal study involving individuals who had a first seizure presumed to be an alcohol withdrawal seizure suggests that one third will have another seizure within three years (Hauser 1990).
All the studies found a pronounced male predominance (80%) and a time lapse of several years (a dozen) between the onset of seizures and the start of alcoholism. Formal demonstration of a direct and proportional relation to the quantity of alcohol consumed was provided by two controlled studies, one of them American (Ng *et al*. 1988) and the other Italian (Leone *et al*. 1997).
In the Harlem Hospital study conducted in New York (Ng *et al*. 1988), and compared to the control group, patients admitted for a generalized tonic-clonic seizure were classified more often as drinkers with a statistically higher rate of alcohol consumption.
Risk of seizures appears in both men and women when daily alcohol consumption exceeds 50g/day (about two glasses of strong alcohol or a half liter of wine).
The multicenter Italian study (Leone *et al*. 1997) examined the relation between alcohol consumption and the occurrence of a partial or generalized seizure, in subjects over 15 years old, as based on questionnaires and behavior scales.
For "idiopathic" seizures (with no identified cause), the relation between alcohol consumption and seizures is very clear. Compared to the control group, subjects with seizures had a higher daily alcohol consumption (59.4 g *versus* 34.5 g) and there was a clear correlation between alcohol consumption and risk of seizures when consumption exceeded 50 g/day for men and 25 g/day for women, pointing to greater susceptibility in the latter.
In all cases, risk is very clearly quantity dependant.

Clinical features

Although their existence has been known for a long time, alcohol related seizures are still poorly understood (Mattson 1990).

Context of occurrence and differential diagnosis of alcoholic epilepsy

There are several possible contexts in which seizures can occur in chronic alcoholics. Several seizure risk factors can coexist in the same patient. Therefore, before discussing alcohol related seizures and alcoholic epilepsy, it is important to eliminate the other causes of seizures in alcoholics.
It is obvious that the same seizure etiologies apply to alcoholics as to the general population, but their life style probably increases the risk of cerebral or metabolic complications that can lead to seizures (Mattson 1990). Complications can be :
– metabolic (hypoglycemia, hyponatremia, hepatic encephalopathy),
– related to other toxic substances (cocaine),
– tumors, cerebrovascular accidents,
– infections (meningoencephalitis),
– cranial trauma (hemorrhage).
These "symptomatic" seizures represent 10 to 12% of seizures (Bartolomei *et al*. 1997, Hillbom 1980, Earnest and Yarnell 1976), and even up to 35% in a recent series (Leone *et al*. 1997). Therefore, basic investigations are required in the case of an alcoholic patient with seizure.
Finally, certain non-epileptic phenomena (fainting, psychogenic seizures) are also possible and have to be eliminated.

Withdrawal seizures

Initially identified by Lennox (Lennox 1941), withdrawal seizures were the focus of studies conducted by Victor and his colleagues (Victor and Brausch 1967, Victor 1990, Victor 1968). Their original description remains valid, although the notion of withdrawal is questionable in some cases (see *infra*).
The authors examined a large series (241 cases) and showed that most patients (89%) presented seizures occurring after a long period of drinking, and during the period when blood alcohol levels were minimal. The majority of seizures occurred from 7 to 48 hours after stopping alcohol intake. Alcohol related seizures developed after several years of alcohol consumption, and were described essentially as generalized tonic-clonic seizures, isolated or, as is frequent in this context, in bursts (55%). Partial seizures, essentially motor seizures, were observed in 5% of cases. In 31% of cases, the subjects presented delirium tremens symptoms following seizures.

EEG was normal in 84% of cases, and in half of the other cases (42% of subjects had EEG exams in the symptomatic phase of withdrawal) showed photoconvulsive or photomyoclonic response.

These two characteristics have remained classic features (Bartolomei *et al*. 1997). Thus, in a study involving 117 patients with "alcohol withdrawal seizures" (Hauser 1982), 97% of the EEGs were normal or only showed non specific abnormalities, showing photoparoxysmal response was observe in one case only.

Photosensitivity is rare, or altogether absent, in most recent studies, probably due to earlier and more widespread use of benzodiazepines (Vossler and Browne 1990). In a recent study, Krauss and Niedermeyer (1991) pointed out another classic feature in alcoholics : an EEG tracing with depressed background activity (< 25 µV). They observed this tracing in 50% of cases (as opposed to 10% in a general population control group), but this feature is not related to occurrence of seizures. In this study, the authors did not find an increased incidence of photoparoxysmal response.

Other authors (Hillbom 1980) have described a particular pattern of withdrawal seizures in week-end drinkers, a common type of alcoholism in Anglo-Saxon countries. The seizures occur mostly the first or second day of the week.

Seizures not related to withdrawal and having no other cause than chronic alcoholism

These isolated seizures, with no apparent relation to actual withdrawal, are the phenomena that gave rise to the notion of alcoholic epilepsy, an old entity, long time recognized in Southern Europe (Giove and Gastaut 1965), but which was completely ignored in subsequent publications, particularly American, which prefer to stress on the effects of withdrawal. According to Devetag (Devetag *et al*. 1983), "alcoholic epilepsy" represents 37% of cases of seizure in alcoholics. The underlying mechanisms are unknown.

The long interval between the start of alcoholism and the onset of seizures in alcoholics (10 years on average) (Devetag *et al*. 1983), argues in favor of the gradual creation of an "epileptogenic" environment. Some authors attempted to correlate this epilepsy with cerebral atrophy observed in 75% of alcoholic patients with epilepsy (Dam *et al*. 1985). However, there is no difference in the ratio of cerebral atrophy in alcoholic patients with or without seizures (Lechtenberg and Worner 1990, Meyer-Wahl and Braun 1982). Other authors have discussed the role of cranial traumatism in increased frequency of seizures. In addition, alcoholics who have stopped drinking can subsequently present seizures. This phenomenon, whose frequency is not known, is compatible with alcohol induced epileptogenesis (Mattson 1990).

Despite the fact that the role of withdrawal in alcoholic seizures seems confirmed at both the experimental and clinical levels, this role has been widely questioned in more recent studies (Ng *et al*. 1988). Thus, the ratio of seizures considered withdrawal seizures has decreased in publications (*figure 1*), and in certain series these seizures no longer represent the majority of chronic alcoholic seizures (*figure 2*).

The withdrawal theory has been largely criticized. In fact all drinkers have "natural" withdrawal periods, lasting 8 to 10 hours a day every day (specifically, when they are sleeping), and most of them do not develop seizures during these periods (Ng *et al*. 1988).

Moreover, the study conducted by Ng *et al.* (1988) shows that onset of seizures in relation to last intake of alcohol is random and is not governed by a probability reflecting a withdrawal effect. Finally, in this series, only 30% of patients had reduced their alcohol consumption before developing a seizure.

Symptomatology of these seizures is, in most cases, generalized tonic-clonic, tending to occur, like withdrawal seizures, in cluster (Bartolomei *et al*. 1997, Chan 1985,

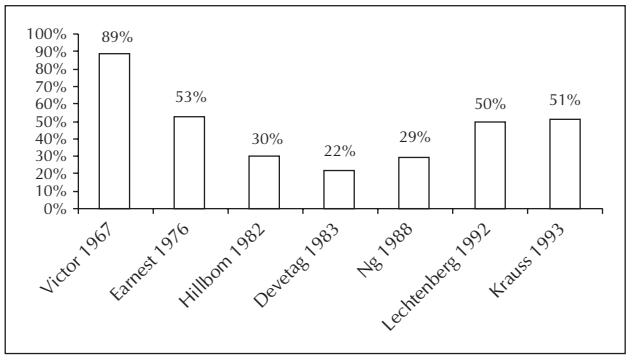

Figure 1. Published series with withdrawal related seizures. The ratio of seizures attributed to withdrawal, very high in the series studied by Victor and Brausch (1967), has decreased in more recent series.

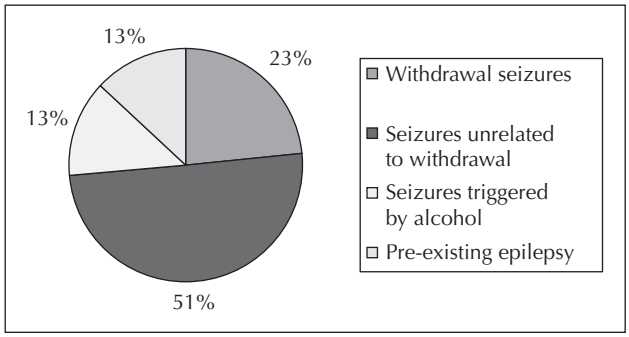

Figure 2. Types of seizures observed in alcoholic patients (44 patients) [5].

Mattson 1990) (*tables 1* and 2). Partial seizures are perhaps underestimated, but have been given more appropriate recognition in more recent series. They represented 16% of seizures in a recent series (Bartolomei *et al*. 1997), essentially in the form of simple partial motor seizures.

Status epilepticus (non convulsive or convulsive) is regularly reported in the series studied. It represents 1 to 10% of seizures in chronic alcoholics.

Alcoholism is an important etiology for status epilepticus (14% (Aminoff and Simon 1980); 10% (Alldredge and Lowenstein 1993)). Prognosis is good in most cases (Alldredge and Lowenstein 1993). Alcohol could contribute to the development of partial complex status epilepticus (Fujiwara *et al*. 1991, Bartolomei *et al*. 1993). A particular picture, combining generalized seizures, action myoclonus and cerebellar signs, is observed particularly during withdrawal. This picture can resemble progressive myoclonic epilepsy, but is reversible after abstinence (Bartolomei *et al*. 1996).

Pathophysiological features in favor of alcohol induced epileptogenesis

As we have pointed out above, certain clinical and epidemiologic observations argue in favor of alcohol induced epileptogenesis. The latter could be facilitated by certain pathophysiological mechanisms summarized below.

Electrophysiological and neurobiological effects of alcohol

It is essential to point out that alcohol has radically different effects when administered in acute single doses as opposed to being administered chronically.

Acute effects

Acute administration of alcohol raises the convulsive threshold (antiepileptic effect) (McQuarrie and Fingl 1954). The withdrawal effect is well known since these early experiments: the convulsive threshold is lowered

Table 1. Clinical data (types of seizures) and EEG data in a series of patients with seizures related to chronic alcoholism (adapted from [5]).

Group	1 : Seizures related to withdrawal	2 : Seizures of random origin	p
Number of patients	14	30	Ns
Sex ratio (F/M)	0,14	0,03	Ns
Age at admission	33 ± 9	45 (± 10)	< 0.005
Type of seizure			
Generalized tonic-clonic (GTC)	12 (85%)	25 (83%)	Ns
GTC in bursts	1 (7%)	11 (36%)	Ns
Complex partial seizures	0 (0%)	0 (0%)	Ns
Simple partial seizures	1 (7%)	5 (16%)	Ns
Status epilepticus	1 (7%)	2 (6%) (focalmotor)	Ns
Normal	12 (86%)	22 (73%)	Ns
Photosensitivity	1 (7%)	2 (6%)	Ns
Focal abnormalities	0 (0%)	3 (10%)	Ns
Generalized abnormalities	1 (7%)	3 (10%)	Ns

Ns = not significant.

Table 2. Clinical data (continued) in a series of patients with seizures related to chronic alcoholism (adapted from [5]).

Group	1: Seizures related to withdrawal	2: Seizures of random origin	p
Number of patients	14	30	
Number of seizures in patient history	2,1	4,8	< 0,05
Associated neurological signs	3 (21%)	19 (63%)	< 0,05
Duration of intoxication:			
< 10 years	10 (71%)	6 (20%)	< 0,05
> 10 years	4 (28%)	24 (80%)	
Brain CTscan:			
Normal	12 (86%)	11 (36%)	
Cerebral atrophy	2 (14%)	17 (56%)	< 0,02
Focal hypodensity	0 (0%)	2 (6%)	

when alcohol administration is stopped. Alcohol delays the occurrence of the kindling effect. In kindled animals, seizures are eliminated by acute administration of alcohol, and are precipitated by withdrawal (Mucha and Pinel 1979). This antiepileptic effect actually depends on dosage. Low doses could produce a different effect, an effect that is pro-epileptogenic (Cohen *et al*. 1993).
Alcohol has very numerous neurobiological effects. We will only discuss certain data regarding alcohol modulation of the physiology of GABA and glutamatergic systems.
Alcohol is a direct agonist of the GABA-A receptor; it stimulates the Cl^- inflowing currents of the receptor and has no effect on the GABA-B receptor (Brailowsky and Garcia 1999, Crews *et al*. 1996, Davis and Wu 2001, De Witt et al. 2003).
In the excitatory systems, alcohol exerts no effect on non-NMDA receptors, but inhibits induced currents, induced calcium influx and toxicity induced by NMDA and its agonists (reviewed in Lovinger *et al.* 1989, Dodd *et al*. 2000).

Chronic effects

Chronic, prolonged administration of alcohol in rodents has very different effects. It is not always easy to distinguish effects related to withdrawal after alcohol administration, from the effects of the alcohol itself. But in any case, the induced modifications tend to increase brain excitability.
In these conditions, reduction takes place through a phenomenon of "under-regulation" of the expression of GABA-A receptors and a reduction of the sensitivity of GABA receptors to agonists (Frye and Fincher 1988, Lui and Deitrich 1998), as well as a reduction of the mRNA of certain receptor subunits (Montpied *et al*. 1991). These modulations correspond, *in vivo*, to the loss of certain inhibitory phenomena, particularly to an amplitude reduction of synaptic inhibitory potentials in the hippocampus (Durand and Carlen 1984).
Chronic administration is associated with an increase in glutamate levels in the cerebral cortex and the limbic system, and an increase in NMDA receptors and their mRNA (Hu and Ticku 1995, Hoffmann et al. 1990, Hoffmann and Tabakoff 1994, Tsai *et al*. 1995, Tsai and Coyle 1998). Here too, there is a functional correlation, with an increase in NMDA responses after chronic alcohol administration (Hu and Ticku 1995, Hoffmann *et al.* 1990, Hoffmann and Tabakoff 1994, Tsai *et al*. 1995, Tsai and Coyle 1998).
In short, acute and chronic effects are opposite. After chronic administration, neurobiological modulations facilitate hyperexcitability, which would be exacerbated in case of withdrawal (*figure 3*).

The kindling hypothesis and alcoholic epilepsy

Ballenger and Post (1978) have advanced the hypothesis that repeated withdrawal (including natural withdrawal such as sleep) in alcoholics can have a "kindling" effect, leading to the gradual lowering of the epileptogenic threshold.
Experimental data seem to confirm this theory. In animals, repeated episodes of withdrawal are associated with the occurrence of spontaneous seizures (Clemmesen *et al*. 1988), with increase in the number of spikes and spike waves in rat hippocampus. These findings are correlated with duration, quantity and number of withdrawal episodes (Veatch and Gonzalez 1996), with appearance of memory disturbances (Poldrugo and Snead 1984) and with prolonged lowering of the convulsive threshold (Kokka *et al*. 1993).
In humans, the evidence is indirect. In a retrospective study (Brown *et al*. 1988), the authors showed that the previous existence of over five hospitalizations for detoxification (that is, abrupt withdrawal) was a risk factor for seizures. A prospective study established a correlation between seizures and the number of previous hospitalizations (Lechtenberg and Worner 1990, 1991, 1992a, 1992b).

Alcoholic epilepsy: a multiple-stage disease?

We are advancing the hypothesis that random seizures and seizures related to withdrawal reflect the same underlying mechanisms, but at different stages of evolution of the same epileptogenic process.
These conclusions are based on a comparative study involving patients with both types of seizures (Bartolomei *et al*. 1997). We separated alcoholic patients with withdrawal related seizures (Group 1), defined by abrupt alcohol withdrawal (24 hours/ 7 days), from random seizures (Group 2).
Tables 1 and *2* summarize the results of this study.

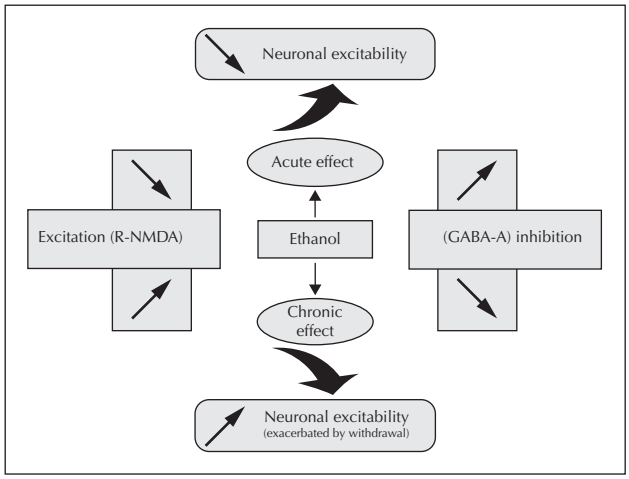

Figure 3. Pathophysiology of neurobiological effects of alcohol. Acute administration has a global inhibitory effect, while chronic administration increases cerebral excitability.

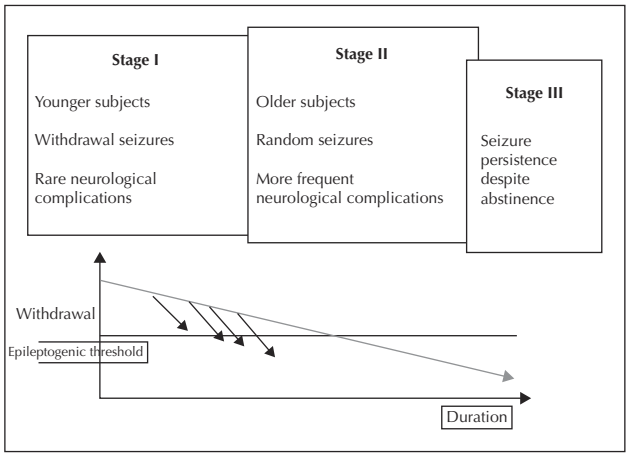

Figure 4. Classification of alcoholic epilepsy in three stages of evolution (see discussion above).

It was demonstrated that patients with seizures not related to withdrawal (random) were significantly older, had had more seizures in the past, and had a longer history of alcoholism. Neurological complications of alcoholism were also more frequent, as was cerebral atrophy.

We also suggest classifying alcoholic epilepsy into three stages of evolution (*figure 4*).

The first stage involves young subjects who only had seizures after actual withdrawal. Complications of chronic alcoholism are not yet present, and the epileptogenic threshold is still high enough to prevent spontaneous seizures in these subjects. The second stage involves more advanced disease (older patients), with a sufficiently lowered epileptogenic threshold for spontaneous seizures unrelated to withdrawal to appear. Of course, withdrawal seizures are possible at every stage. The first stage is reversible, as is the second in all likelihood, at least partly. However, there can be a third stage in which the patient could continue to have seizures despite stopping alcohol intake.

This classification can serve as a basis for a therapeutic approach where, in our opinion, stage I does not require long-term antiepileptic treatment, while stages II and III, in which epileptogenic threshold is lowered, require this type of treatment.

Conclusion

In our opinion, alcoholic epilepsy is an epileptic syndrome whose particularity resides in the fact that it is potentially reversible. Despite its frequency (the major cause of seizures in adults), it is still poorly understood and its pathophysiology requires further examination. □

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