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Alcohol Abuse and Seizures: an Overview of Clinical Notions and Pathogenetic Theories

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Abstract Alcohol abuse is a major causative factor of different neurological disorders, among which seizures and epilepsy have an important burden of disease. Through discussing different pathogenetic mechanisms, scholars have tried to define and describe the diversity of clinical pictures and occurrences that might elicit a convulsive disorder in the alcoholics. An overview of the history of the diagnostic and classificatory attempts is made in the present paper, and distinctions between acute intoxication and withdrawal syndromes are summarized. The influences of ethanol on the cellular level and on the synaptic processes are succinctly mentioned. The authors are focused predominantly in three particularities of the alcohol-related seizures, namely the so-called alcoholic epilepsy, withdrawal seizures, and subacute encephalopathy with seizures in chronic alcoholism (SESA syndrome). Several sources are quoted, and the paper contains a brief overview on the efficacy of benzodiazepines and other antiepileptic drugs in the treatment of this variety of clinical events.

Keywords: *ethanol, seizures, epilepsy, withdrawal syndrome, chronic alcoholism*

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1. Introduction

Effects of alcohol abuse over the nervous system are numerous, and the variety of clinical pictures makes their taxonomy a challenging task. However, if we focus over the influences that ethanol has directly over the neuron, and the nervous cells in general, than a simplifying discussion over its role on the cellular and molecular basis might be helpful.

The correlations between alcohol consumption and abuse, and central or peripheral nervous system pathologies have since long formulated [1]. The direct effects of ethanol on the cellular matrix, namely the fluidification of neuronal membrane has been initially considered as the pathogenetic mechanism leading to neural dysfunction [2]. Last decennia the focus has been moved on the ethanol enhancement of synaptic GABA (gamma-amino-butyric-acid) inhibition; chlorine ions permeability increasing as well as the higher number of membrane calcium channels; with recently more attention given to NMDA (N-methyl-D-aspartate) glutamate receptors [3].

Ethanol has been definitely classified as a central nervous system depressant, and the virtual stimulating condition someone proves during the initial signs of intoxication is due to loss of the inhibitory role that some subcortical structures exercise over the cortical areas. The inhibition of the controlling function of these areas during the first stages of a binge, for example, will explain the asocial behaviors, the aggressive conduct, and the altered excitability of the brain cortex [4]. All these metabolic and neurotransmission changes are complementary, and not necessarily contradictory, when we discuss acute intoxication, chronic intoxication, or withdrawal syndrome.

This is valid as well for the frequent clinical combination of seizures with alcohol consumption, and abuse. As a major public health issue, authors generally have found a link between withdrawal syndrome and seizures. The term of 'alcoholic epilepsy' was proposed in 1881 from Echevarria, and re-discovered in 1967 from Victor and Brausch [5,6]. Serious attempts to classify the type of convulsive activity inside a chronic ethanol intoxication background were made from Devetag in 1983 [7].

Devetag et al. suggested the division of convulsive activity or seizure types among alcoholics in four types: *(a)* solitary convulsive seizures; *(b)* convulsive seizures in the setting of withdrawal syndrome or due to massive intake of ethanol; *(c)* seizures related to the presence of other potentially epileptogenic diseases and *(d)* alcoholic epilepsy, a disorder per se. The definition of the latter, however, has ever since been object to classificatory controversies.

2. Clinical Particularities

Medical staffs and public health institutions have been generally more orientated to treat and prevent liver damages caused from alcohol (cirrhosis); when nervous system is mentioned, the first item to call attention has been peripheral neuropathy. However, alcohol abuse might cause severe central nervous conditions, and its role in provoking seizures, and eventually a form of epilepsy, is uncontestable. Below we'll try to summarize the main forms of alcohol-related conditions on central nervous system, and Table 1 consists of a short synopsis of situations, and eventual pathogenetic mechanisms, that lead to nervous clinical events following alcohol abuse.

Table 1. Clinical Situations of Correlation between Alcohol Abuse, Seizures and Epilepsy [Modified from 8-12]

MAJOR CLINICAL PICTURE AND SUBTLETIES	POSSIBLE PATHOGENETIC MECHANISM
Epileptic crisis elicited or aggravated from alcohol abuse	
Post-traumatic pathology (frequent falls, head trauma following binges)	Micro/macro intracranial post-traumatic hemorrhages
Cerebral vascular accident	Alcohol as a major risk factor for cerebro and cardio-vascular events
Hypoglycemia	Nutritional carencial status
Infectious pathology	High frequency of meningitis in alcoholics [9]
Dilution hyponatremia	Massive beer consumption
Concomitant drug abuse	Benzodiazepines, barbiturates (polytoxicomania)
Alcoholism as a direct causative factor of epileptic disorder	
Convulsions following binges	High levels of ethanolemia; *morbus convivialis* [10]
Withdrawal syndrome	Ethanol long-term effects over GABA transmission and NMDA receptors
Alcoholic epilepsy	Experimental kindling of Carrington [11]
Alcohol abuse in an otherwise known as epileptic patient	
A clinical rarity, since the majority of epileptics remain sober	Sleep deprivation, enhanced photic sensitivity and accelerated metabolism of antiepileptic drugs due to drinking alcohol [12]

2.1. Alcoholic Epilepsy: Still A Valid Term

The issue if alcohol itself is able to produce an epileptic disorder is still a matter of controversy. Of course, there are plenty of clinical occurrences relating alcohol abuse with seizures, but there are as well many authors that believe ethanol is simply a provoking factor, in an otherwise convulsions-predisposed brain. The *morbus convivialis* of Roman age was a depiction of such a disorder, following the consumption of large quantities of alcoholic beverages, wine above all [10].

Another classificatory and definition issue is if *alcoholic epilepsy* should be considered the sequence of seizures during alcohol intake, or if the term should be spared only for patients suffering withdrawal syndrome, and convulsions [6,7]. Sources have reported seizures directly *caused* by alcohol ingestion, but those in fact were mainly case reports, rather than large prospective studies [13]. Of a contrary opinion are authors that suggest refraining from using the term *alcoholic epilepsy* if alcohol is still being consumed at the time of the appearance of convulsions [14]. Due to such misunderstandings, some authorities suggest to avoid completely the term of *alcohol epilepsy*, and to be more specific when reporting and treating convulsive disorders in an alcohol-abuse setting [15].

This is even more important, if we consider that there are other notions very closely related, if not identical, with the alcoholic epilepsy. The most frequently discussed is *alcohol-related seizures* (ARS), which concurs with the chronic alcohol dependence [16]. The overlapping situation with the withdrawal seizures, is however not identical with the latter.

In fact, Bråthen distinguishes at least four subtypes of ARS [14]:

a. Alcohol withdrawal seizures,

b. Post-traumatic epilepsy secondary to alcohol abuse,

c. Alcohol-induced seizures,

d. Latent or pre-existing epilepsy unmasked or complicated by alcohol use.

The acute or chronic alcohol intoxication occasionally might be enough severe to precipitate a *status epilepticus* [17].

2.2. Withdrawal Seizures

Withdrawal seizures during ethanol abstinence are a common occurrence, when a chronic alcoholic refrains from drinking partially or totally. Roughly 90% of the seizures present within 7-48 hours after the last drink, with a peak at 13-24 hours. During this time lapse the patient is highly sensitive toward stroboscopic stimulation, which might cause myoclonic or generalized seizures (the so-called photo-paroxysmal responses) [18]. The convulsive event might be an isolated one, but generally two to six seizures are reported, with some patients falling into an epileptic status (2% of them). Seizures are of the *grand mal* type, albeit focal seizures suggest a localized lesion, mostly traumatic (subdural hematomas during falls after a binge). Almost 30% of the patients suffering from generalized seizures will present thereafter the clinical picture of *delirium tremens* [19]. Seizures will precede the delirium, as a rule.

Some authors have defined the withdrawal seizures as "rum fits", or even "whiskey fits" [20,21]. Electroencephalography (EEG) registrations did not support the suspicion that seizures were merely elicited from alcohol, in a condition of otherwise latent epilepsy. EEG has registered brain electrical activity changes directly provoked from ethanol, such as slow rhythms during chronic intoxication; virtually a normalization of EEG after abstaining from alcohol will be followed from a short period of paroxysms coinciding with the seizures, before an (almost) complete normalization of the brain electrical activity to take place. With regard to the slow rhythms, suggestions that theta waves dominate the scene are numerous, pushing some authors to include theta oscillations in the ever-changing list of biomarkers of alcoholism [22].

2.3. SESA: Subacute Encephalopathy with Seizures in Chronic Alcoholism

SESA is a clinical rarity, but worth mentioning apart, when discussing about the duality seizures – alcoholism. It seems that SESA accompanies chronic consumption of large ethanol quantities. The term was coined in 1981 from Niedermeyer et al, and it became very soon clear that this syndrome differed substantially from other withdrawal conditions such as the rum fits or delirium, and was not even the same clinical picture as Wernicke-Korsakoff encephalopathy or other surrogates related to chronic alcohol abuse [23].

From the clinical point of view SESA presents with multiple neurological deficits, such as hemiparesis or homonymous hemianopsia, as well as recurrent focal seizures that sometimes become generalized ones. EEG is typically characterized with graphic elements defined as periodic lateralized discharges (PLEDs). PLEDs are generally correlated with metabolic factors and alterations; in fact those have been registered in very diverse brain nosologies [24-26]. The appearance of seizures is obviously a major criterion for the diagnosis of SESA to be made.

Although a rarity, SESA represents a challenge for the treating clinician, since it has a very high probability of getting complicated with intercurrent infections or other internal conditions [27]. The prognosis is poor, the course is subacute, and the recovery if successful will be very gradual. The treatment should rely upon antiepileptics, whose efficacy is undisputed in this setting; albeit SESA actually is considered as a form of nonconvulsive status epilepticus [28,29].

3. Conclusive Remarks

Alcohol abuse causes a variety of internal and neurological diseases. Ethanol does it directly, but indirectly as well, through predisposing for other diseases, via different mechanisms which are primarily metabolic in their nature. Albeit the percentage of alcoholics in the general population is estimated roughly to 3%, more than 20% of admissions and hospitalizations inside intensive care units and neurological facilities are in fact, alcohol abusers [30].

Alcohol acts within the nervous system as a depressant; therefore during acute intake this substance will increase the seizure threshold, and contrary to the popular belief, high blood levels of ethanol alone during acute intake might not be responsible for the seizures [31]. The situation will be reversed when the alcohol administration is stopped, with a lowering of the convulsive threshold. In fact, if alcohol causes convulsions during an acute and exaggerated intake, it tends by far to provoke more seizures during the withdrawal syndrome, i.e. when abstaining from its consumption, especially when the cessation has been abrupt [32]. This apparently contradictory combination is explained through different mechanisms that the alcohol abuse carries out over the neuron and neural networks in their entirety. Acute and chronic effects seem to be opposite to each other, whereas different molecular, ionic, metabolic and synaptic changes following chronic consumption will suffice to explain the hyperexcitability status that follows the withdrawal [33,34]. Acutely, alcohol will act as an agonist of GABA-A receptors, and it will inhibit induced ionic currents and calcium influx induced by NMDA [33]. Conversely, during the chronic abuse, an increase of glutamate levels and of the number of NMDA receptors will increase cerebral excitability [33].

The role of other determinants cannot be underemphasized when seizures dominate the clinical picture, such as the concomitant intake of other drugs of abuse, with situations of polytoxicomania apparently being much more complex during withdrawal periods [35]. Obviously, genetic predisposition and sex differences in alcohol-related seizure susceptibility account to a certain degree for the severity of the condition, and its respective frequency. Thus, the enzymatic polymorphism responsible for higher homocysteine plasma concentration has an influence over the withdrawal seizures [36]. On the other hand, in a series of 540 patients, complications of withdrawal syndrome were most frequent in men compared to woman, thus showing significant gender differences [37].

Benzodiazepines remain the mainstay of the treatment of seizures following alcohol abuse or withdrawal, in each case, and different preparations from this group have been tested, such as alprazolam, diazepam, clonazepam, chlordiazepoxide and lorazepam, among others [32,38,39]. The efficacy of other antiepileptics has been scrutinized and validated as well, with studies including carbamazepine, phenytoine, chlomethiazole, valproate, barbiturates and recently, levetiracetam [29,32]. All other necessary supportive measures should of course be adopted, within the frame of intensive care setting and principles [40,41].

Conflict of Interest

None.

Supporting Source

None.

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