The management of alcohol-related seizures: an overview

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Alcohol-withdrawal seizures are one of the common medical emergencies. The seizures are generalized and usually occur abruptly between 6–8 hours after cessation of alcohol use (peak 12–24 hours). These patients are often uncooperative and therefore need careful assessment. Lorazepam is the first-line drug for termination and prophylaxis of alcohol-withdrawal seizures.

The relationship between alcohol use and seizures dates back to the earliest recorded literature. A major effort was made by Bowman and Jellinek in 1939 to review current understanding of the effects of alcohol. The authors cited 33 papers dating back to 1874 that reported cases of epilepsy which were related to alcohol (Mattson, 1990).

INCIDENCE

As many as 37% of patients presenting with seizures at the accident and emergency (A&E) department, University Hospital Aintree, had alcohol-related seizures (*Table 1*). These are either withdrawal seizures or toxic seizures precipitated by alcohol. This figure is close to those reported in literature (Bochner et al, 1986; Morrison and Mcalpine 1997; Roth and Frank 1998). Studies indicate that 25% of alcoholics experience seizures (Mattson, 1990; Tan and Weaver, 1997), which is a much higher than the general population (risk of 2–3%).

According to the literature 15–23% of the alcohol-related seizures are withdrawal seizures (Sullivan et al, 1996; Bartolomei et al, 1997). However, in the authors' experience the percentage of withdrawal seizures is much higher than this. Alcohol-induced seizures are strongly dose dependent: the risk of a seizure occurring without any antecedent event, such as stroke, increases threefold with alcohol consumption of 51–100 g per day, eight times with alcohol consumption of 101–200 g per day, and twenty times with alcohol consumption of 201–300 g per day. The risk of a seizure occurring as a result of stroke, tumour or metabolic cause, with or without a history of increased alcohol intake, is equal if the alcohol consumption is less than 200 g per day. However, the risk of seizures increases significantly if the alcohol consumption is more than 200 g per day — 10 times with alcohol consumption of 201–300 g per day (Ng et al, 1984; Roth and Frank, 1998).

CLASSIFICATION OF ALCOHOL-RELATED SEIZURES

A dynamic classification of alcohol-induced epilepsy was proposed by Bartolomei and colleagues (1997) after comparing patients with seizures related to episodes of alcohol withdrawal with alcoholic patients with seizures unrelated to alcohol withdrawal.

Stage 1

Stage 1 is characterized by younger patients, presenting with seizures provoked exclusively by alcohol withdrawal. The incidence of seizure, brain atrophy and alcohol-related neurological complications are low at this stage.

Stage 2

The second stage is characterized by older patients. Increasing seizure frequency and random seizure occurrence, partial seizures, brain atrophy and alcohol-related neurological complications tend to be more frequent during this stage.

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TABLE 1.
Number of patients with seizures presenting at University Hospital Aintree accident and emergency department

Year	Total number of patients with seizures	Number of patients with alcohol-related seizures	%
1997	80	28	35
1998	85	33	39

It has been speculated that chronic alcohol use could cause a third stage of irreversible brain damage, which might cause epilepsy. There is, however, no good evidence to support this speculation.

The conventional classification of alcohol-related seizures is based on the underlying aetiology (Mattson, 1990), which is as follows:

Alcoholism

1. Acute cerebral or medical disorder
   a. Metabolic (e.g. hypoglycaemia, hyponatraemia, hypomagnesaemia, uremia)
   b. Toxic (cocaine, narcotics)
   c. Infection (meningitis, encephalitis)
   d. Trauma (subdural haematoma, subarachnoid haemorrhage)
   e. Cerebrovascular accident, arteriovenous malformation or neoplasm.
2. Withdrawal syndrome
3. Epilepsy (seizure during prolonged abstinence)
   a. Symptomatic of long-term effects of disorders noted in alcoholism
   b. Coincidental symptomatic epilepsy
   c. Latent epilepsy unmasked by alcoholism
   d. Epilepsy resulting from neuronal damage caused by alcohol?

Epilepsy

1. Alcoholism developing in patients with epilepsy
2. Seizures precipitated by alcohol use in non-alcoholic patients with epilepsy
3. Latent epilepsy unmasked by alcohol use.

Idiopathic generalized epilepsy, particularly juvenile myoclonic epilepsy, and epilepsy with wakening tonic-clonic seizures are those which are likely to be associated with provoked, often alcohol-related, seizures.

PATHOGENESIS OF ALCOHOL-RELATED SEIZURES

Alcohol-induced brain damage is manifest in cognitive, physiological and structural changes in several brain structures (Freund and Anderson, 1996; Sullivan et al, 1996). In a study conducted by Sullivan and colleagues (1996), magnetic resonance imaging scans were done on chronic alcoholics with and without fits. The results showed significant bilateral tissue volume deficit of the anterior hippocampus, frontal parietal and temporal lobe gray matter, relative to controls. It was further noted that temporal lobe white matter volume was significantly smaller in alcoholics with seizures than in alcoholics without seizures.

On a molecular level alcohol affects various neurotransmitter systems in the CNS, but it mainly affects gamma-aminobutyric acid (GABA) receptors and glutamate receptors. GABA is the major inhibitory neurotransmitter in the CNS (Freund and Anderson, 1996; Hall and Zador, 1997; Tan and Weaver 1997; Tsai and Coyle, 1998) and ethanol potentiates GABA-ergic transmission. Chronic alcohol use leads to adaptation and downregulation of GABA receptors. A sudden withdrawal leads to hyperexcitation of neurones, which results in alcohol withdrawal symptoms and seizures. This theory is supported by the fact that GABA-ergic drugs such as benzodiazepines prevent alcohol withdrawal symptoms (Mayo-Smith, 1997; Tan and Weaver, 1997).

Glutamate is the major excitatory neurotransmitter in the CNS. There are four subtypes of glutamate receptor in the CNS, but ethanol mainly affects N-methyl-D-aspartate (NMDA) receptors. During acute exposure ethanol acts as an NMDA antagonist, inhibiting NMDA-stimulated influx of calcium ions and thus decreasing CNS excitability. Prolonged exposure leads to upregulation of NMDA receptors. Sudden withdrawal causes rapid influx of calcium ions, causing hyperexcitability of neurones which results in withdrawal seizures. Repeated upregulation and rapid influx on withdrawal leads to neuronal damage (Freund and Anderson, 1996; Hall and Zador, 1997; Tan and Weaver 1997; Tsai and Coyle, 1998).

ALCOHOL WITHDRAWAL KINDLING

In 1969 Goddard and colleagues described the phenomenon of kindling. This is a process in which repeated sub-convulsive stimulation eventually produces motor seizures and electroencephalogram (EEG) changes. Based on this mechanism, many animal studies have been conducted which show that seizure activity can be kindled pharmacologically by repeated administration of various drugs (Ulrichsen et al, 1997). Alcohol withdrawal kindling was first suggested by Ballenger and Postin in 1978 and it has recently gained considerable support. Studies show that repeated alcohol intoxication and withdrawal episodes result in increased severity and duration of withdrawal, and a decrease in the threshold for seizures (Worner, 1996; Becker et al, 1997; Mahmoudi et al, 1997; Saitz and O'Malley, 1997; Ulrichsen et al, 1997).

The exact mechanism of alcohol withdrawal kindling is not clear but it is hypothesized that repeated ethanol exposure and intoxication leads

to alteration in neuronal activity, which can ultimately lead to neuronal damage. There is a positive relationship between previous history of alcohol-withdrawal seizures and the severity and duration of subsequent withdrawal seizures. This increased sensitization of withdrawal response represents alcohol withdrawal kindling (Becker et al, 1997).

EVALUATION OF ALCOHOL-RELATED SEIZURES

The evaluation of patients with alcohol-related seizures is similar to that for all other seizures with a few additional considerations. These patients are often difficult and uncooperative, but it is important to establish the amount and duration of drinking and also whether drinking has stopped and if so when and why. Medical illness may have prompted alcohol cessation. Alcohol withdrawal appears to be a more important mechanism in causing seizures in alcoholic patients than trauma or true epilepsy.

Alcohol-withdrawal seizures usually occur in the 4th and 5th decades of life, after many years of alcohol abuse, often in binge drinkers. Seizures are usually generalized, occurring abruptly without warning, 6–8 hours after cessation of alcohol use (peak 12–24 hours), often singly or in clusters rarely exceeding five seizures in 6 hours (Roth and Frank, 1998). As many as one-quarter of such withdrawal seizures may be of focal onset. Abuse and ingestion of other medication is a common feature in withdrawal seizures, and infection and hypoglycaemia occur frequently. These patients are also at risk of haemorrhagic stroke, hepatic failure, pancreatitis, peritonitis, gastrointestinal bleeding, arrhythmias and trauma. A history of seizures is pertinent because patients often have a consistent pattern of withdrawal seizures.

Neurological examination of patients should look for focal signs suggesting an intracranial structural lesion. Laboratory studies should include toxic screen, calcium, magnesium, antiepileptic drug levels and alcohol levels. Computerized tomographic (CT) scan of the brain should be obtained in all alcoholic patients experiencing their first seizures, because they are at high risk of a structural lesion. CT scans should be carried out in those who have evidence of raised intracranial pressure and an altered mental status not attributable to intoxication. Patients with fever, raised white cell counts and seizures should have a lumbar puncture to rule out CNS infection. However, it is important to recognize that patients may have a high white cell count and transient fever secondary to seizure.

MANAGEMENT

A large number of patients present in A&E departments with alcohol-withdrawal seizures. Although many different drugs and regimens are mentioned in the literature, there does not appear to be consensus on the management of alcohol-withdrawal seizures. Management of alcohol-withdrawal fits can be divided in to two parts:

- Management of withdrawal seizures
- Prophylaxis of withdrawal seizures.

Management of withdrawal seizures

Alcohol withdrawal seizures are usually self-limiting and of short duration and may not require any treatment (Bochner et al, 1986; Morgan, 1995; Roth and Frank, 1998). However, if a patient develops a prolonged seizure or repeated seizures, recent evidence shows that loading with lorazepam (2 mg) is the treatment of choice for termination of seizures (D'Onofrio et al, 1999). Lorazepam is not only effective in terminating seizures but also prevents seizure recurrence. Evidence shows that lorazepam is better than diazepam as an acute treatment for seizures: it prevents recurrence of seizures and has a longer half-life than diazepam. The incidence of respiratory depression is less with lorazepam than diazepam (Appleton et al, 1995; D'Onofrio et al, 1999; Beyenburg et al, 2000).

Chlormethiazole is a very effective anticonvulsant drug and can be administered intravenously. It has been used quite effectively in resistant alcohol-withdrawal seizures and status epilepticus (Morgan, 1995). However, the use of intravenous chlormethiazole should be limited to resistant cases which do not respond to lorazepam, or in cases where the patient develops status epilepticus. It should be used with caution as it can cause respiratory depression and therefore the aim should be to change to oral medication as soon as the patient can tolerate it (Morgan, 1995).

The conventional antiepiletics do not have a role in the treatment of alcohol-withdrawal seizures. In patients who are known epileptics and develop recurrent alcohol-withdrawal fits, phenytoin can be used with diazepam (Roth and Frank, 1998).

Prophylaxis of alcohol withdrawal seizures

There are number of drugs used for the treatment and prophylaxis of alcohol-withdrawal symptoms. Chlormethiazole and chlordiazepox-

ide are the two most commonly used drugs. As in many hospitals in UK and Scandinavia, the authors favour chlormethiazole for the management and prophylaxis of alcohol withdrawal because it has a relatively short half-life (3–6 hours), and it is less likely than other drugs to accumulate in the liver of patients with liver damage (Lapierre et al, 1983; Morgan, 1995). Chlormethiazole is effective in both the control and prophylaxis of alcohol-withdrawal symptoms (Lapierre et al, 1983).

Conventional antiepileptics have no role in prophylaxis. Phenytoin and carbamazepine have been used in alcohol withdrawal but data supporting these drugs are limited (Mayo-Smith, 1997; Roth and Frank, 1998). Conventional antiepileptics should only be considered in patients who have features suggesting that alcohol is not the only cause of seizures and where there is a history of seizures even after prolonged periods of abstinence, especially if patient is below 30 years of age. Sudden discontinuation of antiepileptics may aggravate alcohol withdrawal.

CONCLUSIONS

In the A&E department at University Hospital Aintree, 30–40% of seizures are alcohol related. Alcohol withdrawal is the leading cause of acute symptomatic seizure in adults. Multiple reasons exist for the occurrence of seizures including metabolic, traumatic and structural changes. Seizures are strongly related to duration and amount of alcohol abuse. Careful diagnostic evaluation is important to delineate the cause in order to select the optimal treatment.

KEY POINTS

- A high percentage of patients with seizures seen in accident and emergency have alcohol-related seizures. Withdrawal seizures are the leading cause of acute symptomatic seizures in adults.
- Alcohol withdrawal seizures occur 6–8 hours after cessation of alcohol use and peak at 12–24 hours.
- Chronic alcohol consumption causes adaptation and downregulation of gamma-aminobutyric acid receptors and upregulation of N-methyl-D-aspartate receptors, sudden withdrawal leads to hyperexcitability of neurone and results in withdrawal seizures.
- There is a positive relationship between previous history of alcohol withdrawal seizures and severity and duration of the subsequent seizures. The increased sensitization of the withdrawal response represents alcohol withdrawal kindling.
- Lorazepam is the drug of choice for the termination and prophylaxis of alcohol withdrawal seizures.

Some clinical issues still need to be resolved. For example, does chronic alcoholism produce cerebral atrophy and other changes which could increase the potential for seizures to occur independent of alcohol withdrawal? Is there a certain amount and duration of alcohol abuse which can cause epilepsy? What is the appropriate long-term treatment and prophylaxis of alcohol-related seizures? Much remains to be learned about the relationship between alcohol use and seizures. **HM**

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