Alcohol withdrawal seizures

This article includes discussion of alcohol withdrawal seizures and rum fits. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Alcohol withdrawal seizures are frequently encountered in the emergency room. Such seizures comprise acute and serious complications to alcohol abuse that need immediate attention. Benzodiazepines should be the first choice in the pharmacological management of such seizures. There is a risk of mistakenly making an epilepsy diagnosis if a thorough alcohol anamnesis is omitted. Any patient with withdrawal seizures should be given thiamine during hospitalization, regardless of nutritional state. In this article, the authors explain the clinical presentation, pathophysiology, diagnostic work-up, and management of alcohol withdrawal seizures and provide clues to the differentiation of withdrawal seizures from seizures due to epilepsy.

Key points

- Alcohol withdrawal is a major seizure-precipitating factor.
- Drinking history is essential; biomarkers such as GGT and CDT may be useful supplements.
- Investigation of first seizures must include neuroimaging.
- Benzodiazepines are safe and effective in alleviating both seizures and general withdrawal symptoms as well as preventing further seizures. High initial doses may be necessary, but treatment should be discontinued within less than a week.
- Parenteral thiamine should be given before any carbohydrate-containing fluids or food.
- The recommended initial preventive thiamine dose is 200 mg; if Wernicke encephalopathy is suspected, give 200 mg three times daily for at least 2 days.

Historical note and terminology

The relation of alcohol to seizures was appreciated by Hippocrates (Lloyd 1978), as well as by the Romans, who even put a name to it, morbus convivialis, or “disorder related to partying” (Lennox 1941). Minimal progress was made to knowledge in this field during the centuries until Magnus Huss introduced the term “alcoholismus chronicus” in 1851 and showed that after prolonged intoxication, alcoholics may have seizures (Huss 1851). He also established that epileptic patients who drink must be differentiated from alcohol abusing patients having epileptic seizures during withdrawal (Jellinek 1943). In 1953 the first systematic article describing the alcohol withdrawal syndrome appeared (Victor and Adams 1953), and later an article exploring the nature of alcohol withdrawal seizures (Victor and Brausch 1967). These have remained landmark articles, forming a basis for our current knowledge.

The lack of a comprehensive definition of clinical entities or a unanimous classification of alcohol-related seizures have been major obstacles to gaining evidence-based knowledge about alcohol and seizures.

"Alcohol-related seizures” describes all types of interrelation between seizures and alcohol use. "Alcoholic epilepsy,” is a confusing term with many different meanings and should be abandoned. “Alcohol-provoked seizures” is a useful term for seizures directly precipitated by a drinking bout, when other etiologies than withdrawal are suspected, eg, metabolic or toxic effects of acute alcohol intoxication, sometimes complicated by drug abuse, head trauma, or
epilepsy. For a comprehensive discussion of seizure types related to alcohol, see (Mattson 1990). The present article deals only with seizures occurring during alcohol withdrawal.

**Clinical manifestations**

**Presentation and course**

The alcohol withdrawal seizure is a symptom of the early alcohol withdrawal syndrome (Victor and Adams 1953), mainly occurring within 48 hours of cessation of drinking (Victor and Brausch 1967; Brathen 1999), during which the seizure threshold is reduced (Tabakoff and Hoffman 1987). The seizure type is predominantly generalized tonic-clonic, single in about 50% of cases or occurring as a series of seizures within a 6-hour period (Isbell et al 1955; Victor and Brausch 1967). Alcohol withdrawal seizures are a strong risk factor for progression into a severe withdrawal state, with subsequent development of delirium tremens in up to 30% of cases if untreated (Victor and Brausch 1967).

**Prognosis and complications**

**Alcohol-related status epilepticus.** Alcohol withdrawal is one of the most common causes of status epilepticus, and status epilepticus may even be the first manifestation of alcohol withdrawal seizures. Although status epilepticus has probably a better prognosis when alcohol-related (Alldredge and Lowenstein 1993), it increases the risk for subsequent epilepsy (Hesdorffer et al 1998). One study indicates that lorazepam may be superior to diazepam for the treatment of out-of-hospital status epilepticus (Alldredge et al 2001). In another study comparing four treatments, lorazepam was considered easier to use but not more efficacious than diazepam, phenobarbital or phenytoin (Treiman et al 1998).

**Clinical vignette**

A 41-year-old Caucasian male had been treated for childhood epilepsy, but was off medication by age 12 years and remained seizure-free through early adulthood. He worked as a carpenter, was married and had a son. Then, at age 32 years, he had his first epileptic seizure at adult age and was investigated for epilepsy with no pathological findings on cerebral MRI or EEG. Subsequent to his second seizure six months later, he was started on carbamazepine, which appeared to keep him seizure-free for a couple of years. Then, soon after the death of his mother, he started having generalized tonic-clonic seizures with increasing frequency, despite still taking carbamazepine. A second investigation revealed no brain pathology on MRI, and EEG was normal, with low amplitude. Although he reported rather high alcohol consumption, he insisted on having seizures unrelated to alcohol use and was sober at every hospital admission. Blood samples drawn at the outpatient clinic showed no blood alcohol and normal liver parameters, and his psychologist confirmed he was not drinking. Consequently, he was treated for epilepsy. Carbamazepine was increased with no effect; then replaced by sodium valproate, and later levetiracetam was added, but he never gained seizure control. The seizures were invariably generalized tonic-clonic, but some unusual features were observed; he would be alert shortly after a seizure with little need for sleep, sometimes he was trembling, and he never stayed in the hospital for many hours.

Then he was hospitalized due to a prolonged seizure, and blood alcohol was highly elevated, as was carbohydrate-deficient transferrin (CDT), indicating current, sustained alcohol abuse. When confronted with the evidence, he admitted to have been drinking for years. Subsequent to detoxification in a rehabilitation clinic, antiepileptic drugs were tapered off and withdrawn. He remained seizure free for some months until recurrent seizures were observed, and it soon became evident that he had started drinking again.

**Biological basis**

**Etiology and pathogenesis**

Alcohol withdrawal seizures normally develop after years of alcohol abuse. Case-control studies convincingly demonstrate the association of first seizures to alcohol use in a dose-dependent manner. For example, the risk was three-fold for people drinking 51 to 100 g alcohol/day and steadily increased to eight-fold and more than 16-fold for people drinking 101 to 200 g/day and more than 200 g/day (Ng et al 1988; Leone et al 1997).

Occasionally, seizures are observed after short binges or even single drinking episodes. In such cases, underlying seizure susceptibility is often present, ie, cortical brain damage from trauma, tumors, or epilepsy.
Alcohol withdrawal seizures typically occur as blood alcohol reaches zero and shortly thereafter, and are rarely seen after two days of abstinence. A temporary fall in blood alcohol levels during sustained drinking could also drive a relative withdrawal state leading to seizures while there is still alcohol in the blood, ie, alcohol withdrawal seizures may sometimes be observed even in intoxicated subjects.

Alcohol acts on the brain through several mechanisms that influence seizure threshold: during prolonged intoxication, the CNS adapts to the influence of alcohol and tolerance develops. The amount of GABAA receptors decreases, whereas the amount of NMDA receptors increases. GABAA receptors become less sensitive to GABA, whereas NMDA receptors become more sensitive to glutamate. These changes may explain the lowered seizure threshold after abrupt cessation of prolonged intoxication, but several other mechanisms have also been proposed.

Experimental research has substantially enhanced our understanding of the molecular basis of these adaptations (Goldstein 1972; Sanna et al 1993; Tan and Weaver 1997).

Alcohol disrupts neuronal signal transduction via alterations of plasma membrane receptor-gated ion channels. It acts like an N-methyl-D-aspartate (NMDA) antagonist (Carboni et al 1993), reducing excitatory glutaminergic synaptic transmission (Nie et al 1993) and inhibits calcium flux through the ion-gated NMDA receptor in a concentration-dependent manner (Lovinger et al 1989). Chronic exposure to alcohol leads to up-regulation of the NMDA receptor function (Iorio et al 1992; Trevisan et al 1994), and the signs and symptoms of the alcohol withdrawal syndrome are thought to reflect this up-regulation (Engberg and Hajos 1992). But alcohol also enhances the gamma-aminobutyrate A receptor (GABAA receptor)-coupled chloride flux, an effect mimicking that of benzodiazepines.

**Epidemiology**

Although there are approximately 0.7% epileptics in populations of developed countries, and the lifetime prevalence of having an epileptic seizure is 2% to 3%, it has been estimated that up to 15% of alcoholics at some stage will have a seizure (Chan 1985).

Consecutive data from several observational studies suggest that approximately one in three patients with seizures leading to hospital admission have consumed a hazardous amount of alcohol prior to the seizure (Brathen 2001).

**Prevention**

Obviously, as alcohol withdrawal seizures are a complication of sustained alcohol abuse and subsequent withdrawal, seizures can be prevented by abstinence. It is not possible to issue general recommendations as to safe drinking levels. Patients with uncontrolled epilepsy should abstain completely from alcohol.

**Differential diagnosis**

Differential diagnoses include epilepsy, psychogenic non-epileptic seizures, and convulsive syncope.

**Diagnostic workup**

As more than 90% of alcohol withdrawal seizures occur soon after the cessation of sustained drinking, whereas general withdrawal symptoms develop gradually, alcohol abuse may not be an obvious cause. It is a common mistake to attribute repeated withdrawal seizures to epilepsy and start treatment with anti-epileptic drugs. Poor compliance, no treatment effect and risk of interaction problems can be expected in such cases (Hillbom and Hjelm-Jager 1984).

**Physical examination.** Clinical features distinctive of either epilepsy or alcohol withdrawal seizures should be focused (Brathen et al 2005). In case of epilepsy, post-ictal symptoms prevail. Most epileptics will be drowsy or in post-ictal sleep, with normal blood pressure and pulse rate and EEG will be pathological in more than 50% showing slow waves or interictal epileptiform discharges (Anonymous 1993). In most cases, the clinical signs and symptoms distinctive of the alcohol withdrawal syndrome will develop shortly (within 24 hours) after the seizure, ie, the patient should be observed for such symptoms. Typical symptoms are anxiety, irritability, unrest, nightmares, sleeplessness, tremor, sweating, elevated blood pressure, and tachycardia. As withdrawal symptoms develop, fever may develop and respiratory alkalosis may be seen in arterial blood (Orringer et al 1977).

**Drinking history.** Alcohol as a seizure precipitant is often missed because patients are not duly questioned, and
when questioned they tend to conceal or under-report their alcohol intake. The time and level of the last alcohol intake prior to the seizure is key information. However unreliable they may be, self-assessment of the approximate amount of alcohol consumed and the recent average weekly alcohol consumption should be recorded. Whenever possible, comparative information about the recent alcohol intake should be sought from a relative or friend.

Questionnaires offer high diagnostic accuracy for alcohol abuse. The most commonly applied instrument is CAGE. It is brief, easily memorized, and has reasonably fair accuracy (Mayfield et al 1974). However, it fails to detect binge drinking, which is a major seizure-precipitating factor (Brathen et al 2000). Binge drinking is probably best assessed by directly asking for the largest number of drinks in a single drinking occasion (Matano et al 2003). A handful of brief versions of the Alcohol Use Disorders Identification Test (AUDIT), eg, AUDIT-C, FAST, AUDIT-PC, or Five-SHOT, have all shown good accuracy compared to AUDIT (Piccinelli et al 1997; Bush et al 1998; Seppa et al 1998; Fiellin et al 2000; Hodgson et al 2003). Many other questionnaires exist; they do not offer better accuracy than the brief versions of AUDIT, and they are more demanding in a routine clinical setting.

**Biomarkers.** For detection of alcohol overuse, questionnaire-based interviews are reported to be more sensitive than any biomarker (Bernadt et al 1982). However, in cases where information on recent alcohol consumption is unavailable or considered unreliable, markers of alcohol consumption can increase the accuracy of the clinical diagnosis (Brathen et al 2000a; Brathen et al 2000b). Carbohydrate-deficient transferrin (CDT) and gammaglutamyl transferase (GGT) are sensitive markers for alcohol overuse; systematic literature reviews have been inconclusive as to which marker is better (Salaspuro 1999; Scouller et al 2000). No biomarker can be recommended for screening of unselected seizure populations (Brathen et al 2000a; Brathen et al 2000b).

As the current intoxication level is important information with potential treatment consequences, blood alcohol concentration should be measured in patients with suspected alcohol-related seizures (Savola et al 2004). Urinary ethyl glucuronide and ethyl sulfate have recently been reported to have high sensitivity and specificity for recent drinking (Dahl et al 2011; Staufer et al 2011).

**Neuroimaging.** As a rule, a first seizure should always lead to a thorough investigation for any underlying cause, including MRI, or cerebral CT without and with contrast. The diagnostic yield of CT after a first alcohol-related seizure is high, mainly due to a high incidence of structural intracranial lesions (Earnest et al 1988; Schoenenberger and Heim 1994). Seizures that occur later than 48 hours after intake of the last drink may indicate other potential etiologies than simple alcohol withdrawal, such as subdural hematoma, brain contusion, or mixed drug and alcohol overuse (Hillbom and Hjelm-Jager 1984). When patients present repeatedly with typical alcohol withdrawal seizures, imaging is not necessary unless changes in seizure type and frequency, seizure occurrence more than 48 hours after cessation of drinking, or other unusual features are present.

**Electroencephalography (EEG).** EEG should be recorded after a first seizure, whereas subsequent to repeated withdrawal seizures, EEG is considered necessary only if an alternative etiology is suspected. The incidence of EEG abnormalities (slow or epileptiform activity) is lower among patients with alcohol withdrawal seizures than in those with seizures of other etiology. Therefore, EEG pathology suggests that the seizure may not have been caused exclusively by alcohol withdrawal (Sand et al 2002).

**Management**

**Seizures.** The acute seizure treatment should follow standard protocol, ie, repeated doses of a benzodiazepine (preferably diazepam or lorazepam) until the seizure stops. If the seizure does not stop (alcohol-related status epilepticus), sodium valproate should be considered before fosphenytoin/phenytoin, as phenytoin has been ineffective in preventing recurrent seizures in three controlled studies (Hillbom et al 2003).

**Thiamine therapy.** Due to the risk of developing the Wernicke-Korsakoff syndrome, which is highly underdiagnosed and may lead to permanent brain damage, patients presenting with known or suspected alcohol overuse should be given thiamine parenterally in the emergency room, before starting any carbohydrate containing fluids or food. The optimal dose is not settled, but because parenteral thiamine administration is generally safe, the diagnosis of thiamine deficiency is difficult, and the potential consequences of not treating are devastating; liberal doses should be administered parenterally. Prophylactic therapy is recommended in all patients with known or suspected alcoholism, malnutrition, or frequent vomiting (for example, in bulimia or hyperemesis gravidarum). Parenteral administration of 200 mg thiamine should be given in the emergency room before any carbohydrates are started. Oral administration is
insufficient as the intestinal thiamine absorption is too low and may be severely impaired in alcohol abuse (Holzbach 1996).

When Wernicke encephalopathy is suspected or manifest, a parenteral administration of 200 mg thiamine three times daily should be started with no delay. An intravenous infusion of thiamine diluted with 100 ml saline or 5% glucose, given over 30 minutes is recommended (Galvin et al 2010). The treatment should continue for at least 2 to 3 days. Patients with manifest Wernicke-Korsakoff syndrome may benefit from a treatment period of up to 2 weeks. It has been speculated that patients who are in a catabolic state or under the influence of alcohol have reduced ability to store thiamine because the enzymes depending on thiamine are downregulated or protein binding is altered by the influence of alcohol (Galvin et al 2010). In such cases, early re-institution of a normal diet may be important.

**Alcohol withdrawal syndrome.** Seizures may be a first symptom of the alcohol withdrawal syndrome and predict a poor prognosis; consequently, patients should be observed for 24 hours ideally or until a clinical improvement is evident. The revised Clinical Institute Withdrawal Assessment Scale (CIWA-Ar) can be applied to grade the severity of alcohol withdrawal (Sullivan et al 1989). It has prognostic value, as patients with scores less than 10 generally do not need pharmacological treatment. However, symptom-triggered therapy based on the CIWA-Ar protocol depends on correct application of the inventory (Hecksel et al 2008). Benzodiazepines should be chosen as the preferred drug class for treatment of the alcohol withdrawal syndrome (Amato et al 2011).

**Electrolyte disturbances.** Hyponatremia in alcohol abusers generally shows a benign clinical course, and usually repairs with cessation of alcohol intake and re-institution of a normal diet (Kelly et al 1998). The serious disorder of central pontine myelinolysis is thought to be triggered by osmotic gradients in the pons, a situation that might result from attempts to correct electrolyte disturbances too rapidly (Lampl and Yazdi 2002). If parenteral treatment is considered necessary, according to a retrospective study, the rate of serum sodium correction should not exceed 10 mmol/l per day (Saeed et al 2002).

Hypomagnesemia and respiratory alkalosis seem to be associated with alcohol withdrawal, and correction of hypomagnesemia may raise the seizure threshold in the initial phase of alcohol withdrawal (Victor 1973). It has been speculated that unresponsiveness to parenteral thiamine therapy may result from hypomagnesemia (Traviesa 1974). Despite the theoretical benefit, there is not sufficient evidence to recommend magnesium supplement.

**Primary seizure prevention.** When a patient is hospitalized for symptoms of alcohol withdrawal, the question arises whether the treatment should aim at preventing epileptic seizures. Patients with mild-to-moderate alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment Scale < 10) and no history of alcohol withdrawal seizures can successfully be detoxified with supportive care only (Whitfield et al 1978). Supportive treatment includes a calm, reassuring atmosphere, coffee restriction, daylight view, and hydration.

Patients with severe alcohol withdrawal symptoms and all those with seizures during previous alcohol withdrawal episodes have higher risk for alcohol withdrawal seizures (Hillbom et al 2003), and may benefit from seizure preventive treatment. When pharmacological treatment is necessary, benzodiazepines should be chosen for the primary prevention of seizures in a person with alcohol withdrawal, as well as for treatment of the alcohol withdrawal syndrome. The drugs of choice are lorazepam and diazepam.

**Secondary seizure prevention.** Following an alcohol withdrawal seizure, the recurrence risk within the same withdrawal episode is 13% to 24% (Hillbom et al 2003). Consequently, there is a good rationale for treating these patients as soon as possible in order to prevent subsequent seizures.

**Drug choice for seizure prevention.** In a meta-analysis of controlled trials for prevention of alcohol withdrawal seizures, a highly significant risk reduction for seizures with benzodiazepines compared to placebo was demonstrated (Hillbom et al 2003). For the purpose of reducing the risk of seizures and rebound withdrawal symptoms after discontinuation, long-acting drugs should be preferred to short-acting ones (Mayo-Smith 1997; Hillbom et al 2003). However, short-acting benzodiazepines may have advantages for patients with respiratory insufficiency. Symptom-triggered treatment has been reported to be as effective as fixed-dose or loading therapy, resulting in lower doses and shorter treatment time (Saitz et al 1994).

Lorazepam has some advantages over diazepam. Despite a shorter half-life it has longer duration of action because it is less accumulated in lipid stores. However, its onset of action is slightly slower than that of diazepam.
Phenytoin may be ineffective in preventing recurrent seizures within a withdrawal episode (Hillbom et al 2003). Many other drugs and drug combinations are being used, including carbamazepine, chlormethiazole, sodium valproate, gamma-hydroxybutyrate, and clonidine, all for which the documentation is generally poor (Robinson et al 1989; Saitz et al 1994; Holbrook et al 1999; Hillbom et al 2003; Minozzi et al 2010).

**Special considerations**

**Pregnancy**

Alcohol is teratogenic. Fetal alcohol spectrum disorders are more prevalent than previously recognized and cause a wide range of birth defects and neurodevelopmental disorders (Riley and McGee 2005).

The risk of fetal damage from generalized seizures during pregnancy is considerable, mainly due to transient hypoxia. Newborns whose mothers are intoxicated prior to or during delivery can experience withdrawal symptoms, such as tremors and even seizures. It is likely that withdrawal also can occur during fetal development. Thus, repeated withdrawals during pregnancy may pose an additional risk to the fetus from that of alcohol exposure in itself. Pregnant women should refrain from drinking alcohol.

**Anesthesia**

During alcohol withdrawal, patients may require higher than normal doses of GABAergic substances (benzodiazepines).

**References cited**

Alldredge BK, Lowenstein DH. Status epilepticus related to alcohol abuse. Epilepsia 1993;34(6):1033-7. PMID 8243353


Salaspuro M. Carbohydrate-deficient transferrin as compared to other markers of alcoholism: a systematic review. Alcohol 1999;19(3):261-71. PMID 10580517


Schoenenberger RA, Heim SM. Indication for computed tomography of the brain in patients with first uncomplicated


Tan CY, Weaver DF. Molecular pathogenesis of alcohol withdrawal seizures: the modified lipid-protein interaction mechanism. Seizure 1997;6:255-74. PMID 9304717


Victor M, Brausch C. The role of abstinence in the genesis of alcoholic epilepsy. Epilepsia 1967;8:1-20. PMID 4961509


**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

**ICD codes**

ICD-9:
Alcohol withdrawal syndrome:291.81
Alcohol dependence syndrome:303
Delirium tremens:291.0
Convulsive seizure or fit NOS: 780.3

ICD-10:
Alcohol withdrawal syndrome: F10.3
Alcohol dependence syndrome: F10.2
Alcohol withdrawal with seizures: F10.31
Other seizures: R56.8

**Profile**

**Age range of presentation**

19-44 years  
45-64 years  
65+ years

**Sex preponderance**

male > female, >1:1

**Family history**

Family history may be obtained

**Heredity**

Heredity may be a factor.

Animal species have long been known to display different susceptibilities to alcohol withdrawal seizures. Selective breeding of mice, for example, has produced lines that are prone and others that are resistant to alcohol withdrawal seizures. There may also be a genetic predisposition to alcohol withdrawal seizures in humans (Sander et al 1997).

**Population groups selectively affected**

none

**Occupation groups selectively affected**

Unemployed

**Differential diagnosis list**

epilepsy  
psychogenic non-epileptic seizures  
convulsive syncope

**Associated disorders**

Acute subdural hematoma  
Alcohol abuse  
Alcohol dependence  
Alcohol intoxication  
Alcohol withdrawal syndrome  
Alcoholic cerebellar degeneration  
Alcoholic myopathy  
Alcoholic neuropathy  
Beriberi  
Central pontine myelinolysis  
Cerebral contusion  
Delirium tremens  
Dementia  
Epidural hematoma  
Epilepsy  
Hepatic encephalopathy  
Hyponatremia
Korsakoff psychosis
Marchiafava-Bignami disease
Pellagra
Subdural hematoma
Substance abuse
Wernicke encephalopathy
Wernicke-Korsakoff syndrome

Other topics to consider

Alcohol abuse: acute and chronic neurologic illness
Alcoholic myopathy
Drug-induced memory disturbance
Drug-induced seizures
Epilepsy
Fetal alcohol syndrome
Korsakoff syndrome
Mental retardation
Nutrition-related neuropathies
Osmotic demyelination syndromes
Sleep disorders associated with alcohol use and abuse