19 NEUROLOGIC COMPLICATIONS OF ALCOHOLISM

Overview

Alcoholism, the addiction to alcohol, is characterized by a craving of alcohol and a tolerance to its intoxicating effects. Worldwide, alcoholism has an enormous impact on society, as it is the number one abused drug in the world. In the United States, there an estimated 8 million people are alcoholics. About 20% of hospital admissions involve medical complications of excessive drinking. The cause of alcoholism remains poorly understood but genetic factors appear to play a role, as alcoholism is 7 times more frequent in first-degree relatives of alcoholics than in the general population. Adoption studies in Sweden found that alcoholism in a biologic parent was more important than growing up in an environment with alcoholism in the adoptive parents. Identical twins have a higher concordance for alcoholism than fraternal twins.

Ethanol enters the circulation within minutes of consumption and rapidly distributes throughout the body. The liver metabolizes over 95% of alcohol via alcohol dehydrogenase, which converts ethanol into acetaldehyde, which is in turn metabolized by aldehyde dehydrogenase into acetate. In the average adult, alcohol metabolizes at a rate of 8 g/h (~8 oz beer/h). Alcohol consumption at faster rates leads to increasing alcohol levels in the blood and brain.

The effects of ethanol on the nervous system are numerous and complex. Which brain interactions are responsible for specific ethanol syndromes remains unclear. Ethanol enters to cell membranes, increasing membrane fluidity and possibly interfering with signal transduction. Significant components of the withdrawal syndrome after chronic alcohol use reflect reduced neurotransmission in the inhibitory type A GABA pathways and enhanced neurotransmission in glutamate (NMDA) pathways. Alcohol withdrawal causes complex decreases in GABA receptor binding, resulting in loss of presynaptic inhibitory control. During alcohol withdrawal, increased dopaminergic transmission may cause hallucinations and increased autonomic activity. Hypomagnesia and hypocalcemia frequently occur during alcohol withdrawal and likely contribute to CNS hyperexcitability by altering neuronal action potentials.

Complications of alcoholism involve many organs, but damage to the CNS and PNS is particularly common. This chapter will review the major neurologic complications from alcohol intoxication and withdrawal (Figure 19-1).

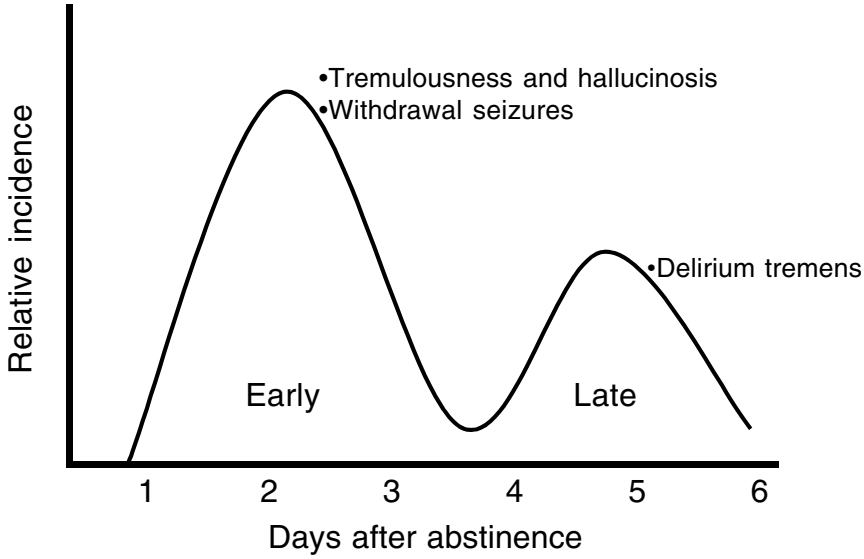

Figure 19-1 *Time course of alcohol withdrawal.*

Drunkenness and Alcoholic Coma

Ethanol readily crosses the blood–brain barrier, enabling brain alterations to begin soon after drinking. Signs of intoxication in nonalcoholic persons begin at blood levels of approximately 60 mg/dL; gross intoxication occurs at levels of 120 to 150 mg/dL. In alcoholics, intoxication may not occur until blood levels are as high as 150 mg/dL. Signs of intoxication consist of varying degrees of euphoria, exhilaration, excitement, loss of restraint, irregular behavior, slurred speech, incoordination of movement, gait ataxia, irritability, and combativeness. While the biochemical effects are incompletely understood, the net result appears to be excitation of brain activity. Consumption of large volumes of beer (beer is hypotonic and ethanol inhibits antidiuretic hormone) may produce a sufficient degree of hyponatremia to cause a generalized seizure.

At higher blood levels, brain functions deteriorate, with the development of lethargy, stupor, and coma, suggesting ethanol now produces inhibition of brain activity. Alcoholic coma is seen at blood levels around 300 mg/dL and respiratory failure develops at levels of >400 mg/dL. Comatose patients often require intubation and mechanical ventilation until the alcohol level lowers.

Alcoholic Tremulousness and Hallucinosis

When alcohol is abruptly reduced, a hyperexcitable withdrawal syndrome develops. The symptoms of alcohol withdrawal can be divided roughly into those from autonomic hyperactivity (tremulousness, sweating, nausea, vomiting, and anxiety) and from neuronal excitation (confusion, agitation, delusions, hallucination, and seizures).

Tremor ("shakes" or "jitters") develops in over 50% of individuals in withdrawal. The tremors begin about 6 hours after the last drink and worsen over the next 2 to 3 days (Figure 19-1). The tremor occurs at rest and with action, and is coarse, irregular, and increases with stress. Patients may also have an increased startle response. The mental status remains relatively clear, but the patient feels uncomfortable. The tremor abates with consumption of more ethanol or use of benzodiazepines.

Alcoholic hallucinosis occurs in 10% of patients in alcohol withdrawal and typically begins from 24 to 36 hours after drinking cessation. Disordered perceptions of vision or sound develop that may frighten or amuse the patient. Occasionally, frank hallucinations occur. Patients feel "shaky" inside, develop tachycardia, and complain of general weakness and insomnia but do not become agi-

tated. This clinical picture persists for several days to weeks. Use of benzodiazepines again relieves most symptoms.

Alcohol-Withdrawal Seizures

Alcohol-withdrawal seizures occur in nearly 5% of individuals who have been drinking steadily for years and then abruptly stop. For example, undiagnosed alcoholics who are hospitalized may experience a seizure the day after admission. The primarily generalized seizure occurs 7 to 72 hours after alcohol cessation, with a peak at 12 to 48 hours (Figure 19-1). Patients tend to have 1 to 4 seizures over several hours. Status epilepticus is rare.

Alcohol-withdrawal seizures are partly a diagnosis of exclusion. The mechanism for withdrawal seizures is unknown but thought to result from a hyperactive brain (due to alcohol withdrawal), accompanying low serum magnesium, and elevated arterial pH from respiratory alkalosis. In keeping with this, $^1/_2$ of patients withdrawing from ethanol have an abnormal EEG manifesting myoclonic or convulsive responses to flashing lights.

Of patients brought to the emergency room with possible alcohol-withdrawal seizures, 50% have another identifiable etiology. These patients often have a seizure aura (implying a focal origin for the seizure), history of serious head trauma while intoxicated, atypical seizures, abnormal neurologic exam, or signs of systemic infection. Neuroimaging studies can identify subdural hematomas, hemispheric contusions or infarctions, intracerebral masses (brain abscess, neurocysticercosis, tumors, and vascular malformations), or meningitis. In patients with known epilepsy, some seizures are actually triggered by drinking alcohol and stopping their anticonvulsant medications. Neurologic exam should not show acute signs that cannot be attributed to chronic alcohol usage. The blood alcohol level should be 0 or very low and the CSF exam, if done, is normal.

Administration of benzodiazepines (lorazepam or diazepam) to patients during alcohol withdrawal usually prevents further seizures during the critical withdrawal period. Phenytoin administration does not prevent seizures. Patients who permanently stop drinking do not have future seizures. Controversy exists as to whether administration of anticonvulsants prevents subsequent alcohol-withdrawal seizures. Since patients often stop their anticonvulsants during drinking spells, the combination of alcohol and anticonvulsant withdrawal may actually increase their risk of future seizures.

Delirium Tremens

Delirium tremens (DTs) is a serious but uncommon complication of alcohol withdrawal (less than 5% of hospital admissions for alcoholism) and presents with profound delirium and autonomic nervous system overactivity. Patients have marked confusion, agitation, hallucinations, tremors, and sleeplessness. Signs of increased autonomic nervous system activity include fever, tachycardia, dilated pupils, and profuse sweating. Clinical signs begin 2 to 5 days after alcohol withdrawal and may be preceded by withdrawal seizures (Figure 19-1). Life-threatening events include high fever, dehydration, hypotension, cardiac arrhythmias, and secondary complications of trauma (from the agitation) or alcohol-associated medical conditions (liver failure, GI bleeding, systemic infection, or pancreatitis).

Treatment aims at reducing agitation and maintaining fluid and electrolyte balance. Lorazepam given repeatedly intravenously or intramuscularly is required for sedation. Patients require fluid replacement of up to 4 to 10 L/24 h to prevent dehydration and circulatory collapse. Serum potassium and magnesium levels are usually low and require correction.

The duration of DTs lasts 2 to 7 days, with most cases ending by day 3. Recovering patients regain alertness and the ability to cooperate but seldom have any memory of the acute illness. The mortality rate is 10%.

Wernicke's Encephalopathy and Korsakoff's Psychosis Syndrome

Introduction

Wernicke's encephalopathy and Korsakoff's psychosis are linked to abnormally low levels of thiamine (vitamin B_1) in the CNS. Chronic alcoholic patients tend toward malnourishment. People with alcoholism may obtain as much as 1/2 their daily

caloric intake from ethanol, resulting in serious nutritional deficiencies, including thiamine, niacin, folate, and protein. Hence, these two disorders are not linked to the direct toxic effects of alcohol or alcohol withdrawal. Thiamine is required for all tissues and is found in high concentration in the brain, heart, skeletal muscle, liver, and kidney. Thiamine is absorbed in the small intestine and transported to the brain by an energy-dependent transport system. A series of phosphorylation reactions produces thiamine diphosphate, a required cofactor in carbohydrate and amino acid metabolism. Thiamine-dependent enzymes are involved in the biosynthesis of neurotransmitters and for the production of reducing equivalents used in oxidant stress defenses.

Manifestations of thiamine deficiency can involve the brain (Wernicke–Korsakoff syndrome), peripheral nerves (dry beriberi), or the cardiovascular system (wet beriberi).

Pathophysiology

Neuropathologic findings in Wernicke's encephalopathy include demyelination, glial and vascular proliferation, hemorrhage, and necrosis. These principally affect gray-matter regions of the medial thalamus, hypothalamus, tegmentum of the pons and medulla, and cerebellum (particularly the Purkinje and granule cells of the anterior-superior vermis). Korsakoff's psychosis shows pathologic brain changes, including hemorrhages and necrosis in the dorsomedial nucleus of the thalamus and/or the mamillary bodies.

Major Clinical Features

Wernicke's encephalopathy is a disease of acute or subacute onset and is characterized by nystagmus, abducens and conjugate gaze palsies, gait ataxia, and a confusional state. The ocular signs consist of nystagmus that is both horizontal and vertical, paralysis of external recti, and paralysis of conjugate gaze. Nystagmus and weakness of the lateral rectus muscles are the most common; total ophthalmoplegia is rare. The ataxia of stance and gait typically produces a wide-based, unsteady, short-stepped, lurching gait. Ataxia of limbs remains less pronounced, and many patients have normal finger-to-nose and heel to shin tests.

Most patients experience a quiet confusional state characterized by apathy, inattentiveness, and indifference to surroundings. Speech is minimal. Drowsiness is common and may progress to stupor if untreated. Mild disorders of perception or hallucinations are experienced by 20% of patients.

Korsakoff's psychosis is a unique mental state in which retentive memory is impaired out of proportion to other cognitive functions in an otherwise alert, fluent, and responsive patient. A selective disorder of memory, Korsakoff's psychosis typically follows ≥1 episodes of Wernicke's encephalopathy. Impaired memory for previously established recent events (retrograde amnesia) and the inability to incorporate new memories (anterograde amnesia) appears, but immediate recall stays preserved. Patients, while disoriented to place and time and unaware of their memory deficits, confabulate or invent material to fill in memory gaps.

Major Laboratory Findings

MRI abnormalities vary in acute patients and include T2-weighted abnormalities in the periaqueductal region, medial thalamus, and mamillary bodies. Later, the T2-weighted abnormalities disappear and atrophic changes occur in the mamillary bodies and cerebellar vermis, with enlargement of the third ventricle.

Principles of Management and Prognosis

Early diagnosis of Wernicke's encephalopathy is critical, as administration of intravenous thiamine can correct the acute neurologic problem. In fact, it is prudent to administer parenteral thiamine to every alcoholic patient seen in the emergency room or hospitalized, since administration of glucose can precipitate the onset of Wernicke's encephalopathy. It is less clear whether thiamine can reverse the memory deficit seen in Korsakoff's psychosis. Poor prognostic factors include severe clinical features, delayed thiamine administration, T2-weighted abnormalities on MRI, and cerebellar or mamillary body atrophy. In countries using thiamine-enriched flour in bread, the incidence of Wernicke–Korsakoff syndrome has fallen but not disappeared.

Alcoholic Cerebellar Degeneration

Chronic alcoholism often leads to slowly progressive gait ataxia similar to that seen in Wernicke's encephalopathy. This is a wide-based, unsteady,

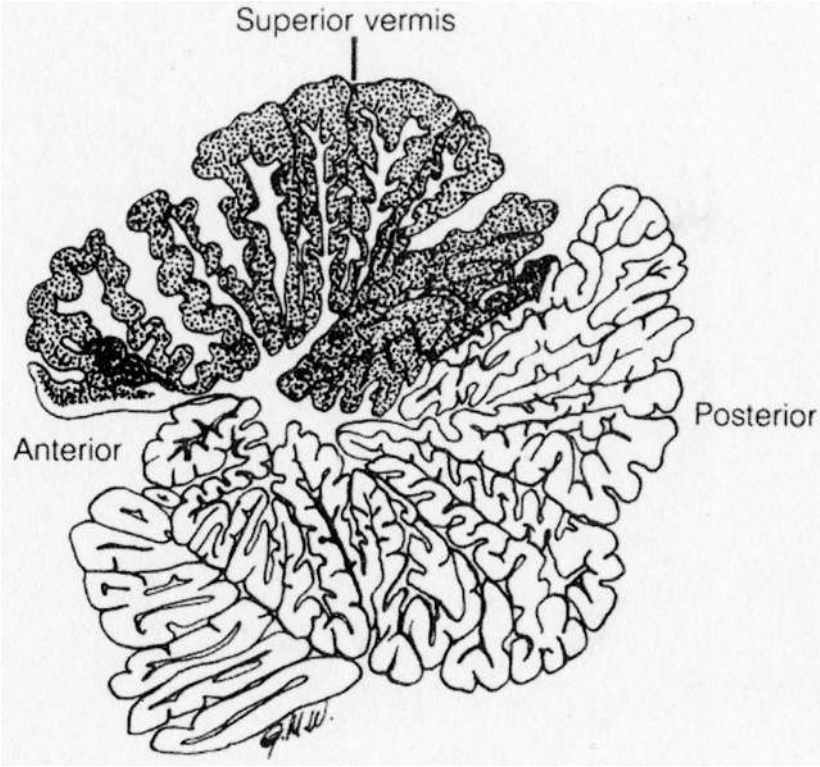

Figure 19-2 Alcoholic cerebellar degeneration.

short-stepped, and lurching gait. Patients often run their hands against the side of buildings or walls to improve their ambulation. Limb ataxia is usually mild. MRI shows atrophy of the superior cerebellar vermis and pathology demonstrates a loss of cerebellar Purkinje cells and other neurons, maximally in the superior vermis and vestibular nuclei (Figure 19-2). Once gait ataxia

develops, no treatment has been shown to reverse it.

Alcoholic Polyneuropathy

A distal symmetrical sensorimotor polyneuropathy is common in chronic alcoholism. The etiology of the neuropathy remains unclear, although direct effects of alcohol on the peripheral nerve and nutritional/vitamin deficiencies have been proposed.

The majority of patients have slowly progressive symptoms of paresthesias, burning dysesthesias, numbness, and muscle cramps in their feet and lower legs. On exam, there is a loss of ankle jerks, diminished vibratory sensation in the feet, and varying degrees of foot numbness and weakness. Loss of pain sensation appears less commonly. As the disease advances, leg weakness and gait apraxia occur from loss of position sense in the feet and possibly concomitant alcoholic cerebellar degeneration. Axonal degeneration, the principal pathologic process, occurs although segmental demyelination can occur. If alcohol consumption stops, the neuropathy may improve. Use of simple analgesics and tricyclic antidepressant medications may alleviate the burning dysesthesias.

Fetal Alcohol Syndrome (FAS)

Introduction

Alcohol is the most common human teratogen. Of the 60% of women who drink alcohol, 16% report drinking during their pregnancy and 4% report drinking more than 7 times per week. An estimated 0.5% (500/100,000) of all live births have some prenatal alcohol damage.

Pathophysiology

The pathophysiology of FAS, while incompletely understood, has several generalizations. Human and animal studies have found that (1) consumption of ≥1 alcoholic drinks per day is highly associated with FAS, (2) alcohol exposure in the first trimester of pregnancy leads to the characteristic congenital malformations of the face and midline brain, (3) third-trimester alcohol exposure decreases brain weight and numbers of neurons, and (4) peak blood alcohol concentrations are more critical than the same dose of alcohol at a lower peak level. The threshold amount of alcohol consumption needed to produce fetal toxicity remains unknown. As such, total abstinence from drinking alcohol is currently recommended for pregnant women and women planning pregnancy.

How alcohol damages the developing fetal brain is poorly understood, but it can kill developing neurons. In early development, excessive cell

Table 19-1 **Characteristic Features of Fetal Alcohol Syndrome**

Facial Abnormalities
Short palpebral fissures
Ptosis (droopy eyelids)
Flat mid-face
Smooth philtrum
Thin upper lip
Growth Retardation
Low relative birthweight
Growth retardation despite adequate nutrition
Low weight relative to height
Central Nervous System Neurodevelopmental Abnormalities
Microcephaly
Agenesis of corpus callosum
Cerebellar hypoplasia
Neurologic signs that may include poor fine-motor coordination, hearing loss, and clumsy gait
Behavioral Abnormalities
Learning disabilities (poor abstract reasoning, math skills, judgment, concentration, and memory)
Poor school performance
Poor impulse control
Hyperactivity
Poor social interactions
Birth Defects
Congenital heart defects
Skeletal and limb abnormalities
Ophthalmologic abnormalities
Sensorineural hearing loss
Cleft lip or palate

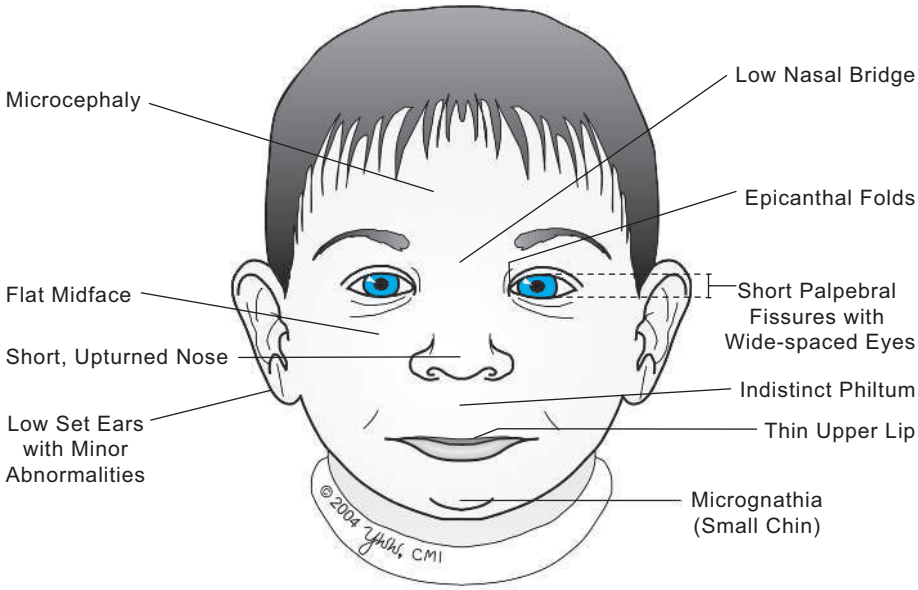

Figure 19-3 *Fetal alcohol syndrome.*

death in the mid-line of the developing embryo may account for mid-line brain defects (agenesis of corpus callosum) and craniofacial abnormalities. In late fetal development, the loss of neurons is more widespread, producing a low brain weight. Hypotheses of the mechanism by which ethanol kills neurons includes formation of toxic acetaldehyde by alcohol dehydrogenase metabolism of ethanol; free-radical formation, which causes cellular damage in the developing brain; and disruption of the L1 cell adhesion molecule (CAM), which is important in the developing brain.

Major Clinical Features

Infants with FAS demonstrate several characteristic abnormalities that involve growth retardation, craniofacial structure, neurodevelopmental abnormalities, behavioral problems, and occasional birth defects (Table 19-1 and Figure 19-3). The average IQ score in FAS is 66, with a range of 16 to 105. These IQ scores are higher than those seen in Down syndrome (25–65) and fragile-X syndrome (30–55). Nearly 60% of FAS children develop significant behavioral problems compared with 25% for Down syndrome children. The cognitive, behavioral, and psychosocial problems persist into adulthood.

Major Laboratory Findings

Clinicians have created categories such as alcohol-related birth defects and fetal alcohol effects or alcohol-related neurodevelopmental disorder for infants damaged by ethanol who do not meet all the criteria for FAS. Presently there is no laboratory test that establishes the diagnosis.

Principles of Management and Prognosis

Patient management begins with an early diagnosis that enables medical intervention, psychologic help, educational evaluation, and access to special education and related services such as speech and language programs and community resource programs. Helping the mother and other family members enables family preservation and helps prevent drinking during subsequent pregnancies.

RECOMMENDED READING

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