Overview of the chronic neurologic complications of alcohol

Author
Michael E Charness, MD

Section Editor
Michael J Aminoff, MD, DSc

Deputy Editor
Janet L Wilterdink, MD

Last literature review version 17.1: January 2009 | This topic last updated: January 28, 2009 (More)

INTRODUCTION — Acute alcohol intoxication is associated with a number of complications including accidents, traffic fatalities, domestic violence, homicide, and suicide. Alcohol dependence is also a chronic disease, associated with malnutrition, trauma, and a wide variety of central nervous system disorders. The chronic neurologic complications of alcohol abuse are reviewed here. The alcohol withdrawal syndromes are discussed separately. (See "Management of moderate and severe alcohol withdrawal syndromes").

Wernicke-Korsakoff syndrome is the best known neurologic complication of thiamine (vitamin B1) deficiency [1]. The term refers to two different syndromes, each representing a different stage of the disease. Wernicke's encephalopathy (WE) is an acute syndrome requiring emergent treatment to prevent death and neurologic morbidity. Korsakoff's syndrome (KS) refers to a chronic neurologic condition that usually occurs as a consequence of WE.

WERNICKE'S ENCEPHALOPATHY — Wernicke's encephalopathy (WE) is a common, acute neurologic disorder caused by thiamine deficiency [1]. It is manifested by a clinical triad of encephalopathy, oculomotor dysfunction, and gait ataxia.

This disorder is discussed in more detail elsewhere. (See "Wernicke's encephalopathy").

KORSAKOFF'S SYNDROME — Korsakoff's syndrome (KS) is a late, neuropsychiatric manifestation of Wernicke's encephalopathy (WE) in which there is a striking disorder of selective anterograde and retrograde amnesia. Although this memory disorder can occur in a variety of conditions that damage the medial temporal lobes, KS is seen most frequently in alcohol abusers after an episode of WE, and most patients with KS show typical WE lesions [1]. (See "Wernicke's encephalopathy", section on Clinical course and prognosis).

In some alcohol abusers, KS develops without a recognized acute episode of WE, although typical WE lesions may be present at autopsy [1-3]. It has been suggested that in these cases, KS may result from a series of subclinical or unrecognized
episodes of WE.

Approximately 80 percent of alcohol abusers recovering from classic WE exhibit the selective memory disturbance of KS. In contrast, KS is a less frequent sequela of WE in non-alcohol abusers [4], an observation that suggests that ethanol neurotoxicity is a contributing factor [5]. However, it is also clear that KS can occur in the absence of ethanol ingestion [5-11].

**Clinical features** — KS is characterized by marked deficits in anterograde and retrograde memory, apathy, an intact sensorium, and relative preservation of long-term memory and other cognitive skills [1,12]. One alcoholic poet passed an hour with me reciting flawlessly the works of Wordsworth, but had no recollection of our meeting one minute after I stepped out of the room. Confabulation is a feature in some but not all cases. Attention and social behavior are relatively preserved. Affected subjects are able to carry on a socially appropriate conversation that may seem normal to an unsuspecting spectator. Patients with KS are as a rule unaware of their illness.

Memory impairment correlates better with lesions in the anterior thalamus rather than mamillary bodies [13]. Nonetheless, atrophy of the mamillary bodies is a relatively specific sign of prior WE, and the finding of small mamillary bodies in a demented patient should raise the possibility that alcohol abuse and malnutrition have contributed to the dementia. (See "Wernicke's encephalopathy", section on Imaging studies).

Some alcohol abusers with WE lesions exhibit a more global abnormality of higher cognitive function [14]. One group identified WE lesions at autopsy in 20 alcohol abusers who had been evaluated by psychiatrists during the course of their illness [15]. Fifteen of the 20 patients were felt to have a global dementia and only five had a circumscribed memory disorder; KS was diagnosed in only three patients and Alzheimer disease (AD) in eight. Twelve of 15 patients diagnosed with dementia showed only the lesions of WE at autopsy, although subtle structural abnormalities were not sought.

The occurrence of global dementia in some patients with KS and the absence of non-WE lesions in some demented alcohol abusers have led some investigators to conclude that most cases of dementia in alcohol abusers are nutritional in origin [1,15,16]. However, other mechanisms including ethanol toxicity, stroke, and head trauma should also be considered as playing a role in these patients. (See "Ventricular enlargement and cognitive dysfunction" below).

**Treatment and prognosis** — Patients with KS rarely recover. Many patients require at least some form of supervision and social support, either at home or in a chronic care facility. There are anecdotal reports of improvement in attention and memory with the use of acetylcholinesterase inhibitors and memantine [17-19], but there is no controlled study.

**Ventricular enlargement and cognitive dysfunction** — Approximately 50 to 70 percent of alcohol abusers have cognitive deficits on neuropsychological testing [20]. Imaging tests, neuropathological observations, and animal studies suggest that ethanol neurotoxicity may contribute to this cognitive dysfunction.
Nevertheless, there is no unequivocal evidence for a brain lesion in humans that is caused solely by chronic ethanol ingestion and that is unrelated to coexisting nutritional deficiency, liver disease, or trauma [1,21,22].

Computed tomography (CT) and magnetic resonance imaging (MRI) show enlargement of the cerebral ventricles and sulci in the majority of alcohol abusers. However, when corrected for the effects of aging, the radiographic indices do not correlate consistently with either the duration of drinking or the severity of cognitive impairment [1]. The ventricles and sulci become significantly smaller within about one month of abstinence, [23-26], while brain water, estimated by MRI or chemical analysis does not consistently change [25,27,28]. Based upon these findings, it has been hypothesized that changes in brain parenchyma, but not brain water, may account for the reversible radiographic and cognitive abnormalities of alcoholics [24,25,29].

There is evidence for regional vulnerability in the brains of alcohol abusers [30]. Neuronal density in the superior frontal cortex was reduced by 22 percent in alcohol abusers compared with nonalcoholic controls in one report [31]. Selective loss of neurons in frontal brain regions is mirrored by regional hypometabolism on PET studies [32,33], and might correlate with deficits in working memory observed in alcohol abusers [30].

Quantitative morphometry suggests that alcohol abusers, including those with liver disease and Wernicke's encephalopathy (WE), lose a disproportionate amount of subcortical white matter compared with cortical gray matter [30,34-36]. The loss of cerebral white matter is evident across a wide range of ages, is not accentuated in the frontal lobes, and is of sufficient magnitude to account for the associated ventricular enlargement [37]. Diffusion-tensor imaging detects microstructural abnormalities in the white matter tracts of alcohol abusers even in the absence of macroscopic lesions [38]. MRI imaging of alcohol abusers shows an increase in white matter volume following three months of abstinence, suggesting that a component of the white matter injury is reversible [39].

Magnetic resonance spectroscopy studies have found metabolic as well as morphologic evidence of brain recovery occurring within two months of sobriety [29,39]. Thus, it is important to determine whether patients with undiagnosed cognitive decline are alcoholic because abstinence and nutritional repletion may prevent further worsening.

**ALCOHOLIC CEREBELLAR DEGENERATION** — Some alcohol abusers develop a chronic cerebellar syndrome related to the degeneration of Purkinje cells in the cerebellar cortex [40]. Midline cerebellar structures, especially the anterior and superior vermis, are predominantly affected, a pattern identical to that in Wernicke's encephalopathy (WE). Alcoholic cerebellar degeneration typically occurs only after 10 or more years of excessive ethanol use.

**Pathogenesis** — Alcoholic cerebellar degeneration may be caused by a combination of nutritional deficiency and alcohol neurotoxicity. A role for nutritional deficiency is suggested by observations that many patients with the disorder are malnourished, and symptom onset has been reported in some patients during periods of abstinence [1]. In addition, identical cerebellar lesions have been observed in a nonalcoholic patient who developed WE associated with malnutrition, suggesting that alcohol was not
required for the development of the cerebellar lesion [41].

One group assessed nutritional status and estimated recent and lifetime alcohol consumption in alcohol abusers and controls [42]. Cerebellar volume, determined by MRI, was progressively smaller in nonalcoholic controls, well-nourished alcohol abusers, poorly nourished alcohol abusers, and alcohol abusers with WE. Regression analysis suggested that both malnutrition and alcohol ingestion (daily intake of more than 140 g of alcohol over 10 years) contributed independently to the development of cerebellar shrinkage. It is noteworthy that alcohol abusers with WE reported higher daily ethanol consumption than asymptomatic alcohol abusers [43]; thus, it is possible that alcohol intake is a covariate of nutritional deficiency.

**Clinical features** — Alcoholic cerebellar degeneration usually develops gradually over weeks to months, but it may also evolve over years or commence abruptly. Mild and apparently stable cases can become suddenly worse. Almost all patients complain first of gait impairment, which is typically characterized as weakness, unsteadiness, or incoordination in the legs [40]. Later, a minority of patients may note incoordination and tremor in the arms, dysarthria, and intermittent diplopia or blurred vision. Vertigo, tinnitus, and deafness have not been reported.

The physical examination in patients with alcoholic cerebellar degeneration demonstrates features of a midline cerebellar lesion, with selective abnormalities of stance, gait, and lower extremity coordination. Patients exhibit ataxia of stance and gait, resembling that of acute alcohol intoxication. Tandem walking is typically impossible, even for those with mild disease. Heel-knee-shin testing is usually abnormal, but finger-nose testing may reveal only mild abnormalities, often associated with more severe impairment of handwriting. Mild dysarthria, characterized as slow, slurred speech, can occur. Some patients also have a coarse, rhythmic, 3 to 5 Hz postural tremor affecting the fingers, arms, or thighs. Cognitive function is usually unimpaired, except in patients with prior episodes of WE.

The clinical course of alcoholic cerebellar degeneration was characterized in 46 patients in the original series reporting the disorder [40]. In general, progression was associated with continued drinking and stabilization with abstinence. In one-half, symptoms appeared and became maximal over a period of weeks to months and then remained stable during many years of abstinence and improved nutrition. Another 16 declined gradually and progressively over many years of continued drinking. A small number exhibited mild, stable symptoms that worsened abruptly with intercurrent illness or malnutrition. Gait did not improve in most patients, and recovery was partial in those who did improve.

**Differential diagnosis** — Sedative hypnotic drug intoxication may be indistinguishable from alcoholic cerebellar degeneration, except for its reversibility. Consequently, some abstinent patients are mistakenly believed to be intoxicated.

The absence of cranial nerve abnormalities differentiates alcoholic cerebellar degeneration from vascular disorders of the posterior circulation, mass lesions, and demyelinating disease. The age of onset and clinical course sets this disorder apart from some of the spinocerebellar ataxias; multiple systems atrophy, including olivopontocerebellar degeneration, may be difficult to distinguish on clinical grounds.
alone.

**Diagnosis** — The diagnosis of alcoholic cerebellar ataxia is based primarily on the clinical history and neurologic examination, although a structural imaging study should be obtained to rule out mass lesions or other diagnoses. CT or MRI scans may show cerebellar cortical atrophy, but one-half of alcoholic patients with this finding are not ataxic on examination [44]. Whether these represent subclinical cases in which symptoms will develop subsequently is unclear.

In contrast, PET studies demonstrate a reduction in cerebral metabolic rate for glucose and a decrease in benzodiazepine receptor binding in the superior cerebellar vermis in alcohol abusers with cerebellar degeneration compared with alcohol abusers without the disorder [33,45]. The magnitude of hypometabolism correlates significantly with the severity of neurologic deficits. However, PET scanning is a research tool and is not indicated for the diagnosis of patients with suspected alcoholic cerebellar degeneration.

**Treatment** — Cessation of drinking and nutritional supplementation are the only treatments available for alcoholic cerebellar degeneration. However, gait does not improve in most patients [40]. Physical therapy, canes, walkers, and wheelchairs are helpful in maintaining mobility.

The effect of abstinence was demonstrated in a study that used posturography in a group of 17 alcohol abusers with cerebellar degeneration [46]. Neurologic examination revealed ataxia of stance and gait, ataxia on knee-heel test, and minimal abnormalities on finger-nose test. Most showed a 3 Hz tremor in the anteroposterior direction, which was accentuated by eye closure. All were tested five days after detoxification and an average of 18.5 months later. Eleven alcohol abusers who remained abstinent showed significant improvements in sway path, sway area, and anteroposterior sway during eye closure; in contrast, six alcohol abusers who continued to drink showed worsening of postural instability.

**MARCHIAFAVA-BIGNAMI DISEASE** — Marchiafava-Bignami disease is a rare disorder of demyelination or necrosis of the corpus callosum and adjacent subcortical white matter that occurs predominantly in malnourished alcoholics [47]. In some cases, there are associated lesions of Wernicke's encephalopathy (WE) as well as selective neuronal loss and gliosis in the third cortical layer. A few cases have been described in non-alcohol abusers, suggesting that alcohol alone is not responsible for the lesion.

The course of the disease may be acute, subacute, or chronic, and is marked by dementia, spasticity, dysarthria, and inability to walk. Patients may lapse into coma and die, survive for many years in a demented condition, or occasionally recover. An interhemispheric disconnection syndrome has been reported in survivors [48]. Lesions appear as hypodense areas in portions of the corpus callosum on CT and as discrete or confluent areas of decreased T1 signal and increased T2 signal on MRI (show radiograph 1) [49]. Alcohol abusers without liver disease, amnesia, or cognitive dysfunction show thinning of the corpus callosum at autopsy [50] and on MRI [51,52], suggesting that alcohol or malnutrition damages the corpus callosum commonly in the absence of the necrotic lesions of Marchiafava-Bignami disease. These findings raise
The possibility that aggressive nutritional supplementation along with a reduction in drinking can prevent the development of Marchiafava-Bignami disease in alcohol abusers.

**NEUROMUSCULAR COMPLICATIONS**

**Peripheral neuropathy** — Alcohol abusers have a high incidence of peripheral nerve disorders, including symmetric polyneuropathy, autonomic neuropathy, and compression mononeuropathies. As an example, peripheral neuropathy was detected in 32 percent and autonomic neuropathy in 24 percent of 107 consecutively examined alcohol abusers in one report [53]. The majority of patients in this series were middle class working men, and evidence of malnutrition was present in only a small minority [54]. The prevalence of autonomic and peripheral neuropathy each correlated best with lifetime alcohol consumption more than with nutritional deficiency [53,55,56].

Pathogenesis — Detailed neuropathologic and electrophysiologic evaluation suggests that alcoholic peripheral neuropathy is primarily an axonal neuropathy, complicated by demyelination when there is coexisting nutritional deficiency [57]. Consistent with these findings, studies have found a predominant reduction in the density of small myelinated and unmyelinated fibers in a group of alcohol abusers with normal thiamine status, a distinctly different pattern from that of beriberi neuropathy [58,59]. In some studies, the degree of slowing in nerve conduction in alcoholic peripheral neuropathy correlated with reductions in erythrocyte transketolase activity, a marker of thiamine deficiency [60,61]. Taken together, these data suggest that alcoholic peripheral neuropathy is caused by alcohol neurotoxicity, but it is sometimes complicated by vitamin deficiency.

Clinical features — Alcoholic polyneuropathy is a gradually progressive disorder of sensory, motor, and autonomic nerves. The clinical abnormalities are usually symmetric and predominantly distal. Symptoms include numbness, paresthesia, burning dysesthesia, pain, weakness, muscle cramps, and gait ataxia. The most common neurologic signs are loss of tendon reflexes, beginning with the ankle jerks, defective perception of touch and vibration sensation, and weakness. Loss of vibratory sensation can be demonstrated in asymptomatic alcohol abusers [62].

Alcoholic polyneuropathy also renders patients susceptible to compression of peripheral nerves at common sites of entrapment, including the median nerve at the carpal tunnel, the ulnar nerve at the elbow, and the peroneal nerve at the fibular head [63]. "Saturday night palsies" occur during bouts of intoxication when the radial nerve is compressed against the spiral groove of the humerus. (See "Overview of upper extremity peripheral nerve syndromes").

Treatment — Specific treatments for alcoholic peripheral neuropathy are not available. Patients should receive thiamine supplementation since malnutrition may contribute to the development of the disorder. Improved nutrition and cessation of drinking have been associated with symptom improvement in cohort studies [64-67], although complete recovery from severe neuropathy is uncommon. Low doses of tricyclic antidepressants, mexiletine [68], or gabapentin are sometimes effective in controlling the burning dysesthesias of alcoholic peripheral neuropathy. (See "Overview of polyneuropathy", section on Treatment of symptoms and prevention of...
complications).

**Myopathy** — Skeletal myopathy is an underrecognized complication of alcohol abuse. In two different studies, almost one-half of alcoholic patients visiting an ambulatory clinic and 60 percent of hospitalized alcohol abusers had biopsy evidence of myopathy [69,70].

Skeletal muscle can be damaged by the administration of alcohol to well-nourished volunteers [71], and most patients with alcoholic myopathy are not demonstrably malnourished [56,72]. Electrolyte abnormalities such as hypokalemia, which are often present in alcoholic patients, can also impair skeletal muscle function. However, studies of alcoholic patients and of ethanol-induced myopathy in rats show no correlation between hypokalemia and muscle damage [73].

Alcoholic myopathy may present as either an acute, necrotizing disorder or as a more indolent process [70,74]. (See "Drug-induced myopathies", section on Alcohol).

**Acute myopathy** — The acute form develops over hours to days, often in relation to an alcoholic binge, and is characterized by weakness, pain, tenderness, and swelling of affected muscles. Animal studies suggest that fasting during a binge may precipitate muscle injury [75]. The vast majority of affected patients are men.

Proximal muscles are often most severely involved, but the distribution of involvement can be asymmetric or focal. Dysphagia [76] and congestive heart failure may occur [77,78]. Laboratory findings include moderate to severe elevation of serum creatine kinase (CK), myoglobinuria, fibrillations, and myopathic changes in the electromyogram, and muscle fiber necrosis on biopsy [70,74,77,79].

Initial treatment is directed at correcting cardiac arrhythmias, renal failure due to rhabdomyolysis, and electrolyte disturbances such as hypophosphatemia or hypokalemia. Abstinence from ethanol is usually associated with gradual, often partial, recovery [80,81].

**Chronic myopathy** — Chronic alcoholic myopathy, which evolves over weeks to months, is a more common disorder [56,70,72]. Pain is less prominent than in acute alcoholic myopathy, but muscle cramps may occur.

On examination, the major findings are muscle weakness and atrophy, which affect predominantly the hip and shoulder girdles. Although a polyneuropathy coexists in many cases, the clinical and laboratory features of this disorder indicate a primary disturbance of muscle. Serum CK is less elevated than in acute alcoholic myopathy, and myoglobinuria does not occur.

Cessation of drinking leads to improvement in most cases, while continued alcohol abuse results in clinical deterioration [81].

NOTE: The author's work is supported by NIAAA and the Medical Research Service, Department of Veterans Affairs.

Use of *UpToDate* is subject to the Subscription and License Agreement.
REFERENCES

39. Shear, PK, Jernigan, TL, Butters, N. Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics [published


GRAPHICS

Marchiafava-Bignami disease

Fifty-nine-year-old female with history of alcohol abuse and diabetes who presented obtundated two days prior to magnetic resonance imaging (MRI) study. T2-weighted axial image (A) shows high signal intensity in the splenium of the corpus callosum, consistent with suspected Marchiafava-Bignami disease. Diffusion-weighted axial images (B) show high signal intensity, which may be expected, as previous studies have shown restricted diffusion in these callosal lesions [1,2].