Neuroimaging Findings in Alcohol-Related Encephalopathies

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OBJECTIVE. Our aim was to review the emergent neuroimaging findings of alcohol-related CNS nontraumatic disorders. Alcohol (ethanol) promotes inflammatory processes, increases DNA damage, and creates oxidative stress. In addition, the accompanying thiamine deficiency may lead to Wernicke encephalopathy. Associated changes in serum osmolarity may lead to acute demyelination.

CONCLUSION. Alcohol-related encephalopathies can be life-threatening conditions but can be prevented or treated, if recognized.

Keywords: alcohol abuse, alcohol withdrawal delirium, central pontine myelinolysis, extrapontine myelinolysis, hepatic encephalopathy, Marchiafava-Bignami disease, nervous system, Wernicke encephalopathy

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Alcohol-related encephalopathies comprise a spectrum of CNS disorders that are directly or indirectly related to chronic alcohol abuse. Chronic ethanol intoxication may lead to atrophy related to loss of subcortical white matter and alterations in the number and size of neurons. Associated malnutrition may cause Wernicke encephalopathy (WE), which is due to thiamine (vitamin B1) deficiency. Marchiafava-Bignami disease (MBD) is a rare entity characterized by acute demyelination of the corpus callosum. Osmotic demyelination syndromes are seen in the setting of altered plasma osmolarity that is associated with alcohol abuse. Hepatic encephalopathy is a potentially reversible syndrome occurring during acute and chronic liver failure that is associated with deposition of neurotoxic substances in the CNS. Alcohol withdrawal syndrome is observed in patients who stop drinking. The aim of this article is to provide an update of the important neuroimaging findings associated with alcohol abuse that can be crucial in helping make these diagnoses.

Wernicke Encephalopathy

WE is a neurologic emergency caused by a thiamine deficiency [1]. It is commonly seen in the alcoholic population but can also be seen with malignancy, total parenteral nutrition, abdominal surgery, hyperemesis gravidarum, hemodialysis, or any situation that predisposes an individual to a chronically malnourished state [2]. If untreated, irreversible brain damage may ensue and could even lead to coma, death, or Korsakoff syndrome, a permanent brain injury that results in antegrade amnesia and confabulation [3]. Postmortem studies indicate that this very treatable disease is underdiagnosed [4].

Pathology

In a thiamine-deficient state, increased metabolic requirements and inability to regulate the osmotic gradients disrupt the blood–brain barrier, resulting in cytotoxic edema and, eventually, permanent neuronal loss in the areas with the highest metabolic demands [5]. In the acute setting, petechial hemorrhage, hypertrophic endothelial changes, and reactive gliosis are identified [6]. Occasionally, necrosis is seen. These findings can then progress to the chronic pathologic changes of gliosis and neuronal loss [7].

Clinical Presentation

The classic triad of WE includes ataxia, global confusion, and opthalmoplegia [8]. However, this triad is often not present in many adult and pediatric patients [9, 10]. The most common presenting symptom is nonspecific mental status changes [9]. This often makes the diagnosis challenging and likely explains its diagnostic elusiveness. Revised criteria have been proposed that take into account dietary deficiencies and may facilitate the clinical detection of this syndrome [3]. A high degree of suspicion for WE is warranted in patients with systemic illnesses, malnutrition, and alcoholism.

Imaging Findings

CT has been shown to have a low sensitivity for the detection of WE, and when findings are present, they are often nonspecific areas of low

density [11]. On MRI, WE typically affects medial thalami, mamillary bodies, the tectal plate, and periaqueductal gray matter in a symmetric fashion [12] (Fig. 1). The differential diagnosis of symmetric lesions of the medial thalami should include ischemia as a result of occlusion of the artery of Percheron and deep cerebral vein thrombosis, influenza A virus infection, primary acute disseminated encephalomyelitis, cytomegalovirus encephalitis, primary cerebral lymphoma, Creutzfeldt-Jakob disease variant, West Nile virus meningoencephalitis, and WE [13]. Involvement of the cerebellum, cerebellar vermis, red nuclei, dentate nuclei, splenium of corpus callosum, fornix, cerebral cortex, cranial nerve nuclei, and basal ganglia have been identified only in the nonalcoholic and pediatric populations [9–13]. Selective alteration of the putamen appears to differentiate the pediatric form of WE from the adult cases [10–13]. MR spectroscopy (MRS) may depict lactate peak and low levels of *N*-acetylaspartate (*N*-NAA)/creatine (Cr) in the affected areas but does not have a clinical prognostic impact [14]. Positioning a single voxel (TE 144 or 244) in the thalami and a control voxel in the normal-appearing gray matter could be helpful in depicting lactate peak. Otherwise, a voxel can be positioned on the midline to include the areas of T2 hyperintensity in the diencephalon [14].

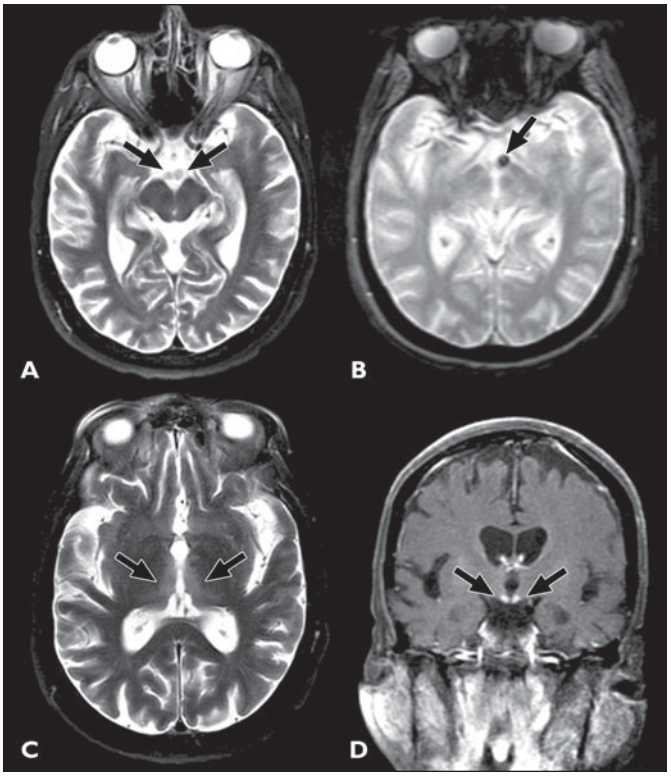

Fig. 1—61-year-old alcoholic man with Wernicke encephalopathy during acute phase of disease.
A, Axial T2-weighted image shows asymmetric edema of mamillary bodies (*arrows*).
B, Multiplanar gradient-recalled image shows blooming consistent with hemorrhage (*arrow*) in left mamillary body.
C, Symmetric involvement of medial thalami (*arrows*) is seen on T2-weighted image.
D, Contrast enhancement of mamillary bodies (*arrows*) is seen on T1-weighted image.

Marchiafava-Bignami Disease

MBD is a rare disorder that results in progressive demyelination and necrosis of the corpus collosum. MBD is generally associated with chronic alcohol abuse but is occasionally seen in nonalcoholic patients [15, 16]. Despite an anecdotal association with red wine, there is no clear evidence that red wine is specifically involved in MBD [17]. MBD is most prevalent in men between 40 and 60 years of age. However, the disease has also been reported in the pediatric population [18].

Pathology

The main pathologic change associated with MBD is degeneration of the corpus callosum, which may vary from demyelination to frank necrosis [17, 19]. Demyelination is accompanied by infiltration of macrophages and, ultimately, thinning of the corpus callosum [17, 20]. Necrosis produces cystic cavities within the corpus callosum, mainly in the genu and splenium [17, 21].

Clinical Presentation

The disease may present in two major clinical forms: acute and chronic. In the acute form, which often results in death, patients present with severe impairment of consciousness, seizures, and muscle rigidity [17–20, 22]. The chronic form of the disease may last for several months or years and is characterized by variable degrees of mental confusion, dementia, and impairment of gait [17, 19, 22]. An intermediate form of MBD, with acute onset of neurologic symptoms followed by regression to the chronic form, has also been reported [21].

Imaging Findings

CT of MBD patients shows diffuse periventricular low density and focal areas of low density in the genu and splenium of the corpus callosum [19]. On MRI, patients with MBD show areas of low signal intensity on T1-weighted images. There is high signal intensity on T2 and fluid-attenuated inversion recovery (FLAIR) images in the body of the corpus callosum, genu, splenium, and adjacent white matter [17, 21]. During the acute phase, the lesions may show peripheral contrast enhancement [21]. As the disease progresses, signal alterations become less evident, but residual atrophy of the involved structure is usually observed [17] (Figs. 2 and 3). MBD may be found in association with other alcohol-related diseases, including WE, Korsakoff syndrome, central pontine myelinolysis (CPM), and Morel laminar necrosis [21, 23]. The differential diagnosis of corpus callosum lesions includes ischemia, diffuse axonal injury, multiple sclerosis, acute disseminated encephalomyelitis, high-altitude cerebral edema, extrapontine myelinolysis (EPM), and lymphoma [18, 24]. Diffusion-weighted imaging (DWI) reveals symmetric hyperintense lesions in the cerebral cortex and corpus callosum [19]. Apparent diffusion coefficient (ADC) mapping yields a marked decrease of ADC values of the involved areas. Although rarely used, MRS may provide additional information on disease pathogenesis and prognosis through evaluation of brain metabolites [17]. To acquire the spectra, a chemical shift spin-echo technique (TR/TE, 1,500/135) has been described, in which the multivoxel was positioned to include the corpus callosum and periventricular white matter [17]. The *N*-NAA/Cr ratio has been reported to decline during the first 4 months of MBD, representing secondary axonal injury following myelin degradation. Lactate, which accompanies inflammatory reactions, was detectable during the subacute phase. After 4 months, lactate was replaced by lipids, indicating necrosis of axons and oligodendrocytes [17].

Osmotic Demyelination Syndrome

Osmotic demyelination syndrome (ODMS) was formerly known as CPM and EPM, or a

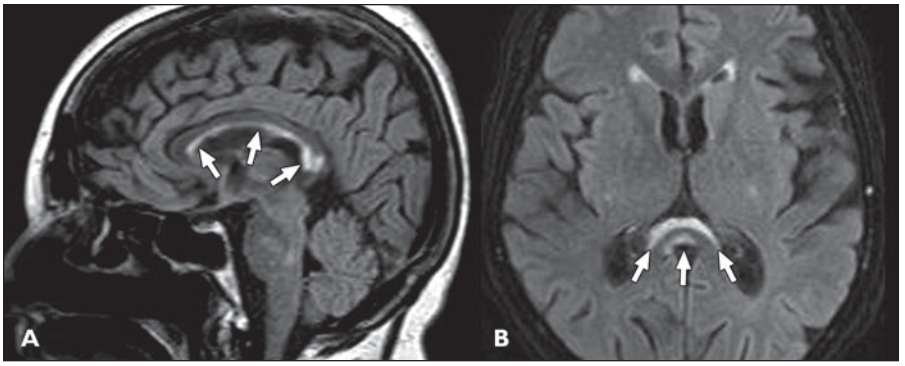

Fig. 2—53-year-old alcoholic woman with Marchiafava-Bignami disease during subacute phase.
A, Sagittal FLAIR image shows signal intensity alteration involving inferior aspect of corpus callosum (*arrows*).
B, Axial FLAIR image depicts two curvilinear hyperintensities (*arrows*) in splenium of corpus callosum.

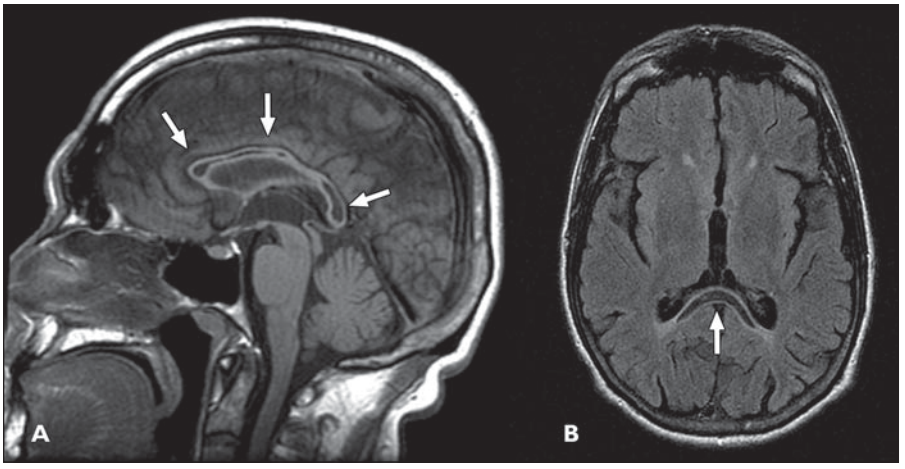

Fig. 3—53-year-old alcoholic man affected by Marchiafava-Bignami disease.
A, Multiple cavitations and atrophy of corpus callosum are noted (*arrows*) on sagittal T1-weighted images.
B, Axial FLAIR image shows cavitations of splenium of corpus callosum (*arrow*).

combination of both [25]. CPM is an acquired condition that results in an osmotic insult and demyelination of the basis pontis [26]. Although the pontine base represents the most common site of involvement, lesions do occur outside of the pons and are termed EPM [27]. The extrapontine lesions are typically seen in the thalami, basal ganglia, lateral geniculate body, cerebellum, and the cerebral cortex [28]. ODMS is most commonly seen in the setting of hyponatremia and its acute correction, or in patients with a history of chronic alcohol abuse and malnutrition [29].

Pathology

The main pathologic finding seen with CPM or EPM is a symmetric area of myelin disruption in areas with admixed gray and white matter [30]. It is most commonly seen in the basis pontis (with CPM) but can also be seen independently in the basal ganglia, thalamus, and neocortical and cerebellar gray/white interface (with EPM) [27]. The demyelinating process is characterized by vacuolization and intramyelinitic splitting with eventual rupture of the myelin sheaths, believed to be caused by osmotic gradient effects [31].

Clinical Presentation

ODMS can present in three distinct ways: isolated CPM, isolated EPM, and combined CPM and EPM. The initial clinical scenario, however, is the same: A patient is treated with IV therapy for an underlying electrolyte dysfunction, as seen with hyponatremia, thus creating the hyperosmolar state that leads to demyelination [30]. Classically, the symptoms of CPM present in a biphasic pattern. Initially, the patient presents with a generalized encephalopathy and electrolytic dysfunction, both of which improve after treatment. Between 2 and 7 days after rapid electrolyte correction, the patient develops neurologic abnormalities associated with myelinolysis, including dysphagia, dysarthria, opthalmoplegia, diplegia, and altered mental status that can eventually progress to coma or death [25, 32, 33].

Imaging Findings

On CT, ODMS typically manifests as low-density lesions in the pons or other affected regions, and occasionally shows enhancement [34]. In acute CPM, MRI shows signal alteration in the central pons with sparing of the tegmentum, ventrolateral pons and corticospinal tracts [35] (Fig. 4). In EPM, symmetric signal alterations can be seen in the basal ganglia, thalami, lateral geniculate body, cerebellum, and cerebral cortex [36] (Figs. 5 and 6). On DWI, mildly restricted lesions can be detected within 24 hours after onset of symptoms and thus provide the earliest indication of this disease entity [32]. The differential considerations include pontine infarcts, which can be distinguished by their asymmetric distribution, involvement of the peripheral pontine fibers, demyelinating disease processes, neoplastic involvement of the pons, and metabolic syndromes such as Leigh disease and Wilson disease. Typically, however, these lesions do

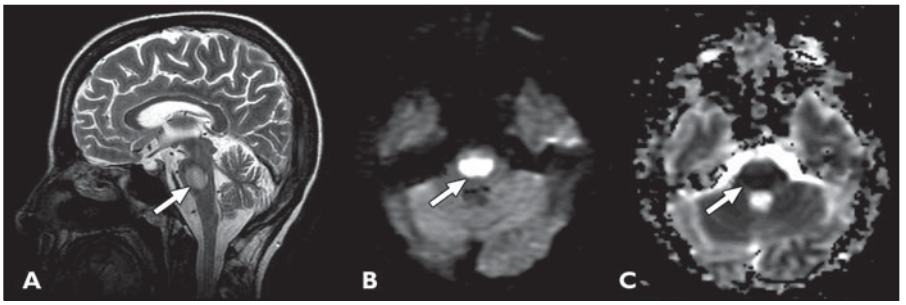

Fig. 4—40-year-old alcoholic woman after rapidly corrected hyponatremia.
A, Sagittal T2-weighted image shows signal prolongation in pontis (*arrow*) typical of central pontine myelinolysis.
B and **C,** Diffusion-weighted image (DWI) (**B**) and apparent diffusion coefficient map (**C**) show restricted diffusion (*arrows*).

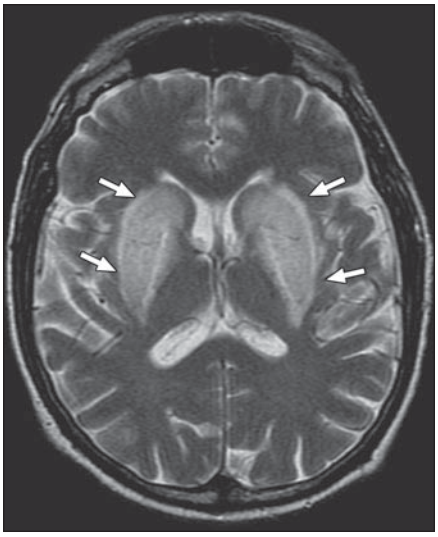

Fig. 5—67-year-old alcoholic man after rapidly corrected hyponatremia. T2-weighted image shows diffuse involvement of basal ganglia (*arrows*) characteristic of extrapontine myelinolysis.

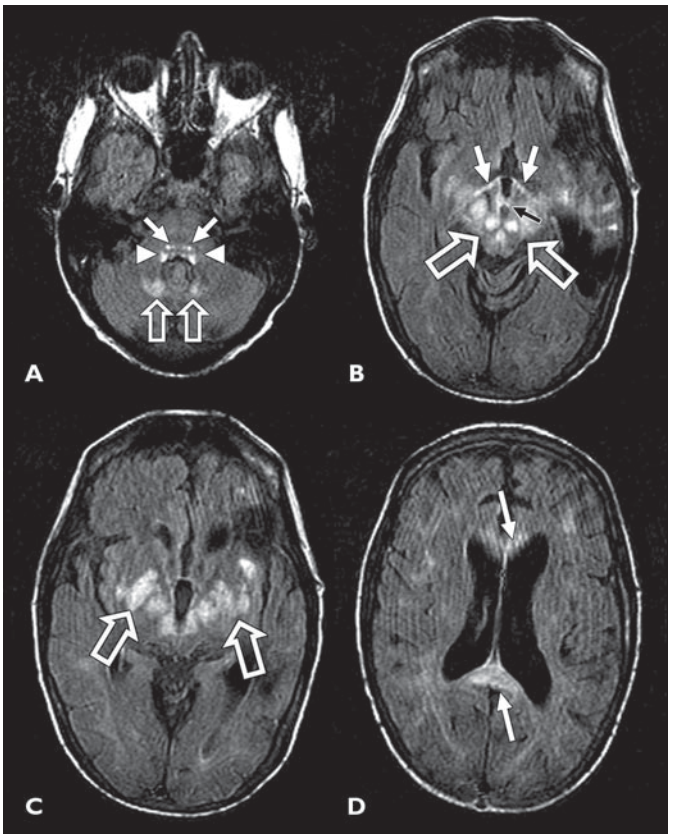

Fig. 6—51-year-old alcoholic man after rapidly corrected hyponatremia showing typical and atypical patterns of extrapontine myelinolysis.
A, Axial FLAIR image reveals selective involvement of facial nerves nuclei (*arrows*), trigeminal and abducens nuclei (*arrowheads*), and dentate nuclei of cerebellum (*open arrows*).
B, Oculomotor nerve nuclei and red nuclei (*open arrows*), cerebral peduncles, mamillary bodies (*black arrow*), and optic tracts (*white arrows*) show signal intensity alterations. Note that alterations in mamillary bodies are also typical of Wernicke encephalopathy.
C, Basal ganglia show high signal intensity alterations bilaterally (*arrows*).
D, Alterations of corpus callosum (*arrows*) are also noted.

not spare the peripheral pontine fibers and frequently have other associated findings [31].

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a functional and potentially reversible syndrome occurring during acute and chronic liver failure or after portosystemic shunt surgery. It is characterized by psychiatric, cognitive, and motor abnormalities [37, 38]. Depending on the duration and degree of hepatic dysfunction, HE may be classified into portosystemic encephalopathy (PSE) or fulminant hepatic failure [37].

Pathology

Pathogenic mechanisms responsible for HE are thought to be related to the accumulation in blood of several compounds that are efficiently metabolized by the liver under normal circumstances. These substances include manganese and ammonia, which can then enter the brain and induce disturbances in astrocyte and neuron function [39–42]. The hypermanganesemia has a neurotoxic effect, inducing reactive gliosis and selective neuronal loss in basal ganglia and midbrain structures [43]. Pathologic examination of HE cases reveals diffuse proliferation of Alzheimer type-II cells in the many gray matter regions [41]. Some patients with acquired hepatocerebral degeneration also have cortical gliosis, laminar neuronal necrosis, atrophy of lenticular nuclei, and polymicrocavitation of the corticomedullary junction, striatum, and cerebellar white matter.

Clinical Presentation

HE can occur during acute liver malfunction from any cause or can complicate chronic liver disease. HE has been further subdivided, based on duration and characteristics of neurologic dysfunction, into episodic, persistent, and minimal subtypes [44]. HE manifests as a neuropsychiatric syndrome encompassing a wide spectrum of psychiatric and behavioral disturbances, as well as motor disorders [44, 45].

Imaging Findings

In acute HE, T2 prolongation may affect the cerebral cortex [46–49]. In chronic hepatic encephalopathy (CHE), foci of T2 prolongation resembles those seen in small-vessel disease [50]. Regression of the MRI lesions after liver transplantation or with the improvement of HE has been shown, providing evidence supporting their reversible nature [51]. The chronic phase is characterized by symmetric T1 high-signal-intensity alterations in the basal ganglia (more often the globus pallidus), the subthalamic nucleus, mesencephalus, tectal plate, hypothalamus, and adenohypophysis [50, 52–54] (Fig. 7). The described T1 hyperintensity is caused by deposition of manganese, which is alleviated on normalization of liver function [53]. Increase in brain water diffusivity has been shown in CHE [55–57]. In acute liver failure, ADC values may be reduced [58], whereas MRS depicts an increase in the glutamine and glutamate peak and a decrease in the myoinositol and choline peaks [59–65]. FLAIR, DWI, and diffusion tensor imaging [66] are more sensitive to changes in brain tissue water content than conventional T2 sequences and have been applied to detect diffuse hyperammonemia-related brain edema in patients with chronic liver disease [49].

Alcohol Withdrawal Syndromes

Alcohol withdrawal syndrome (AWS) is a constellation of symptoms observed in a person who stops drinking alcohol after a period of continuous and heavy alcohol consumption. Delirium tremens represents a distinct clinical entity within the AWS spectrum. It is defined as an acute generalized involvement of the CNS, and is characterized by impairment of consciousness. Patients affected by delirium tremens may experience hallucinations, tremors, convulsions, sweating, and an increase in heart rate and body temperature. In severe cases, hypothermia, cardiovascular collapse, and death are described [67].

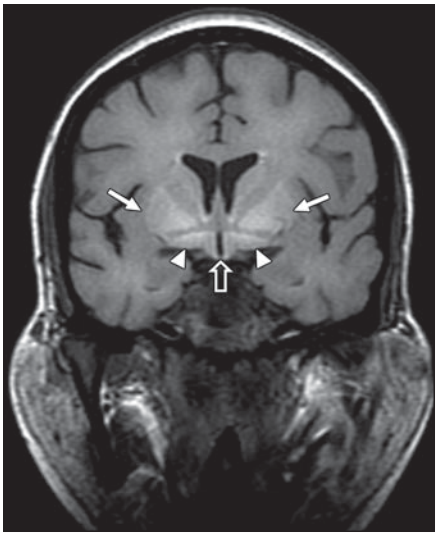

Fig. 7—46-year-old alcoholic woman with chronic liver failure. Coronal T1-weighted image shows high signal intensity of basal ganglia (*solid arrows*), hypothalamic nuclei (*arrowheads*), and mamillary bodies (*open arrow*).

Pathology

Only a few pathologic investigations are available. They show nonspecific changes, lesions typical of alcoholism, or both. These reflect permanent pathologic changes such as axonal Wallerian degeneration, which results in a permanent decrease in white matter volume [68]. Histology shows central chromatolysis of neurons [69], which most often is observed in Betz cells and in the neurons of the pontine nuclei. Circular neurons with peripheral displacement of the nuclei and Nissl substance are depicted [69].

Clinical Presentation

In AWS, disturbances in cognition, perception hallucinations, visual impairment, nausea, and tinnitus are thought to relate to cortical dysfunction. Tremor, sweating, depression, and anxiety are related to effects on the limbic system. Changes in consciousness and gait disorders are associated with brainstem involvement. Alcohol-related seizures were first described in 1981, and are commonly observed in AWS [70]. The term alcoholic epilepsy should not be applied if alcohol is still being consumed. Delirium tremens is the expression of alcohol withdrawal, and seems to be related to kindling phenomenon [67]. A repeated subconvulsive stimulus can accumulate its activity, causing a generalized seizure [67].

Imaging Findings

In alcoholics with withdrawal seizures, MRI depicts cytotoxic edema during the acute and subacute phases (Fig. 8) and significant volume loss in temporal regions [71]. It could therefore be deduced that epileptic seizures affect alcoholic subjects similarly to temporal epilepsy, in which reversible edema with some volume loss and consequent hippocampus atrophy is observed. In a patient affected by AWS, reversible vasogenic edema in the cerebellum; thalami; and cortical, subcortical, and deep parietal white matter has been described in the clinical setting of posterior reversible encephalopathy syndrome [72].

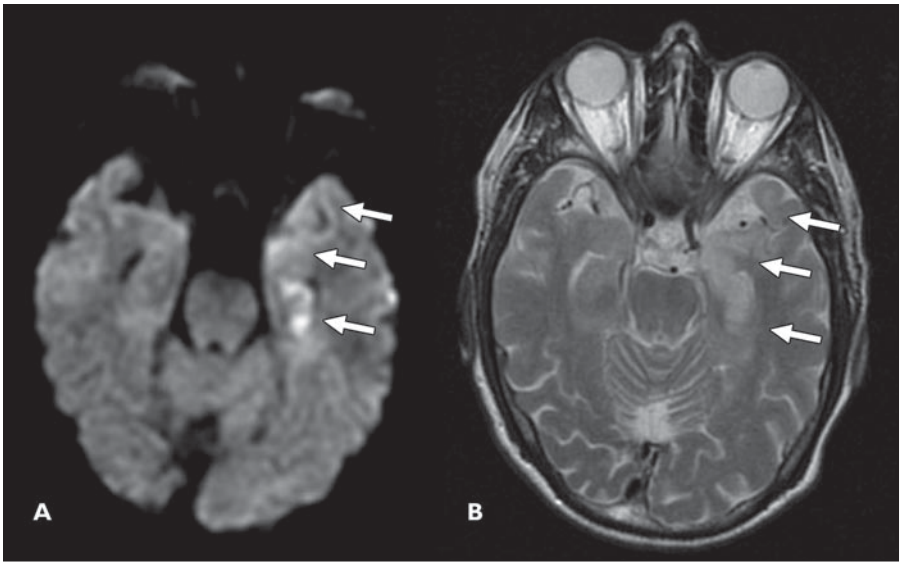

Fig. 8—38-year-old alcoholic man with delirium-tremens-related seizures.
A, Restricted diffusion is noted in left hippocampus (*arrows*).
B, T2 prolongation in left temporal region (*arrows*) is also noted.

Conclusion

Alcohol-related encephalopathies are life-threatening conditions, often characterized by nonspecific neurologic presentation. Neuroimaging represents a useful tool in depicting alcohol-related brain damage. Accurate knowledge of the neuroimaging findings can lead to correct diagnosis and treatment. Alcohol-related encephalopathies may share common anatomic regions and thus seem to represent a continuum more than distinct pathologic entities.

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