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Alcohol-induced changes in the brain as assessed by MRI and CT

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Abstract This review provides an overview of structural magnetic resonance imaging and computed tomography findings of direct and indirect alcohol-related toxic effects on the brain. In addition to ethanol-related changes to the brain, this article will also describe imaging findings in the acute setting of methanol and ethylene glycol poisoning. Alcohol will lead to brain atrophy, osmotic myelinolysis, Marchiafava–Bignami disease and, especially when related to malnutrition, may also cause Wernicke encephalopathy. Brain atrophy can be reversible if alcohol abuse is stopped. If not treated, Wernicke encephalopathy can lead to coma and death and an early diagnosis is important for immediate initiation of thiamine substitution. As clinical symptoms are often unspecific, the radiologist plays an important role in the detection of alcohol abuse and its related clinical conditions.

Keywords Alcohol · Brain · Atrophy · Wernicke encephalopathy · Osmotic myelinolysis · Marchiafava–Bignami disease

Introduction

Alcohol is one of the most commonly abused substances and alcohol dependence is the third leading cause of disease burden in developing countries worldwide as reported by the World Health Organisation [1, 2]. Alcohol metabolism is a complex process with large variations between individuals, and is mainly related to genetic factors. Direct absorption into the bloodstream occurs at the stomach and small intestine. The liver breaks down nearly 90% of alcohol. Alcohol dehydrogenase (ADH) oxidises ethanol into acetaldehyde which is then further oxidised into acetic acid by acetaldehyde dehydrogenase (ALDH) and finally metabolised into CO_2 and water through the citric acid cycle [3]. Alcohol-related brain changes can be separated into two groups. The primary or "direct" effect of alcohol is volume loss due to a toxic effect on neurons often mediated by a compromise of neurotransmitters and/or receptors and electrolytes [4]. Secondary effects, on the other hand, are related to the sequelae of liver cirrhosis, i.e. hepatic encephalopathy and coagulopathies, and problems related to the gastrointestinal (GI) tract, with consequent impairment of vitamin uptake [5, 6]. Finally, in at least three clinical conditions related to alcohol, it remains unclear whether primary or secondary effects (or a combination of both) are the leading pathomechanisms: Wernicke encephalopathy may be due to direct toxic effects of alcohol and/or to alcohol-related malnutrition/malabsorption; osmotic myelinolysis may be directly related to the effects of alcohol or secondarily to changes in the blood electrolyte homeostasis; and Marchiafava–Bignami disease, where the exact pathomechanism is yet to be determined. Finally, chronic alcoholism also produces progressive adaptive mechanisms in the CNS. As a consequence, abrupt

cessation of chronic alcohol intake is responsible for withdrawal syndromes that may manifest themselves as epilepsy and hallucinations (delirium tremens).

In this review, we illustrate the structural magnetic resonance imaging (MRI) and computed tomography (CT) findings of both the direct and indirect effects of ethanol and its withdrawal, describe their pathomechanism and clinical findings and discuss briefly methanol and ethylene glycol.

MRI and CT findings

Volume loss in chronic alcoholism

Direct brain toxicity is caused by up-regulation of *N*-methyl-D-aspartate (NMDA) receptors secondary to abnormal homocysteine catabolism that results in increased susceptibility to excitatory and cytotoxic effects of glutamate. In addition, acetaldehyde and related products of lipid peroxidation can bind to the brain tissue and initiate an immuno-mediated response resulting in neuronal and white matter damage. NMDA receptors also inhibit the function of cell membrane ionic canals. This results in a reduction of intracellular Na^+ and Cl^- and consequent brain volume loss.

Chronic alcohol consumption leads to decreased neurotrophic factors, which results in interference with the normal brain function, dysregulation of neuronal synaptic connectivity and apoptosis. Decreased gene expressions of myelin protein encoding genes in the glia cells are present in the superior frontal cortex and hippocampus, resulting in further volume loss in these regions [3, 4]. This aspect is of particular importance in cases of connatal alcoholism syndrome: Newborns from alcoholic mothers may have diffuse brain atrophy prevalent at the cerebellum. Alcohol inhibits growth of Bergmann's fibres, thus impairing the migration processes from the deep germinative zone (Fig. 1).

From an imaging point of view, a characteristic spread of volume loss is observed. Initial changes can be seen in the cerebellum on either CT or MRI with atrophy of the upper vermis, prominence of the cerebellar fissures without associated pontine atrophy. In later stages, the frontal white matter will be involved leading to prominent sulci and widening of the frontal and temporal horns. In the final stages, global volume loss is seen. Recent studies have demonstrated that brain atrophy is reversible if chronic alcohol intake is stopped [7]. Histology reveals loss of neurons, especially in the superior frontal and motor cortices, a significant decrease in white matter volume and reduction of neuronal dendritic arborisations [8]. Following cessation of chronic alcohol intake, the reversibility of brain atrophy is believed to be due to sprouting of dendrites and axons, glial hyperplasia, or rehydration of brain tissue [9].

It is interesting to note that the regression of brain atrophy and metabolic recovery occur at an early stage after abstinence from chronic alcohol abuse [7]. Quantitative diffusion tensor imaging has shown that excessive alcohol abuse not only causes macrostructural tissue shrinkage, but also fibre microstructure compromise with white matter degradation in multiple different fibre systems including the corpus callosum [10, 11].

Neurochemical changes can occur in the brain even without brain atrophy. In a recent study employing MR spectroscopy, alteration of brain metabolites (choline and creatine decrease and glutamate increase) that correlated with altered short-term memory functions were present in structurally normal-appearing brain [12]. In addition, a decrease in *N*-acetylaspartate (NAA) can be found as a potential marker of axonal damage as well as an increase in inositol that may reflect astrocyte proliferation [13], whereas following abstinence an increase in choline-containing compounds is seen as a potential marker for increased membrane metabolism [14].

Wernicke encephalopathy

Wernicke encephalopathy (WE) or Wernicke–Korsakoff syndrome is a neurological disorder caused by thiamine

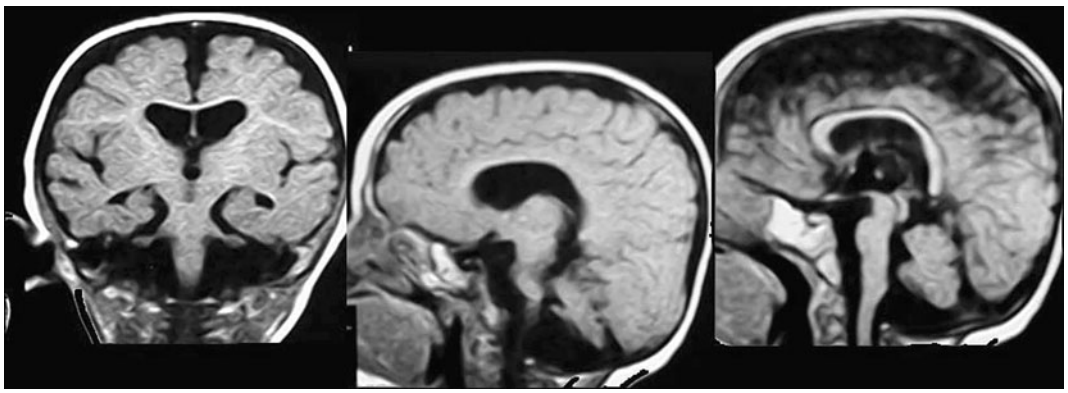

Fig. 1 Coronal T1-weighted IR and sagittal T1-weighted MR sequences demonstrate diffuse brain atrophy and marked diffuse cerebellar atrophy in a 2-year-old boy born from an alcoholic mother

deficiency related to chronic alcoholism. The major pathomechanisms include inadequate nutritional intake, decreased absorption of thiamine through the gastrointestinal tract and decreased thiamine utilization in the cells [15]. The incidence in random autopsies is reported to be 0.8–2% [16, 17]. The classic clinical triad of WE including ocular dysfunction (nystagmus, conjugate gaze palsies, ophthalmoplegia), ataxia and altered mental status is only observed in 30% of patients [18]. If left untreated, patients may develop Korsakoff psychosis, a form of severe amnesia, characterised by memory loss and confabulation, which may occur without other symptoms of WE. These clinical findings are related to damage of the mammillary bodies, anterior thalamic nuclei and interruption of the diencephalic-hippocampal circuits [19]. Rapid thiamine substitution has to be initiated to prevent the otherwise rather high mortality rates.

Several neuropathological changes can be observed in thiamine deficiency. As thiamine is involved in the maintenance of membrane integrity and osmotic gradients across cell membranes, depletion will lead to failure of conversion of pyruvate to acetyl-CoA and α-ketoglutarate to succinate, altered pentose monophosphate shunt and the lack of Krebs cycle will result in cerebral lactic acidosis and to intra- and extracellular oedema with swelling of astrocytes, oligodendrocytes, myelin fibres and neuronal dendrites [20]. Demyelination, glial cell proliferation, capillary endothelium hyperplasia and proliferation with petechial haemorrhage can be seen in the subacute phase, predominantly in the paraventricular region, around the third ventricle in the dorsomedial and pulvinar nuclei of the thalami and hypothalami, mammillary bodies, pineal regions and periaqueductal region of the midbrain, including the third nerve nuclei [21].

On MR imaging, these changes can be seen as bilateral and symmetrical abnormal hyperintensities on T2-weighted and FLAIR images [22, 23]. Reversible high signal changes on diffusion-weighted images (DWI) with either decreased apparent diffusion coefficient (ADC) representing cytotoxic oedema of the neurons and glial cells or increased ADC due to the presence of vasogenic oedema can also be present [24–26]. Enhancement on post-Gd T1-weighted images of the lesions can be seen in approximately 50% of cases in the periventricular and periaqueductal regions, frontal cortex and thalami due to disruption of the blood–brain barrier [27, 28]. Strong enhancement of the mammillary bodies in the acute phase, which is seen in up to 80% of cases, even without the T2 signal changes, is considered pathognomonic for WE [29] (Fig. 2). Reversibility of these changes can be seen after thiamine replacement (Fig. 3). In chronic cases, the T2 hypersignal becomes less prominent because of the diffuse atrophy of the brain, especially at the fornices and mammillary bodies [22, 29]. If haemorrhage is present in the acute form (with petechial T1 hyperintensities in the thalami and mammillary bodies) the prognosis is considered infaust (Fig. 4). It is important to note that while clinical findings do not differ between WE in alcoholic and non-alcoholic patients, imaging findings do: Contrast enhancement in the affected brain regions is found in almost all alcoholic WE patients, whereas contrast enhancement is only rarely present in cases of other aetiologies [30]. In addition, there is a higher prevalence of involvement of the mammillary bodies in patients with alcoholism [31], while atypical MR imaging patterns may be observed in non-alcoholic patients afflicted with WE. A potential explanation for this different distribution refers to a laxity of the blood–brain barrier in the periaqueductal region that may lead to some systemic toxins passing through [32]. Finally, WE can rarely coexist with Marchiafava–Bignami disease as discussed below and/or with cortical laminar necroses (Fig. 5).

Osmotic myelinolysis

Osmotic myelinolysis (osmotic demyelination syndrome, central pontine myelinolysis) is a serious neurological condition, which is classically seen in hyponatraemic patients whose sodium levels are corrected too rapidly [33]. These changes in serum osmolality lead to disruption of the blood–brain barrier and leakage of the hypertonic fluid into

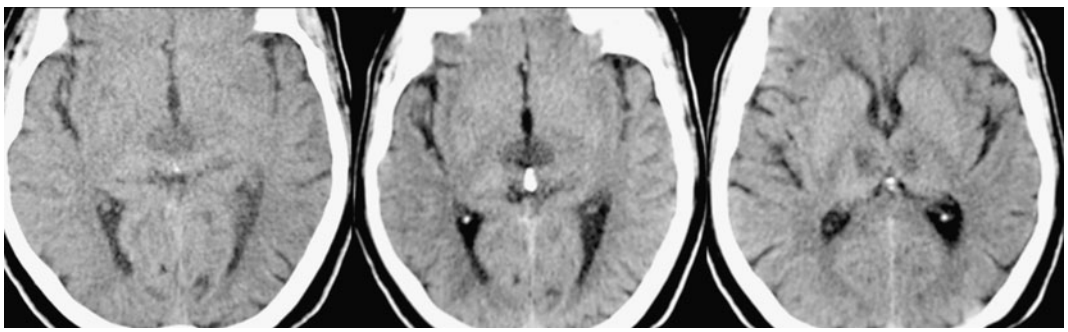

Fig. 2 CT changes in a patient with Wernicke encephalopathy as a result of thiamine deficiency. Bilateral and symmetrical hypodensities on CT in the periventricular thalami and mammillary bodies are seen

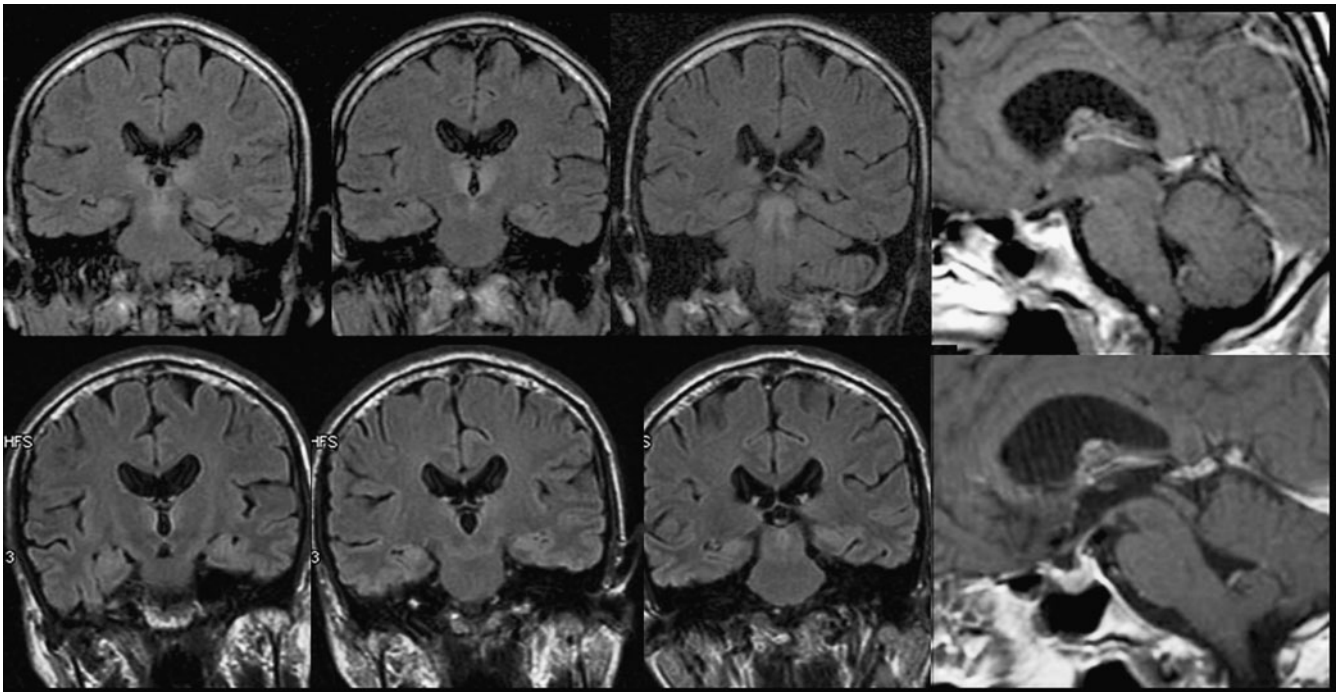

Fig. 3 Reversibility of abnormal signal changes following thiamine substitution in Wernicke encephalopathy. The *upper row* represents coronal FLAIR weighted images and a sagittal T1-weighted contrast-enhanced image before therapy, the *lower row* similar slices 6 months following treatment demonstrating reversibility of contrast enhancement and FLAIR hyperintensities in the pathognomonic regions

the extracellular space resulting in demyelination in the transverse and long fibres of the pons.

The condition can also be seen in chronic alcoholic patients unrelated to changes in the serum sodium level due to a direct toxic effect of the alcohol on the pontine fibres [34]. In alcoholic patients, extrapontine myelinolysis with involvement of the basal ganglia, thalami, deep cerebral white matter or the lateral geniculate bodies and hippocampi is exceedingly rare [35]. The clinical symptoms range from dysphagia, pseudobulbar palsy, dysarthria and movement disorders to seizures, tetraparesis, coma and death.

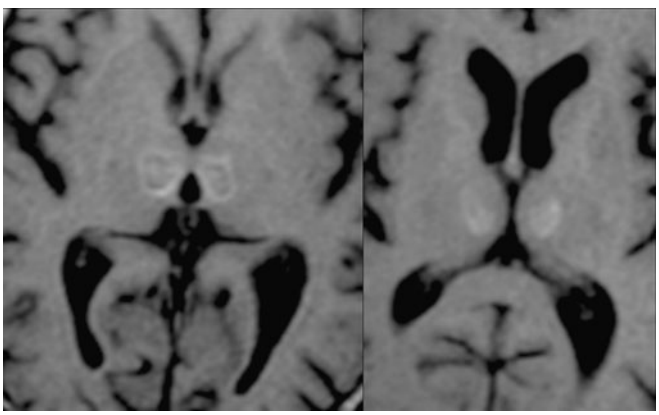

Fig. 4 If petechial hyperintensities are present on unenhanced T1-weighted sequence, the haemorrhagic form of Wernicke encephalopathy has to be considered, which is associated with a poor outcome as presented in this single patient with two subjacent slices

MR imaging in the acute phase will show areas of increased T2 and FLAIR signal in the central portion of the pons with sparing of the ventrolateral aspect and corticospinal tracts, a sign that has been referred to as a "Batman" lesion [4]. These lesions typically have a slight T1 hypointensity and no contrast enhancement, although occasionally enhancement can be present (Fig. 6). Diffusion restriction of these lesions can be observed within 24 h of clinical onset and may precede the changes on conventional MR sequences [36] (Fig. 7). Symmetric T2 hyperintensities can also occur in the basal ganglia, thalami, cerebral peduncles, corticomedullary junctions, cerebellum and spinal cord. In patients who survive the acute phase, residual signal changes or cavitary lesions can be seen within the pons with associated T2 hypersignal in the middle cerebellar peduncles due to Wallerian degeneration of the ponto-cerebellar tracts [37].

Marchiafava–Bignami disease

Marchiafava–Bignami disease (MBD) is a rare complication of chronic alcohol consumption and is characterised by primary demyelination and necrosis of the central part of the corpus callosum [38]. The clinical presentations in the

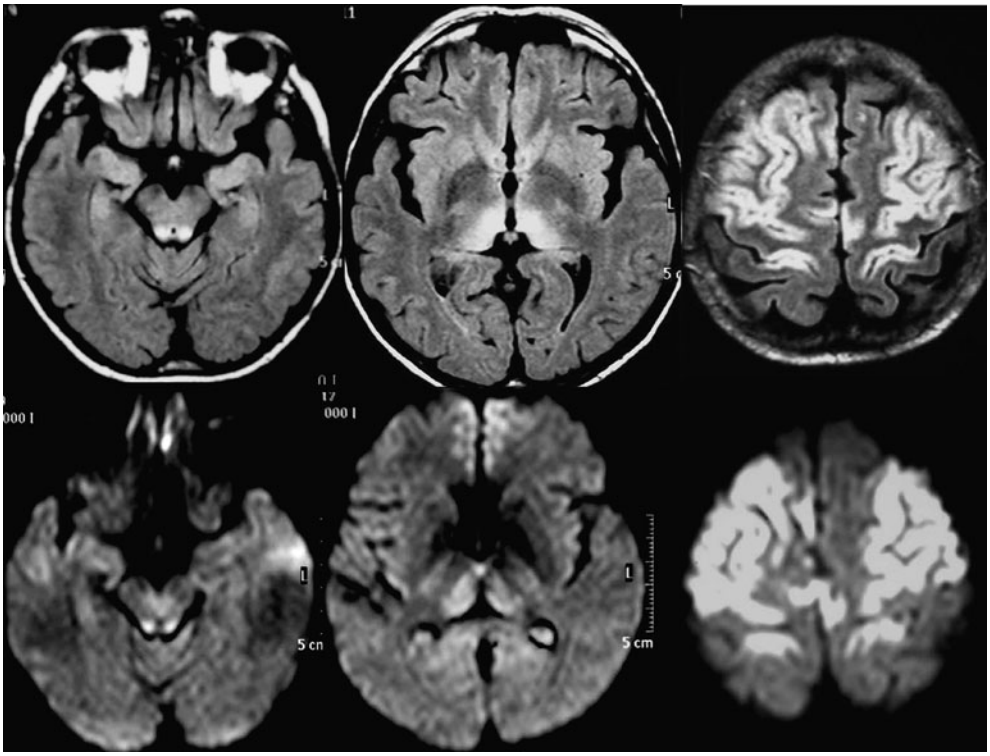

Fig. 5 Coexistence of cortical laminar necrosis diffusely involving the frontal cortex with initial extension in both parietal lobes in a case of alcoholic WE: note also the T2 hyperintense signal in the periaqueductal region and in both pulvinar thalami. *Upper row*: T2-w FLAIR sequences. *Lower row*: DWI sequences obtained during the acute clinical stage. (Courtesy of M. De Donatis, G. Cuonzo, Department of Radiology, Pescara Hospital)

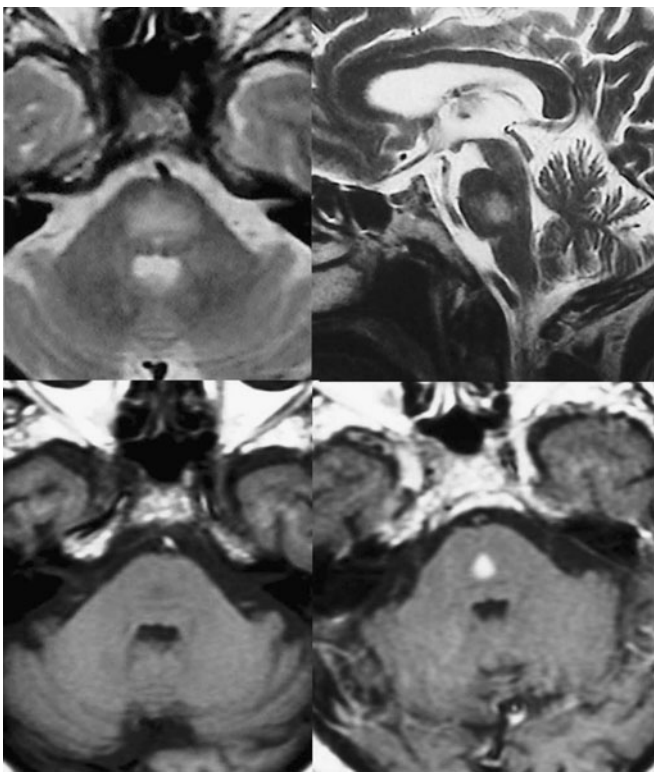

Fig. 6 Osmotic myelinolysis in an alcoholic patient. Contrast enhancement of the centre of the lesion is clearly seen (*bottom right image*)

acute and subacute phase include cognitive impairment, gait disturbance, limb hypertonia, dysarthria and signs of interhemispheric disconnection. Other clinical symptoms include psychosis, depression, hemiparesis and apraxia. Progression to seizures, stupor, coma and death may occur. Symptoms often overlap or coexist with that of Wernicke encephalopathy and can be difficult to differentiate in the acute stage. Residual cognitive impairment, disconnection syndromes and dysarthria will persist in the chronic stage of MBD.

Although the true aetiology of this rare condition is still unknown, toxic agents in low quality red wine and/or vitamin B complex deficiencies have been put forward as potential causes [39]. Pathological features include layered necrosis, degeneration and cystic cavitations of the corpus callosum, predominantly at the body followed by the genu and splenium [40]. Other white matter tracts such as the anterior and posterior commissures, the corticospinal tract, the external capsule, the hemispheric white matter and middle cerebellar peduncles may also be involved. There have been case reports with cortical involvement [41], which is thought to be associated with laminar sclerosis.

The characteristic MR imaging findings are high T2 signal without significant mass effect within the corpus callosum, which may extend to the genu and adjacent white matter (Fig. 8). During the acute phase, peripheral contrast enhancement of these lesions can be seen with restricted diffusion, suggesting cytotoxic oedema. In the acute phase, differential diagnoses include infarctions, shearing injuries,

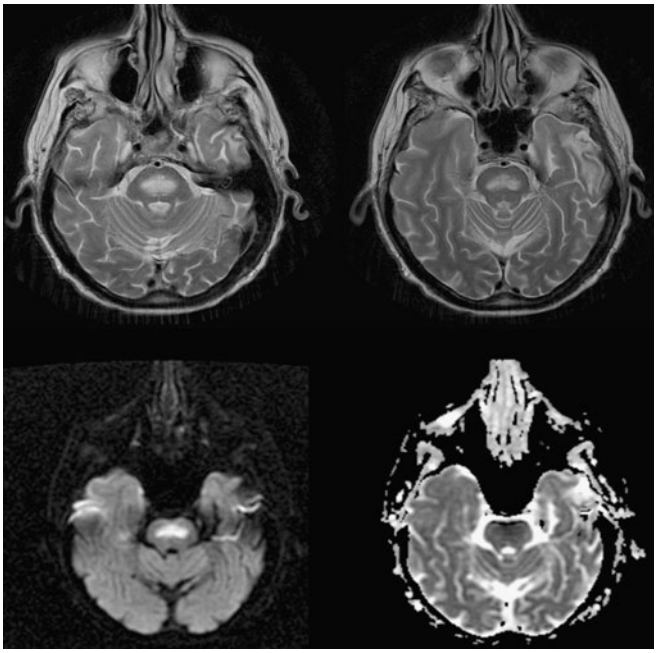

Fig. 7 Osmotic myelinolysis in an alcoholic patient with acute cytotoxic oedema in the central pons crossing the midline visible on T2- and diffusion-weighted sequences

demyelinating processes, seizures and post-radiation changes [42, 43]. In the chronic phase, MBD lesions will eventually become cystic and well marginated. Occasionally they may be reversible [44].

Alcohol withdrawal syndromes

The topic of alcohol withdrawal syndromes (AWS) including delirium tremens and seizures has been recognised for many centuries. Echevarria reported that 45% of patients inflicted with chronic alcoholism experienced a seizure during their lifetime [45]. However, the exact relationship between alcohol and seizures remains uncertain. In most cases, seizures immediately precede delirium tremens [46]. It is known that alcohol promotes electrolyte disturbances and lowers the convulsive threshold. Involvement of NMDA and GABA receptors has been put forward as a potential pathomechanism as during chronic alcohol intake adaptation of NMDA and GABA receptors may occur. Alcohol consumption leads to decreased activity of NMDA and consequent up-regulation of receptors, most evident at the level of the cerebellum and hippocampus. In addition, alcohol consumption also increases the GABA levels in the CNS which further inhibits NMDA receptors. The abrupt interruption of alcohol intake will therefore lead to increased activity of NMDA receptors with subsequent rapid increase of intracellular Ca^{2+} (and Cl^{-}), intracellular oedema and neuronal excitability which may ultimately lead to epilepsy. Moreover, glutamatergic synapses are activated with consequent excitotoxicity [47]. Animal studies demonstrate that epileptiform activity seen in hippocampal sections after prolonged ethanol administration is related to intracellular Ca^{2+} increase and oedema [48, 49].

On MRI a significant volume decrease in the temporal cortical grey and white matter as well as the anterior hippocampus is seen in chronic alcoholic patients who have suffered from withdrawal seizures [47]. It may therefore be deduced that epileptic seizures in alcoholic patients will, similar to temporal lobe epilepsy, lead to reversible intracellular oedema with subsequent volume loss and hippocampal atrophy (Fig. 9). The relationship between delirium tremens and seizures is believed to be due to a kindling phenomenon. According to this theory, delirium tremens is related to an excitotoxic mechanism following alcohol withdrawal that leads to repetitive subconvulsive stimuli that are responsible for the symptoms and can accumulate its activity culminating in a generalised seizure [50]. Clinical presentation of delirium tremens consists of hallucinatory episodes, mostly with micro-zooptic contents, usually preceded by disturbed sleep and irritability and generally takes several days to develop. The patient may experience sweating and increases in heart rate and body temperature, as well as hallucinations, tremors and convulsions. In severe cases, delirium tremens may lead to hypothermia, cardiovascular collapse and death.

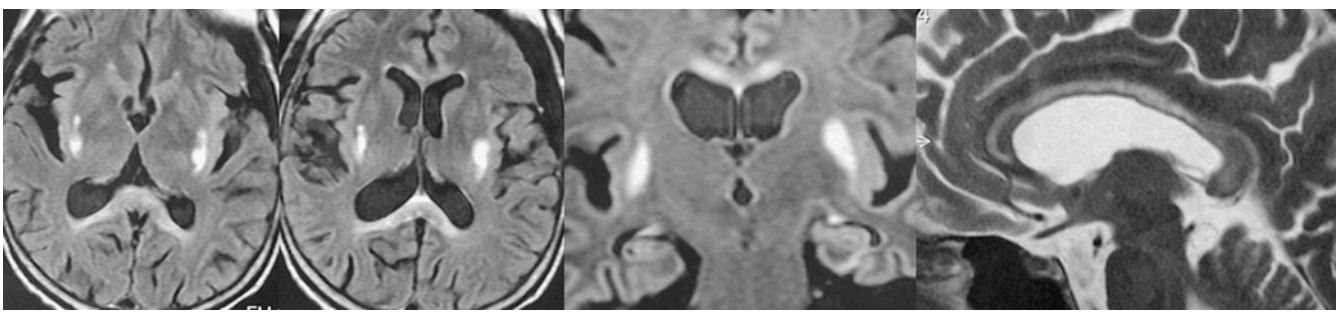

Fig. 8 Marchiafava–Bignami disease with the classic finding of layered necrosis, degeneration and cystic cavitations of the corpus callosum. In addition, extensive involvement of the dorsal part of the external capsule was seen in this patient

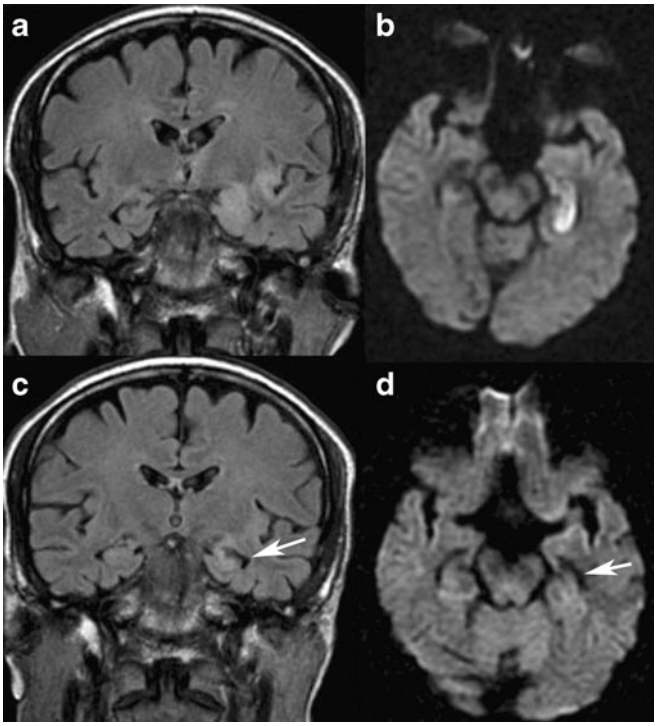

Fig. 9 MRI in a case of alcohol withdrawal. The patient was hospitalised 2 days before the onset of delirium tremens. MRI was performed during the acute phase of delirium tremens. There was no evidence of recent seizures. T2-weighted FLAIR coronal slices at the onset (**a**) and after 1 month (**c**). DWI axial slices at the acute stage (**b**) and after 1 month (**d**). Note the mild enlargement of the left temporal horn which may testify to brain volume loss (*arrow*)

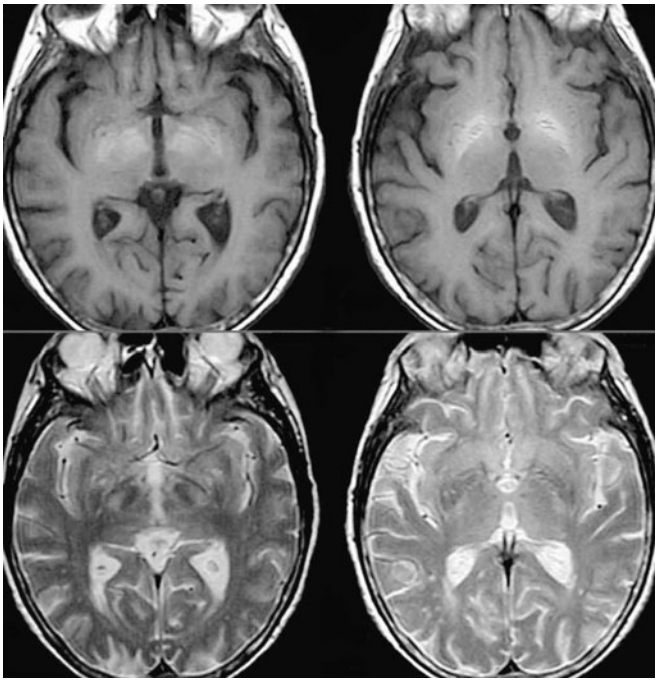

Fig. 10 Hepatic encephalopathy in an alcoholic patient. Anterior midbrain and pallidi are hyperintense on T1-weighted sequences

Chronic hepatic encephalopathy

Chronic hepatic encephalopathy (CHE) is a form of metabolic encephalopathy caused by hepatocellular failure and porto-systemic venous shunting in patients with cirrhosis, resulting in inadequate hepatic removal of nitrogenous compounds from the GI tract and accumulation of ammonia, manganese and mercaptans [51]. Precipitating factors include dietary protein load, constipation and GI haemorrhage [52].

Clinical symptoms are reversible and patients may present with personality changes, shortened attention span, anxiety, depression, motor incoordination and flapping tremor of the hands. Coma and death may occur in severe cases.

MR findings in patients with liver failure include bilateral and symmetrical T1 signal hyperintensity in the caudate nucleus, globus pallidus, putamen, subthalamic nucleus, tectum, adenohypophysis, substantia nigra and red nucleus, attributed to the increased brain tissue concentration of manganese [53] (Fig. 10). However these findings are not closely related to the presence of hepatic encephalopathy [5]. In patients with hyperammonaemia, swelling of the astrocytes may result in mild generalised brain oedema, best seen on FLAIR and DWI. An increase in the glutamine/glutamate peak with a decrease in the *myo*-inositol and choline peaks can be detected on MR spectroscopy [54, 55]. This increase of glutamine/glutamate may be related to hepatic encephalopathy [56].

Coagulopathies related to chronic liver disease

Chronic liver diseases will result in coagulopathies due to a decreased amount and function of platelets, decreased production of coagulation and inhibitor factors, vitamin K deficiency, synthesis of abnormal clotting factors, decreased clearance of activated factors by the reticulo-endothelial system, hyperfibrinolysis and disseminated intravascular coagulation [57]. Although spontaneous bleeding is infrequent in these patients, minor accidents or falling while under the influence of alcohol with decreased protection reflexes will lead more commonly to life-threatening haemorrhage. Presence of fluid–fluid levels within the haematoma due to the haematocrit effect may point towards an underlying coagulopathy. For the same reason, chronic alcoholic patients are also at a higher risk of rebleeding.

Methanol

Acute methanol intoxication can occur either because of illegal, fraudulent adulteration of wine or other alcoholic

beverages or after accidental ingestion of cleaning products, antifreeze or industrial solvents because of their clear and colourless appearance [58]. Following ingestion, a clinically silent period of 12–24 h is present that corresponds to the time required for methanol to be metabolised into formaldehyde and formic acid, which will result in severe metabolic acidosis [59]. The putamen and the visual pathways are the most susceptible regions [60]. Visual disturbances secondary to optic nerve necrosis or demyelination are typically the first symptom in most patients. Other early symptoms, including nausea, vomiting and abdominal pain are non-specific and the neurological symptoms range from mild, such as headaches, dizziness and seizures, to permanent neurological dysfunction, coma and even death. Respiratory arrest is often the terminal symptom and occurs at 6–36 h after intoxication.

Bilateral putaminal necrosis is characteristic and can be visualised on both CT and MR imaging. Haemorrhage is reported in approximately 7–14% of cases [61–63] and is associated with a poor prognosis. On CT, bilateral putaminal hyperdensities (petechial haemorrhage) or hypodensities (due to oedema alone) with surrounding poorly delineated oedema can be seen that may change to cystic necroses in the chronic stage (Fig. 11). MRI shows T1 hyperintensities due to the presence of haemorrhage with T2 hyperintensity of the lateral putamen that may extend into the pallidum, corona radiata and the centrum semiovale [64, 65]. Oedema and necrosis of hippocampi, cerebellum and subcortical white matter, predominantly in the frontal and occipital lobes with sparing of the subcortical U-fibres, have also been described. Restricted diffusion suggests the presence of cytotoxic oedema [66, 67]. Contrast enhancement of these lesions is non-specific and varies from no enhancement to rim and strong enhancement patterns.

Ethylene glycol

Ethylene glycol is a solvent commonly used in paints, dyes, drugs and as an antifreeze solution. As with methanol, accidental (or suicidal) ingestion of ethylene glycol can occur due to its colourless and nearly odourless properties, resulting in severe metabolic acidosis. Severe systemic and neurological complications occur approximately 12 h after ingestion, leading to hepatorenal failure, brain oedema with coma, seizures and peripheral neuropathy [68, 69]. Brain oedema can be seen early on CT and MR; however, necrosis of the white matter, predominantly in the frontal lobe, basal ganglia, thalami, midbrain and upper pons, seen as hypodense areas on CT and hypo T1/hyper T2 signal changes on MR, will develop after 24–48 h and may disappear after 5–35 days. Occasionally enhancement of the cranial nerves may also be detected [70].

Conclusion

Alcohol can cause substantial cerebral damage because of its direct toxic effects and also secondary effects that may

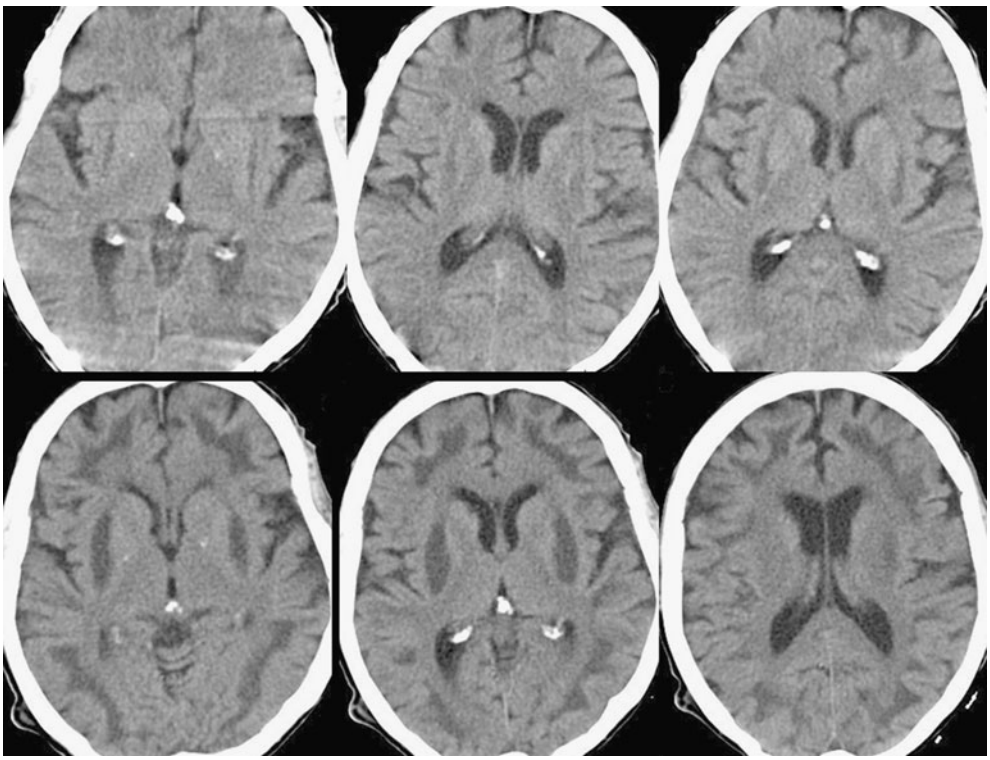

Fig. 11 Acute (*upper row*) and subacute (24 h following ingestion, *lower row*) stages of methanol poisoning. Putaminal oedema is demonstrated on the acute stage CT, while 24 h following the acute ingestion, in addition to the putaminal sharply demarcated hypodensity, diffuse hypodensities are present in the subcortical white matter

be related to malnutrition or alteration of liver functions. While in some instances the pathomechanism is yet to be determined, the early diagnosis of alcohol-related disorders can substantially alter the prognosis of the afflicted patient. Therefore, the radiologist plays an important role in the management of this disorder.

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