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## PICTORIAL ESSAY

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# Magnetic Resonance Imaging of Alcohol-induced Encephalopathies

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### ABSTRACT

Alcohol has direct and indirect toxic effects on the brain, such as oxidative metabolism, inflammatory reactions, and DNA damage. This article describes neuroimaging findings of alcohol-induced encephalopathies including brain atrophy, osmotic demyelination syndrome, Marchiafava-Bignami disease, Wernicke's encephalopathy, hepatic encephalopathy, and alcohol withdrawal syndrome. Symptoms of these disorders are often non-specific, so a thorough understanding of neuroimaging findings is important for prompt diagnoses and treatment.

**Key Words:** Alcohol induced encephalopathy; Magnetic resonance imaging; Marchiafava-Bignami disease; Wernicke encephalopathy

## 中文摘要

### 酒精誘發腦病的磁共振成像

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酒精對腦部有直接和間接的毒性作用，如氧化代謝物、炎症反應和DNA損傷。本文描述多種酒精誘發腦病，包括腦萎縮、滲透性脫髓鞘綜合徵、Marchiafava-Bignami病、Wernicke腦病、肝性腦病和酒精戒斷綜合徵的神經影像。這些疾病的症狀通常是非特異性的，因此全面了解其神經影像對於及時診斷和治療是很重要的。

### INTRODUCTION

Alcohol-induced encephalopathies manifest as various central nervous system (CNS) disorders secondary to direct or indirect alcohol-induced toxic effects.<sup>1,2</sup> Chronic alcohol consumption may result in brain

atrophy secondary to the loss of subcortical white matter and alteration in the number and size of neurons.<sup>3</sup> Associated conditions (such as malnutrition, impaired balance of electrolytes, and alcoholic liver disease) can cause osmotic demyelination syndrome, Marchiafava-

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Bignami disease, Wernicke's encephalopathy (WE), hepatic encephalopathy, and alcohol withdrawal syndrome. Some of these conditions can be fatal, but clinical symptoms are often non-specific. Thus, thoroughly understanding neuroimaging findings can help with prompt diagnosis and treatment. This article reviews the neuroimaging findings associated with chronic alcohol abuse (Table). Images are from patients attending the Gyeongsang National University Hospital and Gyeongsang National University Changwon Hospital between January 2013 and December 2015.

## BRAIN ATROPHY

In chronic alcoholism, direct brain toxicity is caused by the up-regulation of N-methyl-D-aspartate (NMDA) receptors, which inhibit the normal function of cell membranes and ion channels. This inhibition decreases the amount of intracellular sodium and chloride and results in brain atrophy. In addition, acetaldehyde (ethanal) and related products of lipid peroxidation can bind to the brain tissue and induce an immune-mediated response, resulting in neuronal and white matter damage. Alcohol misuse results in decreased neurotrophic factors, disturbance of normal brain function, dysregulation of neuronal synaptic connectivity, and apoptosis. There is volume loss in the superior frontal cortex and hippocampus secondary to decreased gene expression of myelin protein-encoding genes in glia cells.<sup>1,4,5</sup> In the early stages,

there is atrophy of the upper vermis and prominence of the cerebellar fissures without pontine atrophy (Figure 1). In the later stages, the frontal subcortical white matter is involved in enlarged sulci and adjacent horns of the lateral ventricle. In the final stage, there is diffuse brain atrophy. Alcohol-induced brain atrophy is only partially reversible after cessation of alcohol intake.<sup>1</sup> Histological examination reveals a reduction in neuronal dendritic arborisation.<sup>6</sup> There is also a prominent loss of neurons in the superior frontal and motor cortices, and considerable volume reduction in the white matter.

## OSMOTIC DEMYELINATION SYNDROME

Osmotic demyelination syndrome is typically seen after rapid correction of hyponatraemia.<sup>1,3</sup> It is also known as central pontine myelinolysis and/or extrapontine myelinolysis.<sup>7</sup> Its clinical manifestations vary from minimal symptoms to complete locked-in syndrome, coma, or death.<sup>1,3,8,9</sup> Acute correction of hyponatraemia causes changes in serum osmolality and osmotic insults (such as disruption of the blood-brain barrier and leakage of hypertonic fluid into the extracellular space) and demyelination in vulnerable structures. Osmotic demyelination syndrome is caused by demyelination of the transverse and long fibres of the pons.<sup>1,10</sup> This process is characterised by vacuolisation and intramyelinic splitting before eventual rupture of the myelin sheaths.<sup>3</sup>

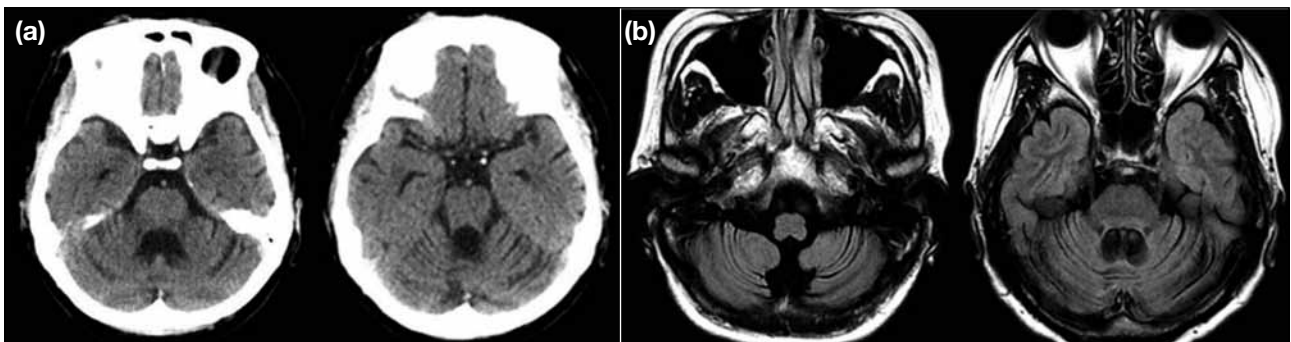
**Table.** Magnetic resonance imaging findings in alcohol-induced encephalopathies.

Condition	Common lesion location	Magnetic resonance imaging findings	Remarks
Brain atrophy	Cerebellum in early stage, frontal subcortical white matter in later stage, diffuse brain involvement in final stage	Prominent cerebellar atrophy (especially upper vermis) without pontine atrophy, diffuse brain atrophy in the final stage	Only partially reversible after cessation of alcohol intake
Osmotic demyelination syndrome	Central pons, also possible at basal ganglia, thalamus, cerebellum, cerebral cortex	T1 hypointensity, T2 and FLAIR hyperintensity, contrast enhancement ( $\pm$ ), mild diffusion restriction ( $\pm$ )	Formerly known as central pontine myelinolysis and/or extrapontine myelinolysis
Wernicke's encephalopathy	Around the 3rd ventricle, dorsomedial thalamus, hypothalami, mammillary bodies, and periaqueductal region of the midbrain	T2 and FLAIR hyperintensity, contrast enhancement ( $\pm$ )	Contrast enhancement common in alcoholic cases and rare in non-alcoholic cases, reversible after thiamine replacement
Marchiafava-Bignami disease	Corpus callosum	T2 and FLAIR hyperintensity, peripheral contrast enhancement ( $\pm$ ), diffusion restriction ( $\pm$ ), cystic cavitations in the chronic phase	Progressive demyelination and necrosis
Hepatic encephalopathy	Basal ganglia, midbrain	T1 hyperintensity, DWI and FLAIR hyperintensity ( $\pm$ ) in acute phase	T1 hyperintensity due to deposition of manganese, DWI and FLAIR changes due to astrocyte swelling
Alcohol withdrawal syndrome	Temporal lobe, anterior hippocampus	Volume loss in the affected regions, diffusion restriction ( $\pm$ ) in the acute and subacute phases	Due to electrolyte imbalance and decreased convulsive threshold

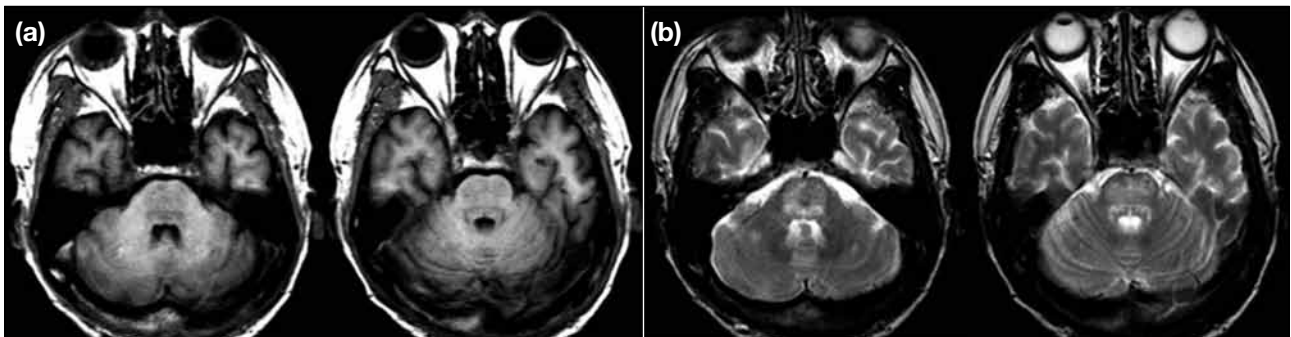
Abbreviations:  $\pm$  = may or may not be present; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery.

There is increased T2 and fluid-attenuated inversion recovery (FLAIR) signal intensity in the central pons with sparing of the tegmentum, ventrolateral pons, and corticospinal tracts (Figure 2). These abnormalities can also be seen in the thalami, basal ganglia, lateral geniculate bodies, cerebellum, cerebral cortex, and spinal cord,<sup>11,12</sup> and are slightly T1-hypointense without contrast enhancement (Figure 3).<sup>1,3,5,9</sup> In the acute phase,

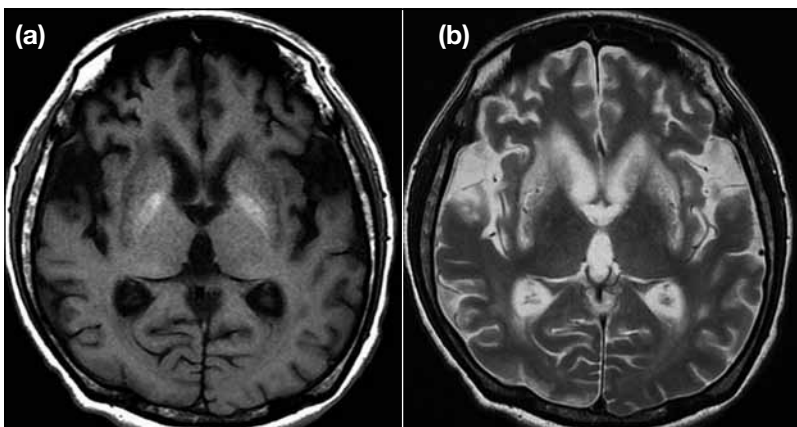
non-homogeneous contrast enhancement is suggestive of an inflammatory mechanism or breakdown of the blood-brain barrier owing to the specific vulnerability of the endothelium.<sup>9</sup> On diffusion-weighted images (DWI), a mild diffusion restriction within 24 hours of onset can be the earliest sign.<sup>13</sup> In the chronic stage, these demyelinating lesions can cause cavitations or Wallerian degeneration of the ponto-cerebellar tracts.<sup>11</sup>



**Figure 1.** Alcohol-induced cerebellar atrophy in a 45-year-old man: (a) non-enhanced computed tomographic scans and (b) fluid-attenuated inversion recovery images showing diffuse cerebellar atrophy without a focal lesion.



**Figure 2.** After rapidly corrected hyponatraemia in a 60-year-old man, (a) T1-weighted images showing hypointensity in the central pons and (b) T2-weighted images showing signal increase in the central pons typical of central pontine myelinolysis.



**Figure 3.** After rapidly corrected hyponatraemia in a 49-year-old woman, (a) T1-weighted image showing hyperintensity in both globus pallidi (suggesting an underlying hepatic encephalopathy) and hypointensity in both the putamina and caudate nuclei, and (b) T2-weighted image showing diffuse involvement of both basal ganglia (characteristic of extrapontine myelinolysis).

## WERNICKE'S ENCEPHALOPATHY

Wernicke's encephalopathy is a neurological disorder caused by thiamine deficiency.<sup>1,3,14,15</sup> It is commonly found in chronic alcohol misuse and chronic malnutrition such as in patients with malignancy or hyperemesis gravidarum, those receiving total parenteral nutrition, and those undergoing abdominal surgery or haemodialysis.<sup>16</sup> The pathophysiology of WE includes inadequate nutritional intake, decreased absorption of thiamine through the gastrointestinal tract, and decreased thiamine utilisation in cells.<sup>15</sup> The classic triad of WE includes ocular dysfunction, ataxia, and confusion, with the latter occurring in only 30% of patients.<sup>3,17,18</sup> The most common symptom of WE is non-specific alteration of mental status.<sup>17</sup>

In a thiamine-deficient state, increased metabolic requirement and inability to regulate osmotic gradients disrupt the blood-brain barrier, resulting in cytotoxic oedema and permanent neuronal loss in areas with the highest metabolic demands.<sup>19</sup> During the acute to subacute phases, demyelination, glial cell proliferation, and hypertrophied endothelial changes with petechial haemorrhage occur in the paraventricular region (around the third ventricle), dorsomedial regions of the thalami, hypothalami, mammillary bodies, pineal regions, and periaqueductal region of the midbrain.<sup>20,21</sup> During the chronic phase, necrosis secondary to gliosis and neuronal loss occurs.<sup>22</sup>

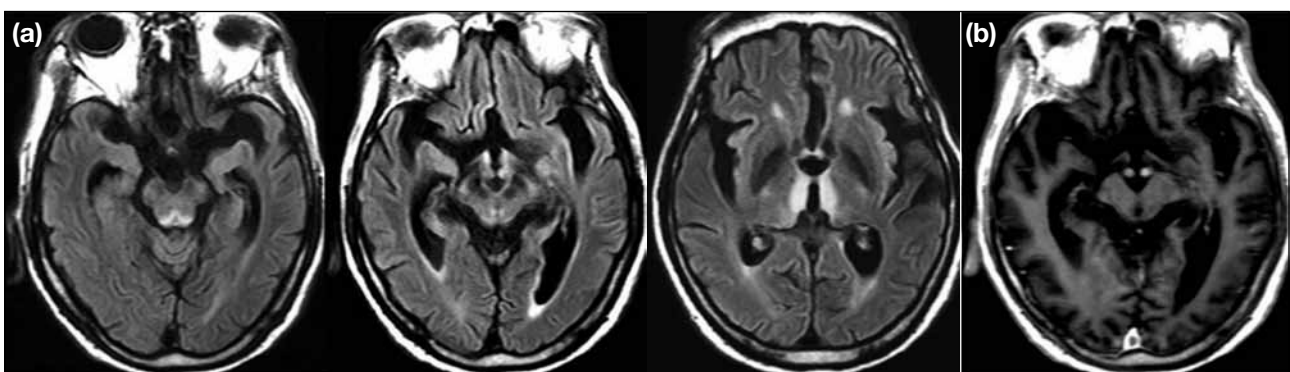
Wernicke's encephalopathy shows a bilateral and symmetrical pattern with abnormal T2 and FLAIR hyperintensities at the medial thalami, mammillary bodies, tectal plate, and periaqueductal grey matter (Figure 4).<sup>18</sup> Contrast enhancement can be observed. Avid

enhancement of mammillary bodies is considered to be pathognomonic for WE, as it is observed in approximately 80% of cases in acute settings.<sup>23</sup> These changes can be reversible after thiamine replacement. In chronic WE, the pre-existing T2 hyperintensity becomes less prominent, with atrophic changes of the affected areas.<sup>1,23</sup> The lesions are contrast-enhanced in almost all alcoholic WE patients but rarely in non-alcoholic WE patients.<sup>24</sup> The mammillary body is more frequently involved in alcoholic WE patients than in non-alcoholic WE patients.<sup>1,17</sup>

## MARCHIAFAVA-BIGNAMI DISEASE

Marchiafava-Bignami disease results in progressive demyelination and necrosis of the central part of the corpus callosum.<sup>25,26</sup> It can also be observed in non-alcoholic patients as WE.<sup>1,3,25</sup> In the acute and subacute phases, its clinical manifestations include severe impairment of consciousness, seizures, and muscle rigidity. In chronic cases, variable degrees of mental confusion, dementia, and gait disturbance are noted. Its main pathological features include demyelination, necrosis, and cystic cavitation, with degeneration of the corpus callosum, predominantly in the body portion. Other white-matter tracts and cerebral cortices may be involved.<sup>3,27-29</sup>

On T2-weighted and FLAIR images, high signal intensities are observed in the body of the corpus callosum without any mass effect. The lesion may extend to the genu portion and adjacent white matter.<sup>1,3,27,28</sup> In the acute phase, peripheral enhancement with diffusion restriction on DWI is suggestive of cytotoxic oedema (Figure 5).<sup>30,31</sup> In the chronic phase, lesion signal changes become less prominent, with cystic changes and atrophy of the affected areas.<sup>28,32</sup>



**Figure 4.** Acute phase of Wernicke's encephalopathy in a 73-year-old man: (a) fluid-attenuated inversion recovery images showing symmetric involvement of the periaqueductal grey matter, mammillary bodies, and medial thalami, and (b) T1-weighted contrast-enhanced image showing diffuse enhancement of both mammillary bodies.

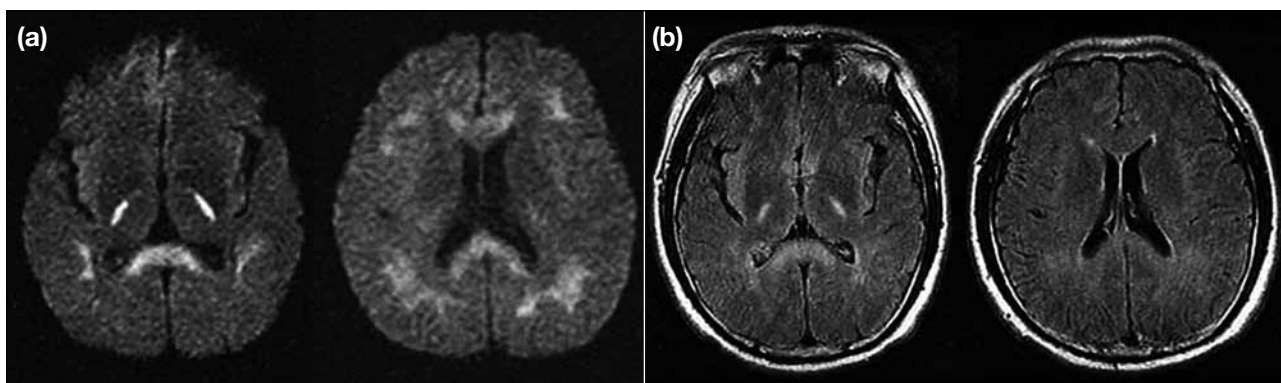
## HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a type of metabolic encephalopathy that occurs during acute and chronic liver failure or after portosystemic shunt surgery, with potential reversibility.<sup>33,34</sup> Its pathophysiology is related to the inadequate hepatic removal of nitrogenous compounds from the gastrointestinal tract and the accumulation of ammonia, manganese, and mercaptans.<sup>1,35</sup> These substances produce neurotoxicity that induces a functional disturbance of astrocytes and neurons and results in reactive gliosis and selective neuronal loss in the basal ganglia and midbrain.<sup>36-38</sup> Its clinical symptoms include psychiatric, cognitive, and motor abnormalities.<sup>1,3</sup> It is characterised by symmetric T1 hyperintensity in the basal ganglia (especially the globus pallidus), subthalamic nucleus, hypothalamus, adenohypophysis, tectal plate, substantia nigra, and red nucleus (Figure 6). The T1 hyperintensity is caused by a deposition of manganese.<sup>39-41</sup> In the acute phase, DWI and FLAIR may show increased signal intensity

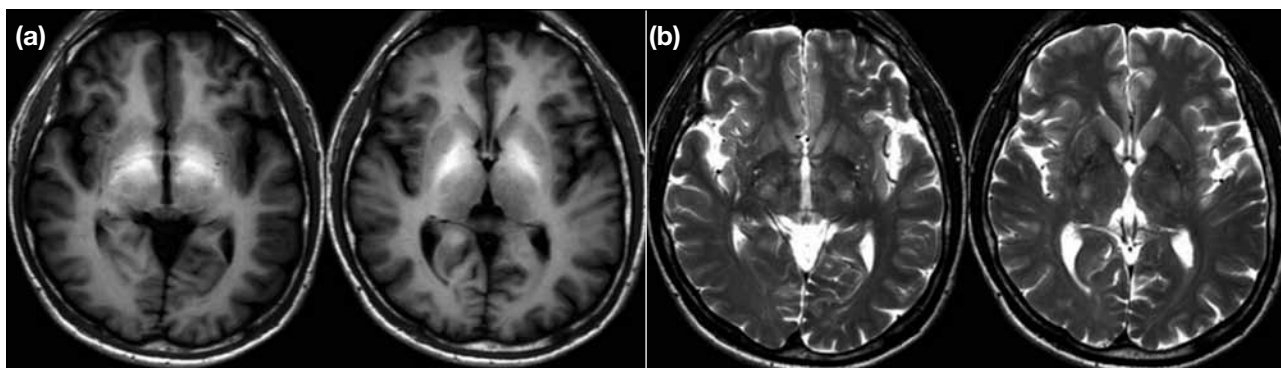
due to swelling of the astrocytes.<sup>1</sup> These abnormalities can be observed in the thalami, posterior limb of the internal capsule, periventricular white matter, and dorsal brain stem, as well as in the cerebral cortices, which can be reversible. Magnetic resonance imaging strongly correlates with the maximal plasma ammonia level, whereas the severity of imaging correlates only moderately with the clinical outcome.<sup>42</sup>

## ALCOHOL WITHDRAWAL SYNDROME

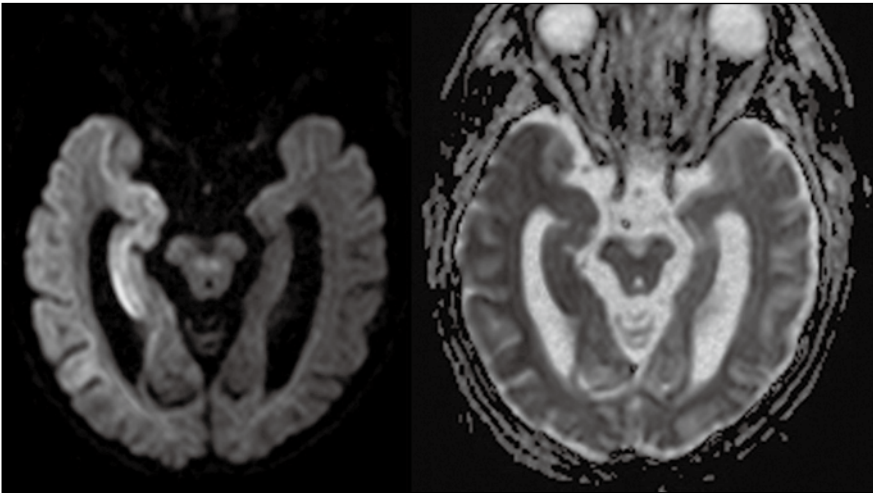
Alcohol withdrawal syndrome is a constellation of symptoms in patients who have experienced an abrupt interruption of alcohol intake after a period of continuous and heavy alcohol consumption. Delirium tremens is defined as acute generalised involvement of the CNS and impaired consciousness.<sup>43</sup> In most cases, seizures immediately precede delirium tremens. Alcohol causes an electrolyte imbalance and decreases the convulsive threshold. Chronic alcohol intake results



**Figure 5.** Acute phase of Marchiafava-Bignami disease in a 48-year-old man: (a) diffusion-weighted images showing bilateral symmetric hyperintensities in both internal capsules (posterior limb), the corpus callosum, and fronto-parietal white matter, and (b) fluid-attenuated inversion recovery images showing mild hyperintensity in the corresponding areas.



**Figure 6.** (a) T1-weighted images of a 54-year-old man showing diffuse T1 hyperintensity in both the anterior midbrain and globus pallidi, suggesting hepatic encephalopathy, and (b) T2-weighted images showing subtle hypointensity in the corresponding areas.



**Figure 7.** In a 38-year-old man with delirium tremens-related seizures: diffusion-weighted images showing diffusion restriction in the right temporal lobe with a decreased apparent diffusion coefficient in the corresponding region.

in decreased activity of NMDA and up-regulation of receptors, which are most abundant in the cerebellum and hippocampus. Alcohol consumption increases the gamma-aminobutyric acid levels in the CNS and inhibits NMDA receptors, resulting in seizures in patients with alcohol withdrawal syndrome.<sup>44</sup> In the acute and subacute phases, there is diffusion restriction by cytotoxic oedema with a significant volume loss in the temporal regions and anterior hippocampus (Figure 7).<sup>45</sup> Vasogenic oedema in the cerebellum, thalami, and parietal white matter is reversible and known as posterior reversible encephalopathy syndrome.<sup>46</sup>

## CONCLUSION

Alcohol can cause CNS damage because of its direct or indirect toxic effects and secondary effects such as malnutrition or hepatic dysfunction. Some types of alcohol-induced encephalopathies can be fatal and clinical manifestations are often non-specific. Therefore, close examination of the neuroimaging features and clinical history can help clinicians make a prompt diagnosis and avoid unnecessary metabolic or toxic screening tests.

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