Diagnosis of Neurological Diseases Associated with Alcohol Consumption

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Learning objectives

• To know the main diseases of the central nervous system (CNS) associated with alcohol consumption, and to identify its classical neuroimaging patterns.
• To keep in mind a simple neuroradiological approach algorithm for these patients.
Background

Alcohol consumption is a public health problem worldwide. The last report of the World Health Organization in 2014 quantifies the consumption in 6.2 liters / year (13.5 grams of pure alcohol / day) in people older than 15 years, finding the highest rates in the developed world, in particular, Europe and America. There is a rise in the alcohol consumption prevalence in the world. On a global level, harmful alcohol use results in 3.3 million deaths / year; and 5.9% of the deaths globally are attributed to alcohol \[1\].

Patients with harmful alcohol use, both in acute and chronic forms, can suffer serious complications of the CNS, some of which may even be fatal. During clinical evaluation, the symptoms of these complications are non-specific and may overlap. Also, the alternative differential diagnoses are varied (ischemic or hemorrhagic stroke, trauma, etc.). In this setting neuroimaging becomes a fundamental pillar to obtain an opportune diagnosis and guide the treatment.

The injury that alcohol induces in the CNS can be separated into two types:

1. Primary injury (direct): neurotoxicity of alcohol on the encephalic parenchyma. It is related to neurotoxic effects mediated by glutamate and other alterations that lead to an ionic imbalance of the neuronal cell membrane, activation of inflammatory phenomena, demyelination and apoptosis, with consequent neuronal loss.

2. Secondary injury (indirect): neurotoxicity mediated by the dysfunction that alcohol produces in other systems. Two subtypes: A) Derived from hepatic failure - cirrhosis, which can cause hepatic encephalopathy and coagulopathy. B) Derived from the deficiency in the absorption of nutrients at the digestive tract (eg. thiamine deficiency in Wernicke encephalopathy) \[2\].
Findings and procedure details

We carried out a literature review of the main diseases of the CNS associated with alcohol consumption: cerebellar degeneration, osmotic demyelination syndrome, Wernicke encephalopathy, Marchiafava-Bignami disease and hepatic encephalopathy. We performed a brief review of its pathophysiology, its most important clinical manifestations and its classical neuroimaging patterns. We exemplify the main diseases with neuroimaging of our case series.

Cerebellar degeneration:

This cerebellar atrophy predominates initially in the upper anterior vermis, then progresses to the upper anterior portion of the cerebellar hemispheres, and finally to the lower portions of the cerebellum\[^3\]. It manifests as prominence of the interfoliar spaces, whose normal width in healthy subjects is around 0.5 mm\[^4\]. A cut-off point of 2 mm is defined as an increased amplitude value of the interfoliar subarachnoid space\[^5\].

The pathophysiology is debated. A direct toxic effect of alcohol on the Purkinje cells of the cerebellum is proposed as a mechanism. Other authors think that it is more related with the combination of alcohol and thiamine deficiency\[^6\].

Patients with cerebellar atrophy, in the context of alcohol consumption, show a progressive clinical course characterized by instability, widened base of support and ataxic gait.

*Imaging findings:*

In the evaluation of computed tomography (CT) and magnetic resonance imaging (MRI), we recommend routinely observing the cerebellar volume and the width of the interfoliar spaces, considering the alcohol etiology in case of cerebellar atrophy that predominates in the upper aspect of the vermis (Fig. 1 on page 9). Normally there is no alteration in density or signal intensity of the cerebellar parenchyma.

Some differential diagnoses to consider in case of observing cerebellar atrophy are the loss of encephalic volume due to aging, the use of drugs (eg. phenytoin), cerebellar-type multisystemic atrophy (MSA-C) and spino-cerebellar ataxias (eg. Friedreich ataxia), among others.

Osmotic demyelination syndrome:
Osmotic demyelination syndrome (ODS) corresponds to changes derived from an electrolyte imbalance, the most common: hyponatremia with quick correction. Alcoholic patients are a risk group for this condition. Currently it is called ODS and not pontine myelinolysis, because, although the involvement of the brainstem is more frequent, other sites of the CNS, such as the basal ganglia and thalami, can also be affected in up to 50% of cases [7]. Extrapontine lesions can appear even without being associated with pontine involvement.

The pathophysiology is not completely elucidated. It is known that patients have an electrolyte imbalance with oligodendrocyte involvement (these cells are particularly sensitive to osmotic changes). Alteration of oligodendrocytes would lead to secondary demyelination [6].

The clinical manifestations of ODS are non-specific, with the majority of patients presenting with altered state of consciousness and/or seizures. Other clinical presentations include dysarthria, dysphagia and movement disorders. This last finding is commonly seen in patients with basal ganglia involvement.

**Imaging findings:**

Characteristically, the pontine involvement is predominantly central, with sparing of the ventrolateral pons and the cortical spinal tracts, acquiring triangular or trident-shaped morphology (Fig. 2 on page 9). On CT we see a hypodense area on the pons, without hemorrhage or enhancement with contrast media. On MRI the lesions are mildly-moderately hypointense on T1 and hyperintense on T2 / FLAIR. They may present enhancement with the use of Gadolinium; also in the first 24 hours lesions may show diffusion restriction. In cases of extrapontine involvement, the findings are similar, with potential involvement of the basal ganglia, thalami, cerebellum (especially dentate nuclei), brain deep white matter and brain cortex (Fig. 3 on page 10). In case of negative findings and clinical suspicion persistence, it is recommended to repeat the images because initial studies may be normal [7].

Within the differential diagnoses we must consider ischemic lesions, demyelinating diseases, neoplasms and other metabolic diseases.

**Wernicke encephalopathy:**

Wernicke encephalopathy is a metabolic disorder caused by thiamine deficiency (vitamin B1). Alcoholic patients are a risk group for this vitamin deficiency, due to a sum of factors: decreased intake, impaired intestinal absorption, increased utilization and increased systemic needs of this nutrient. Alcoholism is not the only cause of thiamine deficiency, other less frequent are prolonged fasting, bariatric surgery and hyperemesis gravidarum [8].
Thiamine is a coenzyme for the metabolism of carbohydrates and for the citric acid cycle, so vitamin B1 deficiency affects oxidative metabolism. An increase in metabolic requirements and involvement of the osmotic regulation mechanisms of the blood-brain barrier has been observed. These alterations result in neuronal damage with cytotoxic edema, demyelination, gliosis and neuronal loss.

The classic clinical triad corresponds to encephalopathy, ataxia, and oculomotor dysfunction, although this triad occurs in a smaller percentage of patients. This disease is associated with high mortality if not treated promptly; it can also evolve to Korsakoff syndrome (permanent brain injury with antegrade amnesia and confabulation).

*Imaging findings:*

The sensitivity of CT is low, and MRI is preferred for diagnosis.

The classic findings correspond to T2 / FLAIR hyperintensity of the mammillary bodies, mesial aspect of the thalami and walls of the third ventricle; the periaqueductal gray matter may also be involved (Fig. 4 on page 11). Less commonly, the basal ganglia, the pons and medulla oblongata, as well as the cerebral cortex, can be compromised. The lesions may present restricted diffusion and enhancement with the use of Gadolinium. In the chronic phase of the disease, atrophy of the mammillary bodies and dilation of the third ventricle is observed.

The differential diagnosis includes symmetric bilateral lesions of the mesial portion of the thalamus, such as Percheron’s artery infarction, cerebral deep vein thrombosis and the variant of Creutzfeldt-Jakob disease.

*Marchiafava-Bignami disease:*

Marchiafava-Bignami disease corresponds to a progressive degeneration of the corpus callosum, with demyelination and subsequent necrosis. It is an entity that has historically been related to alcoholic patients. Initially described in red wine drinkers, it has not been possible to demonstrate exclusive association with this type of drink. It also may present in nonalcoholic patients with malnutrition.

Its pathophysiological mechanism is not completely known. Microscopically there is an extensive loss of myelin, with relative preservation of neuronal axons, decreased number of oligodendrocytes and abundant lipid-laden macrophages in the initial stages. It may present gliosis and cyst formation, especially in the most severe forms.
The clinical manifestations are variable. In literature there are three forms described: acute, subacute and chronic. The three forms present with altered state of consciousness as a common marker.

**Imaging findings:**

The classical location of the Marchiafava-Bignami disease lesions is the corpus callosum. Lesions may even extend to the adjacent deep white matter.

On CT the lesions are hypodense. In MRI are hyperintense in T2 / FLAIR and hypointense in T1. In acute phase, the lesions may present restricted diffusion and peripheral enhancement with the use of Gadolinium (Fig. 5 on page 12). In chronic phase, residual atrophy of the corpus callosum predominates [7, 10].

In the differential diagnosis should be considered ischemic lesions, diffuse axonal damage, vasculopathies (eg. Susac syndrome), and neoplasms with involvement of the corpus callosum [7, 13].

**Hepatic encephalopathy:**

Brain damage derived from alcoholic liver failure - cirrhosis can occur during acute liver malfunction or can complicate chronic liver disease. Is more common in chronic than in acute setting.

In pathophysiological terms, in cirrhotic patients, in addition to primary (direct) brain injury, there is a secondary (indirect) injury, mainly derived from hepatic insufficiency and porto-systemic shunt. Hyperammonemia is one of the main neurotoxic agents, having association with astrocyte dysfunction, oxidative stress, neuroinflammation, alteration of the blood-brain barrier, and finally vasogenic and cytotoxic edema.

Hepatic encephalopathy is characterized by psychiatric, cognitive and motor abnormalities. The severity of encephalopathy tends to correlate with plasma ammonia levels. Patients usually present behavioral changes such as irritability, associated with a decrease level of consciousness. If encephalopathy progresses, patient can present seizures and even reach a coma.

**Imaging findings:**

A common finding is progressive encephalic atrophy, which usually involves the cerebellum and brain parenchyma, especially the frontal lobes. Later the atrophy is generalized.

In MRI a classic finding is the T1 hyperintensity of the basal ganglia, specially the globus pallidus, and less frequently the subthalamic region - cerebral peduncles, quadrigeminal
plate and adenohypophysis (Fig. 6 on page 13). This finding is due to manganese accumulation, and there is not a demonstrated correlation between its magnitude and the severity of hepatic encephalopathy\[^{14}\].

The presence of hyperintense T2 lesions, focal and confluent in the white matter of the corona radiata and centrum semiovale is also a frequent finding; it resembles small vessel disease. In MR-spectroscopy, these lesions are associated with an elevation of glutamine / glutamate peak and decrease in myoinositol and choline peaks; and probably represent alterations in cell volume homeostasis secondary to hyperammonemia. Regression of these MRI lesions after liver transplantation or with the improvement of hepatic encephalopathy has been shown, providing evidence supporting their reversible nature\[^{10, 14}\].

In cases of hyperammonemia due to acute or chronic hepatic insufficiency, alterations that correlate with the ammonia metabolism may be seen. In acute hyperamonemic encephalopathy, the role of neuroimaging is mostly limited to excluding other neurological diseases, although in some cases it is possible to see compromise of the thalamus and posterior arm of the internal capsules, and diffusion restriction of the cerebral cortex (insula and cingulate gyrus). In cases of recurrent or chronic hyperamonemic encephalopathy, diffuse or localized cerebral edema is usually seen, specially affecting the cortico-spinal tracts (Fig. 7 on page 14).

Finally we propose a simple neuroradiological approach algorithm for these patients (Fig. 8 on page 15). This algorithm considers:

- To evaluate neuroimagenological markers of chronic alcohol consumption, that will give you clues that you are in front of a patient with harmful alcohol use: A) Cerebral stigmas of chronic liver disease (eg. manganese deposition). B) Cerebellar atrophy.
- To evaluate the involvement of specific encephalic structures, that will suggest you specific diagnoses: A) Mammillary bodies = Wernicke encephalopathy. B) Corpus callosum = Marchiafava-Bignami disease. C) Pons = Osmotic demyelination syndrome.
- If there is no involvement of specific encephalic structures, then check plasma ammonia levels: A) High = Look carefully for signs of hyperamonemic encephalopathy (eg: brain cortex diffusion restriction, cortico-spinal tracts edema). B) Low (normal) = Think in cerebral edema or other toxic-metabolic encephalopathies.

We suggest following these steps in order to carry out a systematic analysis of the different pathologies associated with alcohol consumption in an appropriate clinical context.
Fig. 1: Brain MRI (A: sagittal T1, B: axial T2). Widening of the interfoliar spaces of the superior vermis (red arrows) in a 32 years-old alcohol consumer patient.

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**Osmotic demyelination syndrome (central pontine)**

![Brain MRI images](image)

**Fig. 2:** Brain MRI (A: axial T2, B: axial FLAIR). Symmetric hyperintense trident-shaped area in the central pons, with sparing of the ventrolateral pons and corticospinal tracts (red arrows).

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Fig. 3: Brain MRI. Axial FLAIR (A, B and C): bilateral high signal intensity alterations of the basal ganglia (red arrows) and dentate nuclei (yellow arrows). There is also involvement of the splenium of the corpus callosum (red arrowheads). Axial DWI and ADC map (D and E respectively): lesions in the basal ganglia show diffusion restriction (yellow arrowheads).

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**Wernicke encephalopathy**

**Fig. 4:** Brain MRI. A) axial FLAIR: hyperintensity of the hypothalamus and mammillary bodies (red arrows), and also hyperintensity of the periaqueductal gray matter and tectal plate (yellow arrows). B) axial T1 with Gadolinium: enhancement of the mammillary bodies (red arrowheads) and enhancement of the periaqueductal gray matter (yellow arrowhead). This clinical case is courtesy of Dr. Alex Rovira, Hospital Vall d’Hebron, Barcelona - Spain.

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**Marchiafava-Bignami disease**

**Fig. 5:** Brain CT, A): hypodense lesion of the corpus callosum (red arrows). Brain MRI B), C), D) and E): the lesion is hyperintense on T2 (yellow arrows) and has restriction on DWI (red arrowheads). This clinical case is courtesy of Dr. Alex Rovira, Hospital Vall d´Hebron, Barcelona - Spain.

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Hepatic encephalopathy (deposition of manganese)

Fig. 6: Brain MRI (A: axial T1, B: sagittal T1). Bilateral and symmetric hyperintensity of the globus pallidus.

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Hepatic encephalopathy (corticospinal tract involvement)

**Fig. 7:** Brain MRI: Dashed lines in the coronal T2 image correspond to the levels of the axial FLAIR sequence (A, B and C). Bilateral and symmetric hyperintensity of the corticospinal tracts (red arrowheads in the coronal image and red arrows in the axial images).

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Fig. 8: The proposed algorithm considers: 1) to evaluate neuroimagenological markers of chronic alcohol consumption (cerebral stigmas of chronic liver disease and cerebellar atrophy), 2) to evaluate the involvement of specific encephalic structures that suggests specific diagnoses (mammillary bodies, corpus callosum, pons), 3) to know the plasma ammonia levels.

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Conclusion

It is important for radiologists to know the classical neuroimaging patterns of diseases associated with alcohol consumption. A memory aid, based on a simple neuroradiological approach algorithm is a useful tool.
Personal information

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