

Advances in Imaging Studies of Brain Structural and Functional Impairment in Chronic Alcohol Dependence

Sun Yuting¹, Yin Changhao², Xu Zheng¹ and Zhu Xiaofeng³

¹Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang

²Department of Neurology IV, Hongqi Hospital affiliated to Mudanjiang Medical University, Heilongjiang Province, Mudanjiang 157000, and Heilongjiang

³Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang

*Corresponding author

Zhu Xiaofeng, Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang

Fund Project: National Key R&D Program of China (2018YFC1314400).

Submitted: 27 Aug 2020; **Accepted:** 02 Sep 2020; **Published:** 15 Sep 2020

Abstract

Chronic alcohol dependence (CAD) is a chronic, recurrent, and highly prevalent disease that causes significant health and financial burden. Chronic alcohol exposure affects all organ systems, especially the central nervous system, which is often manifested in a range of neurological and psychiatric symptoms. Therefore, the problem of brain damage caused by alcohol dependence needs to be solved urgently. In recent years, imaging has been widely used in the study of substance addiction, especially the study of alcohol dependence has made significant progress, which is of great significance for the early diagnosis and prognosis evaluation of the disease. This article reviews the progress of imaging studies on brain structure and function damage in CAD patients.

Keywords: Alcohol dependence; Brain damage; Imaging

Introduction

Chronic alcohol dependence (CAD) is a syndrome characterized by a series of symptoms and behaviors, including uncontrolled alcohol consumption, dangerous drinking patterns, and cravings for alcohol in the absence of alcohol [1]. In 2018, the World Health Organization announced that harmful use of alcohol caused about 3 million deaths in 2016, and CAD accounted for 4% of the global disease burden. It is one of the common mental disorders affecting millions of people around the world [2]. Long-term drinking will not only affect the peripheral organs, but also cause serious neurological consequences, including Wernicke's encephalopathy (WE). If left untreated, it can develop into Korsakoff syndrome (KS) and hepatic encephalopathy (HE), central pontine myelinolysis (CPM), Marchiafava-Bignami disease (MBD) and other diseases. In addition to direct effects, high levels of alcohol consumption are associated with an increased risk of seizures, stroke, and traumatic brain injury.

Brain damage caused by alcohol dependence is a chronic process. The impairments of nerve cells and microstructures, structural changes and the abnormalities of cerebral perfusion

and metabolism are not easily detected in the early stage, and often delay diagnosis and treatment. Imaging examination can effectively solve this problem. Longitudinal observation of CAD patients during the entire disease process, to unlock the disease process, to help early detection, diagnosis, and treatment, to better understand the physiological changes and molecular mechanisms of CAD [3].

Alcohol can cause cell degeneration, demyelination and axonal degeneration of the central and peripheral nerves through various mechanisms; and lead to vascular endothelial cell apoptosis, thickening of the vessel wall, mild stenosis of the lumen, reduction of cerebral blood flow, and ischemic deficiency Oxygen changes, inflammatory edema of brain tissue, etc.

Image characteristics of changes in brain structure

Structural magnetic resonance imaging (MRI) is currently the most effective and commonly used tool for identifying and diagnosing neurological diseases caused by long-term drinking. Relevant studies used MRI to find that, compared with healthy controls, untreated CAD patients had volume defects in the

frontal cortex, thalamus, and papillary body; uncomplicated CAD patients had thinning of the corpus callosum and reduced pons; The structure of the basal ganglia is affected, including the caudate nucleus, putamen and nucleus accumbens [3]. Changes in the reward circuit nodes of the basal ganglia may promote the gradual progress of alcohol dependence, because these structures involve habit formation, reward evaluation, etc [4]. Before the appearance of clinical symptom syndrome, neurological diseases such as WE, KS, CPM and MBD progressed continuously in the course of dynamic alcohol damage. Longitudinal structural MRI studies have shown that some brain morphological changes are reversible after stopping drinking. After a period of abstinence, many areas of the brain that had previously shrunk increased in size, including the temporal, insular and anterior cingulate cortex, amygdala, thalamus, hippocampus, brainstem, and cerebellar cortex. Full recovery is difficult to judge, because the older you are, the weaker the brain function associated with alcoholism: for example, the older you are, the weaker your ability to recover is compared to the younger CAD patients. White matter hyperintensity is believed to be due to changes in the fluidity and water content of interstitial fluid, which may mean demyelination or axonal damage. A large number of structural and diffusion-weighted MRI studies have proven that brain white matter is susceptible to the negative effects of drinking. Cause brain white matter damage. WE is caused by a deficiency of vitamin B1 associated with long-term drinking, and if left untreated, it may develop into KS. On the T2 image, the brain aqueduct, papillary body, and midbrain gray matter around the third ventricle showed symmetrical hyperintensity changes (Figure A) [5]. In general, structural MRI has a great advantage in the observation of brain structural changes. The obtained images have three-dimensional characteristics, so the measured results can be more accurately compared with the internal boundary markers. However, it has limitations in the detection of early microstructure changes.

Images of the brains of alcoholics with WE (Figure B) from left to right are FA pseudo-color images and MK pseudo-color images. Male patient, 54 years old, with significant memory loss, chronic alcoholism and MBD patient.

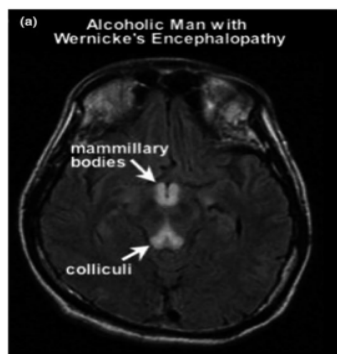


Figure A

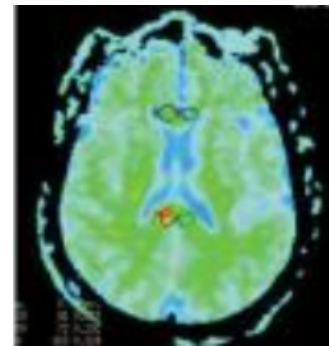
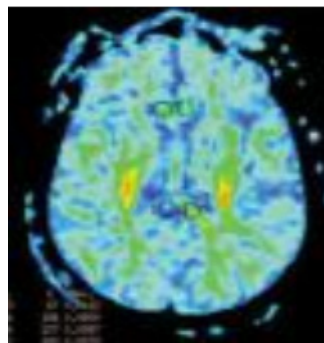


Figure B

Diffusion kurtosis imaging (DKI) and diffusion tensor imaging (DTI) can detect white matter changes before they become obvious on conventional MR images, and can be used to detect white matter changes in CAD patients. The commonly reported DTI measurement methods are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD); DKI scanning can get average kurtosis (MK). FA is thought to reflect axon diameter, axon density, and myelination. The decrease in FA is usually associated with an increase in RD (related to demyelination) or a decrease in AD (reflecting axon damage) [6]. Studies have shown that, compared with CAD patients without KS, KS patients show a decreased FA value in the fornix, hippocampal memory circuit, and medial marginal circuit [7]. Studies have shown that the MK of the corpus callosum, the cerebellar hemisphere, and the bridge arm of CAD patients is lower than that of the control group. The results suggest that DKI technology can detect early changes in the microstructure of the brain tissue of CAD patients. Ordinary imaging examinations are difficult to diagnose MBD with mild chronic alcoholism, and DTI and DKI can make up for the above shortcomings. Figure B shows a typical image of chronic alcoholism MBD [8]. More and more evidences indicate that white matter abnormalities may be the core of the pathophysiology of mental disorders. Alcohol is related to white matter abnormalities, but the data of impact on white matter microstructure for CAD patients is very limited, especially in the early stages of the disease. Research results show that young people who drink regularly (more than one drink a week) have lower FA values in left thalamic radiation, left hippocampal and left amygdala white matter [9]. DKI and DTI can reflect the changes in the microstructure of the whole brain of CAD patients, and provide imaging evidence for the diagnosis of alcohol dependence. Although DKI is still in the research stage, a large amount of clinical data and more accurate diffusion models are needed to further evaluate its value, but it has become an important part of multiparameter imaging of brain damage in CAD patients.

Image Characteristics of Changes in Brain Function

Functional magnetic resonance imaging (fMRI) is based on the blood oxygen level dependent (BOLD) imaging principle to reflect neuronal activity. BOLD-fMRI signals have been used in CAD

patients to explore the functional activities of the brain related to cue response, craving, impulse, and self-control and to characterize the dynamic characteristics of brain activity. fMRI studies have shown that, compared with healthy controls, alcohol can cause CAD patients' attention bias [10]. Some fMRI studies have linked visual alcohol signals to hemodynamic responses in brain areas related to reward circuits, including the anterior cingulate cortex, medial prefrontal cortex, ventral striatum, and insula. Other studies reported that the brain areas of CAD patients have undergone tremendous changes in areas related to self-control, memory, and reflective thinking, indicating significant changes in circuits related to decision-making. The resting state default mode network describes a network of connected brain regions. When the individual is not performing tasks, these regions are particularly active, consisting of the ventral medial prefrontal cortex, cingulate gyrus, inferior parietal lobe, lateral temporal cortex, dorsal. Composed of the medial prefrontal cortex and hippocampus, alcohol dependence changes the default mode network of the resting state, from the connection between the posterior cingulate cortex and the middle cingulate cortex to the increased connection between the midbrain and the middle cingulate cortex. The results show that the execution control is compromised [12]. A large amount of evidence from fMRI research shows that the anterior cingulate cortex and the lateral prefrontal cortex are important nodes that assist cognitive control. A study based on fMRI has shown that alcohol is harmful to the neural synchronization that promotes cognitive control [13]. It can interfere with goal-oriented behavior, and goal-oriented behavior may lead to lack of self-control and compulsive drinking. fMRI is mainly used for the monitoring of brain function activities. It can detect abnormalities before the brain structure changes in CAD patients and intervene as early as possible. It is also of great significance in the research on the mechanism of brain damage caused by CAD.

Arterial spin labeling (ASL) provides a non-invasive method to quantify cerebral blood flow, using autologous arterial blood as a natural endogenous tracer, and ASL cerebral blood flow is widely used as a marker of brain function. In a study of haloperidol in the treatment of alcohol-induced mental disorders, cerebral perfusion was examined before and after treatment, and it was found that blood flow in the left caudate nucleus and left frontal lobe increased after treatment, and the frontotemporal parietal occipital lobe, thalamus and cerebellum changes in local blood flow are significantly negatively correlated with the severity of symptoms, suggesting that there may be dysfunctions in these brain areas, leading to a series of neurological and cognitive impairments, such as reduced executive control and memory impairment [14]. The influence of alcohol on brain perfusion can be monitored by ASL. ASL technology has the advantages of repeatability and facilitating follow-up. It can be used for longitudinal observation of CAD patients, and abnormal cerebral blood flow can be found before clinical symptoms appear, which is convenient for early treatment and intervention.

The cause of abnormal electroencephalogram (EEG) in CAD

patients with brain damage is non-specific diffuse changes [15]. The study found that, among 80 CAD patients, 49 had abnormal EEG, with an abnormality rate of 61.25%; other studies have shown that the abnormal rate of EEG is about 63.8%. The results suggest that alcohol damages brain function diffusely. Therefore, EEG analysis is used to provide certain information and basis for disease research and diagnosis. With the emergence of non-invasive brain imaging technologies such as EEG and fMRI, we can objectively determine the neural connection of drinking cravings, thereby highlighting the reward effect of drinking on the brain. This can be achieved by using resting state EEG and task-based functional magnetic resonance imaging to study the resting state and responsiveness of CAD patients' brains to images of alcoholic and non-alcoholic beverages [16]. Previous studies have shown that in the limbic reward system, such as the nucleus accumbens, ventral striatum, and amygdala, alcohol-related cues can increase BOLD signals. At the same time, the BOLD signal in other cortical areas also increased, such as dorsal anterior cingulate cortex, anterior cingulate anterior knee, posterior cingulate cortex, orbitofrontal cortex, precuneus, insula and parahippocampus. These findings are consistent with the results of a study that reported abnormal brain resting states in CAD patients after a period of abstinence. Several EEG studies in the resting state reported that the cravings of CAD patients are related to increased β -wave spontaneous brain activity [17, 18]. There are relatively few studies of EEG used for brain damage in CAD patients, and the accuracy rate is slightly lower than other tests. When no abnormality is found in an EEG examination, the brain damage cannot be completely ruled out and regular review is required. However, the status of EEG in the study of alcohol dependence cannot be ignored, and it is still important in the diagnosis of brain damage caused by alcohol.

Imaging Features of Changes in Brain Metabolism

Magnetic resonance spectroscopy (MRS) is quantified in vivo based on the molecular structure of neurometabolites. The most commonly detected metabolites are N-acetyl aspartic acid (NAA), creatine phosphate (tCr), choline-containing compounds (Cho) and so on. Most MRS studies on alcohol dependence have focused on these three main metabolites. NAA exists only in neurons and is a sign of neuron density and survival [19]. The level of NAA reflects the functional status of neurons, and Cho represents the metabolic state of cell membranes. Long-term heavy drinking is closely related to the abnormal concentration of brain metabolites, but the mechanism is still unclear [20, 21]. Neuroimaging studies have used proton magnetic resonance spectroscopy (^1H MRS) to study neurometabolic changes associated with heavy drinking and/or alcohol dependence. These studies usually report low levels of NAA and Cho in CAD patients [22]. However, in the only report of MRS on a case of alcoholism-related CPM, a 53-year-old man developed gait disturbance and hearing loss, and developed voxels in the pons (conventional MRI showed lesions), showing elevated Cho/tCr. It is interpreted as edema or demyelination [23]. A preliminary study of the neurometabolic changes caused by alcohol in the ^1H MRS study showed that long-term heavy drinking could lead to homeostasis, that is, abnormal transfer of

the “set point” of the nervous system [24]. A study showed that in the frontal lobe, medial temporal lobe, cerebellum, and thalamus, CAD patients had lower NAA/tCr and Cho/tCr levels than normal controls. A case study of a Japanese man who drank alcohol for 50 years and suffered from insufficient diet for several days. Acute WE due to vitamin B deficiency showed that the level of NAA/tCr in the thalamus and cerebellum is low, and the cerebellum lactic acid peak is usually undetected (ie healthy controls). In various brain regions (such as frontal lobe, parietal white matter, anterior cingulate gyrus, basal ganglia, and occipital white/gray matter), the results of MRS showed significant consistency in alcohol-related HE compared with healthy controls. Compared with non-alcoholic HE, it shows a lower level of Cho/tCr [25]. FRISCHKNECHT et al. studied the hippocampal metabolism of CAD patients and found that the hippocampal NAA/tCr decreased significantly and the hippocampal gray matter volume decreased [26]. MRS detects brain tissue metabolism and biochemical changes, which can be used for early intervention and clinical research on CAD patients. The MRS technology has the advantages of safety, non-invasiveness, accuracy and effectiveness, and dynamic monitoring, which provides a basis for alcohol dependence research.

Positron emission tomography (PET) is a non-MRI imaging method that uses specific radiotracers to study the brain’s glucose metabolism, the availability of neurotransmitter receptors, or the use of competitive receptor binding instead of indirect measurement of neurotransmitter levels, which can be used for evaluation relative changes in the extracellular levels of specific neurotransmitters. A study showed that compared with the control group, CAD subjects showed decreased brain glucose metabolism, which was evident in the medial frontal and parietal cortex regions. Acute alcoholism also reduced brain glucose metabolism. Long-term drinking leads to a decrease in GABA receptor activity and the dopaminergic pathway is de-inhibited [27]. Human PET studies have found that dopamine signals in CAD patients are contradictory. For example, a study reported that intravenous alcohol administration caused a significant increase in dopamine in the right abdomen striatum of non-therapeutic alcoholics (as measured by [¹¹C] raclopride competitive D2/D3 receptor binding), but was not effective for social drinking. The other has no such effect [28]. In contrast, the increase in extracellular dopamine in the ventral striatum and caudate nucleus caused by alcohol is related to the pleasurable effect of alcohol, and this difference may be caused by genetic polymorphism [29]. One of the most consistent reported findings in CAD research is the reduction of dopamine D2/D3 receptors throughout the brain [30]. The lack of inhibitory dopaminergic receptors can explain some of the behavioral characteristics of CAD patients, such as lack of impulse suppression and compulsive behavior patterns. However, if this change continues after a long period of prohibition, it is still controversial. D2/D3 receptors in the striatum continued to decrease after 4 months of abstinence, while in the subgroup of CAD patients who had abstained for 1 year, D2/D3 receptors were significantly upregulated [31]. Studies

using PET have found that long-term alcohol consumption leads to reduced availability of the marginal metabotropic glutamate receptor (mGluR5), and lower mGluR5 is associated with less craving [32]. The decreased availability of mGluR5 in the brain of CAD patients partially recovered during abstinence, and mGluR5 levels have changed significantly after two months. PET shows the metabolism, function, blood flow and other conditions of the brain cells of CAD patients from the molecular level. It is more comprehensive and systematic than other examinations, and can provide more physiological and pathological diagnostic information for the clinic.

Summary

The brain damage caused by long-term drinking of CAD patients is increasing. Early detection, early diagnosis, and early treatment are necessary for such patients. Imaging has the advantages of non-invasive, convenient, and accurate. It is of great value for the pathogenesis, pathological changes, disease progression, diagnostic evaluation, and clinical research of CAD patients. Although some examinations are not widely used in the clinical work of CAD, they are still in the experimental research stage, but with the continuous advancement of imaging technology, there will be more technologies applied to alcohol dependence, showing greater value.

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