Chronic Alcoholic Toxic Cerebral Encephalopathy manifested as Acute Marchiafava-Bignami Disease: a case report

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Case report

Keywords: Acute Marchiafava-Bignami Disease, magnetic resonance imaging, entire callosal lesions, prognosis

Posted Date: October 4th, 2019

DOI: https://doi.org/10.21203/rs.2.15535/v1

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Abstract

Background: Marchiafava-Bignami Disease (MBD) is a alcohol-related disorder, its acute form is rather rare that is characterized by acute edema and demyelination of the corpus callosum, manifested as severe disorder of consciousness like coma, which can be accompanied by an increase in muscle tone.

Case presentation: We report a 57-year-old man with a 40-year history of chronic and heavy alcohol abuse who progressively developed bilateral lower limb weakness and slurred speech for 3 days. On admission, neurological examination revealed abnormal mental status and cognitive deficits. His left nasolabial groove appeared shallow. The muscle power of the bilateral upper and lower limbs was only grade 4+ with lead-pipe rigidity of muscle. Deep tendon reflexes in the lower limbs were increased, and Babinski reflexes were positive bilaterally and negative Hoffmann reflexes and the forced grasp reflex.

He was diagnosed with erosive gastritis two years ago without any treatment. The immediate brain computed tomography(CT) showed hypodensity in the genu and splenium of the corpus callosum, which suggested an acute cerebrovascular disease, however, the laboratory tests were almost normal except for decreased serum level of folic acid (7.63mmol/L; normal range 11.8-56.2mmol/L), and MRI revealed bilateral hyperintensity on T2, T2 FLAIR and DWI in the entire corpus callosum, with corresponding hypointensity on ADC images. Based on his medical history, physical examination, and imaging features, the definitive diagnosis of acute MBD was reasonable. But after nearly 5 months of treatment, the symptoms did not relieve significantly, which could be attributed to entire callosal lesion etc.

Conclusions: MBD is mainly caused by chronic alcoholism. MRI findings, especially the DWI sequence, are critical for the early diagnosis of MBD in the acute stage, which prevent disease progression from irreversible callosal lesion.

Background

MBD is a very rare and typically fatal disease associated with chronic, heavy alcohol consumption and malnutrition, and is characterized by callosal lesions like necrosis and demyelination, which was originally described in middle-aged men living in the Chianti region of Italy[1,2]. To date, the pathogenesis of MBD has not been well clarified. Some researchers pointed out that several factors, like genetic factors, direct and indirect toxic effects mediated by alcohol consumption, liver disease and so on, have influenced the pathophysiology of MBD. A few reports that investigated the mechanism of alcohol-related disorders suggest that inflammatory reactions accompanying demyelination and micronecrosis and secondary axonal damage might be involved in the acute stage of MBD[3,4]. The syndrome consists of altered mental status, impaired gait, dysarthria, apathy, amnesia, apraxia, coma, cortical disconnection syndrome, seizures and pyramidal tract symptoms. These symptoms are all related to specific corpus callosum involvement, with particular involvement of the splenium[3,5,6].

Acute lesions were frequently found in the body of the corpus callosum, the genu, and the splenium. However, the entire corpus callosum is rarely involved[7]. Other sites which have been described include...
the periventricular white matter, the basal ganglia, the internal capsules, subcortical areas, the cerebral cortex, optic tracts, as well as cerebral and cerebellar peduncles[3,8,9]. As many experts conclude, cortical involvement, complete corpus callosum lesions, and some other extra-callosal lesions in acute MBD are poor prognostic indicators[6,7,10,18].

The following pathognomonic MRI findings are critical for the diagnosis of MBD: hyperintense signal lesions on T2 weighted imaging (T2WI), fluid attenuated inversion recovery (FLAIR) and DWI within the corpus callosum without significant mass effect[11]. DWI is sensitive to cytotoxic edema[18]. During the acute phase, the involved regions become oedematous with or without demyelination and reduced diffusion is often shown on DWI with corresponding hypointensity and decreased values on apparent diffusion coefficient (ADC) mapping[12,15,16].

Here we report a case with acute lesions confined to the entire corpus callosum. Various MRI modalities, especially DWI, were performed sequentially to facilitate the diagnosis. According to the mode of symptom onset and neurological signs presented, most importantly, the MRI manifestations, the final diagnosis was MBD.

**Case Presentation**

A 57-year-old male, with a 40-year history of heavy alcohol abuse (500g of distilled spirit per day), was admitted to the hospital due to the acute onset of bilateral lower limb weakness and slurred speech for 3 days. Initially, he had a slurred speech when he woke up (he had drunk 250g 6 hours ago), with bilateral lower limbs weakness that led to his inability to independently stand up. Simultaneously, he presented symptoms of dysarthria, nausea, and incontinence, and no disturbance of consciousness, dizziness, visual rotation and paresthesia. The symptoms were persistent without remission. Subsequently, these symptoms and signs progressed to altered mental status with confusion, bradyphrenia, as well as deterioration in standing capacity within the next two days. His family noted that he fell and had involuntary hand movements half a month before the onset of illness. The patient had a history of haematemesis and was diagnosed with erosive gastritis two years ago without any treatment. He had no history of poison contact, drug abuse, head trauma, recent fever, or infection. There was also no similar family.

On admission, blood pressure was 134/87 mmHg and body temperature was normal. Neurological examination revealed a slurred speech with abnormal mental status and cognitive deficits. Both pupils were round and equal, light reflex corneal reflex and eyeball motion were normal, without nystagmus. Weakness of the frontalis muscle, masticatory muscles and orbicularis oculi was not found. His left nasolabial groove appeared shallow. There was normal gag reflex and palate elevation. His overhang and tongue was in the center. Neither tongue atrophy nor fasciculation were found. The muscle power of the bilateral upper and lower limbs was only grade 4+ with lead-pipe rigidity of muscle. The patient did not cooperate with the sensory function test and coordination movement. Deep tendon reflexes in the lower limbs were increased, and Babinski reflexes were positive bilaterally. Hoffmann reflexes and the forced
grasp reflex were negative. He displayed no abnormalities in his autonomic system except sphincter dysfunction.

Routine blood, urine, liver and kidney function, blood coagulation tests, glycosylated hemoglobin (GHb), electrolytes tests and tumor series as well as other laboratory tests showed no obvious abnormalities. His serum level of folic acid (7.63 mmol/L; normal range 11.8–56.2 mmol/L) was low, the level of vitamin B12 (209.26 pmol/L; normal range 133–675) was in the normal range (180–914 pg/mL). The serum level of vitamin B1 could not be detected.

He underwent immediate brain computed tomography (CT) that showed strongly hypodensity in the genu and splenium of the corpus callosum, which suggested an acute cerebrovascular disease (data not shown). His brain MRI obtained 1 day after admission showed bilateral abnormal hyperintensity on T2 and T2 FLAIR in the entire corpus callosum and partial corona radiata (Figure1) (the data on T1 weighted imaging (T1WI) is not available). The DWI showed the complete corpus callosum to be strongly hyperintense with corresponding hypointense on ADC images (Figure1). Sagittal MRI showed hypointense on T1 Flair and hyperintense T2WI in the central layer of the corpus callosum. Magnetic resonance angiography (MRA) of the head showed normal intracranial vessel status (data not shown).

Suspected diagnosis was MBD, simultaneously, the initial diagnosis of “acute cerebrovascular disease” was excluded based on his history of chronic alcoholism and specific brain MRI findings. On the basis of the medical history, findings on physical examination, laboratory tests, and imaging features, the final diagnosis of acute MBD was reasonable.

Before the results of the various tests, agathuban (60 mg a day was administered by micro pump for 24 hours), atorvastatin (40 mg, before going to bed apart), edaravone (30 mg, intravenous) were administered to treat acute cerebrovascular disease for 2 days. Then, vitamin B complex (vitamin B 1, B 6, B 9, and B 12) was commenced immediately after make the diagnosis of acute MBD. Due to the positive result of the skin test, thiamine (vitamin B 1) was administered through the stomach tube at a dose of 60 mg/d. Vitamin B9 (20 mg, three times a day) was administered through the stomach tube. Vitamin B6 (300 mg a day), B12 (5 mg, three times a day) and vitamin C (1 g a day) were administered intravenously.

Furthermore, he was administered with eperisone (50 mg, three times a day) / baclofen (the initial dose was 5 mg, then increased by 5 mg every three days until 15 mg), citicoline (0.2 g, three times a day) and donepezil (10 mg, one time a day) to improve the muscle tone and cognitive function. After 7 days of treatment, the patient’s symptoms did not relieve significantly, and his family requested to be discharged. Upon discharge, his mental status improved slightly, but other symptoms remained constant. During hospitalization, he did not report any side effects of thiamine administration. After discharge, the patient continued to take eperisone, citicoline, vitamin B1, vitamin B6 and donepezil as usual. A phone follow-up, four months later, revealed little improvement in his symptoms, except for a decrease in muscle tone. Further brain MRIs have not been arranged due to the patient’s condition.

**Discussion And Conclusions**
MBD is a rare acute to chronic disorder that most frequently occurs in chronic alcoholics, followed by malnourished people. In terms of its pathophysiology, MBD can be attributed to the direct and indirect toxic effects derived from chronic alcohol consumption as well as malnutrition. Drinkers generally eat less food, and furthermore, alcohol-induced gastrointestinal injury inhibits the absorption of multiple vitamins, like B-vitamins. Of the B-vitamins, B1 plays an important role in human body in the form of pyrophosphate thiamine (TPP). TPP is an important coenzyme of glycolysis pathway and pentose phosphate pathway, which contributes to the energy supply and phospholipid metabolism of nerve tissue. Deficiency of TPP affects the function of nerve tissue and leads to demyelination and axon loss of the nerve tissue. In addition, deficiency of vitamin B1 can also increase the activity of cholinesterase and accelerate the hydrolysis of acetylcholine (ACh), which can affect the normal conduction of impulses in nerve tissue. The latter can decrease the liver’s ability to clear toxic metabolites in the blood, which can further increase oxidative stress and neurotoxicity [1]. An emerging mechanism of direct neurologic injury suggests that the metabolites of ethanol accumulate to disrupt function of lipid, mitochondrial, endoplasmic reticulum and so on. This can cause strong oxidative stress accompanied by production of stress-response proteins and reactive oxygen species as well as activation of intracellular signal cascade reactions to initiate neuronal cell death. Simultaneously, ethanol can also directly decrease the production of brain-derived neurotrophic factor, promoting neuronal cell growth and differentiation, and thus leading to the death of neurons. Chronic alcohol use may cause disorders of neurotransmitters, including dopamine, GABA, glutamate, noradrenaline, opioids and serotonin. For instance, ethanol can suppress the NMDA receptor and thus reduce the excitatory effects of glutamate. The indirect effects of alcohol consumption arise from thiamine deficiencies and hepatic dysfunction. The former can lead to disorders in synthesis and metabolism of substances that are essential to neurogenesis[1,3].

The corpus callosum is a fiber-rich white matter tract that connects left and right cerebral hemisphere and has a relatively high myelin content. The corpus callosum, especially the splenium, is vulnerable to a variety of external and internal risk factors, like alcoholic toxicity and thiamine deficiency[8]. Neurologic defects are mild when the corpus callosum lesions are small or the sites involved are few. On the contrary, when the corpus callosum lesions are diffuse or involved in multiple sites, the neurologic defects are very serious [12]. Meanwhile, there are also many other sites which have been described and can be involved (mentioned above)[3,8,9]. So the clinical manifestations of MBD are diverse and unspecific and thus, difficult to diagnosis.

This study describes a patient diagnosed two years previously with erosive gastritis and had a 40-year history of heavy alcohol abuse. Considering the above risk factors, we infer that the serum level of vitamin B1 was decreased. Thus, it can be speculate that the patient’s MBD may be closely associated with chronic alcoholism and/or malnutrition, and especially B-vitamins (Mainly vitamin B1, Thiamine) deficiencies.

There are three types of MBD: (1) acute MBD, which is characterized by severe disturbance of consciousness, such as coma[6] and dizziness, which may be accompanied by increased muscular
tension, disorientation, seizure, dysarthria, and frontal lobe symptoms; (2) subacute MBD, which is characterized by a rapid progression of dementia, inability to stand and walk, behavioral abnormalities, apathy, visual hallucinations, and likely progressing into chronic disease. (3) chronic MBD, which is characterized by progressive dementia, behavioral abnormalities, disturbance of intelligence, and interhemispheric disconnection syndrome[7,11]. Whereas the above mentioned clinical classification of Brion et al is still widely used, Heinrich et al proposed a clinicoradiologic classification[6]. Considering the patients' clinical status as well as the radiological severity of cerebral changes detectable on MRI, it was recommended that the disease could be classified as type A and type B. Type A is characterized by alterations of consciousness and diffuse swelling of the entire corpus callosum on imaging. Type B is characterized by mild impairment of consciousness and small callosal lesions associated with good prognosis. According to clinicoradiologic manifestations, most MBD cases can be assigned to one of these two groups.

The patient in this case study can be classified as type A from a clinicoradiologic point of view (acute onset with suspected expressive aphasia, alterations of mental status, pyramidal tract syndromes and the strong affection of the complete corpus callosum). Type A has a worse prognosis [6]. Considering his short medical history and clinical manifestations, the patient was likely in the acute stage.

The role of MRI is essential in making the diagnosis, differentiating the different subtypes, identifying degree of involvement, and predicting prognosis in vivo. Conventional MRI in MBD typically detects lesion areas of low T1 signal intensity and high T2 signal intensity as well as FLAIR and DWI in the body of the corpus callosum, followed by the genu and the splenium. However, the entire corpus callosum is rarely involved [7,13]. Degeneration of the corpus callosum mainly involves the middle layer rather than the upper and lower margins[17]. The best method to assess callosal lesions is sagittal MRI which offers the ability to visualize the entire corpus callosum. By contrast, accurate visualization of the body of the corpus callosum is difficult in the axial planes, limiting the diagnostic yield of axial MRI and particularly CT[14]. In sagittal MRI, like T1WI and T2WI, we observe that MRI of MBD are characterized by symmetrical lesions of the corpus callosum situated in the central layer sparing the dorsal and ventral layers, resulting in a sandwich-like appearance(Figure2)[13]. As mentioned earlier, the DWI, which displays a limited extent of diffusion, is sensitive to cytotoxic edema. During the acute phase, the involved regions become oedematous. Reduced diffusion and hyperintensity are often seen on DWI with decreased values on ADC mapping[12].

The MRI of the patient in the present case was quite typical, and consistent with those expected for MBD. Although MRI revealed hyperintensity on T2WI and FLAIR in the entirety of corpus callosum and corona radiata (Figure1 a, b, c, d), only the corpus callosum appeared to be hyperintense on DWI (Figure1 e, f). A possible explanation for this phenomenon is that the corona radiate lesion was mild and insufficient to limit diffusion. It may also be that the damage in the corona radiate was an obsolete cerebral injury. That is to say, the callosal lesion was the main reason for this hospitalization.
The diagnosis of MBD is based on the callosal lesions. Differentiation of MBD from infarction of the corpus callosum may be difficult. However, selective involvement of the entire length of the corpus callosum without significant mass effect and focal cystic necrosis confined to its central layer are more likely to be attributed to MBD. Many other diseases that involve the corpus callosum like paraneoplastic syndrome (PNS), multiple sclerosis (MS), Wernicke's encephalopathy (WE) and so on had to be excluded based on the clinical manifestations, laboratory findings and imaging features prior to a diagnosis of MBD. The combination of chronic alcoholism, clinical features, laboratory tests and MRI findings (showing the detailed parts involved in the diseases) were used to exclude those diseases and support the correct diagnosis[12].

After treatment with vitamin B complex (vitamin B 1, B 6, B 9, and B 12), the patient’s symptoms did not relieve significantly. Reviewing his treatment process, it was speculated that this might be due to the mode of administration (stomach tube) and dosage (60mg/d) of vitamin B1 (personal opinion). In addition, poor prognosis may be related to the brain areas involved in the MBD. It is still controversial whether the appearance of extra-callosal lesions, like in the cerebral cortex, subcortical white matter or corona radiate etc., can be used to predict a poorer prognosis[6,18]. A review by Heinrich and Menegon stated that involvement of the entire callosum and of the cortex were poor prognostic factors[6,7]. When the entire corpus callosum is involved, the function of the corpus callosum cannot be compensated (personal opinion), which may explain the poor prognosis of our patient. Although there is no conclusive evidence, we speculate that corona radiate injury is also involved in the poor prognosis. Otherwise, Ménégon P et al reported that cytotoxic edema on DWI and the ADC map might also predict poor outcome[7]. All in all, the risk factors that could potentially lead to poor prognosis were prevalent in our patient, likely explaining his poor prognosis.

MBD should be considered in the evaluation of alcoholic or malnourished patients who present acute, subacute or chronic neurological symptoms. MRI findings, especially the DWI sequence, are critical for the diagnosis of MBD. Early diagnosis and treatment may prevent irreversible corpus callosum damage. What we must keep in mind is that prevention is the key to disease. So we should pay attention to health education in order to maximize the prevention of disease.

**Abbreviations**

MBD: Marchiafava-Bignami disease; T1WI: T1 weighted imaging; T2WI: T2 weighted imaging; FLAIR: Fluid attenuated inversion recovery; DWI: Diffusion-weighted image; MRI: Magnetic resonance imaging ; ADC: Apparent diffusion coefficient; CT: Computed tomography; MRA: Magnetic resonance angiography; GHb: Glycosylated hemoglobin; TPP: pyrophosphate thiamine; Ach: Acetylcholine; PNS: paraneoplastic syndrome; MS: multiple sclerosis; WE: Wernicke's encephalopathy .

**Declarations**
Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the guardian of the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interest

The authors declare that they have no competing interests.

Funding

Not applicable

Authors’ contributions

All authors have read and approved the final manuscript. ZZ and XL acquire patient data; ZZ, XL, LW, XJ, JN and CS analyzed and interpreted patient data; ZZ was a major contributor in writing the manuscript. Critical revision of the manuscript for important intellectual content: ZZ, XL, LW, XJ, JN and CS.

Acknowledgements

We are very grateful to Dr. W. Z. Duan and J. Dong from Hopkins University for providing a critical reading of this manuscript.

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Figures

Figure 1

Axial T2WI (a, b), FLAIR(c, d), DWI(e, f) and ADC(g,h) images. T2WI and FLAIR showed hyperintensity in the genu, splenium (a, c) and body(b, d) of the corpus callosum, as well as corona radiate(b,d). DWI showed the complete corpus callosum to be hyperintense (e, f). ADC-mapping showed hypointense signal corpus callosum lesion (g, h).
Figure 2

Sagittal T1 Flair(a) and T2WI(b) images. T1 Flair(a) and T2WI(b) showed typical “sandwich-like appearance” with T1 Flair hypointensities(a) and T2WI hyperintensities(b) in the central layer of the corpus callosum.

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