Retrospective analysis of 21 cases of Marchiafava-Bignami disease in alcoholic in Southwest China

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Abstract

Marchiafava-Bignami disease (MBD) is a rare disease with only a few reports worldwide. To describe clinical features and identify difficulties in the treatment of alcohol-related MBD, we performed a retrospective study of 21 MBD inpatients at a hospital in Southwest China. The interquartile range (IQR) for age was 53-66, with a mean age of 59 years. The IQR for drinking duration was 30-40, with a mean drinking length of 35.5 years. Cognitive impairment and unconsciousness were the most common symptoms (n=13, [61.9%]). Consciousness disorders, delirium, irritability, and ataxia are more prevalent in type A MBD patients; seizures, cognitive impairment, and limb weakness are more common in type B MBD patients. Routine blood and biochemical tests in alcoholic MBD patients may demonstrate orthocytic hypochromic anaemia and impaired liver function. Patients' uric acid (UA), potassium, and sodium levels may be normal. Eight patients received thiamine, while one received steroids. The average stay was 15 days. At the time of discharge, there had been no deaths. One patient died six months after being discharged, while another died two years afterwards. Indeed, MBD is a rare alcohol-related disorder with a variety of clinical symptoms. With thiamine treatment, prognosis is positive.

Introduction

Although Marchiafava–Bignami disease (MBD) has been identified for over 100 years since 1903, by 2001, only about 250 cases had been reported worldwide.[1] MBD, also known as primary corpus callosum degeneration is a rare disease characterized by degeneration and necrosis of the corpus callosum. [2] Injury to the corpus callosum can result in decreased cortical function, altered consciousness, and impairments in behavior and cognition. These manifestations may overlap with the other clinical symptoms of alcoholism-related encephalopathy. [3] MBD can be classified into subtypes A and B based on the type of symptoms observed. [2, 4] MBD can also be categorized as acute (≤ 2 weeks), subacute (> 2 weeks), or chronic (> 3 months) based on the time of onset. [4] The diagnose of alive patients relies heavily on imaging findings and correlation with a drinking history. Magnetic resonance imaging (MRI) is the gold standard imaging study of choice, and symmetrical lesions in the corpus callosum are typical pathognomonic characteristics on MRI.[5] There are no standard guidelines or validated treatments for managing MBD. Most reported cases of MBD have been treated with thiamine, vitamin B complexes, and steroids. [6, 7] The prognosis of patients varies, ranging from recovery to death. [7, 8]

Alcoholism is the most widely accepted causes of MBD.[6] The disease was first detected in 1903 in the autopsies of three Italians who had been drinking wine.[9] Patients with MBD who drink heavily appear to have a worse prognosis compared to non-drinkers. Hillbom, M. et al. reviewed 153 MBD cases reported between 1981 and January 2012, 142 of them were related with alcohol intake, and compared the proportion of patients who recovered to those with non-alcoholic, 9.9% (14/142) and 63.6% (7/11), respectively.[10] In China, it is estimated that 4.0%-6.0% of adults (over the age of 15) have an alcohol use disorder.[11] However, information on alcohol-related MBD is not readily available. In this study, we aimed

to assess clinical manifestations, magnetic resonance imaging (MRI) findings, treatment, and prognosis in patients with MBD. In turn, will promote awareness of MBD management in alcoholics for clinicians

Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Research Approval No. 2021-54). As this was a retrospective investigation, written consent was waived as per the First Affiliated Hospital of Chongqing Medical University Ethics Committee.. All records were anonymous and confidential. This was an evaluation of all alcohol-related MBD hospitalized cases from January 2012 to October 1, 2021, at the first affiliate hospital of Chongqing medical university. Alcoholics cases were identified based on the diagnosis codes and drinking history recorded in medical records. The coders encoded the alcohol dependence, alcoholism, acute alcoholism, chronic alcoholism and alcoholic encephalopathy according to the international Classification of diseases (ICD-10). The diagnosis of MBD relies on symmetrical lesions on the corpus callosum in MRI. Information such as demographic, medical history, clinical symptom, radiographic features, laboratory-test results, therapeutic regimens, and the outcomes were available in the medical records. Patients with great disturbance of consciousness, hyperintense swelling of the corpus callosum and poor prognosis are classified as type A, while the opposite is true for type B. A follow-up phone call was conducted with the participants. The Glasgow Outcome Scale (GOS) was used to assess prognosis in each patient. All 21 patients were followed up to March 2022 or with the patient's death as the follow-up endpoint. GOS is divided into 5 grades, Grade 5 Return to normal life, albeit with mild impairment. Grade 4 Mildly disabled but can live independently; able to work under protection. Grade 3 Severe disability, awake, disabled, requires care in daily life. Grade 2 Vegetative survival, only minimally responsive (e.g., eyes open with sleep/wake cycle). Grade 1 Death.

Data analysis

The medical records were analyzed, with descriptive analysis conducted for clinical data. The results were presented in terms of IQR and average according to age and drinking year, as well as in terms of medians and percentages with respect to the categorical variables.

Analyses were performed using IBM SPSS version 25.0. Statistical significance was set at $P < 0.05$.

Results

Baseline information and state at time of retrospective

The sample consisted of 21 men (Type-A 5 cases, Type-B 16 cases) with MBD and drinking history; these cases were documented between January 2012 to October 1, 2021, at the first affiliate hospital of Chongqing medical university. Fourteen patients came with acute episode, 5 with a subacute phase, and 2 with a chronic condition. The IQR of age was 53–66 (mean age 59, range 41-82). The average length of alcohol intake for the 21 patients was 35.5 years, (IQR year 30-40, range 20-60) and 4 patients (19.1%)

had ceased drinking before to the visit. In addition to alcohol, all patients were also addicted to tobacco. Five patients (23.8%) combine hypertension, 2 had malnutrition (9.5%) and 1 had diabetes (4.8%). Ten patients developed pneumonia during their stay in hospital. Six individuals had concurrent alcohol-related disorders, including 3 with alcoholic hepatitis, 2 with alcoholic polyneuropathy, and 1 with both hepatitis and polyneuropathy. (**Table 1)**.

Table I. Patients' characteristics

Case/Sex	Age(y)	Drinking time(y)	Complications	Follow-up time(y)	Return to regular drinking
1/M	41	20	Pneumonia	6	N
2/M	46	20	N	Lost	
3/M	46	30	Intracerebral hemorrhage; Pneumonia	5	Y
4/M	51	35	Alcoholic polyneuropathy; Alcoholic hepatitis	4	Y
5/M	52	30	Pneumonia	2	Y
6/M	54	40	Alcoholic polyneuropathy; foot ulcer	3	N
7/M	54	30	Hyperuricemia	3	Y
8/M	54	30	Pneumonia	1	N
9/M	56	30	N	1	N
10/M	57	40	N	Lost	
11/M	57	40	Alcoholic hepatitis; Pneumonia	1	N
12/M	60	40	Alcoholic hepatitis	Lost	
13/M	61	30	Pneumonia; Undifferentiated connective tissue disease	2	N
14/M	62	40	Pneumonia	8	N
15/M	63	40	Pneumonia	Lost	
16/M	65	40	Alcoholic polyneuropathy; Pneumonia; Urinary tract infection; Skin infection	6	Y
17/M	67	40	Pneumonia	0.5	N
18/M	67	40	N	4	Y
19/M	69	40	Chronic superficial gastritis	5	Y
20/M	75	30	Alcoholic hepatitis	4	Y
21/M	82	60	N	2	N

Cognitive impairment and unconsciousness were the most prevalent symptoms observed among the 21 patients (n=13, [61.9%]). Other common symptoms include irritability (n=12, [57.1%]), seizures (n=9, [42.9%]), delirium (n=9, [42.9%]), dysarthria (n=8, [38.1%]), ataxia (n=6, [28.6%]), and limb weakness (n=2, [9.5%]). Type A MBD patients did not report limb weakness.(**Figure 1**). Disorders of consciousness, delirium, irritability and ataxia are more common in type A MBD patients; seizures, cognitive impairment

and limb weakness are more public in patients with type B MBD. Dysarthria is shared by both types of MBD. (**Figure 2**)

Lesion distributions and MRI sequences

The main MRI findings were long T1 (n=16, 76.2%) and long T2 (n=18, 85.7%) signal changes in the corpus callosum. T2 fluid-attenuated inversion recovery sequence (Flair) (n=17, 81.0 %) and diffusion-weighted imaging (DWI) (n=14, 66.7 %) showed high signal. Two patients showed enhanced MRI. Lesions were found in the genu of the corpus callosum in 76.2% (16/21) of the patients, followed by the splenium in 71.4% (15/21). Two (9.5%) patients also had cerebellum lesions. The distribution of lesions is depicted in Figure 3.

Laboratory indicators

Table 2 shows the main statistical indicators for the admission laboratory tests. The following conclusions can be drawn: Orthocytic hypochromic anemia, a mild form of anemia, can occur in patients with alcoholic MBD. Elevated aspartate transaminase (AST), alanine transaminase (ALT), direct bilirubin (DBil), and decreased serum albumin (Alb) levels are indicators of possible abnormal liver function. Uric acid (UA) and electrolyte (kalium and Natrium) levels in the patient were both within normal ranges.

Table 2 Laboratory indicators of alcoholic Marchiafava-bignami Disease.

Laboratory indicators	Average	Median	Minimum	Maximum	Reference interval#
RBC (*10^12/L)	3.92	3.83	3.19	4.85	4.30 5.80
Hb(g/L)	128.5	129.5	74.0	159.0	130.0 175.0
Hct (%)	38.18	38.15	27.1	46.1	40.00 50.00
MCV (fl)	97.77	99.2	80.4	110	82.0 100.0
MCH (pg)	32.85	32.75	22	38.9	27.0 34.0
Alb(g/L)	37	36	29	47	40 55
TBil(μmol/L)	17.2	16.1	6.3	46.6	3.4 20.5
DBil(μmol/L)	10.5	5.9	2.5	88.0	0.0 6.8
ALT(U/L)	72.6	38	10	302	9 50
AST(U/L)	99	56	14	526	15 40
UA(μmol/L)	322	307	98	578	208 428
K(mmol/L)	3.9	3.85	3.2	4.7	3.5 5.3
Na(mmol/L)	143	143	139	147	137 147

#Normal reference ranges for all laboratory indicators are from the Department of Laboratory Medicine, The First Hospital of Chongqing Medical University.

RBC: red blood cell; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; Alb: Albumin; TBil: Total Bilirubin; DBil: Direct Bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; UA: Uric acid; K: kalium; Na: Natrium

Treatment and outcomes

Eighting patients were given thiamine (100mg im qd, 120mg im qd, 100mg im tid or 200mg im tid, treatment occurred daily for 5-20 days) and one was given steroids (Methylprednisolone 1000mg qd for 3 days). The average length of hospital stay is 15 days. During follow-up (0.5–8 years), 4 patients (19.0%) were lost to follow-up. Nine patients abstained from drinking, whereas 8 resumed drinking. At discharge, there were no fatalities. One patient (67 years old) died six months after discharge and the other (82 years old) died two years later. Data of the GOS score are detailed in Figure 4.

Discussion

Alcohol use disorder remains a major worldwide public-health problem, posing a large threat to human health. Marchiafava-bignami disease is a rare condition found in alcoholics, characterized by degeneration and necrosis of the corpus callosum.[12] Unlike other alcohol-related encephalopathies such as Wernicke's encephalopathy and Korsakoff's syndrome, we know remarkably less about the MBD. This is problematic, as delays in diagnosis can adversely affect treatment outcomes.[13] Different treatment options may also have a negative impact on the prognosis of patients. In this study, 21 inpatient cases of alcoholic MBD over a ten-year period in a hospital in west China with a large alcohol use disorder incidence seemed relatively small, suggesting a large number of cases were missed. In this study, we detailed the manifestations of 21 alcoholic MBD in a hospital at west China, as well as the treatment and prognosis in affected patients.

This study included twenty-one male patients, ages 59 on average, with 20–60 years of alcohol use and comorbid tobacco addiction. MBD is most commonly seen in patients who have a history of chronic alcohol consumption. According to a 2003 study on alcohol consumption in China, the general population's annual drinking rates were 74% for men and 38% for women. These rates rose with age, peaked at 40 to 50 years old, and then began to fall. Daily drinking rates were higher for men than for women, at 22.2% for men and 2.5% for women, and men consumed more alcohol on average than women. [14] consistent with those reported by Dong, X et al. in northeastern China with alcoholic MBD (age at onset 37–62 years, mean age 47.00 years ± 14.50 years).[15] One survey suggests that alcoholics who were 45 years of age or older had a significantly smaller corpus callosum area than age-matched controls, [16] indicating that men in this age group are more likely to develop alcoholic MBD. The China Report on the Health Hazards of Smoking 2020 reports that the smoking rate in China in 2018 was 26.6% for people aged 15 and over, with 50.5% of men smoking.[17] In this survey, all patients had a history of smoking and drinking. Studies have found that smokers have higher fractional anisotropy (FA) than

nonsmokers. Increased FA levels were showed in the corpus callosum (genu, body, and spenium), internal capsule, and superior longitudinal fasciculus.[18] Elevated FA may be a consequence of more myelin being formed, [19] or of long-term nicotine exposure causing vasogenic edema in the white matter bundles. [20] Demyelination of the corpus callosum is the primary cause of Marchiafava-bignami disease's pathological foundation.[2] Does nicotine, thus, act as a preventative against the development of MBD? Or does smoking make alcoholic MBD more likely to form? All require more research.

The corpus callosum is a white matter fiber that connects the cerebral cortex and is linked to higher brain functions.[21] A 53-year-old woman presenting with callosal disconnection syndrome (CDS) as a result of a stroke presents with ideomotor apraxia, and tactile anomia with the left hand, cross-replication of hand postures, cross-localization of the fingers, and constructional impairment with the right hand.[22] Epilepsy has been reported in up to two-thirds of people with corpus callosum hypoplasia or partial hypoplasia. The corpus callosum is the main pathway of epileptic generalization.[23] Reversible splenic corpus callosum lesions have also been discovered in patients who developed neuropsychiatric symptoms after steroid treatment.[24] MBD presents with a wide range of clinical manifestations, including altered cognition, motor impairment, sensory impairment, visual impairment, and psycho-behavioral abnormalities. [15] Unconsciousness and cognitive dysfunction are the most common clinical manifestations. [25] The corpus callosum projection neurons are pyramidal cells that use mainly glutamate or aspartate as neurotransmitters.[21] Vascular and non-vascular factors can both result in corpus callosum lesions. Tumors, trauma, demyelination, abscesses, ischemic and hypoxic injuries, etc. are examples of non-vascular causes.[26] The basic idea for how alcohol intake causes MBD involves thiamine shortage, oxidative damage, and the toxic effects of ethanol, with thiamine being the primary culprit.[27] Patients who consume alcohol have an impaired ability to absorb and utilize thiamine, and thiamine deficiency interferes with myelin synthesis, thereby damaging the corpus callosum, which has high myelin content. [27] Thiamine deficiency, rather than chronic alcohol intake, has been speculated to decrease glutamate uptake in the prefrontal cortex, leading to neurochemical dysfunction. [28] Vitamin B1 testing was seldom performed in our patients since vitamin B1 were given to the majority of patients who consumed alcohol.

Starting thiamine therapy within 2 weeks of MBD onset has been reported as beneficial for recovery, [4] Collectively, these findings suggest that thiamine therapy should be actively initiated upon MBD diagnosis regardless of the disease course. In previous studies, patients who eventually made a full recovery received a therapeutic thiamine dose of 60–1,500 mg/day. [29] No uniform guidelines for determining the optimal thiamine dose in MBD have been established, and the most common reference is the dosing regimen for Wernicke’s encephalopathy. [2] The dose (100 mg/day to 600 mg/day) and duration (5–20 days) of thiamine treatment in our patients varied widely, but 94.4% (17/18) of patients who received thiamine treatment had a positive prognosis. Does this imply that the dose and duration of thiamine therapy have no bearing on patient prognosis? However, there is a paucity of monitoring of patients' thiamine levels during therapy, which should be addressed in future research.

The current view is that alcoholic MBD appears to have a poorer prognosis than non-alcoholic MBD. [30] One study compared the prognosis of patients with corpus callosum abnormalities identical to MBD but not related with drinking or malnutrition to that of patients with alcoholic MBD, indicating that non-alcoholic patients had a better prognosis.[13] But each of the conclusions came from a review of the literature on previous findings. Due to the rarity of non-alcoholic MBD cases, there are very few reports on the prognosis of non-alcoholic MBD. The fact that non-alcoholic participants with MBD are younger [13] may also contribute to a better overall prognosis than alcoholic MBD. Our study tracked patients' alcohol consumption after they were discharged from the hospital. There were 17 patients who reported whether or not they continued to drink, eight of whom did and nine of whom did not. Six (66.7%) patients who denied continuing to drink had a good prognosis and two died, whereas 7 (87.5%) patients who continued to drink had a good prognosis. Except for one patient who was 82 years old, all 17 patients were similar in age. At the follow-up, all patients reported to drinking much less alcohol after discharge and, in order to avoid malnutrition, would frequently eat while drinking. This could explain why our drinking patients have a better prognosis.

MBD patients have a high mortality rate, particularly type A MBD patients, with some studies claiming death in up to 8% of cases.[31] In our study, two patients died. Patient 1 was an 82-year-old male with a 60-year history of alcohol consumption who was discharged with complete symptom improvement and died 2 years later of natural causes. Patient 2 was 67 years old and was treated with methylprednisolone during his hospitalisation, and was discharged with improved symptoms, but died 6 months after discharge. The University Hospital of Buenos Aires in Argentina also reported a death following intravenous methylprednisolone treatment, in which the patient's vitamin levels had corrected to normal levels but there was no sign of clinical improvement.[32] Patients with nonalcoholic MBD reported the death of an 80-year-old woman with Marchiafava-Bignami disease, which was discovered at autopsy.[33] Patient mortality appears to be linked to old age and methylprednisolone treatment. And a 34-year-old patient with alcoholic MBD who died of a lung infection seems to emphasize the importance of being on the lookout for pneumonia.[34] Steroids are considered to reduce brain edema, inhibit corpus callosum demyelination, and reduce inflammatory damage in patients with acute MBD. [35] Steroids also exacerbate underlying conditions such as infection and the risk of gastrointestinal bleeding, [28, 36, 37] which may increase the risk of poor prognosis. Therefore, steroids should be used cautiously in patients with MBD.

This research has some limitations. Firstly, the sample size was quite small. The First Hospital of Chongqing Medical University is one of the large hospitals in southwestern China, and most of the patients were from southwestern China. Alcohol-related MBD would have been fully represented if the sample size had been increased and diverse. Another limitation is the lack of testing for thiamine levels in patients, which makes it impossible to determine whether thiamine levels correlate with treatment levels in patients.

Declarations

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Author contributions

Zhi-Qin XI: Conceptualization; data curation. Xiaohui WU: Conceptualization; data curation; formal analysis. Wenju LI: Formal analysis. Yuzhu WANG: Data collection; data curation. Xuan CHEN: Data collection; data curation.

Data availability statement

Data are available on request. Correspondence and requests for materials should be addressed to X.W(email:huiczhde33@163.com)

Competing interests

The authors declare no competing interests.

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Figures

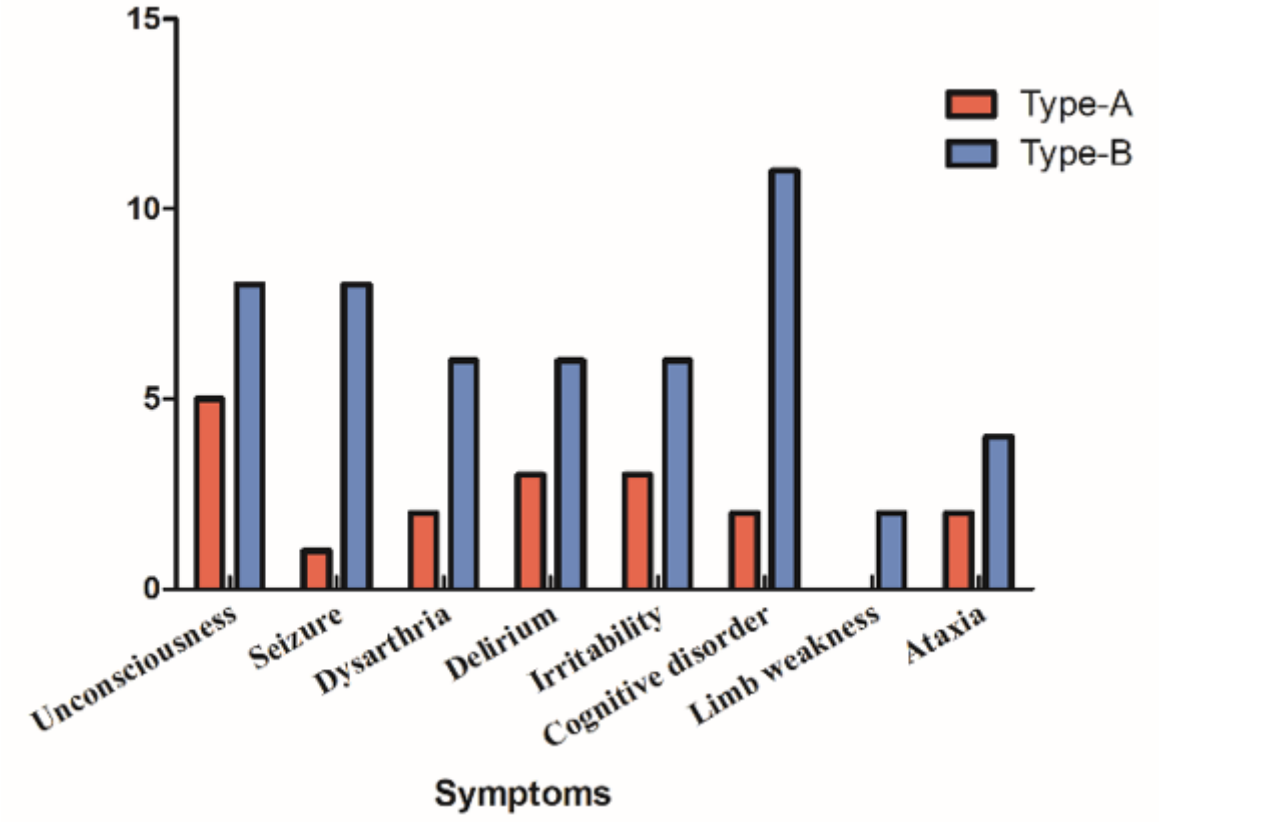

Figure 1

The histograms represent the numbers of each symptom between type A a-MBD and type B a-MBD.

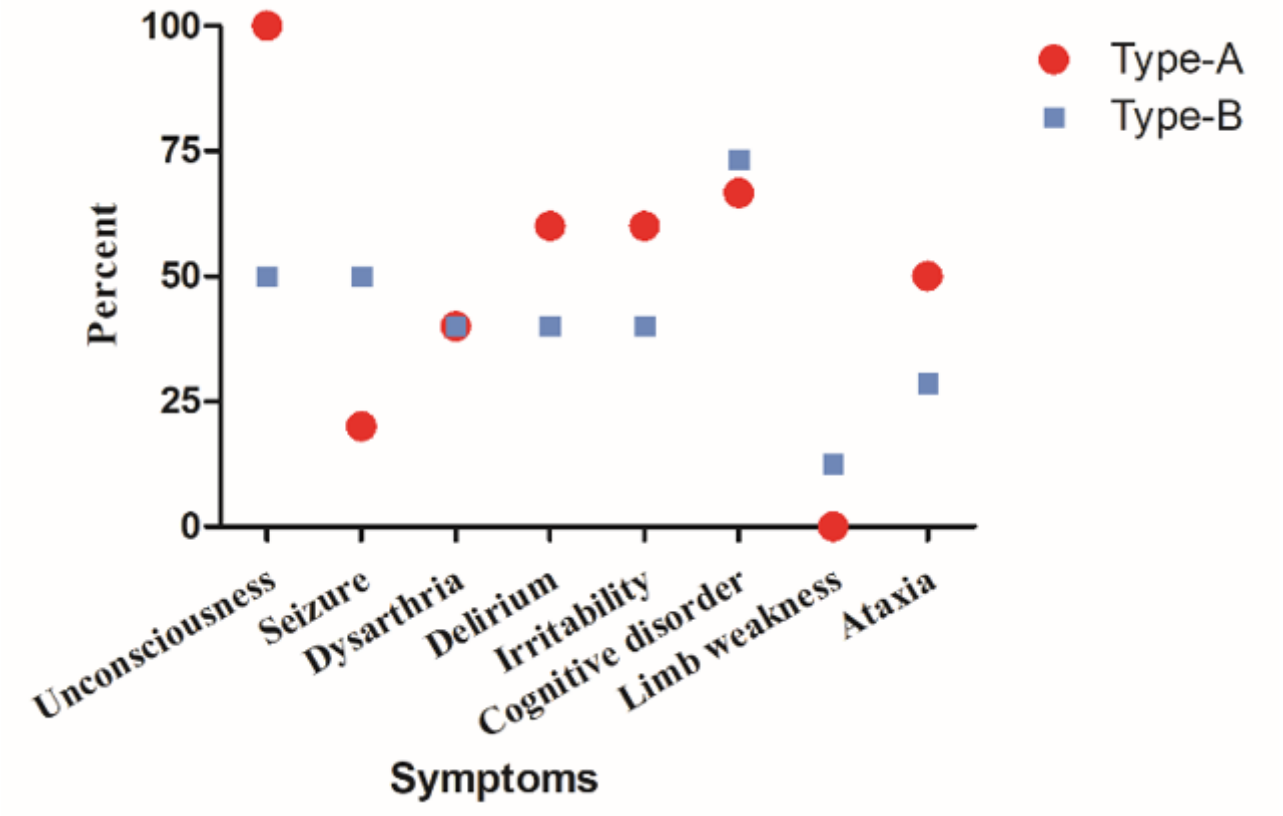

Figure 2

The Scatter Chart represent the distribution of symptom between type A a-MBD and type B a-MBD.

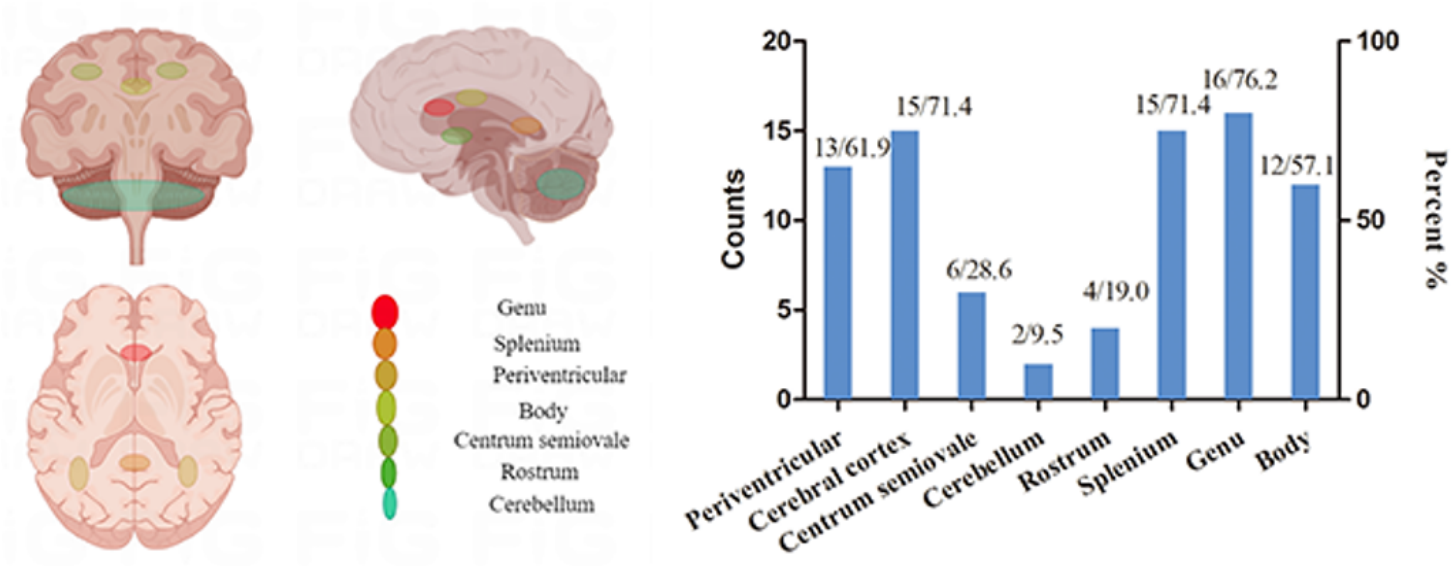

Figure 3

The lesions in the 21 patients with a-MBD were mainly located in the corpus callosum (genu, splenium, rostrum and body), periventricular, centrum semiovale and cerebellum. The most common lesions were located in the corpus callosum genu.

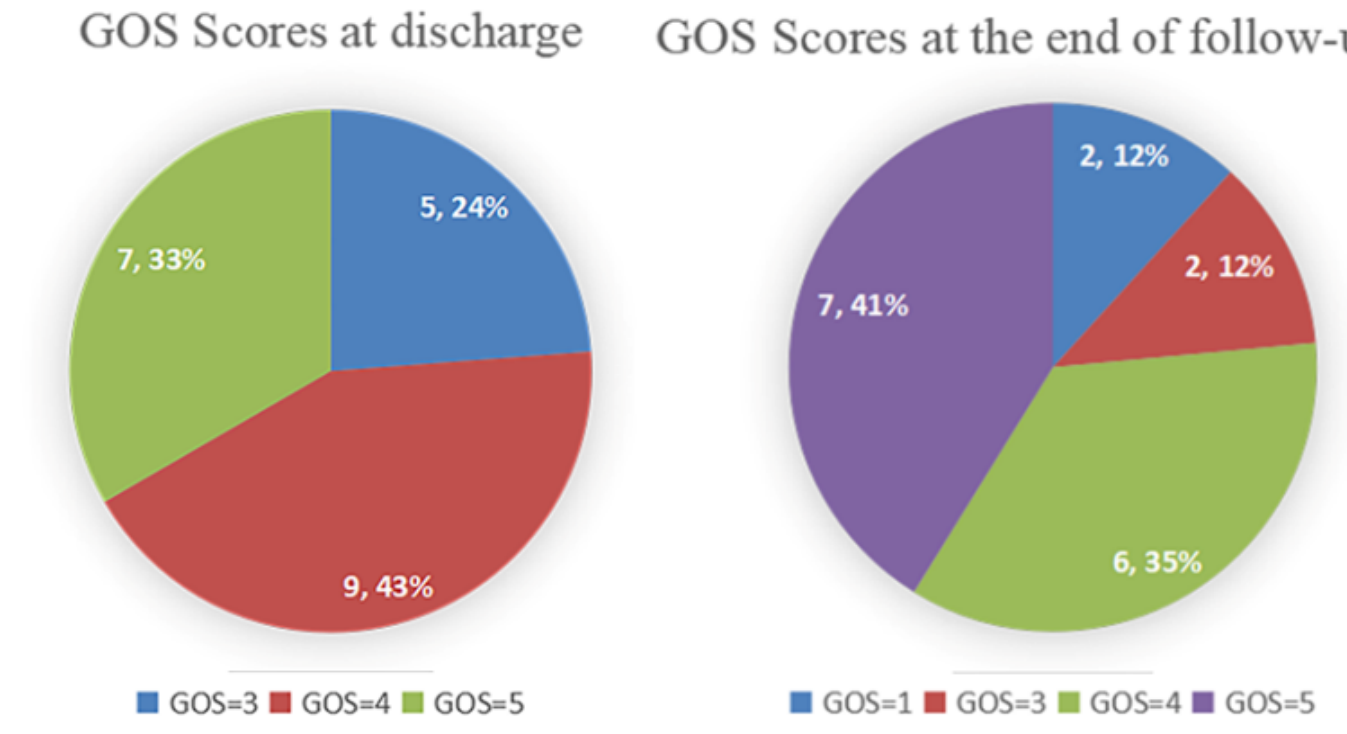

Figure 4

Figure 4 depicts the GOS scores of 21 patients at discharge and 17 patients at the end of their follow-up period (March 2022). The majority of patients had a favorable prognosis(GOS ≥4).