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From Mild Gait Difficulties to a Sudden Coma: A Rare Case of Marchiafava-Bignami Disease

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Abstract: In this case report we describe the case of a 66-year old man with subacute gait difficulties, with a progression to confusion coma with multiple generalised epileptic seizures during the following days. Biochemical analysis showed hyperglycaemia, cerebrospinal fluid (CSF) testing showed a mild lymphocytic pleocytosis and an elevated protein and lactate. Broad-spectrum antibiotics and antiviral therapy where initiated. However, all other CSF testing remained negative. Magnetic resonance imaging of the brain showed remarkably symmetric hyperintense T2 white matter lesions most noticable in the corpus callosum. The lesion pattern was suggestive of a metabolic or toxic encephalopathy, the preponderance for the corpus callosum was furthermore suggestive for Marchiafava-Bignami disease (MDB), as was the clinical course since admission of the patient. A high dose IV substitution of vitamin B1, B6 and B12 was started and antibiotic and antiviral therapy was discontinued. After one day the patient showed progressive regaining of consciousness and he returned to premorbid functioning in a matter of 1-2 weeks. MRI of the brain after 1 week showed notable improvement of the white matter lesions. At routine follow-up two weeks later he presented with icterus and a diagnosis of Epstein-Barr virus (EBV) hepatitis was made, lymph node biopsies showed an EBV positive diffuse large cell B-cell lymphoma (DLCBL). MDB is mostly associated with severe alcoholism, with malnourishment being the second leading cause, however there are case reports describing MDB in patients with chronically poorly controlled diabetes mellitus. We hypothesize that his condition may have been precipitated by his poorly controlled diabetes mellitus. However it is also possible that weight loss (probably related to the DLCBL diagnosis) might have contributed to a state of malnourishment and therefore played a role in the aetiology as well.

(*Top Magn Reson Imaging* 2023;32:1–4)

Marchiafava-Bignami disease is a rare condition characterized by demyelination and necrosis predominantly of the corpus callosum.[1] It is seen most frequently in patients with a history of alcohol abuse and has various nonspecific clinical manifestations.[2] We present a nonalcoholic, diabetic patient with subacute gait difficulties, followed by confusion and rapid evolution to coma and seizures, with full recovery after vitamin B substitution.

HISTORY OF PRESENTATION

A previously healthy 66-year-old man was admitted through the emergency service with subacute confusion, preceded by mild gait difficulties since a week. Clinical examination showed an agitated patient, but aside from bilateral pathological plantar reflexes, no significant abnormalities were found. During the observation, his condition worsened, with evolution to coma a day after admission. The second day of hospitalization, our patient had multiple generalized epileptic seizures, for which antiepileptic therapy was initiated. Owing to sedative effect of the antiepileptic therapy, intubation and mechanical ventilation were required.

INVESTIGATIONS

Routine biochemical analyses showed an important hyperglycaemia (plasma glucose level of 344 mg/dL and HbA1c of 11.7%). Computed tomography scans of the brain and the extracranial and intracranial arteries were unremarkable (Fig. 1). Cerebrospinal fluid (CSF) testing demonstrated a mild lymphocytic pleocytosis with elevated protein and lactate levels (16 WBC, glucose 175 mg/dL, protein 413 mg/dL, and lactate 3.2 mmol/L), for which broad-spectrum antibiotic and antiviral therapy was initiated at once. Cultures and testing for common viruses, bacteria, and fungi remained negative. Onconeural antibodies and autoimmune antibodies to neuronal cell surface and synaptic proteins remained negative in serum and CSF.

Magnetic resonance imaging (MRI) of the brain showed faint ill-defined hyperintense T2 signal, most remarkable on FLAIR sequence in the corpus callosum, the deep white matter in the frontoparietal regions, the periventricular regions, and middle cerebellar peduncles (Figs. 2–4). The alterations were remarkably symmetric. There was mild restricted diffusion in the posterior part of the corpus callosum (Figs. 5 and 6), but no contrast enhancement nor alterations on perfusion-weighted imaging. The lesion pattern was made suggestive of a metabolic or toxic encephalopathy. The preponderance for the corpus callosum was furthermore suggestive for Marchiafava-Bignami disease, as was the clinical course since admission of the patient.

TREATMENT

Antibiotic and antiviral medications were discontinued, and high-dose IV substitution of vitamin B1, B6, and B12 was started after measuring serum levels (which were in the lower normal range). One day after the start of vitamin substitution, the patient's condition improved, showing progressive regaining of consciousness after being in a comatose state for 3 days. He returned to premorbid functioning in a matter of 1–2 weeks. Repeat CSF analyses showed a stable cytosis, with declining protein count and lactate levels. MRI of the brain after 1 week showed notable improvement of the white matter lesions (Figs. 7 and 8).

FOLLOW-UP

Because the patient mentioned a significant, unwanted weight loss the past year, a whole-body fluorodeoxyglucose positron emission tomography was planned which showed multiple pathological lymphadenopathies. After a biopsy was performed, the patient was put on oral vitamin B substitution and could be discharged. At routine follow-up 2 weeks later, he presented with fulminant icterus. After extensive hematological and gastrointestinal investigations were performed, a diagnosis

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Received for publication July 3, 2022; revision received October 14, 2022; accepted October 25, 2022.
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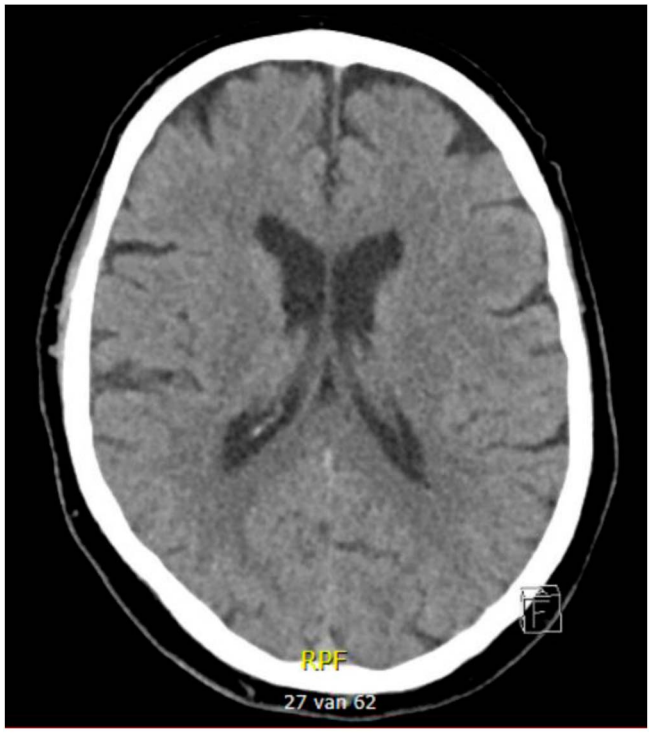
The authors declare no conflicts of interest.

DOI: 10.1097/RMR.0000000000000301



CT-scan

FIGURE 1. Computed tomography scan.

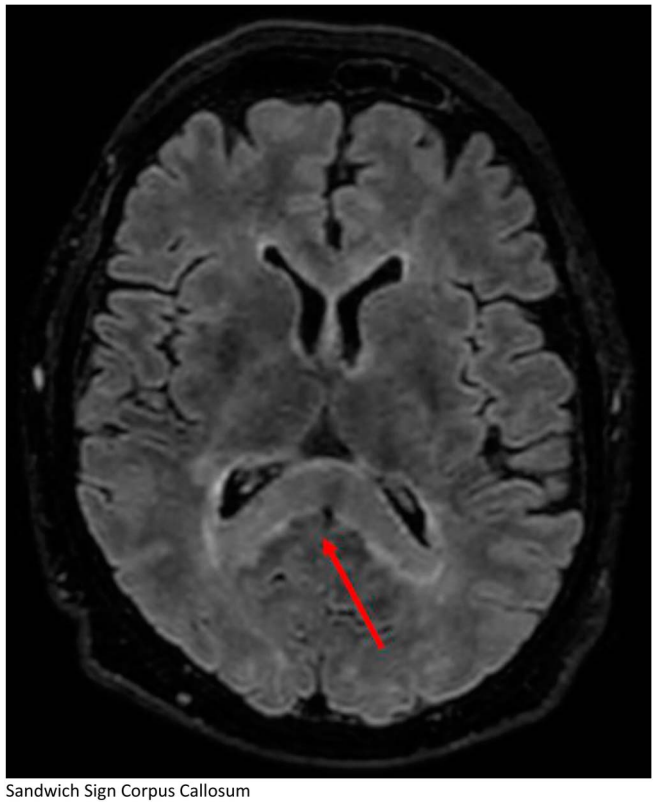


FIGURE 2. Sandwich sign corpus callosum.

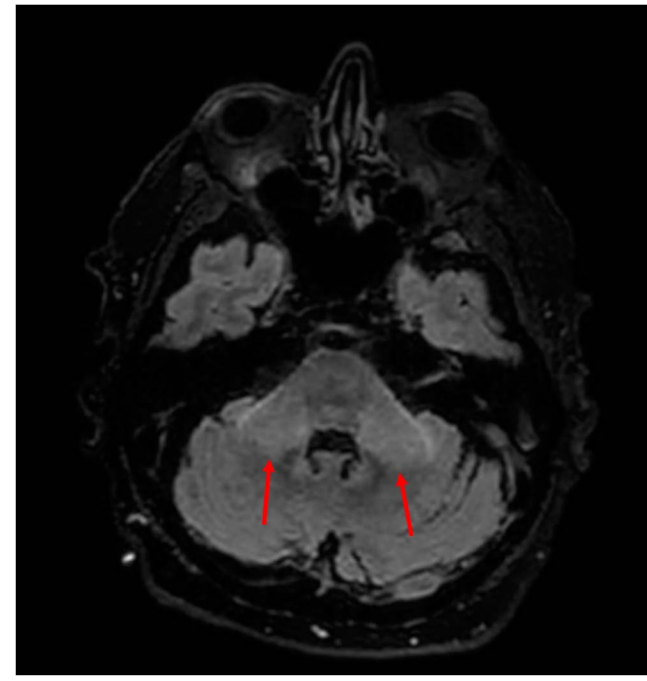


FIGURE 3. Hyperintensity middle cerebellar peducle.

of Epstein-Barr virus hepatitis was made. Lymph node biopsies demonstrated an Epstein-Barr virus positive diffuse large cell B-cell lymphoma (DLCBL), for which rituximab was initiated.

DISCUSSION

Marchiafava-Bignami Disease (MBD) is mostly associated with severe alcoholism, with malnourishment being the second leading cause (which often coincides with alcohol abuse). The

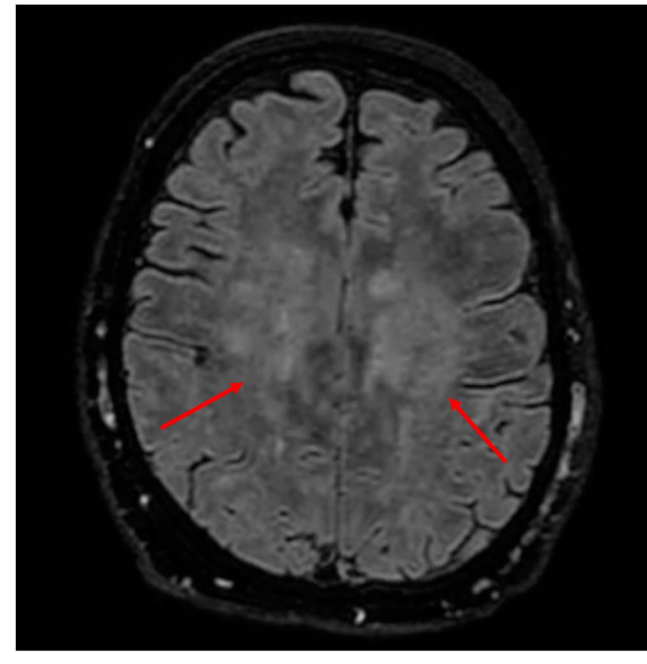


FIGURE 4. Deep white matter lesions.

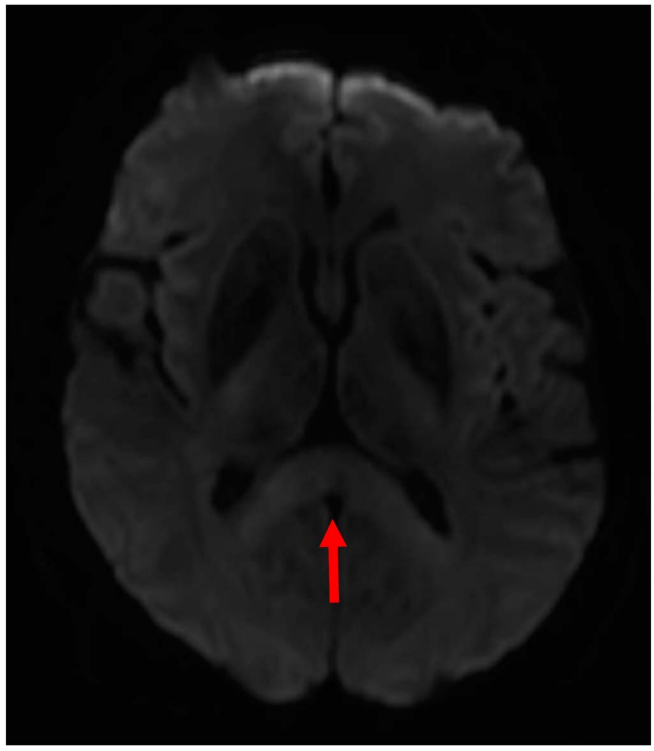


FIGURE 5. Diffusion weighted imaging hyperintensity.

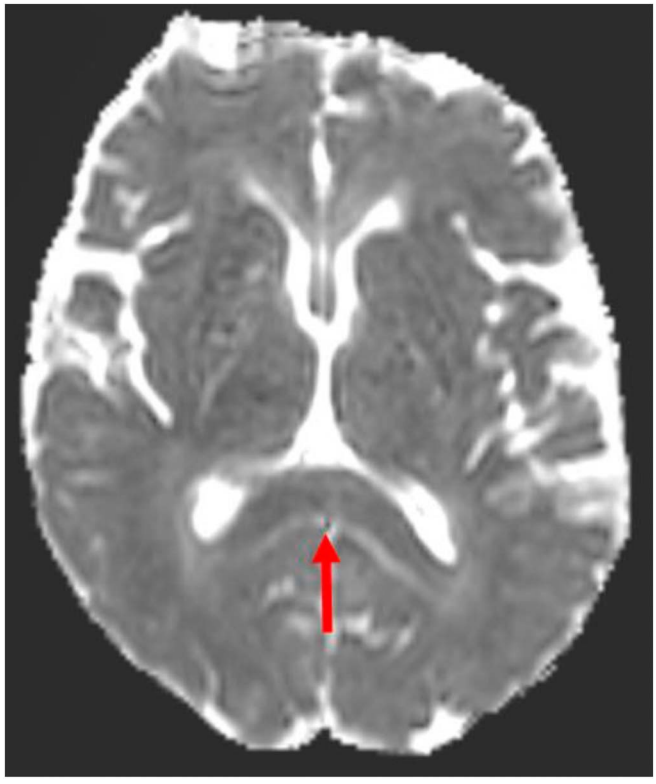


FIGURE 6. Apperent diffusion coefficient hypointensity.

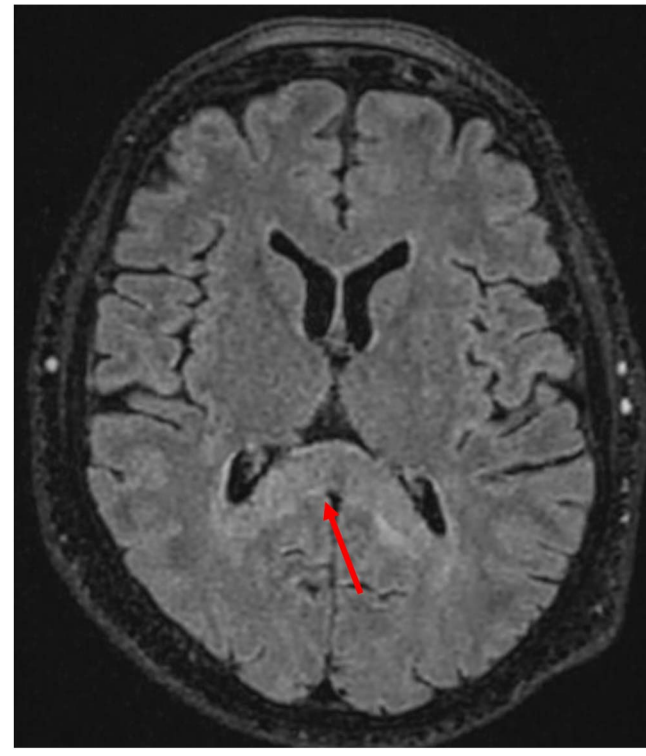


FIGURE 7. Sandwich sign follow-up MRI after 1 week.

pathophysiology is not fully understood. Alcohol-induced neurotoxicity is believed to play a role but is as itself insufficient as the disease can also occur in nonalcoholic patients. In addition, a deficiency of the vitamin B complex has also been considered an important damaging factor.[2] There are however also case reports describing MBD in patients with chronically poorly controlled diabetes mellitus. This is believed to originate from fluctuations in glycemia, causing osmotic stress in oligodendroglial cells and leading to callosal myelinolysis.[3–5]

MBD has a variable clinical spectrum, and 2 types of classifications are currently in use. The first one recognizes 3 subtypes and is mostly based on the acuteness of onset and disease progression: (1) acute onset MBD generally presents with sudden loss of consciousness with seizures and rapid progression to coma, (2) subacute forms can have varying prodromes ranging from depression to ataxia or spasticity, and (3) chronic MBD presents as a progressive dementia, generally with behavior abnormalities, hallucinations, and delusions.[6] A second newer classification uses clinical presentation, with an emphasis on the level of consciousness.[1] It recognizes type A MBD, with severe impairment of consciousness, seizures, and spasticity. This is associated with diffuse, severe lesions of the corpus callosum on MRI. By contrast, type B MBD has less impairment of consciousness, presents with milder symptoms, and has fewer callosal lesions. Type B is therefore believed to have a better prognosis as compared with type A.[7–11]

Diagnosis nowadays is mainly made using MRI, characteristically demonstrating symmetrical, confluent lesions of the corpus callosum. The lesions typically start in the body, later spreading to the genu and the splenium, and show diffusion restriction and appear hyperintense on T2 and FLAIR images. Typically, these hyperintensities are observed in the central region of the body and the splenium, sparing the peripheral dorsal and ventral layers (sometimes referred to as the "sandwich sign"). They may also spread to other parts of the brain, such as the cerebral cortex (considered to indicate Morel laminar

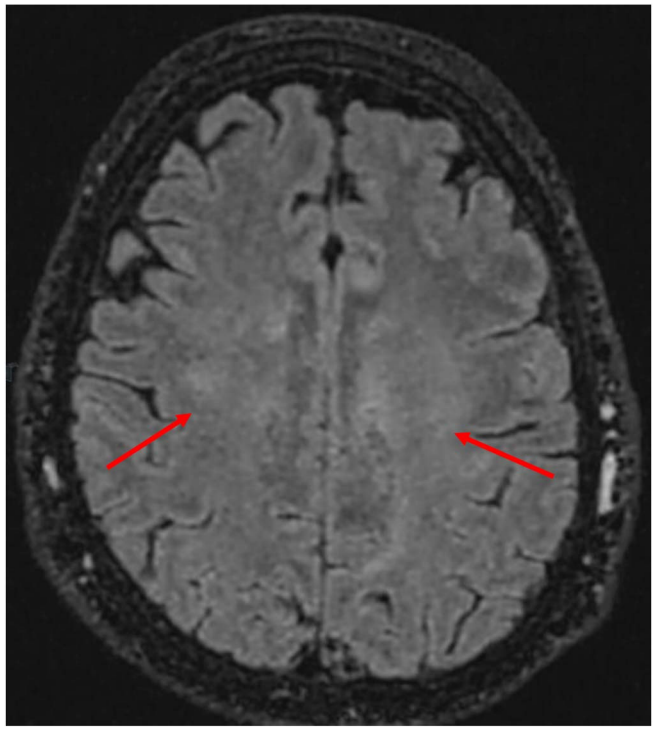


FIGURE 8. Deep white matter in the frontoparietal regions, follow-up after 1 week.

sclerosis, a pathological finding in chronic alcoholics believed to be caused by thiamine deficiency), and the hemispheric white matter of basal ganglia.[12] Bilateral involvement of the middle cerebellar peduncle, as observed in our case, has also been reported.[11,13] Sometimes, the "Ears of the Lynx" sign can be observed, consisting of cone-shaped T2/FLAIR hyperintensities located at the tip of the frontal horn of the lateral ventricles.[14] In subacute stages, the lesions may become T2/FLAIR hypointense because of hemosiderin deposition. In the chronic phase, complete resolution can be observed in treated patients. In untreated patients or those not responding to therapy, permanent demyelination and necrosis may appear as atrophy and cystic transformation of the corpus callosum, often appearing hyperintense on T2 images and hypointense on FLAIR images.[8,9,15]

This case report describes a patient who presented with type A Marchiafava-Bignami disease. We hypothesize that his condition may have been precipitated by his poorly controlled diabetes mellitus. However, it is also possible that his weight loss (probably related to the DLCBL diagnosis) might have contributed to a state of malnourishment and therefore played a role in the etiology as well. We found no reports on previous cases of MBD that suggest a direct relation to DLCBL. Nevertheless, vitamin B12 deficiency is not uncommon in hematological malignancies. Serum vitamin B12 levels might even appear falsely elevated, pointing to a functional deficit because of rapid proliferation of hematological cells and increased oxidative stress. This might have played a role in the pathophysiology of MBD in our patient. However, homocysteine and methylmalonic acid levels were usually elevated when there is a functional vitamin B12 deficit, which was not the case in our patient.[16–18]

It is notable that despite a number of unfavorable prognostic factors, including the presence of extracallosal lesions, cerebral lobe impairment, and severe disturbance of consciousness, the patient had a remarkably fast and complete recovery.[7,12] Early diagnosis and treatment may have played an important role in this; however, it should be noted that the poor prognosis attributed to MBD stems from the pre-MRI era. At that time, case confirmation could only be made by performing an autopsy, which might have led to underdiagnosis and selection bias.[7]

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