Marchiafava-Bignami Disease with frontal cortex involvement and late onset, long-lasting psychiatric symptoms: a case report

Malattia di Marchiafava-Bignami con coinvolgimento della corteccia frontale e insorgenza tardiva di sintomi psichiatrici resistenti: un caso clinico

Caso clinico

Marchiafava-Bignami Disease (MBD) is a rare idiopathic syndrome characterized by symmetrical demyelination and necrosis of the corpus callosum, described worldwide in less than 300 patients, mostly with a history of chronic alcoholism, as well as in poorly nourished nondrinkers. Although the first case of MBD was likely described by Carducci in 1898, the disease was eventually named after Marchiafava and Bignami, who originally described the typical symptoms in Italian men and were the first to associate the disease with increased consumption of inexpensively manufactured Chianti red wine. The etiology of MBD has long been considered to be either toxic or nutritional. Apart from alcohol consumption, other causes of MBD have been described in literature, including for example anorexia nervosa or even traumas. Overall, alcoholism-related MBD seems to have a poorer outcome compared with the MBD due to other causes.

The actual mechanism of the callosal lesions of MBD is still unclear. It has been hypothesized that a toxin in the alcohol may be responsible for demyelination, or that severe liver dysfunction in chronic alcoholics may lead to elevated serum ammonia levels and encephalopathy, callosal edema, and demyelination. Various vitamin deficiencies and overall malnourishment, which are common in heavy drinkers, have also been linked with MBD. Additionally, in

SUMMARY. Aims. To describe the case and management of a patient with Marchiafava-Bignami Disease (MBD) with frontal cortical lesions, no specific symptom at first referral to the Emergency Room, and late onset of atypical psychiatric symptoms. Methods. We report the case of a 44-year-old patient with a history of chronic alcohol abuse, eventually diagnosed with MBD. Results. Magnetic Resonance showed lesions in the splenium and the body of corpus callosum and bilateral lesions of the frontal cortex. The patient showed late-onset atypical psychiatric symptoms which were drug resistant. Discussion. The case we describe seems to support the existing few ones describing cortical involvement in MBD, which suggest that this is associated with a poorer prognosis. Psychiatric symptoms may be challenging to treat because of drug resistance. Conclusion. The involvement of psychiatrists together with neurologists and radiologists, with a consultation-liaison approach proved important for the achievement of diagnosis and of the most appropriate management and treatment for this patient.

KEY WORDS: Marchiafava Bignami Disease, cortical involvement, psychiatric symptoms, chronic alcohol abuse.

BACKGROUND

Marchiafava-Bignami Disease (MBD) is a rare idiopathic syndrome characterized by symmetrical demyelination and necrosis of the corpus callosum, described worldwide in less than 300 patients, mostly with a history of chronic alcoholism, as well as in poorly nourished nondrinkers. Although the first case of MBD was likely described by Carducci in 1898, the disease was eventually named after Marchiafava and Bignami, who originally described the typical symptoms in Italian men and were the first to associate the disease with increased consumption of inexpensively manufactured Chianti red wine. The etiology of MBD has long been considered to
non-drinkers, it has been suggested the exposure to some kind of toxin from a different source.

Differential diagnosis with other pathologies involving the corpus callosum (e.g., ischemic stroke, diffuse axonal injury, inflammatory demyelination, brain tumors, Wernicke encephalopathy, Wallerian degeneration) is based on clinical history, physical examination, and Magnetic Resonance Imaging (MRI). Indeed, modern brain imaging techniques provide a reliable in-vivo diagnosis, allowing early detection of MBD. Two clinic-radiologic subtypes of MBD have been described, differentiating between either acute or chronic onset: Type A and Type B, with significant differences as far as clinical course and prognosis are concerned. Type A is characterized by major impairment of consciousness, T2-hyperintense swelling of the entire corpus callosum on early MRI, and poor outcome; Type B shows at most slight impairment of consciousness, partial callosal lesions on MRI and, usually, a favorable outcome. As far as outcome is concerned, it is also likely that predominant bifrontal cortical involvement and lesions are a marker of very poor prognosis. Further data are needed to support this evidence; moreover, the reason underlying the vulnerability of frontal cortices to chronic alcoholism and/or thiamine deficiency is not clear; in animal experiments thiamine deficiency, but not chronic ethanol consumption, was reported to decrease glutamate uptake in the prefrontal cortex, leading to elevation of glutamate and neurochemical dysfunction.

Clinically, patients hospitalized with MBD are predominantly male, with a mean age of 46 years, even if the age range is wide, spanning from 14 to 79 years. MBD has not a typical clinical presentation. The disorder may present with a wide range of severe neuro-psychiatric symptoms, including non-specific mental state disorders such as confusion, delirium, unconsciousness, impaired memory and/or disorientation. Impaired walking, dysarthria, mutism, signs of disconnection or split brain syndrome, pyramidal signs, primitive reflexes, rigidity, incontinence, sensory symptoms, and gaze palsy or diplopia can be also found. Split brain syndrome has been reported as a characteristic feature: anyway, signs of interhaemispheric disconnection may be difficult to detect, particularly in subjects with a lower level of consciousness.

The treatment of suspected MBD is similar to the treatment of the Wernicke-Korsakoff syndrome, and is basically based on nutritional supplementation with B-group vitamins, including folate (B9), thiamine (B1), and vitamin B12. A high-dose corticosteroid therapy has been reported to cause clinical improvement. So far, there is no specific gold-standard treatment for MBD and for its possible psychiatric symptoms. Nonetheless, there is evidence of better outcome in thiamine-treated patients, while those treated with steroids showed no better outcome; thiamine supplementation during the acute phase of the disease leads to a significantly better outcome than treatment in the chronic phase.

Our aim is to describe the case and the specific management of a patient with MBD with frontal cortical lesions, no specific symptom at first referral to the Emergency Room (ER), and late onset of atypical psychiatric symptoms.

CASE PRESENTATION

The patient, a 44-year-old male, was referred to the ER of the Maggiore della Carità Hospital, Novara, Italy, due to decrease in visual acuity, asthenia and hypoxia that had persisted for about two weeks. The patient’s relatives complained that his food intake had decreased significantly during the last 20 days and that he was fasting since a week; they reported also reduced autonomy in carrying out common daily tasks.

It was reported chronic, heavy alcohol consumption for about 25 years (2 liters/day of wine and 2 spirits/day), which the patient stopped abruptly 4 days before he came to the ER. He had no history of drug abuse; he had about 8 months of depressive symptoms in 2008, after separating from his wife; apart from this, no other previous psychiatry history was reported, and he had never been treated by psychiatrists. From 2009 to 2010 he was followed by a Service for Drug Addiction and was prescribed Disulfiram 200 mg/die, which he stopped later on.

When the patient first referred to our ER, the brain Computerized Tomography (CT) scan revealed multiple hypodense areas without perilesional edema. The patient refused hospitalization, so he was discharged and went back home. The next day he came back to the ER again; diagnosis was not clear and hospitalization was proposed again to allow a more thorough clinical assessment and to exclude psychopathological disorders such as depression or catatonic states; the patient accepted and was admitted to our Psychiatry Ward to complete the diagnostic and therapeutic procedures.

PHYSICAL, PSYCHIATRIC AND NEUROLOGICAL EXAMINATION

The patient was malnourished and dehydrated (body weight: 48 kg, Body Mass Index: 14.2 kg/m²). Cardiac, abdomen and chest examination did not show any alteration. At the interview in the Psychiatry Ward, he exhibited a dull expression with a hypomimic face; spontaneous speech was absent and he was globally slowed; he spoke slowly but correctly, the speech was poor but correct as far as logic and form are concerned. He was alert, lucid, conscious, quiet and cooperative. No psychopathological alteration was found in cognition, sensperception, memory, and consciousness of self. Form and content of thought were normal. He was appropriate in expression, affectivity and behavior.

The neurological examination highlighted diffuse muscle hypotrophy with weakness (more proximal than distal) and ataxic gait disturbance, hyporeflexia (plantar responses were flexor), bradykinesia; cranial nerve examination revealed dysarthria and no other disturbances; the motor coordination was normal; there were no sensibility deficits. No neck rigidity was elicited.

No specifically psychiatric symptoms were recorded during an observation period of 24 hours, hence the patient was transferred to the Neurology Ward in order to further investigate a clinical condition which seemed related to an organic disease rather than to a primary psychopathological condition.

LABORATORY TESTS AND IMAGING

At admission to the ER, laboratory results revealed anemia and a slight decrease in total serum proteins (6.1 g/dl)
and albumin (3.3 g/dl); liver function test showed an increase of gamma glutamyl transferase (86 U/l). No alterations of coagulation were found. Inflammatory markers were increased: Reactive C Protein 1.62 mg/dl, Erythrocyte Sedimentation Rate 43 mg/dl. Thyroid Stimulating Hormone was in range. Blood alcohol and drugs were negative.

In order to exclude an infectious etiology, serology of Borrelia Burgdorferi, HIV, syphilis, hepatitis B and C was performed and found negative. Urinalysis showed no major changes. Cerebrospinal fluid analysis was normal (no alteration in proteins and cells number). The first electroencephalography (EEG) showed pathological alterations (diffuse slow waves of 6-7 Hz with sporadic epileptiform discharge) which persisted at the following EEGs performed during hospitalization. Chest X-ray was negative, and the total body CT did not show any relevant alteration as well.

Cranial CT, performed in the ER, showed low density lesions, without perilesional edema, in the frontal lobe, bilaterally, together with a characteristic low density lesion of the splenium of the corpus callosum. Cranial MRI in Diffusion-Weighted sequences, performed during hospitalization at the Neurology Ward, revealed a restricted water diffusion in the splenium and the body of corpus callosum. In T2 weighted images hyperintense lesions in the splenium and the body of corpus callosum were present, with relative sparing of dorsal and ventral layer. MRI confirmed, in T2 weighted images, hyperintensity of frontal lesions, with restricted water diffusion in diffusion-weighted sequences, in particular of the upper and middle frontal gyrus and of the cingulate gyrus, bilaterally. Hyperintensity signal in T2 weighted images, likely due to edema, was found in these sites in subcortical white matter. The patient was eventually diagnosed with MBD on the basis of the clinical features and the imaging (CT and MRI) findings.

**TREATMENT AND CLINICAL COURSE**

During the patient’s stay in the Psychiatry Ward, treatment was started to control any withdrawal symptoms from alcohol: intravenous infusion of saline 1500 ml per day, delorazepam 9 mg per day, then tapered to 6 mg per day, and supplementation with thiamine hydrochloride 100 mg per day. On the basis of the EEG, levetiracetam was introduced to avoid convulsions, and later replaced with carbamazepine. Hypovitaminosis D was corrected with an injection of cholecalciferol (100,000 IU), and subsequent oral supplementation; hypokalemia was treated with the introduction of potassium per os. A concurrent urinary tract infection was treated with ciprofloxacin, which was then stopped because of erythema of the lower limbs and trunk.

During hospitalization in the Neurology Ward, the patient presented episodes of nocturnal psychomotor agitation; after a couple of weeks, sensorperception disorders and confabulations started, and were still persistent at discharge. Episodes of nocturnal psychomotor agitation were treated with promethazine. Sensorperception disorders and confabulations were treated first with haloperidol 1.5 mg daily, later replaced (after a couple of week, due to poor effectiveness) by risperidone 1 mg in the evening. It should be noted that even if psychiatric symptoms are frequently associated with MBD, there are only few reports about this issue and the role of psychiatric medications, and specifically of antipsychotic, is not yet clearly established.

Despite the onset of psychomotor agitation, sensorperception disorders and confabulations, during hospitalization it was observed a gradual clinical improvement including reduction of the ideomotor slowdown and increase of the muscular strength. At discharge, autonomous ambulation was allowed, and the patient had put on weight (weight at discharge: 56 kg). After about a month of hospitalization, the patient was transferred to a long-term care structure near Novara.

Here, despite the amelioration of his organic conditions, it was observed a gradual worsening of psychiatric symptoms. The patient’s behavior became aggressive against either the staff and other inpatients; he was confused, confabulations and sensorperception disorders persisted despite therapies.

In the following days, patient’s clinical conditions worsened drastically: he became more and more slowed down and stuporous and he died after about 10 days of hospitalization in the long-term care structure. Since no autopsy has been performed, we cannot report the exact reason of the patient’s decease.

**CONCLUSIONS**

There is increasing evidence of the diagnostic value of MRI in the MBD. MRI may allow an early diagnosis, even in the ER setting. As described above, the main, typical MRI findings in MBD are the symmetrical lesions of the corpus callosum; these may coexist with symmetrical cortical lesions in the frontal region, which have been suggested to have a negative prognostic value, although there are currently only a few cases describing MBD with cortical involvement. Cortical lesions are more frequently described in association with Wernicke encephalopathy, and in these cases the main MRI findings include lesions of the mammillary bodies, and in other medial thalamic and periaqueductal areas. Nonetheless, in milder cases a normal MRI does not exclude the diagnosis of Wernicke encephalopathy.

The case we have described adds to the few ones supporting the hypothesis that cortical lesions could be a predictor of poorer outcome in MBD: moreover our patient showed late onset and enduring psychiatric symptoms (sensorperception disorders and confabulations) which are not so common in MBD. However, a limitation of this hypothesis is the difficulty to discriminate whether cortical lesions are related to MBD or to a milder form of Wernicke encephalopathy which may present with hallucinations and confabulations. It would be interesting to understand the pathophysiology of the alteration of sensorperception in cases of MBD and its possible overlap and co-occurrence with Wernicke encephalopathy, which is still poorly described in the current literature.

Some considerations about the clinical approach to patients with these non-specific, neuropsychiatric symptoms may be useful as well. As often happens in everyday clinical practice, psychiatrists have been involved together with neurologists in the management of this patient, and it eventually turned out that the patient’s disease was a rare but organic, neurological disorder. After the ER assessment, despite the lack of a clear psychiatric symptomatology, admission to the Psychiatry Ward was the way to get a differential
diagnosis and to start treatment. In fact, as described above, the patient had referred to the same ER the day before hospitalization for the same reasons, but refused hospitalization and was sent back home.

The only relevant anamnestic features suggesting the need to involve psychiatrists were a history of alcoholism and a reported period of not otherwise specified “depressed mood”. After 24 hours in the Psychiatric Ward, the patient was then transferred to the Neurology Ward and diagnosed with MBD, a form of dementia secondary to alcoholism, after MRI was performed. Only in the following days, psychiatric symptoms emerged indeed, including symptoms of delirium (visual hallucinations, confabulation, psychomotor agitation) and psychiatric consultation was required before starting treatment with typical neuroleptics and atypical antipsychotics.

Psychiatrists may find themselves involved in cases which are not within their strict clinical competence, but needing highly specialized skills in medical-patient relationship because of the complexity of the symptoms and clinical picture. A consultation-liaison psychiatry approach seems to be the first choice diagnostic and therapeutic approach in cases like this, as it allows collaboration and dialogue among different specialists (ER clinician, psychiatrist, radiologist, neurologist) with the aim of identifying the most appropriate management and treatment for the patient. As consultation-liaison professionals, psychiatrists may help adjust the procedures of the whole healthcare team to treat neuropsychiatric complications that may affect patients, and this may be particularly relevant in secondary dementias as the MBD, requiring a multidisciplinary approach for the successful treatment of patients.

REFERENCES