Primary degeneration of the corpus callosum (Marchiafava—Bignami disease): 2 unusual clinical presentations☆

Degeneración primaria del cuerpo calloso (Marchiafava-Bignami): 2 formas inusuales de presentación clínica

Dear Editor:

Marchiafava—Bignami disease was first described in 1903 by 2 neuropathologists who observed that 3 alcoholic patients had presented acute symptoms of psychomotor agitation, seizures, and decreased level of consciousness, followed by death. Neuropathological studies revealed that these patients exhibited demyelination and atrophy of the corpus callosum.[1] Since then, short series have provided additional information about this disease. It appears in the sudden-onset form described by Marchiafava and Bignami, and also in a chronic form characterised by signs of interhemispheric disconnection, sensory hemispatial neglect, and signs of alien limb syndrome. These signs are frequently associated with cognitive impairment and sometimes coincide with Korsakoff syndrome, which is another common finding in alcoholic patients.[2—4]

Pathophysiology of the disease has been attributed to numerous types of ischaemic lesions and demyelination of the corpus callosum in both the acute-onset and progressive varieties. It is often associated with vitamin B12 and folic acid deficits, alcoholism, and hyporexia of any aetiology. Many patients with this disease present cognitive impairment with a potentially reversible cause, which highlights the importance of early diagnosis and treatment.[5—9] In this article, we describe 2 cases with unusual presentations (1 acute, the other chronic) and provide a review of medical literature.

The first patient was a female aged 74 with a history of controlled mild arterial hypertension, hypothyroidism, and dyslipidaemia. She had no history of alcoholism or malnutrition, performed activities of daily living independently, and her prior cognitive state appeared to be normal. The patient came to the emergency department due to disorientation in time and space, anomic aphasia in spontaneous conversation, anterograde amnesia, and a mild headache over the previous 6 hours.

Upon admission, the patient's status was afebrile and good overall, although blood pressure was 140/85 mm Hg. Neurological examination showed that the patient was disoriented in time and space, with no meningeal signs or motor deficits. Cranial nerves were normal and superficial sensitivity was intact. Plantar cutaneous reflexes exhibited bilateral flexion; gait and coordination were normal. We detected left sensory hemispatial neglect (sensory extinction).

The cranial CT performed in the emergency department revealed a haematoma of the splenium of the corpus callosum (Fig. 1). Brain MRI with MR angiography ruled out expansive lesions and arteriovenous malformations; last of all, conventional arteriography excluded AVM and other lesions. EEG showed slow left temporal intermittent theta activity (TIRTA). Analyses did not initially show any relevant abnormalities; folate and vitamin B12 levels were acceptable. Neuropsychological examination showed mild cognitive impairment with a dysexecutive component.

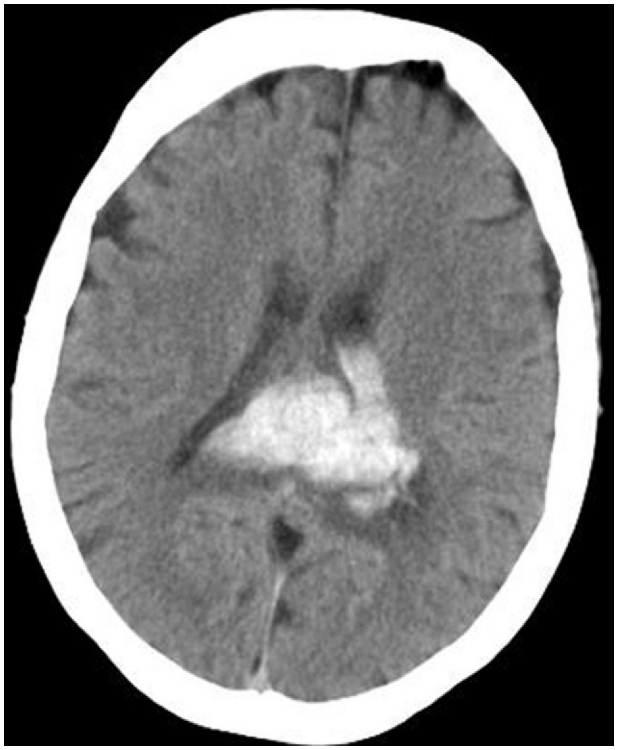

Fig 1 Computed tomography showing a haematoma of the splenium of the corpus callosum in the patient with acute presentation.

Clinical evidence of left hemispatial neglect remained 8 months later, with neuropsychological tests showing few changes. A new routine brain MRI showed multiple ischaemic lesions in the splenium of the corpus callosum and an area of the splenium with haematoma reabsorption. Laboratory tests showed a vitamin B12 deficit. Medical history and physical examination revealed hyporexia and loss of 8 kg in 6 months. According to the family, the patient had experienced periods of apparently psychogenic hyporexia over the past few years and was under psychiatric study.

The second patient, a 62-year-old female, was admitted for convalescence and functional recovery following knee prosthesis surgery. Her medical history included bariatric surgery 5 years before which was indicated due to morbid obesity. Weight loss in the 3 years prior to knee surgery amounted to 55 kg. Despite resolution of obesity, the patient became progressively housebound and gave up her habitual activities, citing her chronic degenerative arthropathy (right knee pain) as the motive. The patient also displayed frequent forgetfulness, repetitive conversations, and difficulty getting dressed and using kitchen implements (apraxia), including ''not knowing how'' to cut bread. Physical examination showed an involuntary creeping movement in her left arm which the patient did not notice, although family

☆ Please cite this article as: Salazar G, Fragoso M, Español G, Cuadra L. Degeneración primaria del cuerpo calloso (Marchiafava-Bignami): 2 formas inusuales de presentación clínica. Neurología. 2013;28:587—589.

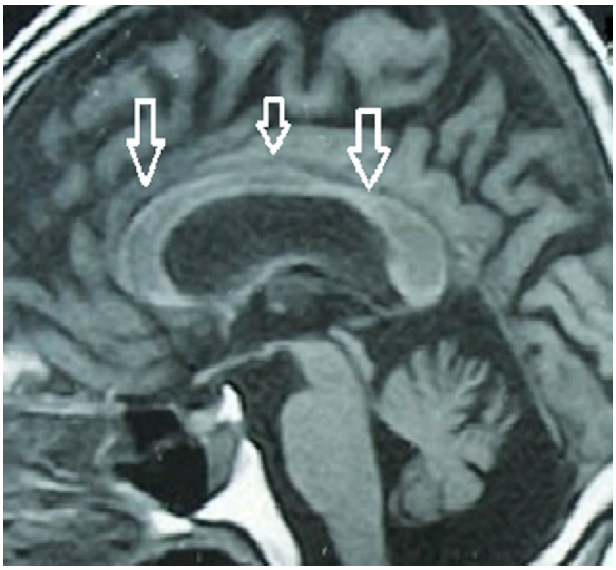

Fig 2 Brain MRI showing atrophy along the entire corpus callosum, indicated with white arrows, in the patient with chronic presentation.

members said it had been present for several months. This movement was suggestive of alien limb syndrome. Results for cranial nerves and muscle strength were normal, as were superficial and deep-tissue sensitivity, even though the patient displayed patent left hemispatial neglect.

Cognitive assessment yielded an MMSE score of 26/30 (2 amnestic errors and 2 executive errors). We performed a brain MRI that showed multiple confluent infarcts in the splenium of the corpus callosum (Fig. 2). EEG revealed left temporal intermittent rhythmic theta activity (TIRTA), and the analysis detected low vitamin B12 and folic acid levels. We started the patient on intramuscular vitamin B12 and folic acid. While hospitalised, the patient experienced 3 right-sided motor simple partial seizures with secondary generalisation. As a result, she was treated with antiepileptic drugs (levetiracetam IV), and symptoms resolved completely.

Three months later, the patient's executive functions showed definite improvement (she was able to dress herself and complete daily activities that had previously exceeded her abilities). She continued experiencing difficulties with drawing tasks (clock drawing test and pentagon copying). MMSE score was 27/30. We observed no involuntary movements of the left arm, no sensory hemineglect, and no agnosia. Routine laboratory tests showed normal folic acid and vitamin B12 levels.

Marchiafava—Bignami syndrome is defined as primary degeneration of the corpus callosum associated with chronic alcohol consumption and other situations eliciting nutritional deficiencies.[10] Consensus holds that the disease is due to a deficiency in vitamin B12 and folate, since many patients recover upon taking these supplements.

We present 2 clinical cases, one with acute onset (first case) and the other with a chronic onset (second case); both show unusual forms of presentation. The case with acute onset began with a haemorrhagic infarct in the splenium of the corpus callosum. Progression was very benign despite the presence of a large cerebral haematoma, and the patient presented only a few symptoms, including hemispatial neglect and anomic aphasia. The other case, the one with gradual onset, manifested with slow, progressive cognitive impairment with frank apraxia and amnestic deficit. One remarkable feature was alien limb syndrome, which is related to the interhemispheric disconnection that occurs in cases of corpus callosum injury, according to earlier descriptions.[11] Regarding aetiology, neither of the patients had a history of alcoholism, although both had nutritional deficits. The patient with acute onset had lost 10 kg in 3 months in association with depression and very low levels of vitamin B12 and folic acid. In the second case, the patient underwent bariatric surgery to correct morbid obesity. After the procedure, she experienced progressive cognitive decline with memory loss and apraxia. Many patients with vitamin and/or folic acid deficiency may present cognitive impairment similar to Wernicke—Korsakoff syndrome, which is frequent in alcoholics. Nevertheless, the corpus callosum lesions viewed by MRI in both cases, plus the presence of clear signs of interhemispheric disconnection, were sufficient to distinguish between cognitive impairment caused by Wernicke—Korsakoff and CI caused by MB.

To the best of our knowledge, there are few published cases of patients with Marchiafava—Bignami disease secondary to bariatric surgery. We do not know if vitamin B12 and folic acid deficiencies are common in these patients, but we recommend performing neuropsychological assessments and measuring plasma levels of these dietary minerals at the slightest clinical sign of a deficiency in these patients.

Our patients demonstrated asymmetrical temporal intermittent rhythmic theta activity. One of our patients presented partial seizures with secondary generalisation and therefore had to be treated with antiepileptic drugs. Epileptic seizures have been described repeatedly in patients with MB; in fact, the initial cases described by Marchiafava and Bignami in 1903 included epileptic seizures.

Regarding pathophysiological changes, we believe that the lesions in these patients are demyelinating and ischaemic. Vitamin deficiency probably elicits small vessel necrosis, which in turn causes loss of white matter and atrophy of the corpus callosum. Nevertheless, demyelination may extend to other areas of the brain.[6]

Lastly, we conclude that the disease described by Marchiafava and Bignami is a clinical syndrome that may be seen in non-alcoholic patients. Its most important feature is poor absorption of vitamin B12 and folic acid, which elicits secondary demyelination. Doctors should carefully examine patients with prolonged hyporexia and those undergoing bariatric surgery for any reason, since they may experience poor vitamin absorption and demyelinating lesions of the corpus callosum.

References

1. Marchiafava E, Bignami A. Sopra un alterazione del corpo calloso osservata in soggetti alcoolisti. Riv Patol Nerv. 1903;8:544.
2. Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava—Bignami disease. J Neurol. 2004;251:1050—9.

3. Gimeno MJ, Lasierra R, Pina JI. Marchiafava—Bignami disease. Four case reports. Rev Neurol. 2002;35:596—8.
4. Vázquez C, Salamano R, Legnani C, Cardinal P. Marchiafava—Bignami disease in Uruguay. Neurologia. 2008;23:322—8.
5. Rusche-Skolarus LE, Lucey BP, Vo KD, Snider BJ. Transient encephalopathy in a postoperative non-alcoholic female with Marchiafava—Bignami disease. Clin Neurol Neurosurg. 2007;109:713—5.
6. Tuntiyatorn L, Laothamatas J. Acute Marchiafava—Bignami disease with callosal, cortical, and white matter involvement. Emerg Radiol. 2008;15:137—40.
7. Celik Y, Temizoz O, Genchellac H, Cakir B, Asil T. A non-alcoholic patient with acute Marchiafava—Bignami disease associated with gynecologic malignancy: paraneoplastic Marchiafava—Bignami disease? Clin Neurol Neurosurg. 2007;109:505—8.
8. Gimeno MJ, Lasierra R, Pina JI. Enfermedad de Marchiafava—BigmaniA propósito de cuatro casos. Rev Neurol. 2002;35:596—8.
9. Navarro JF, Noriega S. Enfermedad de Marchiafava—Bignami. Rev Neurol. 1999;28:519—23.
10. Hund E. Neurologic sequelae of chronic alcoholism. Anaesthesiol Reanim. 2003;28:4—7.
11. Rosa A, Demiati M, Cartz L, Mizon JP. Marchiafava—Bignami disease, syndrome of interhemispheric disconnection, and right-handed agraphia in a left-hander. Arch Neurol. 1991;48:986—8.

G. Salazar[a,*], M. Fragoso[a], G. Español[b], L. Cuadra[c]

[a] *Servei de Neurologia, Hospital Terrassa, Barcelona, Spain*
[b] *Servei de Psiquiatria, Hospital Terrassa, Barcelona, Spain*
[c] *Servei de Geriatria, Hospital Terrassa, Barcelona, Spain*

* Corresponding author.
E-mail address: gsalaz64@gmail.com
(G. Salazar).

Yawning as a dose-dependent side effect of treatment with escitalopram☆

Bostezos como efecto secundario dependiente de la dosis del tratamiento con escitalopram

Dear Editor

The neurobiological processes involved in yawning are complex. Yawning is controlled by the dopaminergic[1] and oxytocinergic systems.[2] These systems activate the cholinergic system,[1,2] which may also be activated by the serotonergic system.[2] On the neuroanatomical level, yawning involves motor centres of the brainstem (V, VII, IX, X, XI, and XII) and the spinal cord, which are controlled by the paraventricular nucleus of the hypothalamus.[1,2] A group of oxytocin neurons situated in the parvocellular region of the paraventricular nuclei and extending towards the hippocampus facilitate yawning, in conjunction with the locus coeruleus and the spinal cord.[1,2] Yawning results when these neurons are stimulated by dopamine or dopaminergic agonists, histamine, or oxytocin[1]; it is inhibited by opioids and γ-aminobutyric acid.[1,2] The serotonergic system also facilitates yawning.[1] Serotonergic activation and dopaminergic inhibition may work together in the event of yawning.[1,2] In addition, the serotonergic system also interacts with the cholinergic system, since the serotonin reuptake inhibitor citalopram (Lu 10-171) favours yawning induced by physostigmine (a cholinergic antagonist).[1] Yawning is also indicative of numerous pathological processes that generally go unnoticed in clinical practice[2] (intracranial hypertension, migraine, cerebrovascular accidents, frontal lobe tumours, temporal lobe epilepsy, progressive supranuclear palsy, multiple sclerosis, thalamotomy, liver and kidney failure, opiate withdrawal, etc.).[2] Some drugs,[1,2] such as dopaminergic agonists[1] or serotonin reuptake inhibitors,[3—14] may provoke yawning as a side effect (Table 1). According to some drug safety reports, paroxetine may also cause yawning (5 cases).[15]

We present the case of a woman aged 37 who was first monitored by the psychiatric department in 2010 due to obsessive thoughts and egodystonic compulsions. The rest of her medical history was anodyne. She met DSM IV-TR criteria for obsessive-compulsive disorder, and doctors decided to treat her with escitalopram in increasing doses over a 3-week period until reaching 20 mg/day. The patient was not taking any other drugs. Treatment initially resulted in clinical improvement and the patient reported frequent yawning as a side effect, with episodes occurring regularly throughout the day. This was the only side effect, and it had very little repercussion on the different aspects of the patient's life. After escitalopram was reduced to 15 mg/day, yawning frequency decreased and had disappeared completely after 10 days. At present, the patient remains stable on a dose of 10 mg/day, with good level of tolerance and no adverse effects.

This 37-year-old woman therefore experienced yawning as a dose-dependent side effect of escitalopram. This case coincides with a published case involving citalopram.[8] Yawning is a side effect of both non-selective[4,7,8,12,14] and selective[3,5,6,8,10,11,13] serotonin re-uptake inhibitors (SSRIs). The literature contains only a few cases due to their low frequency and/or non-detection of this sign.[4] Yawning does not seem to be sex-related (Table 1). Yawning is an easily observable clinical sign that may be an adverse drug effect or an alarm sign indicating central nervous system disease or other neuropsychiatric disorders.[1,2] However, yawning is underinvestigated and rarely examined in the clinical setting.[2]

Early detection of the temporal relationship between onset of excessive yawning and treatment with serotonergic agents[1] allows doctors to offer simple remedies such as decreasing dosage or changing the treatment. This serves to prevent unnecessary healthcare spending on more complex complementary tests and also lets doctors rule out serious diseases.[1,2]

☆ Please cite this article as: Roncero C, Mezzatesta-Gava M, Grau-López L, Daigre C. Bostezos como efecto secundario dependiente de la dosis del tratamiento con escitalopram. Neurología. 2013;28:589—590.