CASE REPORT

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Atrophy of the corpus callosum in heavy alcoholic patients

Taysa Benítez-Delgado[1], Daniel Martínez-Martínez[1], Candelaria Martín-González[1], Lucía Romero-Acevedo[1], J.R. Muñiz-Montes[2], Geraldine Quintero -Platt[1], Jorge A. López-García[3], Emilio González-Reimers[1]

[1]Servicio de Medicina Interna, Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, Canary Islands (Spain), [2]Servicio de Radiodiagnóstico, Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, Canary Islands (Spain) , [3]IMETISA-Complejo Hospitalario Universitario de Canarias, Tenerife, Canary Islands (Spain)

SUMMARY

Atrophy of the corpus callosum among alcoholics was classically restricted to patients affected by Marchiafava-Bignami (MB) disease. It was further observed in patients with thiamine and/or niacin deficiency, or in alcoholics who had consumed alcoholic beverages for a long period. A 42-year-old alcoholic patient was admitted with a full-blown alcohol withdrawal syndrome. After recovery, unstable gait and marked pyramidal signs were observed. A brain magnetic resonance was performed, which revealed corpus callosum atrophy. At discharge the patient was placed under ambulatory care. Nevertheless, he never attended his appointments and he was readmitted several times with withdrawal syndrome. Repeated MRI studies showed no remarkable changes besides progressive atrophy of the corpus callosum. Indeed, the area of corpus callosum was markedly reduced when compared with that of 20 alcoholics and 5 further patients with Wernicke´s encephalopathy. Therefore, the clinical picture is consistent with classic MB disease, and the more severe atrophy than that observed in the remaining alcoholics suggests that additional mechanisms may play a role in MB disease.

Key words: Marchiafava-Bignami – Alcoholism – Corpus callosum atrophy

Corresponding author: Emilio González-Reimers. Servicio de Medicina Interna, Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, Canary Islands (Spain). Phone: 34 922678600. E-mail: egonrey@ull.es

INTRODUCTION

Brain atrophy is one of the most outstanding manifestations of alcoholism. Both grey matter and white matter atrophy have been described in alcoholics. Neuronal death and altered neurogenesis affect nearly the whole brain, but especially frontal lobes, hippocampus, and cerebellum. White matter affectation is also widespread (de la Monte and Kril, 2014). Corpus callosum, as the largest white matter tract in the brain becomes also severely damaged in these patients.

Atrophy of the corpus callosum among alcoholics was classically restricted to patients affected by Marchiafava-Bignami disease (MBD). This is an uncommon neurologic disorder, mainly observed among heavy alcoholics, characterized by demyelination and central necrosis of the corpus callosum (Ironside et al., 1961). In 1898, A. Carducci, a pupil of Marchiafava, described the first case in a 50-year-old alcoholic patient in whom the middle part of the corpus callosum showed severe demyelination and necrosis. This case and two additional ones were reported by Marchiafava and Bignami in 1903, underscoring the affectation of the central part of the corpus callosum, and stressing the differences with Wernicke´s encephalopathy (Marchiafava and Bignami, 1903). Affected patients were middle-aged men with a protracted history of cheap red wine consumption, and only a few scattered cases were described since then, nearly always in heavy alcoholics, and usually associated with a poor prognosis (Ironside et al., 1961). The exact mechanism is unknown. The per-

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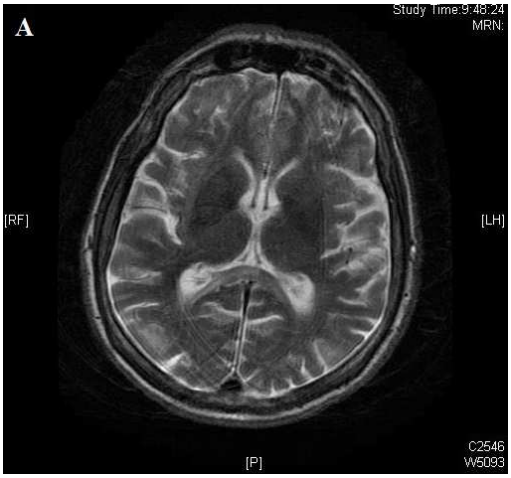
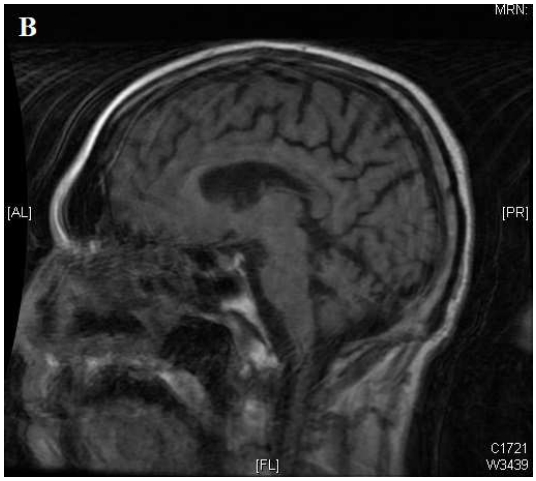
icallosal artery, derived from the anterior cerebral artery, irrigates the central part of the corpus callosum, so that it was hypothesized that vascular changes affecting callosal vessels could be involved in MB pathogenesis. However, numerous anastomoses between the pericallosal artery and branches of the posterior cerebral artery generally guarantee an adequate blood supply of the body of the corpus callosum (Li et al., 2015). Moreover, atrophy of the corpus callosum was further observed in patients with thiamine and/or niacin deficiency, or in alcoholics who had consumed alcoholic beverages for a long period. Therefore, ethanol-mediated neurotoxicity, and/or disrupted energetic metabolism caused by thiamine deficiency may also contribute. In this sense, a case of a patient affected by MB who recovered with thiamine supplementation was reported (Pasutharnchat and Phanthumchinda, 2002). However, clinical evolution and severity of MBD among alcoholics, with intense callosal atrophy and a high mortality, strongly suggest that it truly constitutes a distinct entity. In this study, we report the case of a 49-year-old patient, followed up during 7 years with a severe atrophy of the corpus callosum. Area of corpus callosum (in the mid sagittal view in magnetic resonance, MR) was measured and compared with the values observed in a series of 20 alcoholics without MB and 11 controls (Fernández-Rodríguez et al., 2016), and in 5 patients with Wernicke-Korsakoff.

CASE REPORT

A 49 year-old male patient consumer of 200-300 g ethanol daily since the last 25 years was brought by his family to this hospital reporting a forty eight-hour history of disorientation followed by visual hallucinations (microzoopsia), tremor and anxiety. The patient had not drunk any alcoholic beverage since forty eight-hours before admission following medical advice, because he was under observation due to gait disorders, repeated falls and difficulty on walking in the previous few weeks. Physical examination was consistent with severe malnutrition, bilateral Dupuytren's contracture and lower limbs amyotrophy. After admission the patient developed a full-blown withdrawal syndrome that was treated with benzodiazepines and thiamine. One week later the patient still presented behaviour disorder, dysarthria, cognitive impairment, disorientation and ataxia. No data regarding muscle tonus and reflexes are available for this first admission. Laboratory evaluation disclosed low serum levels of folic acid and the following biochemical alterations: aspartate aminotransferase (ASAT) 393 IU/L and alanine aminotransferase (ALAT) 96 IU/L. Brain MR showed on T2, FLAIR and diffusion -weighted sequences a high signal lesion diffusely affecting corpus callosum, consistent with demyelination and necrosis of the corpus callosum, and cortical cerebral atrophy (Fig. 1). After discharge





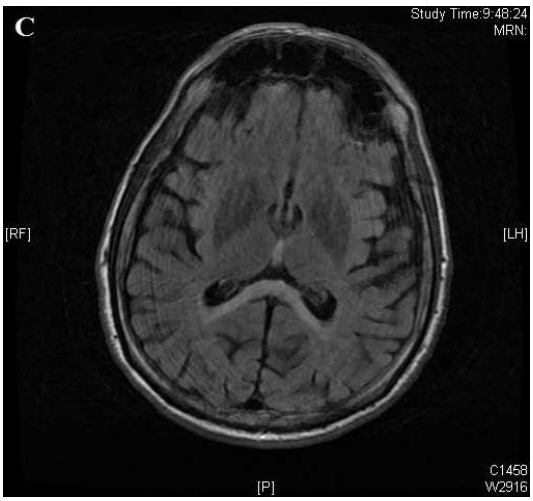


Fig. 1. MR images obtained one month after the onset of symptoms. **(A)** Axial T2-weighted image shows a hyperintense image in the splenium of the corpus callosum. **(B)** Sagittal T1-weighted shows hypointensity of the splenium of the corpus callosum. **(C)** Axial fluid-attenuated inversion recovery image shows hyperintensity of the splenium.

the patient did not follow ambulatory clinical assistance, but was readmitted again to the emergency room of this hospital with two new episodes of alcohol withdrawal syndrome. The patient continued with heavy alcohol consumption, was admitted to the emergency room two years before his last admission, being discharged shortly after. Physical examination at his last admission, about 6 months ago, showed marked spasticity and generalized hyperreflexia with inextinguishable achylian and patellar clonus. A new MR showed a severely atrophied corpus callosum, and also moderate cortical atrophy (Fig. 2). Amyotrophy and raised idiomuscular response were still present. Therefore an electrophysiological study was performed, yielding a mixed sensitive-motor polyneuropathy. At discharge the patient, although able to walk a short distance without aid, still showed mild cognitive impairment, despite thiamine treatment. Globally, as derived from the analysis of the clinical records, the neurologic situation of the patient regarding mobility has not varied substantially from the first admission until the last one, but after this last, prolonged hospital stay, mental status showed some improvement.

Area of corpus callosum, in mm^2 (divided by the distance between the inner cortical table of the frontal bone and that of the occipital bone (in mm)) was 2.7104 mm^2/mm in the first study (2009), 2.1527 mm^2/mm in the second one (2014), and 1.5404 mm^2/mm in the last, 2016). Area of the corpus callosum of 11 controls, aged 56.2 ± 6.0 years was 4.7002 ± 0.6735 mm^2/mm; that of the 20 alcoholics, aged 45.2 ± 19.1, was 3.8751 ± 0.7311 mm^2/mm, and that of the 5 patients with Wernicke-Korsakoff syndrome, aged 56.0 ± 6.0, was 3.4347 ± 0.8491 mm^2/mm. In Figs. 3, 4a, and 4b we show, for comparative purpose, midsagittal MR images of a normal control, with an area of corpus callosum of 5.210 mm^2/mm, and 2 alcoholic patients, one of

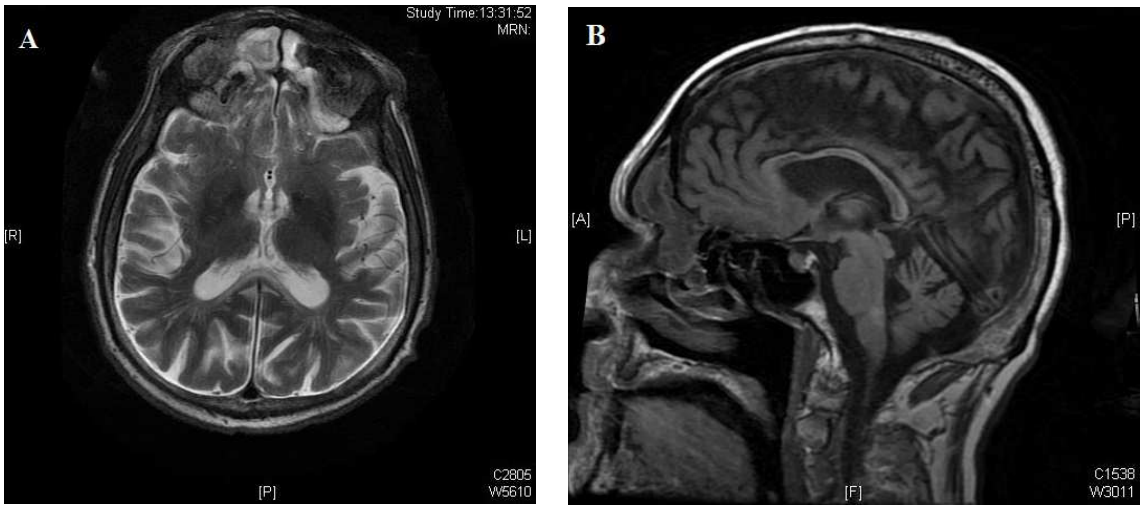


Fig. 2. Follow-up MR images obtained six years after the initial study. **(A)** Axial T2-weighted shows atrophy and hyperintensity of the splenium of the corpus callosum. **(B)** Sagittal T1-weighted MR image shows multiple areas of decreased signal intensity involving the entire corpus callosum, which appears atrophic.

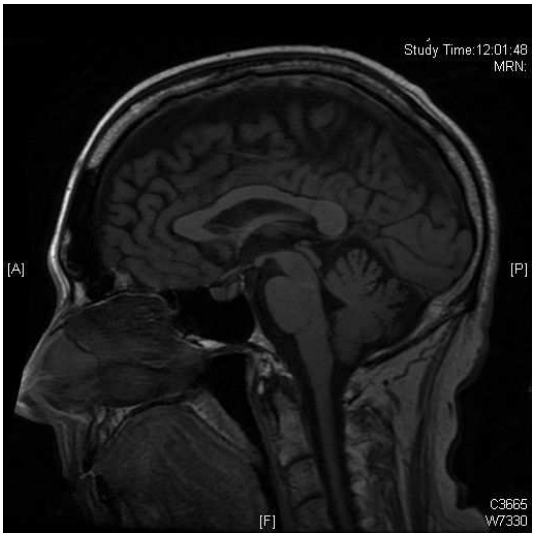


Fig. 3. Sagittal T1-weighted RM image of a normal individual, with an area of corpus callosum of 5.210 mm^2/mm.

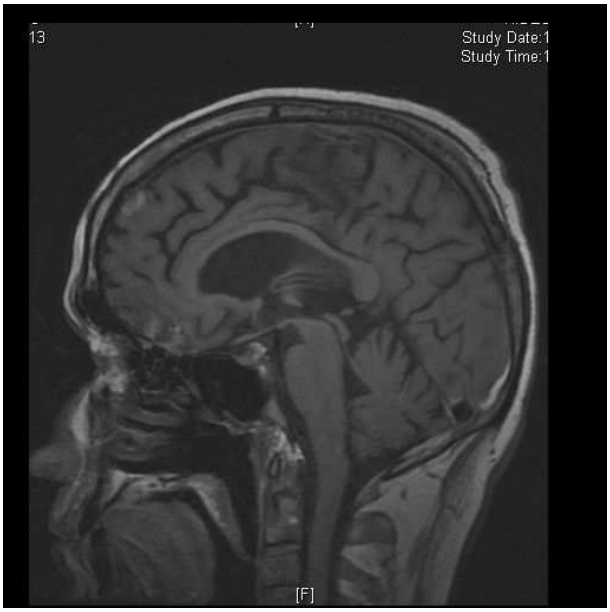


Fig. 4 (A) Sagittal T1-weighted RM image of an alcoholic patient, with severe atrophy of corpus callosum (area= 3.9847 mm^2/mm).

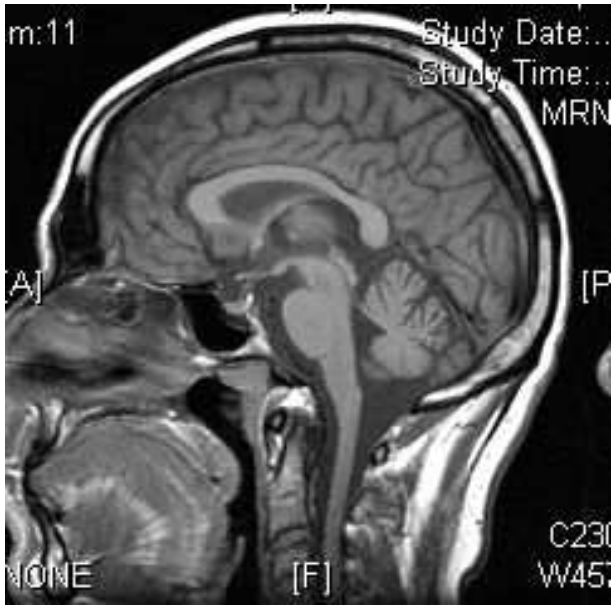


Fig. 4 (B) Sagittal T1-weighted RM image of an alcoholic patient, with severe atrophy of corpus callosum (area= 4.9542 mm^2/mm).

them with severe atrophy (area of corpus callosum=3.9847 mm^2/mm), and another without atrophy (area of corpus callosum=4.9542 mm^2/mm).

COMMENTS

We here describe the case of a heavy alcoholic patient with an intense atrophy of the corpus callosum. From a clinical point of view, the patient had difficulty in walking, with spasticity, and there were also other striking signs consistent with pyramidal lesion, such as marked hyperreflexia and bilateral Babinski sign. There were also some data derived from peripheral nerve affectation that was objectively evidenced by electrophysiological study. MR imaging (especially the last one) showed intense atrophy of the corpus callosum, especially at its middle zone. Both clinical picture and MRI findings are fully compatible with the classic description of Marchiafava-Bignami disease.

This entity was initially reported in some Italian patients consumers of red wine (Carducci, 1898; Marchiafava and Bignami, 1903). It was hypothesized that perhaps certain compounds specifically contained in this kind of beverage were responsible for the necrosis of the corpus callosum presented by these patients, although etiology and pathophysiology remained obscure. Interestingly, in the commented series of 20 alcoholic patients the mean and standard deviation of callosal area obtained in sagittal view of magnetic resonance (MR) was 3.8751 ± 0.7311 mm^2/mm. Although the number is relatively short, the lower limit of the 95% confidence interval of this parameter among alcoholic patients is 2.4228 mm^2/mm, still higher than that observed in the MB patient, whose corpus callosum (in the last MR study) was also more atrophied than the lower limit of the corpus callosum of the Wernicke´s patients (1.7706 mm^2/mm). Differences are even more striking if we consider that the mean value of controls is 4.7002 ± 0.67352 mm^2/mm, leading to a lower limit of the 95% confidence limit of 3.3801 mm^2/mm. The more severe atrophy of this patient suggests that other unknown factors add to the ethanol-derived neurotoxicity and thiamine-deprivation associated disturbed energetic balance that may underlie the atrophy of corpus callosum observed in alcoholics without MB disease.

Along with the widespread use of MRI in the clinical practise, in recent years several cases of focal and/or reversible cases of corpus callosum affectation detected by MRI have been reported (Bulakbasi et al., 2006), especially among patient with seizures, encephalitis, antiepileptic drugs withdrawal, metabolic disturbances such as hypoglycaemia and hypernatremia, among others (McLeod et al., 1987). In contrast with the classic Marchiafava-Bignami disease, these last patients usually recovered completely both clinically and regarding the MRI findings in a short-time period ranging from three days until two months. Probably these cases represent another disease. In fact the term Reversible Splenial lesion Syndrome (RESLES) has been coined (Garcia-Monco et al., 2011).

Ethanol-associated, chronic form of MBD is a rather uncommon disease. In a review article published in February 2014 only 153 patients had been reported (Hillbom et al., 2014). There are controversial results regarding prognosis. Helenius et al. (2001) comment on unfavourable outcome in

90% of patients, whereas other authors address a rapid recovery of the reported patients (García-Monco et al., 2011). These disparate results probably reflect that, in fact, classic, chronic, MBD and the so called acute MBD or RESLES syndrome constitute different entities.

In some studies, the presence of coexisting cortical atrophy was associated with a worse prognosis (Namekawa et al., 2013). Probably cortical atrophy represents another illness related to heavy alcoholism independent of Marchiafava-Bignami disease. In fact, brain cortical atrophy has been reported in 50-80% of chronic alcoholics (Bates et al., 2002). It usually manifests as cognitive impairment and/or dementia and is reversible with alcohol abstinence (Demirakca et al., 2011). Brain cortical atrophy has been also reported to occur in patients affected by thiamine deficiency (Wernicke -Korsakoff syndrome; Sullivan and Pfefferbaum, 2009). Again, considerable debate exists regarding this item, since probably brain atrophy in alcoholics with thiamine deficiency also represents an independent lesion, in possible relation with a direct effect of ethanol and/or ethanol-mediated inflammatory response (Gonzalez-Reimers et al., 2015).

Brain atrophy was indeed observed in the patient here described. Although we cannot fully exclude the possibility that it truly represents a complication of Marchiafava-Bignami disease, we believe that it rather depends on a direct effect of ethanol, in a way similar to the sensory motor peripheral nerve affectation. Due to the severe neurological impairment of this patient and the fact that he was waiting for a sociosanitary facility, the duration of this last hospital admission was quite long (two months). During this period, the patient has notably recovered cognitive functions, and is able to walk, but there is no change in muscle rigidity and pyramidal signs, despite treatment with thiamine.

Therefore, we here present a patient with the chronic form of MBD, and entity classically associated to a very high mortality. This was not the case in the patient here presented, despite intense ethanol consumption. Possibly in relation with the perseveration in the alcoholic habit, a marked atrophy of the corpus callosum, with necrosis of its central area was clearly evident, constituting a striking example of this uncommon entity. Also, illustrating the co-existence of several ethanol mediated alterations in a same patient, diffuse cortical atrophy and peripheral nerve affectation were also evident. The more severe atrophy observed in this patient when compared with that observed in other alcoholics, and the clinical picture, strongly suggest that MB is in fact a distinct entity in which pathogenesis other unknown factors may play a role in addition to the commented neurodegeneration and energetic unbalance described in alcoholics without MB disease. Further studies are needed to assess whether the intensity of corpus callosum atrophy differs in patients with thiamine deficiency, or with uncomplicated heavy alcoholism, or in MB patients, as this study points out.

REFERENCES

BATES ME, BOWDEN SC, BARRY D (2002) Neurocognitive impairment associated with alcohol use disorders: implications for treatment. *Exp Clin Psychopharmacol*, 10: 193-212.

BULAKBASI N, KOCAOGLU M, TAYFUN C, UCOZ T (2006) Transient splenial lesion of the corpus callosum in clinically mild influenza-associated encephalitis/ encephalopathy. *Am J Neuroradiol,* 27: 1983-1986.

CARDUCCI A (1898) Contributo allo studio delle encefaliti non suppurate. *Riv Psicol Psichiat Neuropat,* 8: 125-135.

DE LA MONTE SM, KRIL JJ (2014) Human alcohol-related neuropathology. *Acta Neuropathol,* 127: 71-90. doi: 10.1007/s00401-013-1233-3.

DEMIRAKCA T, ENDE G, KÄMMERER N, WELZEL-MARQUEZ H, HERMANN D, HEINZ A, MANN K (2011) Effects of alcoholism and continued abstinence on brain volumes in both genders. *Alcohol Clin Exp Res*, 35: 1678-1685.

FERNÁNDEZ-RODRÍGUEZ C, MUÑIZ-MONTES JR, GONZÁLEZ-ARNAY E, DÍAZ-FLORES-VARELA L, MARTÍN GONZÁLEZ C, QUINTERO-PLATT G, PÉREZ-HERNÁNDEZ O, GONZÁLEZ-REIMERS E (2016). Altered iron metabolism and atrophy of hippocampus and corpus callosum among alcoholics. *Trace Element Electrol*, 33: 22-27.

GARCIA-MONCO JC, CORTINA IE, FERREIRA E, MARTÍNEZ A, RUIZ L, CABRERA A, BELDARRAIN MG (2011) Reversible splenial lesion syndrome (RESLES): what's in a name? *J Neuroimaging*, 21: 1-14.

GONZALEZ-REIMERS E, QUINTERO-PLATT G, FERNANDEZ-RODRIGUEZ C, GONZALEZ-ARNAY E, MARTIN-GONZALEZ MC, PEREZ-HERNANDEZ O (2015) Oxidative damage and brain atrophy in alcoholics. *Oxid Antioxid Med Sci,* 4: 61-72.

HELENIUS J, TATLISUMAK T, SOINNE L, VALANNE L, KASTE M (2001) Marchiafava-Bignami disease: two cases with a favourable outcome. *Eur J Neurol,* 8: 269 -272.

HILLBOM M, SALOHEIMO P, FUJIOKA S, WSZOLEK ZK, JUVELA S, LEONE MA (2014) Diagnosis and management of Marchiafava-Bignami disease: a review of CT/MRI confirmed cases. *J Neurol Neurosurg Psychiatry,* 85: 168-173.

IRONSIDE R, BOSANQUET FD, MCMENEMEY WH (1961) Central demyelination of the corpus callosum (Marchiafava-Bignami disease) with report of a second case in Great Britain. *Brain,* 84: 212-230.

KAWARABUKI K, SAKAKIBARA T, HIRAI M, YOSHIOKA Y, YAMAMOTO Y, YAMAKI T (2003) Marchiafava-Bignami disease: magnetic resonance imaging findings in corpus callosum and subcortical white matter. *Eur J Radiol,* 48: 175-177.

KOLLÁR J, PÉTER M, FÜLESDI B, SIKULA J (2001) Is

every sharply defined, symmetrical, necrotic-demyelinating lesion in the corpus callosum an actual manifestation of Marchiafava-Bignami disease? *Eur J Radiol*, 39: 151-154.

LI S, SUN X, BAI Y, QIN H, WU X, ZHANG X, JOLKKONEN J, BOLTZE J, WANG S (2015) infarction of the corpus callosum: a retrospective clinical investigation. *PLoS One,* 10: e0120409. doi:10.1371/journal.pone.0120409.

MAEDA M, TSUKAHARA H, TERADA H, NAKAJI S, NAKAMURA H, OBA H, IGARASHI O, ARASAKI K, MACHIDA T, TAKEDA K, TAKANASHI JI (2006) Reversible splenial lesion with restricted diffusion in a wide spectrum of diseases and conditions. *J Neuroradiol,* 33: 229-236.

MARCHIAFAVA E, BIGNAMI A (1903) Sopra un'alterazione del corpo calloso osservata in soggetti alcoolisti. *Riv Patol Nerv Ment,* 8: 544-549.

MCLEOD NA, WILLIAMS JP, MACHEN B, LUM GB (1987) Normal and abnormal morphology of the corpus callosum. *Neurology*, 37: 1240-1242.

NAMEKAWA M, NAKAMURA Y, NAKANO I (2013) Cortical involvement in Marchiafava-Bignami disease can be a predictor of poor prognosis: a case report and review of the literature. *Intern Med,* 52: 811-813.

PASUTHARNCHAT N, PHANTHUMCHINDA K (2002) Marchiafava-Bignami disease: a case report. *J Med Assoc Thailand*, 85: 742-746.

SULLIVAN EV, PFEFFERBAUM A (2009) Neuroimaging of the Wernicke-Korsakoff syndrome. *Alcohol,* 44: 155-165.

TADA H, TAKANASHI J, BARKOVICH AJ, OBA H, MAEDA M, TSUKAHARA H, SUZUKI M, YAMAMOTO T, SHIMONO T, ICHIYAMA T, TAOKA T, SOHMA O, YOSHIKAWA H, KOHNO Y (2004) Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. *Neurology*, 63: 1854-1858.