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Case Report

Marchiafava-Bignami Disease: Longitudinal MR Imaging and MR Spectroscopy Study

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Summary: A case of Marchiafava-Bignami disease was serially evaluated with MR imaging and MR spectroscopy at 1, 2, 4, and 11 months after the onset of symptoms. The first MR imaging study showed extensive abnormal signal intensity of the corpus callosum without macroscopic changes; a diagnosis of Marchiafava-Bignami disease was made, and vitamin therapy was initiated. Follow-up studies showed progressive reduction of signal intensity abnormalities and residual callosal atrophy. MR spectroscopy revealed progressive reduction of the *N*-acetylaspartate:creatine ratio, with partial recovery in the last study, and a normalization of the choline:creatine ratio, which was initially slightly increased. Lactate was detectable during the subacute phase and was replaced by lipids after 4 months. This study confirmed the role of MR imaging in diagnosing Marchiafava-Bignami disease and particularly the value of MR spectroscopy in focusing the pathogenesis of the disease, monitoring its evolution and changes related to therapy.

Marchiafava-Bignami disease is a rare complication of chronic alcoholism, even though some cases not related to alcohol abuse are described. Since 1903, when the first case of Marchiafava-Bignami disease was reported, approximately 150 cases have been described. Early reports were based mainly on postmortem pathologic evidence (1–3), whereas the advent of CT and MR imaging allowed in vivo analysis of neuroimaging findings.

The main pathologic change associated with Marchiafava-Bignami disease is a degeneration of the corpus callosum with different degrees of damage, from demyelination with preservation of axons to necrosis accompanied in few cases by bleeding during the subacute phase. The genu of the corpus callosum is more frequently involved, but the degeneration can extend to the entire corpus callosum, preferentially involving fibers of the central portion. Necrosis produces cystic lesions within the corpus callosum, mainly in the genu and splenium with gliotic walls and content of foamy macrophages (4). Astrocytes filled with iron-positive granules may be present within the gliotic tissue, indicating previous bleeding (4).

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Demyelination is accompanied by infiltration of lipid (Lip)-laden macrophages distributed around naked axons and blood vessels (1). The corpus callosum becomes thinner because of axonal loss, which may extend to the radiations in the centrum semiovale. Occasionally, other structures of the CNS may be involved: optic chiasm and tracts, putamen, anterior commissure, cerebellar peduncles and, rarely, cortical gray matter (laminar sclerosis) (5) and U fibers. Some cases of reversibility are described (6, 7).

The pathogenesis is still unclear; a toxic factor present in cheap red wine has been advocated but never identified. Deficiency of essential nutritional factors, especially of vitamins, is frequent in alcoholics and contributes to the neurologic complications, even though it does not seem to be directly implied in the pathogenesis. However, vitamin supply, in particular B complex and folic acid, has been reported to have a positive effect on clinical outcome.

Marchiafava-Bignami disease may present in various clinical forms. Acute Marchiafava-Bignami disease includes seizures, impairment of consciousness, and rapid death. Subacute Marchiafava-Bignami disease includes variable degrees of mental confusion, dysarthria, behavioral abnormalities, memory deficits, signs of interhemispheric disconnection, and impairment of gait (5, 8). Chronic Marchiafava-Bignami disease, which is less common, is characterized by mild dementia that is progressive over years (8, 9).

Because clinical signs are nonspecific, the role of CT and MR imaging is essential to confirm the diagnosis. The corpus callosum appears hypoattenuated on CT scans, with the exception of cases that are characterized by subacute bleeding, in which it may be iso-hyperattenuated (4, 10).

The corpus callosum appears hyperintense on T2- and proton density-weighted MR images during the acute phase, hypointense on T1-weighted images, with possible foci of T2 proton density hyperintensity in the centrum semiovale. During the subacute phase, cystic lesions and small foci of T2 hypointensity can develop, most likely because of hemosiderin (11). After a few months, signal intensity alterations become less evident but residual atrophy of the involved structure (and, in some cases, also of the cortex) usually is present (9, 11).

To our knowledge, proton MR spectroscopy has not yet been applied to the study of this disease. The aim of our serial MR imaging and MR spectroscopy study of a patient with Marchiafava-Bignami disease was to note changes after vitamin therapy and to

Main MR imaging signal changes and correspondent metabolic profile of MR spectroscopy during the evolution of the disease

Months after Onset	MR Imaging	Cho/Cr	NAA/Cr	Lactate	Lipids
1	T2 hyperintensity of the entire corpus callosum; foci of in the centrum semiovale	1.35	1.98	++	−
2	Unchanged	1.17	1.67	+	−
4	Persistent hyperintensity in the splenium and posterior half of the body of the corpus callosum; corpus callosum slightly atrophic	1.06	1.26	−	+
11	Slight hyperintensity of the splenium; moderate atrophy of the corpus callosum	0.87	1.45	−	−
Normal range		0.9–1.3	1.8–2.4	−	−

Note.—Cho indicates choline; Cr, creatine; NAA, *N*-acetylaspartate.

assess the contribution of spectroscopy to the in vivo study of the disease.

Case Report

A 49-year-old man with a 10-year history of alcohol (red wine) abuse developed progressive behavioral and mood changes during the month before the observation. At general examination, he appeared ill nourished. A neuropsychologic evaluation showed apathy, psycho-motor impairment, long- and short-term memory deficits, decreased attentive function, visuospatial agnosia, and oral apraxia. He showed nonspecific neurologic signs, such as, hyperreflexia, mild ataxia, Babinski sign, and hypopallesthesia.

MR imaging and MR spectroscopy were performed with a 1.5-T magnet (Siemens Vision; Siemens, Erlangen, Germany) at 1, 2, 4, and 11 months after the onset of symptoms. Fast double spin-echo sequences (2600/14, 85 [TR/TE, second TE]), T1-weighted images (600/14), fluid-attenuated inversion recovery images (9999/105), and inversion recovery sequences (TR, 9520; inversion time, 60 ms) were obtained in the axial, coronal, and sagittal planes.

Spectra were acquired by using a chemical shift imaging spin-echo technique (1500/135). The multivoxel of 80 × 80 × 20 mm was positioned to include the corpus callosum and periventricular white matter. Postprocessing software was used to measure peak areas of choline (Cho), creatine (Cr), *N*-acetylaspartate (NAA), lactate (Lac), and lipids (Lip) in the area of the splenium because of the better resolution of peaks in this area of the corpus callosum. Cr was used as internal standard for the relative quantitation of NAA and Cho. The mean value of four voxels in the splenium was calculated and the data compared with those of three control participants. The results are summarized in Table 1.

One Month after Onset of Symptoms

MR imaging showed a selective involvement of the corpus callosum, which appeared markedly hyperintense on T2-weighted, proton density-weighted, and fluid-attenuated inversion recovery images and hypointense on T1-weighted images, from the genu to the splenium, with sparing of superficial fibers. On the coronal inversion recovery sequence, the corpus callosum was hypointense and the central midportion of fibers was spared. On T2- and proton density–weighted images, two foci of slight hyperintensity in periventricular white matter were also seen. The sulci and ventricular system were moderately enlarged in both infra- and supratentorial compartments (Fig 1).

Proton MR spectroscopy revealed a well-defined Lac peak at 1.3 ppm. The Cho/Cr ratio was slightly increased (1.35 ± 0.26), and the NAA/Cr ratio was normal (1.98 ± 0.30).

MR imaging suggested the diagnosis of Marchiafava-Bignami disease. The clinical presentation suggested a subacute form of disease. A supplementary therapy with B-complex vitamins and folic acid was started. The patient stopped alcohol consumption.

Two Months after Onset of Symptoms

Although MR imaging showed no changes, MR spectroscopy revealed an initial reduction of the NAA/Cr ratio (1.67 ± 0.32), the Cho/Cr ratio returned to the normal range (1.17 ± 0.22), and the area of Lac peak was reduced to half its initial value.

Four Months after Onset of Symptoms

Except for a global thinning of the corpus callosum, the splenium and the posterior half of the body were still hyperintense on T2-weighted images, whereas the genu and the anterior half of the body showed a slight prolongation of T2. The focal involvement of periventricular white matter was no longer detectable (Fig 2 A–C).

MR spectroscopy metabolite ratios confirmed the previous trend: the NAA/Cr ratio continued to decrease, reaching a minimum value (1.26 ± 0.12), and the Cho/Cr ratio was still within the normal range, even if at its inferior limits (1.06 ± 0.06). Lac was no longer detectable, whereas Lip peak became evident at the same resonance frequency as that of Lac.

Eleven Months after Onset of Symptoms

MR imaging showed global moderate atrophy of the corpus callosum and persistent slight hyperintensity limited to the splenium (Fig 2D and E). MR spectroscopy revealed that the Cho/Cr ratio was at the inferior limit of the normal range (0.87 ± 0.15), that the NAA/Cr ratio had partially recovered (1.45 ± 0.25), and that neither Lac nor Lip peaks were evident (Fig 3). The clinical conditions of the patient improved, and the memory and cognitive functions were recovered almost completely.

Discussion

MR imaging is the most adequate technique with which to evaluate CNS changes induced by Marchiafava-Bignami disease and to monitor the evolution toward partial or total regression. Some studies correlating MR imaging changes to the pathologic substrate have shown that the distinctive element of Marchiafava-Bignami disease is selective demyelination of the corpus callosum, with or without necrosis.

T2 prolongation is due in part to edema in addition to myelin damage. For this reason, during the acute phase, the corpus callosum appears clearly hyperin-

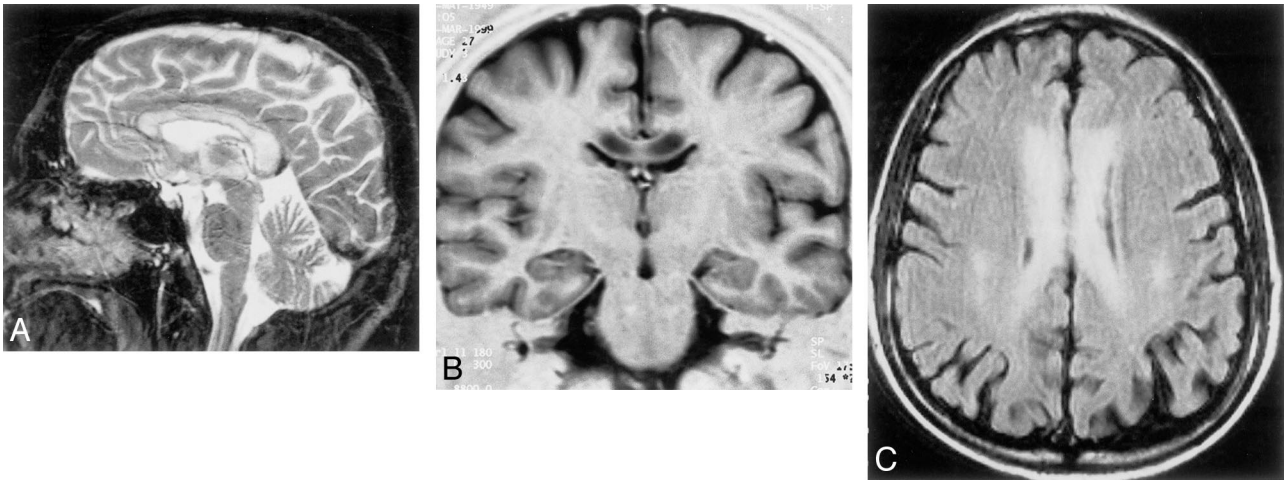

FIG 1. MR images obtained 1 month after the onset of symptoms.
A, Sagittal T2-weighted MR image (2600/14, 85/2 [TR/TE, second TE/NEX]). Hyperintensity of the entire corpus callosum is present.
B, Coronal inversion recovery image (9520/60/2 [TR/TI/NEX]). The corpus callosum appears hypointense, with sparing of fibers in the superficial and central portion.
C, Axial fluid-attenuated inversion recovery image (9999/105/1). Bilateral foci of hyperintensity in the white matter of the centrum semiovale.

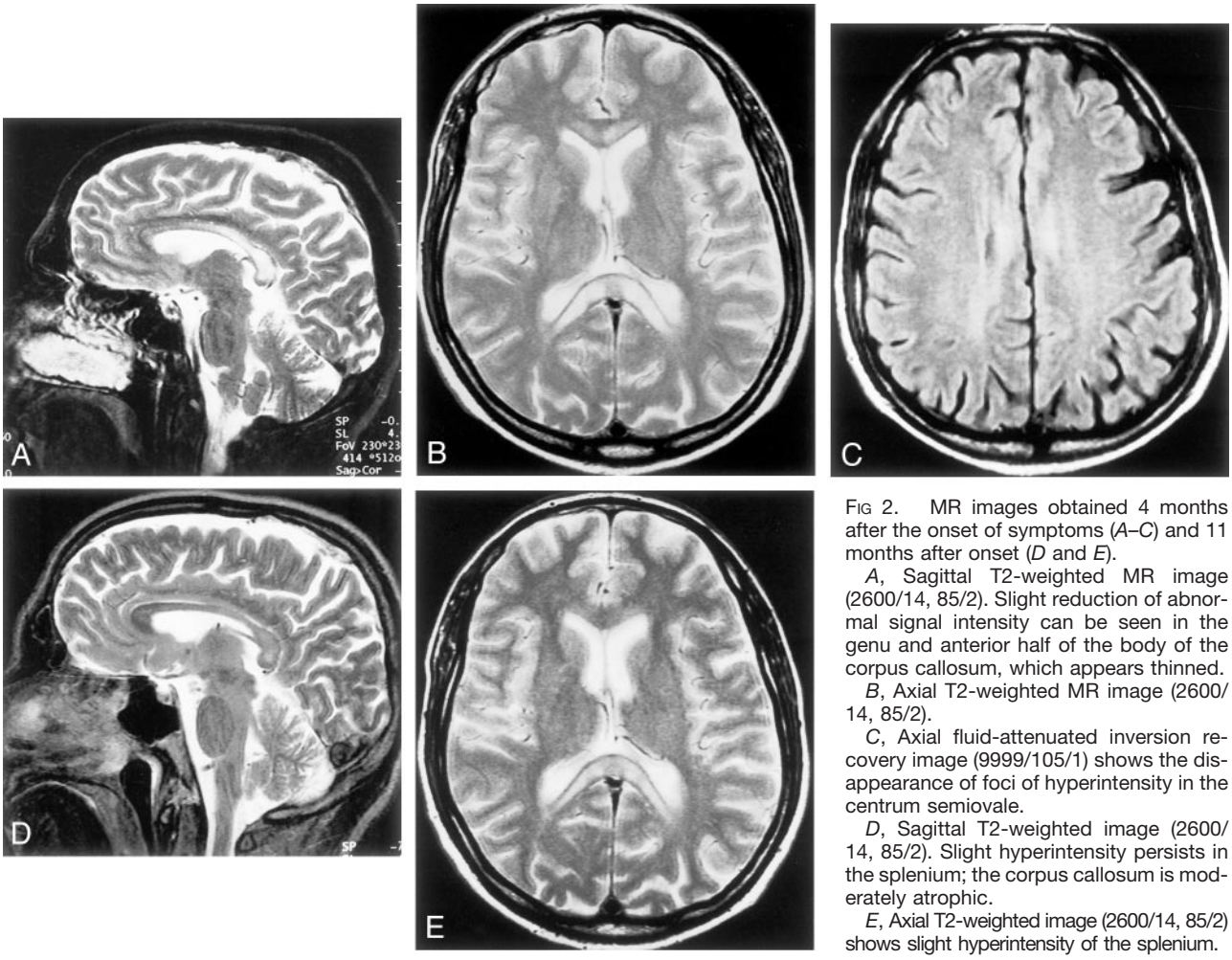

FIG 2. MR images obtained 4 months after the onset of symptoms (*A–C*) and 11 months after onset (*D* and *E*).
A, Sagittal T2-weighted MR image (2600/14, 85/2). Slight reduction of abnormal signal intensity can be seen in the genu and anterior half of the body of the corpus callosum, which appears thinned.
B, Axial T2-weighted MR image (2600/14, 85/2).
C, Axial fluid-attenuated inversion recovery image (9999/105/1) shows the disappearance of foci of hyperintensity in the centrum semiovale.
D, Sagittal T2-weighted image (2600/14, 85/2). Slight hyperintensity persists in the splenium; the corpus callosum is moderately atrophic.
E, Axial T2-weighted image (2600/14, 85/2) shows slight hyperintensity of the splenium.

tense (7). T2 signal intensity alteration progressively reduces over time, in parallel with decreasing edema (7). The corpus callosum may remain hyperintense for permanent myelin damage or may recover its normal signal intensity in cases of total remyelination (7). Necrosis can occur, especially in the genu and

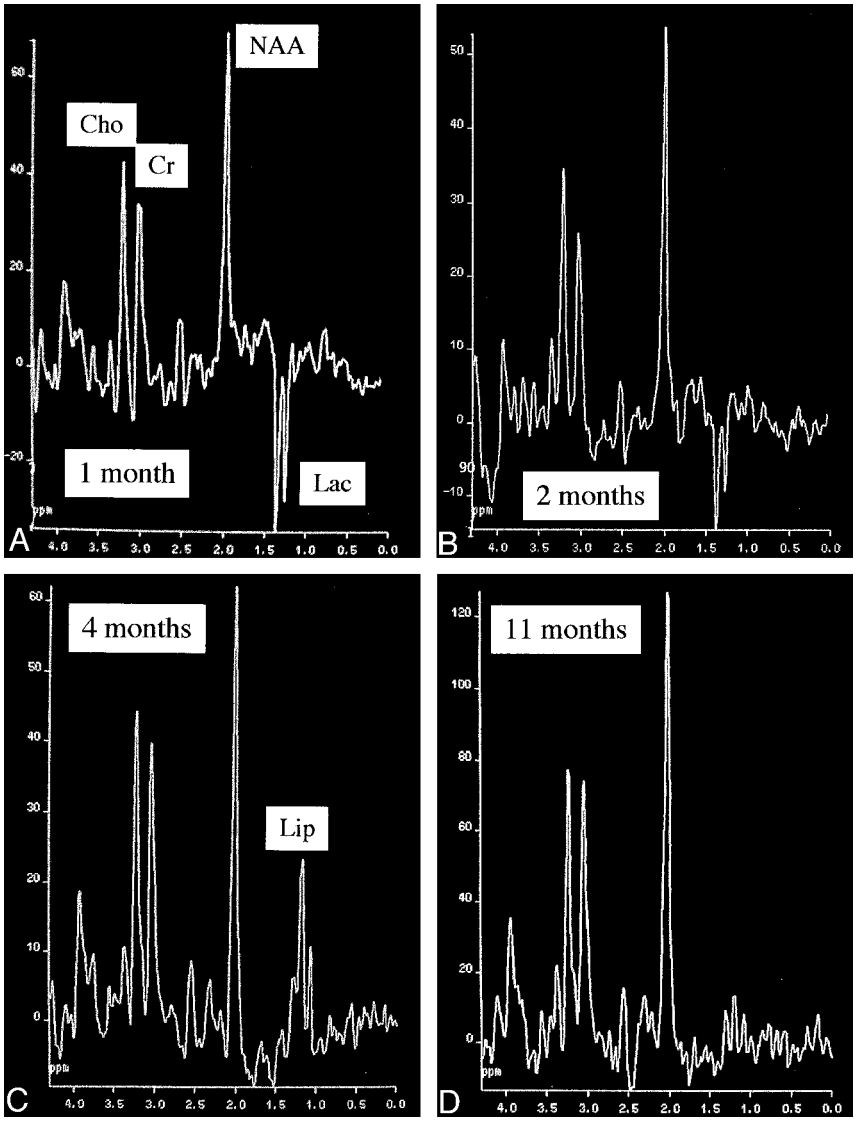

FIG 3. Evolution with time of metabolic profile of the splenium of the corpus callosum. Progressive normalization of the Cho/Cr ratio is initially slightly increased; progressive reduction of the NAA/Cr ratio, with a minimum at 4 months and a partial recovery at 11 months; presence of Lac at 1 and 2 months replaced by Lip at 4 months.

A, Metabolic profile at 1 month.
B, Metabolic profile at 2 months.
C, Metabolic profile at 4 months.
D, Metabolic profile at 11 months.

splenium, inducing the formation of cysts. Superficial and central fibers of the corpus callosum are characteristically spared by the process (1, 2). Residual callosal atrophy is described to occur during the chronic phase (11). Some authors report callosal bleeding during the subacute phase (10, 11), evidenced by hypointensity on T2-weighted images, consistent with hemosiderin deposition (6).

In our case, we observed a globally hyperintense corpus callosum on T2-weighted images, with sparing of superficial and central fibers; there was no evidence of bleeding nor of macroscopic necrosis. The process showed a progressive involution, resulting in residual moderate atrophy and persistent slight hyperintensity on T2-weighted images in the splenium. A moderate diffuse enlargement of the subarachnoid sulci and ventricular system and two focal hyperintensities on T2-weighted images of periventricular white matter were noticed. The former may be considered expression of mild brain atrophy as a possible consequence of the toxic action of alcohol. The latter are nonspecific and have been described in other cases of Marchiafava-Bignami disease (12) as probably representing extension of the damage to the radiations of the corpus callosum (secondary degeneration).

Even though clinical signs and symptoms are hardly explained by this kind of brain alteration, the clinical conditions of our patient improved in parallel with the reversion of MR imaging changes. The most interesting data of this study are represented by the serial evaluation of brain metabolites by MR spectroscopy, because this technique may provide additional information to help in understanding the pathogenesis of the disease and in evaluating brain damage and prognosis. To our knowledge, no spectroscopic studies of Marchiafava-Bignami disease have been published to date.

It is known that an increase in Cho-containing compounds occurs during the acute phase of demyelination because of the active myelin breakdown and the consequent release of phosphocholine and glycerol-phosphocholine (13). Cr resonance intensity is considered to be stable so that this metabolite is usually used as an internal standard to make relative

quantitation of the other metabolites (13). Cr peak can be focally reduced in association with some destructive pathologic abnormalities, such as malignant tumors (13), whereas it is shown that in demyelinating processes, it remains stable (14). However, some authors describe that in cases of severe demyelinating processes, a decrease of Cr during the hyperacute phase may be observed, with normalization occurring within a few days (15).

In our study, we observed only an initial slight increase of the Cho/Cr ratio, which subsequently returned to the low normal range. It is possible that we did not find a marked increase of Cho because the first measurement was performed during the subacute phase of the disease (at 1 month from the onset of symptoms). The progressive normalization of the Cho/Cr ratio is in keeping with the chronic phase of demyelination.

Lac was present in the first two studies. This metabolite accompanies inflammatory reactions, which cause a temporary shift from aerobic to anaerobic glycolysis. Lac is usually present during the acute/subacute phases of demyelination, as in our case.

The NAA/Cr ratio showed a progressive decrease to a minimum level after 4 months and a partial recovery after 11 months. Because NAA is a specific neuronal marker, its reduction suggests the secondary axonal injury after myelin destruction. The axons are subject both to temporary dysfunction and to irreversible damage, which explains the partial recovery of the NAA/Cr ratio in the last study.

After 4 months from the onset of symptoms, spectra revealed the presence of Lip, which could have hidden a residual peak of Lac. Lip were present only at this time, contemporary with the major axonal damage. Neuropathologic studies report that at this time, the damaged tissue is invaded by macrophages enriched in Lip because of their phagocytic activity of cellular membranes (1), so the Lip peak is likely to be the expression of micronecrosis of axons and oligodendrocytes.

Conclusion

This study confirms that during the course of Marchiafava-Bignami disease, MR imaging is the appropriate technique with which to evaluate morphologic and metabolic changes of the corpus callosum, including their evolution with time and after treatment. MR spectroscopy can support the pathogenetic theory, suggesting that an "inflammatory" reaction may accompany demyelination and micronecrosis. These data, however, need confirmation by further studies.

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