

**Marchiafava-Bignami disease with dementia:  
severe cerebral metabolic depression revealed by PET**

*Case Report*

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Accepted July 21, 1994

**Summary.** The Cerebral Metabolic Rate of Glucose (CMRGlu) was measured with positron emission tomography and <sup>18</sup>F-FDG in a patient with Marchiafava-Bignami Disease (MBD)-related dementia. Despite MRI evidence of lesions essentially limited to the corpus callosum (CC), but consistent with the cognitive pattern of cortical dementia, the CMRGlu was markedly reduced in the frontal and temporo-parieto-occipital association cortices.

Disruption of cortico-cortical networks crossing the CC presumably contributed to, but may not in and by itself explain, the severity of the clinical-metabolic findings in this patient. An additional role could be played by microscopic white matter lesions and/or neocortical neuronal loss, which have been occasionally observed in post-mortem studies of MBD patients.

**Keywords:** Marchiafava-Bignami disease, corpus callosum, brain glucose utilization, Positron Emission Tomography, alcoholism.

**Introduction**

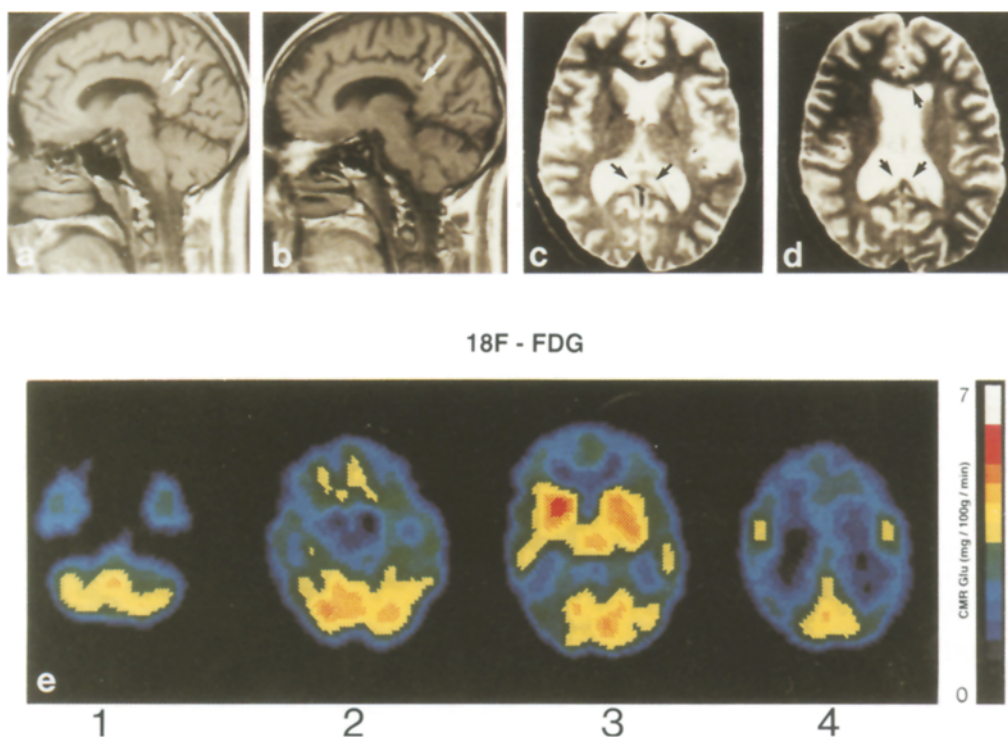
Marchiafava-Bignami Disease (MBD) is a rare complication of chronic severe alcoholism. Its pathological hallmark is damage of the corpus callosum (CC) (Castaigne et al., 1971). The advent of CT and MRI imaging has allowed a better delineation of clinical presentations of MBD other than the classic letal form, notably a “benign” form with permanent cognitive impairment or even dementia (superimposed on classic disconnection syndromes) despite apparently limited CC lesions (Canaple et al., 1992; Nicoli et al., 1994). This contrast between residual cognitive impairment and apparently limited CC lesions is intriguing and raises the issue of the associated damage to the cortex and hemispheric white matter that has been occasionally reported post-

mortem (Castaigne et al., 1971) but rarely by MRI (Nicoli et al., 1994); though not mutually exclusive, a role for strategically located lesions of the CC, globally disrupting cognitive function, does however remain an intriguing possibility.

This report is the first to present cerebral glucose utilization (CMR<sub>Glu</sub>) data in a patient with MBD-related dementia. Its interest lies in the demonstration of a striking disruption of synaptic activity in the entire association neocortex, which was coherent with the clinical presentation of dementia but less expected in view of the limited chronic-stage CC lesions revealed by the MRI. A preliminary account of this work has been presented earlier (Pappata et al., 1992).

### Case report

The patient was a 39 year-old unemployed, right-handed male with a long history of severe alcoholism. He underwent a post-traumatic amputation of the right hand at age 17 years. He was admitted to the hospital three days after sudden onset of confusion and behavioral changes, without gait disturbances. His family stated that he had been cognitively normal prior to this episode. At admission, clinical examination showed a severe global mental deterioration with language and memory disturbances but without alteration of consciousness, delirium or tremor. The patient showed major impairment with naming objects to confrontation, word-finding in spontaneous speech, verbal comprehension (both oral and written), and writing. He was disoriented for both time and space and had a severe anterograde and retrograde amnesia. The rest of the neurological examination, including gait, was normal apart for absent ankle jerks bilaterally; at careful examination of the external ocular movements, there was no gaze palsy and no nystagmus was elicited. The standard laboratory and cerebro-spinal fluid data were normal. The admission CT Scan showed a clear-cut hypodense lesion of the splenium of the CC, consistent with the diagnosis of MBD; there was also a generalized, moderate widening of the cerebral sulci. The patient was treated with detoxification by withdrawal of alcohol, parenteral B1–B6 vitamins and a combination of meprobamate and haloperidol to prevent anxiety and night-time agitation. He underwent a PET study one month later. By that time, he had shown some improvement, but was still demented. In addition to mild neocortical and superior cerebellar atrophy, the MRI T1 – weighted images showed several small, and one larger, hypointense areas in the splenium of CC; the thickness of the CC appeared normal, except perhaps at its anterior 2/3 – posterior 1/3 junction which appeared thinned (Fig. 1a,b). However, in the mid-sagittal cut, there was also a faintly visible slit-like hypointensity running antero-posteriorly within the body of the CC (not shown). The T2 sequences disclosed more conspicuous splenial lesions, and one small hyperintense area in the genu (Fig. 1c,d). There was no evidence of MRI abnormalities known to be associated with Wernicke encephalopathy (e.g., increased T<sub>2</sub> signals near, or dilatation of, the third ventricle and the aqueduct, or atrophy of the mammillary bodies) (Gallucci et al., 1990). Neuropsychological evaluation revealed a Wechsler Adult Intelligence Scale verbal IQ of 62 and a Wechsler Memory Scale score of 53. Compared to admission time, there was an improvement in language performances; he could name 4 out of 5 objects, and better understand verbal orders and write. The spatioconstructive abilities were altered with “closing in” (placing lines too close to each other). There was major frontal lobe dysfunction. The verbal fluency was reduced, and the learning of sequences of hand gestures according to Luria was altered. He showed mental slowness, abulia and imitation behavior. Severe dementia and amputation of the right hand prevented detailed investigation of inter-hemispheric disconnection but there was definite left apraxia without tactile naming deficit. A PET study was repeated 3 months later. At that time the patient showed an essentially unimproved cognitive status.



**Fig. 1.** **a-d** Magnetic Resonance Imaging (GE 1.5 Tesla), and **e** Parametric PET CMRglu images, obtained 1 month after onset of dementia. **a,b** Sagittal MRI views showing two lesions in splenium of the corpus callosum (arrows) (Partial Saturation T1 weighted images, TR: 600 msec, TE: 20 msec). **c,d** Axial MRI views, showing extensive hyperintense lesions in the splenium (arrows) and one small lesion in the left part of the genu of the corpus callosum (arrow) (Spin Echo T2 weighted images, TR: 2,000 msec, TE: 80 msec). **e** PET images of CMRglu at four selected brain levels (orbito-meatal plane +10 mm, +25 mm, +55 mm, and +70 mm, from left to right, respectively). The pixel-by-pixel parametric CMRglu images are displayed according to a pseudo-colour scale that ranges from zero (black) to 7 mg/100 g.min (white). They show a bilateral cortical hypometabolism, more marked in the prefrontal and temporo-parietal-occipital association cortices than in sensori-motor, auditory and visual primary areas (planes 3 and 4). The cerebellum (planes 1 and 2) and the deep gray matter structures (plane 3) also appear relatively spared (see Results and Table 1 for quantitative results)

### Methods

PET and  $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG) were used to measure the CMRglu, according to a procedure detailed elsewhere (Martinot et al., 1990). PET scans were performed with the LETI TTV01 time-of-flight four-ring seven-slice camera with axial and lateral resolutions of about 13 mm. The subject's head was positioned in a head-holder so that the lowest slice was 10 mm above the orbito-meatal plane. Correction for attenuation was carried out using a germanium 68-gallium 68 transmission scan. Plasma  $^{18}\text{F}$ FDG curves were obtained from twenty-four arterial blood samples collected from the radial artery over one hour after the i.v. injection of 5 mCi of the radiotracer. PET images were acquired from 50 to 60 min post injection. Parametric pixel-by-pixel images of CMRglu (mg/100 g/min) were obtained using the autoradiographic method and the FDG rate constants and lumped constant derived from normal subjects (Martinot et al., 1990); this procedure is valid, as the  $^{18}\text{F}$ FDG in vivo autoradiographic model is not sensitive

to small variations in these constants, i.e. in the absence of acute non-physiological conditions.

For PET data analysis, the five brain levels passing through the cerebellum, the orbito-frontal cortex, the basal ganglia, the corona radiata and the centrum semi-ovale, respectively, were selected (Martinot et al., 1990). Circular regions of interest (ROIs) were placed over the cortical structures, thalamus, striatum and cerebellum on the right side and automatically copied on the left side with respect to, and after appropriate rotation of, the antero-posterior sagittal axis; due to the limited spatial resolution of the PET device used, the hippocampal area was not assessed in this study. The data from cortical ROIs were subsequently averaged according to a limited number of anatomical – functional brain areas (Martinot et al., 1990). In addition to the absolute CMRglu values so obtained, we also evaluated the cortical metabolic “distribution pattern”, which is a classical method for characterizing disease processes relative to one another in a more sensitive way (Rapoport, 1991). To do this, the absolute cortical regional CMRglu values were normalized for the occipital cortex values, i.e. the cortical region that showed least decrease in CMRglu in our patient (see below) (Sawle et al., 1991; Schapiro et al., 1993). The patient’s results were compared to those of 31 age matched controls (mean  $\pm$  one SD:  $37 \pm 13$  years). Statistical significance was assessed using the 95% or 99% individual prediction limits (IPL) calculated for each brain region (both for absolute CMRglc and for normalized metabolic values) from the control values according to the following formula:

$$\text{IPL} = \text{mean} \pm \text{SD} \cdot t,$$

with Student’s two-tailed *t* values of 2.042 and 2.750 for  $p = 0.05$  and  $p = 0.01$ , respectively.

## Results

The parametric CMRglu images (Fig. 1e) displayed a clear-cut global hypometabolism, more marked in the anterior and posterior association cortices, with relative sparing of the cerebellum, the deep gray nuclei and the primary neocortex. The CMRglu in the basal ganglia, the thalamus and the cerebellum was in the low range but did not reach statistical significance relative to controls (4.82, 4.01, and 3.55 mg/100 g.min, respectively, versus  $6.05 \pm 1.29$ ,  $5.61 \pm 1.21$  and  $4.57 \pm 1.04$  mg/100 g.min, respectively).

Table 1 shows the absolute neocortical metabolic values. The CMRglu was significantly decreased for the whole neocortex ( $\sim 50\%$  of controls,  $p < 0.05$ ). All cortical regions were hypometabolic, with the lateral prefrontal, medial frontal (including the anterior cingulate gyrus) and posterior associative (i.e. parieto-temporo-occipital) cortices reaching statistically significant ( $p < 0.05$ ) metabolic depression bilaterally; the sensori-motor, lateral temporal (which includes the primary auditory cortex) and the visual cortices were not significantly hypometabolic. The visual cortex was least reduced (65% of controls).

The analysis of normalized metabolic values (Table 1) revealed essentially similar findings, but with enhanced significance. Significant decreases were found for the lateral prefrontal ( $p < 0.01$ ), medial frontal, orbito-frontal and posterior associative cortices ( $p < 0.05$  for each), but not for the sensori-motor and lateral temporal cortices.

Essentially unchanged metabolic alterations were found at follow-up PET study (data not shown). When seen at clinical follow-up at six and 10 months

**Table 1.** Average CMRGlu (mg/100 g/min) in whole cortex and cortical areas, and regional relative metabolic values (cortical region/visual occipital cortex)

Structures	CMRGlu		Region/visual cortex	
	Controls	Patient	Controls	Patient
Whole cortex	5.59 ± 1.25	2.93*	NA	NA
Lateral prefrontal	5.87 ± 1.37	2.57*	0.92 ± 0.09	0.62**
Medial frontal	6.10 ± 1.45	2.96*	0.96 ± 0.09	0.71*
Orbito-frontal	5.52 ± 1.39	2.77	0.87 ± 0.09	0.66*
Sensori-motor	5.63 ± 1.29	3.01	0.88 ± 0.08	0.73
Posterior associative	5.33 ± 1.22	2.83*	0.84 ± 0.07	0.68*
Lateral Temporal	5.17 ± 1.13	3.06	0.82 ± 0.06	0.74
Visual	6.33 ± 1.25	4.15	1	1

\*  $p < 0.05$  and \*\*  $p < 0.01$ , two tailed probability with respect to 31 age-matched control subjects (see Methods). *NA* not applicable

after onset of cognitive impairment, the patient remained demented despite sustained, though mild, improvement.

### Discussion

This patient had the rare presentation of protracted dementia of acute onset with only partial subsequent improvement, together with CT and MRI lesions of the CC consistent with the diagnosis of MBD (Castaigne et al., 1971; Nicoli et al., 1994). The PET studies performed one and three months after onset showed a conspicuous metabolic depression that was global but preferentially affected the association neocortex bilaterally, relative to primary neocortex and subcortical structures. This striking distribution of hypometabolism is quite consistent with the neuropsychological pattern of “cortical dementia” observed in this patient, including major frontal lobe dysfunction, memory impairment, and disturbances of language and spatio-constructive abilities, and resembles that reported in advanced Alzheimer’s disease (Rapoport et al., 1991) as well as in one demented patient with neuropathologically-proven Parkinson’s disease but without cortical pathology (Schapiro et al., 1993), indicating it is specific neither for disease nor for lesion topography.

These major changes in brain glucose metabolism found in our patient stand in striking contrast with the apparently relatively limited callosal lesions. Could a widespread disruption in transcallosal-based cortical function result from strategically located callosal lesions and underly, at least in part, this clinical-metabolic presentation? In favour of this idea, the distribution of cortical hypometabolism in our patient would be consistent with the regional pattern of callosal connections, which are dense for associative, and sparse for primary sensory, cortices (Innocenti et al., 1986). In addition, the frontal and temporo-parieto-occipital transcallosal fibers cross at the level of the genu and the splenium, respectively (De Lacoste et al., 1985), which bear the brunt of the damage in this case. Finally, corpus callosotomy in epileptic subjects often induces a confusional state (Spencer, 1988; Oepen et al., 1988), and in the

baboon results in a 30% reduction in CMRGlu in the fronto-temporal regions (Yamaguchi et al., 1990). However, there are two major inconsistencies with this hypothesis. *First*, these effects of corpus callosotomy, both in epileptic subjects and in baboons, are transient (Spencer, 1988; Oepen et al., 1988; Yamaguchi et al., 1990), as compared to sustained in our case. *Second*, though the MRI suggested somewhat extensive CC lesions, the most conspicuous damage affected the splenium, which would be expected to chronically impair almost exclusively the specific transcallosal transfer functions (Geschwind et al., 1962). It is tempting, therefore, to suggest that other lesions, in addition to CC damage, contributed to the clinical – metabolic picture in this case. Post-mortem studies in MBD occasionally show hemispheric white matter lesions and/or cortical neuronal loss (Castaigne et al., 1971); although these findings come from severe MBD cases going to autopsy, it is possible that such lesions were present in our case but, as reported recently (Nicoli et al., 1994), escaped detection by chronic-stage MRI (which showed only a mild and diffuse cortical atrophy which presumably antedated the episode, as suggested by the admission CT-Scan). However, chronic alcohol abuse *per se*, would not appear to have played a direct role, as previous PET studies have shown this does not result in brain metabolic alterations of either the severity or the distribution pattern seen in this patient (Samson et al., 1986; Volkow et al., 1992; Adams et al., 1993). Likewise, the metabolic pattern in our patient differed considerably from that reported in Korsakoff's syndrome, which is characterized by relative sparing of the neocortex with thalamic-limbic system hypometabolism (Heiss et al., 1992); furthermore, neither the MRI findings nor the cognitive impairment profile were suggestive of Korsakoff's syndrome in our case.

*In conclusion*, in this patient with MBD and with MRI evidence of lesions limited to the CC (apart from associated mild diffuse cortical atrophy), the dementia was subserved by a striking brain hypometabolism preferentially affecting the association cortex. The extent to which the CC damage and the potentially associated white matter and/or neocortical lesions each contribute to these major clinical-metabolic alterations remain uncertain. Further experimental studies combining callosal and extra-callosal lesions might shed light on this issue.

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Received April 25, 1994