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Marchiafava-Bignami Disease

A Correlative Computed Tomography and Morphological Study

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Summary. The subacute development of Marchiafava-Bignami disease (MBD) is reported in a 60-year-old patient from Southern Germany with a history of chronic alcoholism and severe malnutrition. Computed tomography scans showed progressive white matter destruction over a period of 8 months, ranging from diffuse hypodensities to well-delineated, strongly hypodense areas in the central hemispheric white matter of both frontal and parietal lobes and in the corpus callosum. Autopsy revealed an identical pattern of demyelinated, partially necrotic lesions in addition to small cystic necroses in the genu corporis callosi. The temporal evolution of MBD, criteria for early diagnosis and pathogenetic aspects are discussed.

Key words: Marchiafava Bignami disease – Demyelination – Corpus callosum – Computed tomography – Alcoholism

Introduction

Chronic alcoholism is the most prevalent form of self-induced intoxication and is associated with numerous medical and socio-economical problems. The nervous system can be involved by a great variety of syndromes which are either a direct consequence of ethanol toxicity (e.g. polyneuropathy) or are secondary to vitamin deficiency, for example Wernicke's encephalopathy which is known to develop in alcoholic and non-alcoholic patients with thiamine deficiency (for review, see Nakada and Knight 1984). Despite the increasing incidence of chronic alcoholism in most countries, Marchiafava-Bignami disease (MBD) remains a very rare complication. Interest in this disease has lately been intensified due to progress in neuroradiological imaging techniques which now allow clinical diagnosis in the early stages of the disease (Bracard et al. 1986). The first patient with MBD in Germany was reported by Walter in 1978. An additional two cases were reported by Dilmac and Klein (1981). In this paper we describe the case of a patient from Southern Germany in whom the progression of the disease was clinically assessed by computed tomography (CT) scans and verified by postmortem studies.

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Materials and Methods

Brain slices were fixed in 10% formalin and embedded in paraffin. The tissue was examined using H & E, luxol-Nissl (Klüver-Barrera) and Bodian silver impregnation. Expression of glial fibrillary acidic protein was assessed using the immunoperoxidase technique (Sternberger 1979) with rabbit antiserum from Dakopatts (dilution, 1:200) and swine anti-rabbit immunoglobulins (1:50) as secondary antibody.

Case Report

The patient was a 60-year-old German male with a 20-year history of heavy drinking. He had been working as a civil servant but was dismissed because of severe alcoholism 15 years before he died. He had generally consumed large amounts of brandy but more latterly had also drunk Italian red wine from the Southern Tirol and the Chianti region. In 1982 he was operated upon for a perforated duodenal ulcer. During the last 3 years

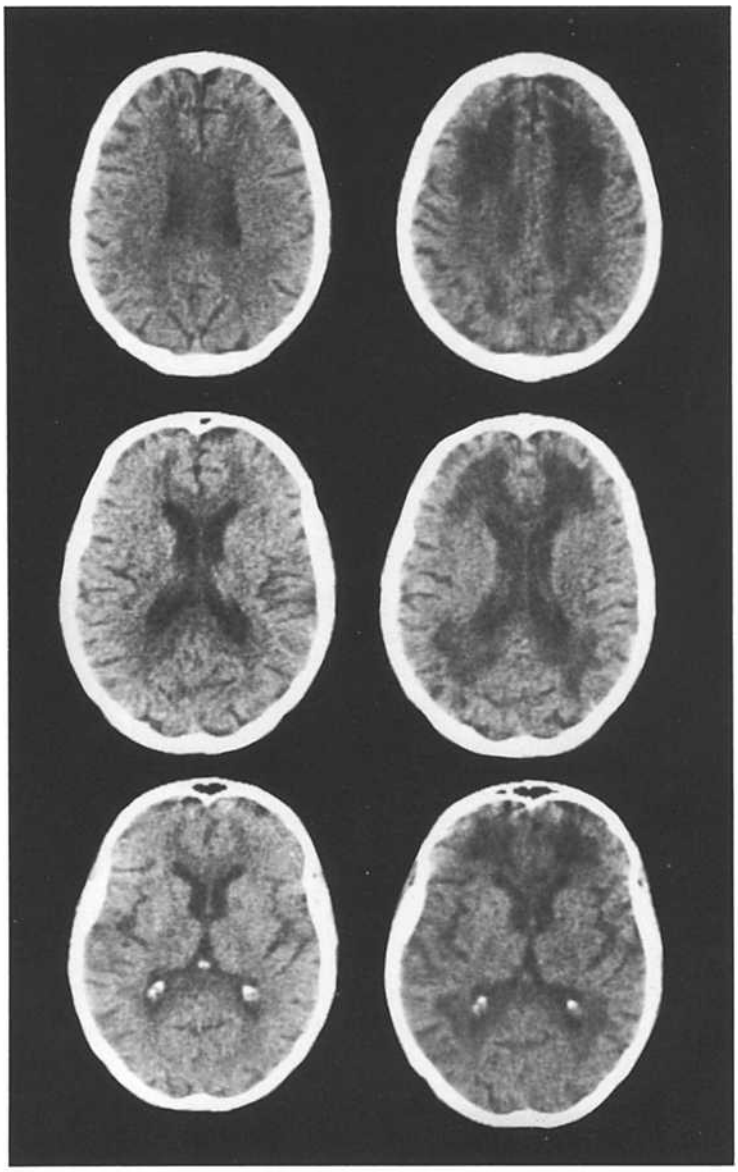

Fig. 1. The first series of computed tomography scans (September 1985) is shown on the *left*. Note the moderate ill-defined hypodensities in the central hemispheric white matter. The corpus callosum is also involved and shows two small cysts in its central portion *(middle)*. The second series *(right)* is from April 1986. The hypodense areas in the hemispheric white matter are now larger, more pronounced and well-defined. A cystic cavity is detectable in the centre of the callosal lesion

of his life he was extremely malnourished. On several occasions he was found in an unconscious state and admitted to hospital. In September 1985 he was treated as an out-patient for alcoholic neuropathy. At this time he presented with a psycho-organic syndrome, unsteady gait and tremor. CT scans revealed symmetrical ill defined hypodensities in the central hemispheric white matter (Fig. 1, left) and small cysts in the central portion of the corpus callosum (Fig. 1, middle left). In April 1986 the patient was found unconscious at home. On admission he was cachectic, dehydrated, unrousable and unresponsive to painful stimuli. His pupils were equal and reacted normally. Neurological examination revealed a flaccid tetraplegia. CT scans showed a moderate cerebral atrophy and well-defined hypodense areas of demyelination in the hemispheric white matter and in the corpus callosum (Fig. 1, right). Radiography showed a patchy bronchopneumonia. *Staphylococcus aureus* and *Escherichia coli* were isolated from the sputum. He was unsuccessfully treated with antibiotics for 2 weeks. The patient did not regain consciousness and died in May 1986.

Postmortem findings. Autopsy revealed a confluent alveobronchiolitis with incipient intraalveolar fibrosis and a fibrous pleurisy with a hydrothorax. There was advanced micronodular cirrhosis of the liver and moderate splenomegaly due to portal congestion. The heart was dilated and there was a pericardial effusion. In addition, the patient had moderate coronary arteriosclerosis and complicated aortic atheroma. In the duodenum there was a chronic ulcer, previously perforated and oversewn. The right kidney showed a double pelvis with a double ureter. There was chronic cystitis and a thrombosis of the prostate venous plexus.

The brain weighed 1,286 g. Gross examination revealed moderate cortical atrophy and slight fibrosis of the leptomeninges. Horizontal sections through the brain showed symmetrical well-demarcated greyish areas of demyelination in

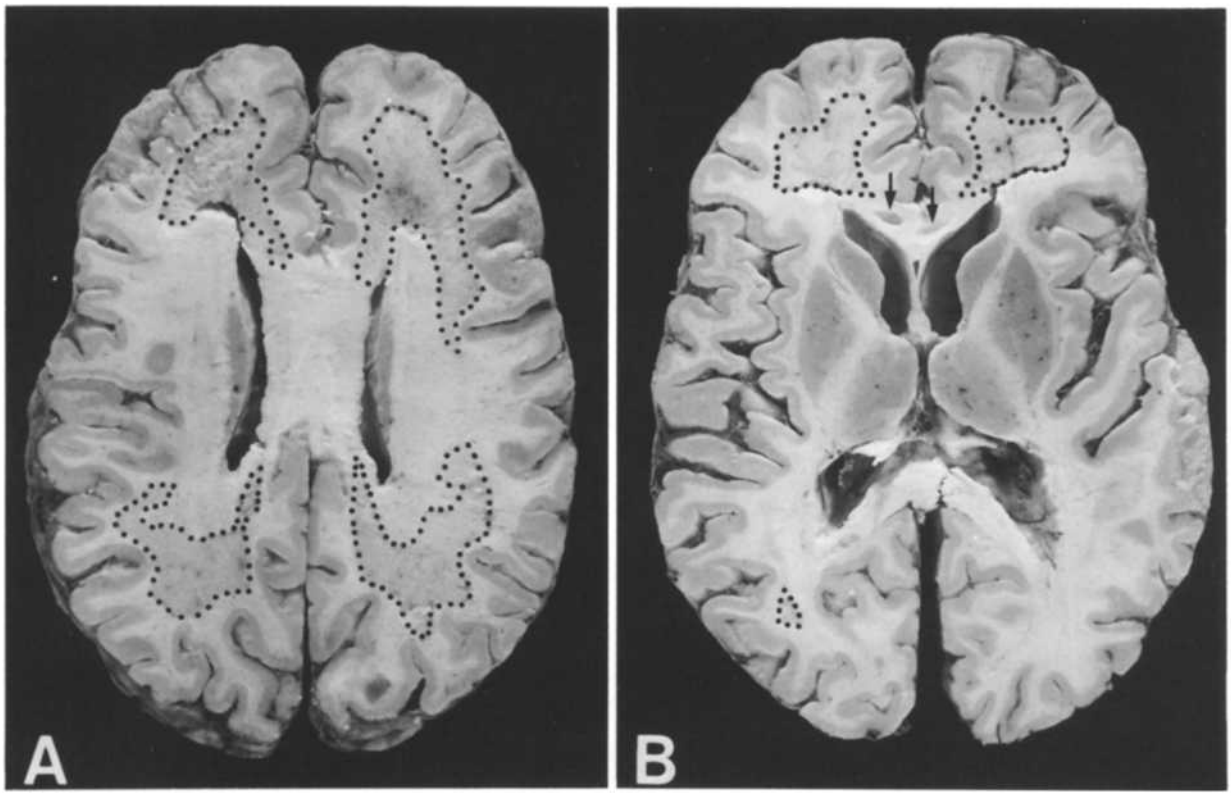

Fig. 2A, B. Horizontal sections through the cerebral hemispheres at the level of the truncus corporis callosi **(A)** and the basal ganglia **(B)**. The white matter shows extensive, symmetrical greyish areas of demyelination *(encircled by dots)*. The subcortical U-fibres are spared. The central portion of the genu corporis callosi **(B)** shows two small cysts *(arrows)*

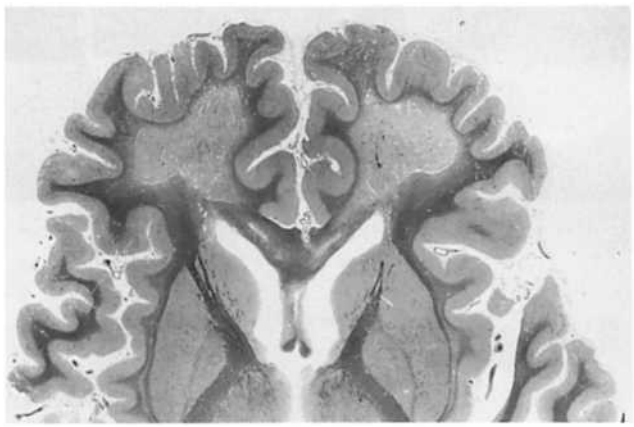

Fig. 3. Horizontal section through the frontal lobes. The well-defined demyelinated areas in the frontal white matter and the cavities in the corpus callosum are surrounded by areas of diffuse myelin pallor. Subcortical U-fibres and the internal capsule are not affected. H & E and Klüver-Barrera stain

the frontal and occipital hemispheric white matter (Fig. 2A, B). The subcortical U-fibres were spared. The most striking features were bilateral cystic cavities in the central portion of the rostral corpus callosum (Fig. 2B, 3). In the right temporal lobe an old contusion was found. The mamillary bodies were inconspicious. No pathological changes were found in the cerebellum and brainstem.

Histopathologically, the central portion of the corpus callosum showed demyelination, reactive gliosis and well-defined cystic necroses (Fig. 3) with numerous macrophages. In the frontal and occipital hemispheric white matter there were extensive, sharply demarcated areas of demyelination (Fig. 3, 4A). In the centre of these lesions there was almost complete loss of myelin and oligodendrocytes and a relative reduction in the number of astrocytes. The capillaries showed moderate proliferation and there were numerous macrophages, particularly in the periphery of the lesion (Fig. 4A). Axons were relatively spared even in the centre of the demyelinated areas (Fig. 4B). The foci of demyelination were surrounded by a wall of glial fibrillary acidic protein positive reactive astrocytes (Fig. 4A). Subcortical U-fibres and compact myelinated fibre tracts other than the corpus callosum, the anterior and posterior commissure (i.e. capsula interna, pedunculi cerebri) were not affected (Fig. 3). The frontal cortex showed occasional clusters of eosinophilic neurons, particularly in the third and fifth cortical layer. The optic tracts showed small foci of demyelination with some fat-laden macrophages.

Discussion

This case shows the typical clinical and morphological hallmarks of MBD. Following heavy exposure to

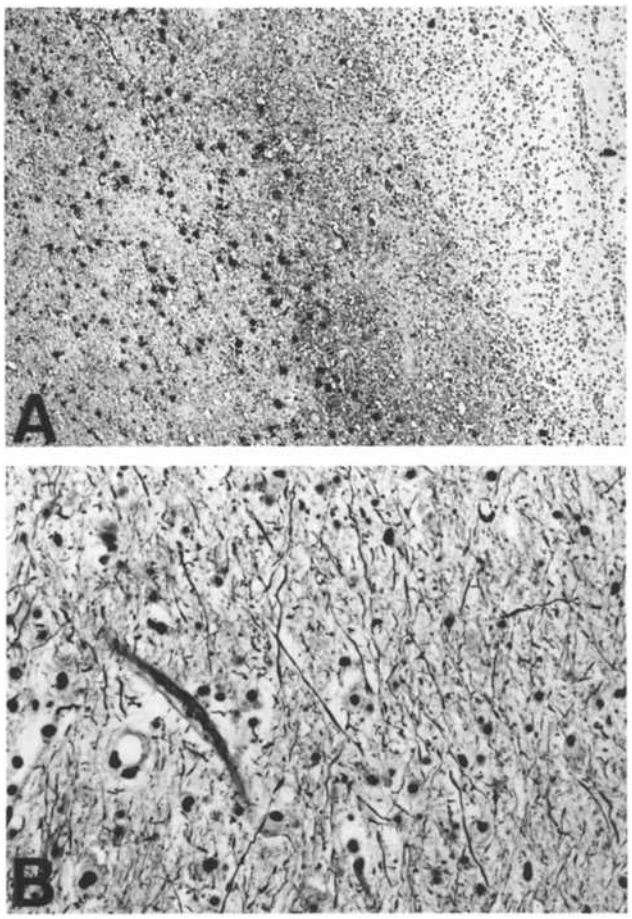

Fig. 4A, B. Periphery of a lesion in the frontal white matter (**A,** *right*) with numerous macrophages. The adjacent white matter *(left)* shows a wall of reactive astrocytes expressing GFAP (immunoperoxidase stain for glial fibrillary acidic protein, × 32). Bodian silver stain **(B)** reveals that most axons within the demyelinated area are well-preserved (× 200)

ethanol over a period of more than 20 years, the patient became malnourished and eventually developed a leucoencephalopathy which in CT scans presented as bilateral symmetrical hypodense areas in the hemispheric white matter and the corpus callosum. Eight months before his death they were still ill-defined (Fig. 1, left) but 6 months later these areas were more prominent, had enlarged, and were well-delineated. The central portion of the corpus callosum (Fig. 1, right) was again included in the demyelinating process. Clinically, this was paralleled by a severe psycho-organic syndrome. Due to his poor compliance, no detailed neurological examination was carried out until shortly before his death when he was admitted in a comatose state from which he was unrousable. Subacute development over several months appears to be the most frequent form of MBD (Brion 1976). The neurological deficit varies considerably and must be regarded as largely unspecific. However, CT scans reliably reveal typical symmetrical hypodense areas in the hemispheric white matter. Although these may be present in a variety of neurological diseases (including leucodystrophies, Binswanger's progressive subcortical encephalopathy, progressive multifocal leukoencephalopathy, AIDS encephalopathy, heroin intoxication), their association with similar lesions in the central portions of the corpus callosum must be regarded as being diagnostic for MBD (Bourrat et al. 1984). Recent clinical studies by Kawamura et al. (1985), Bracard et al. (1986), and Clavier et al. (1986) indicate that nuclear magnetic resonance imaging is superior to X-ray CT in early diagnosis of the disease. The pathological correlate to these findings are well-defined foci of demyelination in the central layer of the corpus callosum and the anterior commissure with an almost complete loss of myelin and oligodendrocytes, whereas axons are relatively well preserved.

No specific therapy exists and this is largely due to our ignorance concerning the aetiology of MBD. Early studies of the pathogenesis of this disease concentrated on vascular factors. Seitelberger and Berner (1955) observed a distinct vascular proliferation and postulated a primary lesion of the blood-brain barrier leading to oedema and demyelination. Brion (1976) disagreed and said that the vascular proliferation "seems purely reactive and not more than would be seen in a necrotic area". Based on our findings in the present case, we would agree with this view. However, it must be conceded that demyelination with preservation of axons as present in MBD is a typical feature of vasogenic oedema damage. Feigin and Budzilovich (1980) discussed the pathogenesis of focal, well-defined oedema of the white matter in relation to the distribution of the extracellular ground substance. The latter consists of mucopolysaccharides composed of long chains of polyanionic glycosaminoglycans. These macromolecules occupy a vast molecular space, their domain, in which they bind anions and restrict the flow of water. These authors found that the distribution of interstitial mucopolysaccharides correlated with water content, the highest amounts being present in cerebral cortex, followed by subcortical U-fibres and central white matter. As the tendency of cerebral tissues to become oedematous is assumed to be inversely related to their normal water content (Adachi and Feigin 1966), a regionally specific vulnerability could explain the pattern of well-defined oedematous lesions in the central white matter. Although this hypothesis may explain the pathogenesis of the lesions, it does not clarify the primary cause of demyelination in MBD.

A pattern of lesions strikingly similar to MBD has been observed in experimental cyanide encephalopa-

thy. In rats, chronic subcutaneous administration of potassium cyanide (Lumsden 1950; Smith et al. 1963; Hirner 1969) or acute cyanate poisoning by inhalation (Levine and Stypulkowsky 1959) causes symmetrical necroses or spongiform lesions in the centre of the corpus callosum, in the central portion of the hemispheric white matter, the anterior and posterior commissures and the optic nerves. Lesions induced by exposure to sublethal doses also include the neocortex, striatum, hippocampus, cerebellum, substantia nigra and diencephalon (Levine and Stypulkowsky 1959). Lumsden (1950) in his experiments described a primary swelling and nuclear pyknosis of oligodendrocytes which later on were notably reduced in number. Hirner (1969) found a swelling of the inner and outer oligodendrocytic covering of the myelin sheaths, indicating that demyelination could be a secondary phenomenon following damage to oligodendrocytes. Most authors agree that inhibition of cytochrome oxidase is involved in the mechanism of cyanide poisoning since the cyanide ion transiently binds to the iron of the iron-porphyrin prosthetic group of cytochrome oxidase. The higher vulnerability of the white matter may be explained by its 3–5 times lower content of cytochrome oxidase, compared with that of the cerebral cortex (Darriet et al. 1986). Since regional differences in the distribution of cytochrome oxidase activity corresponding to the pattern of white matter lesions are not known, the vascular anatomy may play an additional role (Levine 1967; Funata et al. 1984).

Since cyanide administration lowers hepatic vitamin B_{12} activity, it has been suggested that "a disorder of cyanide metabolism may be implicated in those diseases in which demyelination occurs within a picture of vitamin B_{12} deficiency" (Smith et al. 1963). It has, therefore, been proposed (Brion 1976) that cyanide metabolism may play a role in the pathogenesis of MBD. Severe chronic alcoholism might interfere with vitamin B_{12} metabolism thus enhancing vulnerability to cyanide. A nutritional factor in the pathogenesis of MBD would be compatible with the fact that many patients have been reported to be severely malnourished. Most of the early reports on MBD concerned male Italians drinking Italian red wine.A racial predisposition or a toxic ingredient of Italian red wine were, therefore, for many years considered to be important aetiological factors. In the early fifties, however, the disease was observed in non-Italians who drank other alcoholic beverages (McLardy 1951). Moreover, MBD has been reported in severely malnourished patients not exposed to ethanol (Leong 1979; Kosaka et al. 1984). There is, however, no significant coincidence between MBD and funicular myelosis (subacute combined degeneration), a characteristic neurological manifestation of vitamin B_{12} deficiency. Although the precise aetiology of MBD remains obscure, combined severe chronic alcoholism and malnutrition appear to be the most consistent extrinsic factors.

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