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REVIEW

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Clinicoradiologic subtypes of Marchiafava-Bignami disease

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Abstract The clinical diagnosis of Marchiafava-Bignami disease (MBD) has considerably changed during recent decades with brain MRI providing the opportunity of a reliable in-vivo diagnosis. However, semiologic and neuroimaging characteristics of the currently known spectrum of MBD have not been investigated systematically, and knowledge of clinicoradiologic associations is sketchy. We report an illustrative case with limited callosal involvement on MRI and a favorable outcome and have reviewed literature on clinical and radiologic features in 50 cases of MBD diagnosed in vivo since 1985. Our reviewed data suggest the differentiation of two clinicoradiologic subtypes: Type A is characterized by major impairment of consciousness, T2-hyperintense swelling of the entire corpus callosum on early MRI and poor outcome. Type B shows at most slight impairment of consciousness, partial callosal lesions on MRI and a favorable outcome. Differentiation of these clinicoradiologic subtypes may help resolve inconsistencies of the established clinical classification resulting from new insights into the clinical course and prognosis of MBD by structural neuroimaging.

Key words Marchiafava-Bignami disease · classification · subtypes

Introduction

Marchiafava-Bignami disease (MBD) is a rare alcohol-associated disorder characterized by demyelination and necrosis of the corpus callosum [6, 9]. Clinical features include neuropsychiatric disorders, dysarthria, tetraparesis, astasia-abasia, impaired consciousness and symptoms of interhemispheric disconnection. Whereas the diagnosis previously could only be ascertained by autopsy, today computed tomography (CT) and particularly magnetic resonance imaging (MRI) provide the opportunity of a reliable in vivo diagnosis. Derived from observations of varying courses of clinical progression in the pre-imaging era, a classification established by Brion in 1977 [6] categorizing the disease into acute, subacute and chronic forms is still widely used today [33]. Although underlying notions of the clinical course and prognosis of MBD have increasingly been questioned by the results of cases diagnosed in vivo, semiologic and neuroimaging characteristics of the currently known clinical spectrum of MBD have not yet been investigated systematically. Encouraged by the findings and the course of a patient suffering MBD, which we found illustrative of limited corpus callosum involvement on MRI, rapid reversibility of neuroimaging abnormalities and favorable outcome, we reviewed literature on cases of MBD diagnosed in vivo in order to summarize clinical and neuroimaging characteristics.

JON 1566

Case report

A 51-year-old, malnourished, chronic alcoholic woman with a history of polyneuropathy and curatively treated breast cancer was referred to our hospital for rapid onset of mental confusion and dysarthria, deterioration of standing and walking, and a generalized tonic-clonic seizure. On admission, she was alert but confused, disoriented, and showed marked memory impairment. Oculomotor and cranial nerve functions were normal, speech was severely dysarthric. There was a slight tetraparesis accentuated proximally and on the lower limbs. Tendon reflexes were normal on the upper limbs and weak on the lower limbs, ankle jerks were absent. Plantar responses were flexor. There was distal symmetric sensory loss of the legs. Truncal and limb ataxia was noted, standing and walking was impossible. Neuropsychological examination 1 week after admission revealed psychomotor and cognitive slowing but no signs of interhemispheric disconnection.

Laboratory testing showed macrocytic anemia, elevated γ-GT and slightly diminished serum vitamin B_1 and B_6 levels. CSF studies were normal. Electrophysiological examination was consistent with moderate axonal neuropathy. Fluid-attenuated inversion-recovery (FLAIR) and T2-weighted cerebral MRI performed two days after symptom onset showed a hyperintense lesion affecting the central layers of the splenium of the corpus callosum which was not visualized on T1-weighted images and showed no contrast enhancement (Fig. 1a–d). Steady clinical recovery was noted on treatment with vitamins B_1 and B_6. MRI on day 9 (Fig. 1e–f) showed greatly diminished signal abnormality. After 6 weeks of rehabilitation, a slight distal and symmetric sensorimotor deficit of the lower extremities attributable to polyneuropathy was the only neurological abnormality.

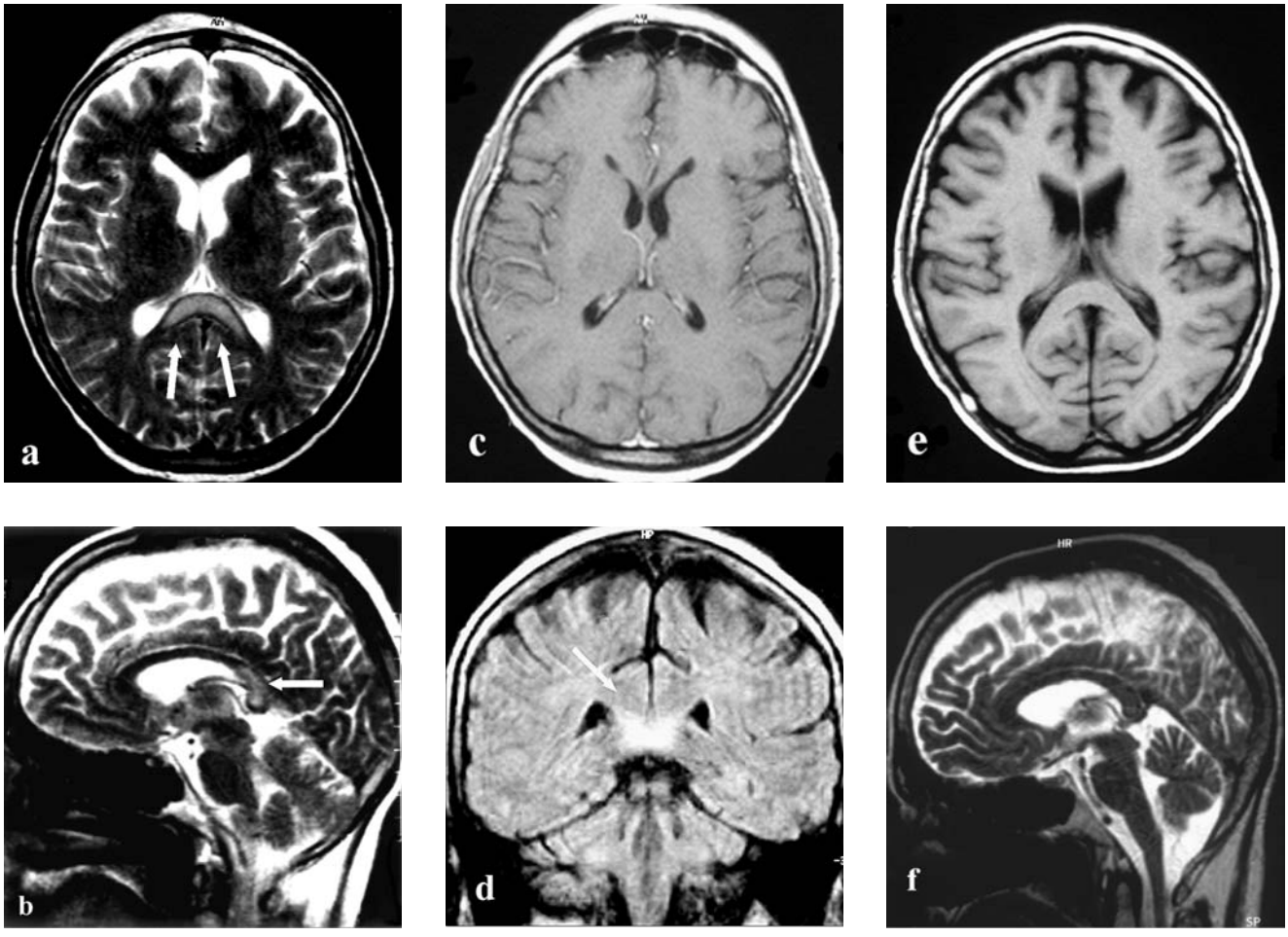

Fig. 1 MRI findings two days after symptom-onset (**a, b, c, d**) and 1 week later (**e, f**). (**a**) axial and (**b**) sagittal T2-weighted images (TR = 3760ms/TE = 120ms) and (**d**) coronal FLAIR images (TR = 6700ms/TE = 105ms) showing a hyperintense lesion in the splenium of the corpus callosum, (**c**) axial T1-weighted images (TR = 627ms/TE = 17ms) showing no contrast enhancement. (**e**) Axial T1-weighted images (TR = 570ms/TE = 14ms) one week later without detectable lesion. (**f**) Resolved lesion on sagittal T2-weighted images (TR = 5244ms/TE = 128ms)

Methods

We searched the literature database "Medline" for cases of MBD diagnosed in vivo utilizing CT and MRI from 1985 until October 2003. All abstracts were sighted, all publications in English, French or German language were retrieved as full original articles and included for review. Age, sex, clinical signs and symptoms in the prodromal, acute to subacute, and chronic stage were extracted. Cognitive impairment was registered when deficits in one or several of the following domains were reported: attention, orientation, memory, spatial ability, language and executive ability. Signs of interhemispheric disconnection were recorded separately. Neurological outcome was determined using the Modified Oxford Handicap Scale (MOHS) [2]. Patients were then classified into two groups corresponding to "minor disability" (MOHS ≤ 2) and to "major disability" (MOHS ≥ 3). Patterns of callosal and extracallosal lesions were analysed based on the results of CT and T2-weighted MRI performed on day 0–13 after symptom onset and T1-weighted MRI performed ≥ 14 days after symptom onset. In cases presenting with coma or stupor, onset of impairment of consciousness was defined as symptom onset. We compared clinical and neuroimaging features of a subgroup presenting with sopor or coma in the acute stage with a subgroup with no or minor impairment of level of consciousness. Fisher's exact test and the Wilxocon two-sample test were used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

Results

53 cases were identified in 44 publications [1, 3–5, 7, 8, 10–40, 42–44, 46–49]. Three publications [17, 22, 40] containing one case each were excluded from analysis for one of the following reasons: insufficient clinical data [22], highly uncertain diagnosis [17] or unavailability of the full manuscript [40]. 50 cases, identified in 41 publications, 38 males and 12 females (m:f = 3.2:1), mean age 46.6 years, (range 26–66, median 45) were included for further analysis.

Of these 50 cases reviewed in detail, 48 patients were examined in the acute or subacute stage of their disorder, while two patients [27, 33] were only reported as in their residual neuropsychiatric status. Demographic, clinical and radiologic data of all patients are presented in Table 1 and are summarized for the 48 patients excluding the two chronic cases in Table 2.

Clinicoradiological features in cases presenting with major impairment of consciousness

Coma or stupor of acute to subacute onset was the predominant clinical finding in 19 cases (14 men, 5 women, mean age 48.5 years, range 26–66, median 48). In ten of these nineteen patients, a prodromal stage with cognitive impairment (10/10) and gait disturbance (7/10) preceded the onset of coma by several days to several weeks (median: 2 weeks). Coma was often accompanied by pyramidal tract symptoms and limb hypertonia. Other symptoms recorded before onset or after recovery from coma included seizures, gait disturbance, signs of interhemispheric disconnection, dysarthria and cognitive deficits (Table 2). Fifteen patients regained consciousness, the majority (13/15) within one week, whereas further deterioration with a lethal course was reported in four patients (21 %) after a mean period of 15 days after admission (range 5–27 days, median 14.5 d). Residual symptoms in the chronic stage were reported in fourteen of fifteen non-fatal cases. Cognitive impairment, dysarthria and disconnection syndromes were predominantly noted, while patients tended to recover from pyramidal tract symptoms and gait disturbance (Table 3).

Sufficient information to estimate clinical outcome according to the MOHS was given in sixteen of nineteen cases. The mean value determined after a median of three months was 3.9 (range 0–6, median 4), a favorable outcome (defined as MOHS ≤ 2) was determined in only three of sixteen cases (19 %).

Early CT-findings were reported in fifteen cases. Hypodense areas were detected in the corpus callosum in twelve patients (80 %), affecting the splenium and the genu in eleven cases. Compared to MRI, which was additionally performed in thirteen patients, callosal abnormalities were found on early CT in ten cases (77 %).

Early T2-weighted MRI-findings obtained on average 2.7 days after onset of stupor or coma (range 0–10 days, median 1, not specified in 1 case) were reported in eight cases, including sagittal planes in five cases. Hyperintense signal abnormality of the entire corpus callosum with a variable degree of swelling was reported in all of these patients. In three cases lacking results of sagittal MRI in the original manuscript, involvement of the entire corpus callosum was confirmed by autopsy [35] or sagittal [10] or coronal [21] imaging results provided to the authors of this article following direct communication. Focal areas of T2-shortening indicating callosal hemorrhage were found in 2 patients [11, 31].

T1-weighted MRI in the subacute to chronic stage was performed in twelve of fifteen non-fatal cases after a median of 49 days (range 15–150 days, not specified in 2 cases). T1-hypointense cystic-necrotic lesions in the corpus callosum were found in eleven cases. In eight cases, they affected all parts of the corpus callosum, in two other cases, lesions were confined to the genu and body of the corpus callosum and in one case to the splenium. In one patient, no cystic lesions were found.

Fourteen cases were assessable for callosal atrophy by T1- or T2-weighted MRI performed in the chronic stage, which was found in eleven patients (79 %). Extracallosal lesions were reported in nine of nineteen cases (47 %), involving predominantly the periventricular white matter (8 patients) or the basal ganglia (1 patient). In two patients, T2-hyperintense extracallosal lesions re-assumed their normal signal intensity.

Table 1 Demographic, clinical and neuroradiologic features in 50 reviewed cases of MBD

author/year [Ref]	age (years)	sex	imaging mode	day after onset	extent of lesions					clinical signs/symptoms								outcome MOHS
					genu	body	splenium	extracall lesions	callosal atrophy*	Prodromal stage	Gait disorder	Dysarthis	Hypertonia	Pyramidal signs	Seizures	Disconnection	Cogn deficits	
Type A; n = 19																		
Kawamura 1985 [32] & Shiota 1996 [44]	35	m	CT	3	+	x	–	–	x	–	–	+	–	+	–	+	+	3
			MRI (T1)	89	+	+	+	–	+									
Bracard 1986 [5]	39	m	CT	2	+	x	+	–	x	+	+	+	+	–	–	–	+	x
			MRI (T1)	150	+	+	+	–	+									
Bracard 1986 [5]	56	m	CT	3	+	x	+	+	x	–	–	–	+	+	–	–	+	6
Bracard 1986 [5]	44	m	CT	1; 23	+	x	+	+	x	–	+	+	+	+	+	–	+	4
Mayer 1987 [36]	50	m	CT	0	+	x	+	–	x	–	–	–	+	+	–	+	+	3
MRI (T1)				58	+	–	–	–	+									
Baron 1989 [3]	48	f	CT	0	–	–	+	–	x	+	+	–	+	+	–	–	+	3
			MRI (T1, T2)	44	–	–	+/+	–	–									
Ikeda 1989 [26]	62	m	CT	1	–	x	–	–	x	+	+	–	+	–	–	+	+	6
			CT	3	–	x	+	–	x									
			CT	11	+	x	+	–	x									
			MRI (T2)	10	+	(+)	+	–	x									
Rosa 1991 [42]	54	m	CT	0	+	x	+	–	x	–	+	–	+	–	–	+	+	2
			MRI (T1)	15	+	+	+	+	–									
Chang 1992 [11]	56	m	MRI (T1,T2)	0	+/+	+/+	+/+	–	x	+	+	+	–	–	+	–	+	x
			MRI (T1,T2)	54	+/+	+/+	+/+	–	+									
Marjama 1994 [35]	34	m	CT	0	–	x	–	–	x	+	+	–	+	+	–	–	+	6
			MRI (T2)	4; 25	+	<+>	+	+	x									
Kamaki 1996 [31] & Kamaki 1993 [30]	43	f	CT	0; 29	+	x	+	–	x	+	–	+	+	+	–	+	+	3
			MRI (T1,T2)	34	+/+	+/+	+/+	–	+									
Logak 1996 [34]	26	f	CT	0	–	x	+	–	x	+	+	+	+	+	–	–	+	5
			MRI (T2)	xa	+	+	+	+	x									
			MRI (T1)	xc	+	+	+	–	+									
Yamashita 1997 [49]	64	m	MRI (T1, T2)	4	+/+	+/+	+/+	–	x	–	–	+	–	–	–	–	+	0
			MRI (T1, T2)	64	–/–	–/+	–/–	–	–									
Diraison 1999 [15]	39	m	CT	0	–	–	–	–	x	+	+	–	+	+	–	+	+	2
			CT	xc	–	x	+	+	x									
			MRI (T2)	30	–	x	+	–	+									
Diraison 1999 [15]	43	m	CT	1	+	x	+	–	x	–	–	+	–	–	–	+	+	x
			MRI (T1)	xc	+	+	+	–	+									
Gabriel 1999 [18]	49	m	CT	xa	+	x	+	+	x	–	–	+	–	+	–	–	+	4
			MRI (T1,T2)	35	+/+	+/+	+/+	+	+									
Celik 2002 [10]	48	f	CT	0	–	x	–	–	x	+	–	–	+	+	+	–	+	6
			MRI (T2)	10	<+>	<+>	+	–	x									
Hayashi 2002 [23]	65	m	MRI (T1,T2)	0	+/+	+/+	+/+	+	x	+	+	+	+	+	–	+	+	4
			MRI (T1,T2)	15	+/+	+/+	–/–	(+)	+									
Gerlach 2003 [21]	66	f	MRI (T2)	0; 40	+	<+>	+	+	+	–	–	–	+	+	–	–	+	5
Type B; n = 29																		
Delangre 1986 [14] & Clavier 1986 [12]	35	f	CT	0	+	x	+	–	x		+	–	+	–	–	+	+	0
			MRI (T1)	180	+	–	+	–	–									
Mayer 1987 [36]	54	m	CT	3	+	x	–	–	x		–	–	–	–	+	+	+	2
			MRI (T1)	14	+	+	–	–	–									
Meyrignac 1987 [37]	45	f	CT	xa	+	x	–	–	x		+	–	+	–	–	+	+	1
			MRI (T1)	33	+	+	–	–	–									
Canaple 1992 [7]	37	m	CT	xa	+	x	–	–	x		+	–	–	–	–	+	+	1
			MRI (T2)	15	+	x	+	–	x									
Canaple 1992 [7]	50	m	CT,MRI(T2)	xa, 21	+	x	+	–	x		+	+	+	–	–	+	+	1
Humbert 1992 [25]	43	m	CT	4	+	x	+	–	x		+	–	+	–	–	+	+	3
			MRI (T1)	50	+	–	–	–	–									
Izquierdo 1992 [28]	33	m	CT	xa	+	–	–	–	x		+	+	–	–	–	–	+	2
			MRI (T1,T2)	xc	+/+	–	–/+	–	–									
Izquierdo 1992 [28]	59	m	CT	xa	–	–	–	–	x		+	–	–	–	–	+	+	2
			MRI (T1,T2)	xc	–/–	+/+	+/+	+	x									

Table 1 *Continued*

author/year [Ref]	age (years)	sex	imaging mode	day after onset	extent of lesions					clinical signs/symptoms								outcome MOHS
					genu	body	splenium	extracall lesions	callosal atrophy*	Prodromal stage	Gait disorder	Dysarthis	Hypertonia	Pyramidal signs	Seizures	Disconnection	Cogn deficits	
Chang 1992 [11]	45	m	MRI (T2)	6	+	+	+	–	x		+	+	–	–	–	+	+	1
			MRI (T2)	13	+	–	+	–	x									
			MRI (T1,T2)	80	–/–	–/–	+/+	–	+									
Berek 1994 [4]	45	m	CT	90	–	–	–	–	x		+	–	+	–	–	+	+	3
			MRI (T1,T2)	120	+/+	–	+/+	–	–									
Nicoli 1994 [39]	43	m	CT	0	–	x	+	+	x		+	–	–	–	–	+	+	2
			MRI (T2)	8	–	+	+	+	x									
			MRI (T2)	32	–	x	–	–	x									
Caparros-Lefebvre 1994 [8]	53	m	CT	1; 8	+	x	+	–	x		–	–	–	–	+	+	+	2
			MRI (T1,T2)	9; 21	+/+	–	+/+	–	–									
			MRI (T1,T2)	300	+/+	–	+/+	–	–									
Caparros-L. 1994 [8]	35	m	CTc	2	–	x	+	–	x		–	–	–	–	+	+	+	1
			MRI (T1)	23; 240	+	–	+	–	–									
Kalkreuth 1994 [29]	40	m	CT	85	+	x	x	–	x		+	+	+	–	+	+	+	3
			MRI (T1)	96	+	+	+	–	+									
Dano 1996 [13]	45	m	CT	xa	+	–	+	–	x		–	–	–	–	–	+	+	0
			MRI (T1, T2)	20	–/–	–/–	+/+	–	–									
Dano 1996 [13] & Tomasini 1993 [47]	54	m	CT	xa	+	x	+	–	x		+	+	+	–	+	+	+	2
			MRI (T1)	xc	+	+	+	–	+									
Moreaud 1996 [38]	45	m	CT	xa	–	–	–	–	x		+	+	+	–	–	–	+	3
			MRI (T1)	xc	+	–	+	–	–									
Tobita 1997 [46]	44	f	CT	7	–	–	+	–	x									
			MRI (T2)	7	–	+	+	+	x		+	+	+	–	+	–	+	0
			MRI (T2)	28	–	–	(+)	–	–									
Gass 1998 [20]	43	m	CT,MRI (T2)	0	+	–	+	–	x		+	–	+	–	–	+	+	2
			MRI (T2)	210	–	–	–	–	–									
Ferraci 1999 [16]	42	f	CT	10	–	–	–	+	x		+	+	–	–	–	+	+	x
			MRI (T1,T2)	xc	+/+	+/+	–	+	x									
Diraison 1999 [15]	43	f	CT	2	–	–	+	–	x		–	+	–	–	–	–	+	0
			MRI (T2)	6	–	–	+	–	x									
Gabriel 1999 [18]	39	m	MRI (T2)	2	–	+	+	–	x		+	+	+	+	+	–	+	2
			MRI (T2)	18	–	(+)	(+)	–	x									
Ruiz-Martinez 1999 [43]	61	m	CT	xa	–	–	+	+	x		+	+	–	–	–	–	+	1
			MRI (T1,T2)	xa	+ /x	–/x	+ /x	–/+	x									
			MRI (T1,T2)	60	–/–	–/–	+ /x	–/–	–									
Yamamoto 2000 [49]	56	m	MRI (T1,T2)	1	–/+	x	+/+	–	x		–	+	–	+	–	–	+	2
			MRI (T1,T2)	50	–/+	x	+/+	–	+									
Alla 2000 [1]	36	f	CT	xa	–	–	+	–	x		+	+	+	+	–	+	+	1
			MRI (T2)	xa	–	–	+	–	x									
Alla 2000 [1]	42	m	MRI (T2)	xa	–	–	+	–	x		+	–	–	+	+	–	+	1
Helenius 2001 [24]	44	m	CT	xa	–	–	–	–	x		+	+	–	–	–	–	+	2
			MRI (T2)	19	–	–	+	–	–									
Helenius 2001 [24]	40	f	MRI (T2)	4	–	+	–	–	x		–	–	–	+	–	+	+	1
			MRI (T2)	10	–	+	–	–	x									
Gambini 2003 [19]	49	m	MRI (T1,T2)	30	+/+	+/+	+/+	–	–		+	–	–	+	–	–	+	1
			MRI (T2)	120	(+)	(+)	+	–	+									
			MRI (T2)	330	–	–	+	–	+									
chronic cases; n = 2																		
Ishii 1999 [27]	54	m	MRI (T1,T2)	xc	+/+	+/+	–/+	+	+		–	+	+	–	–	–	+	3
Kohler 2000 [33]	52	m	MRI (T1,T2)	xc	–/–	–/–	+/+	+	+		+	+	+	–	–	+	+	4

* Determined by sagittal MRI performed ≥ 14 days after symptom onset

+: indicates the presence of a radiologic feature or clinical sign; –: indicates the absence of a radiologic feature or clinical sign

(+) indicates weak or partial presence of a radiologic feature; x: not specified in the text body and figures of the original manuscript; <+>: confirmed by direct communication or autopsy; xa/xc: not specified, acute/chronic stage

MOHS Modified Oxford Handicap Scale

Table 2 Demographic, clinical and neuroradiologic features in 48 reviewed cases of acute and subacute MBD

	Type A[a, d] (n = 19)	Type B[b, d] (n = 29)	All (n = 48)[d]	*p* Value[c]
Age, years ± SD	48.5 ± 11.3	44.8 ± 7.3	46.3 + 9.2	0.25
Female	5 (26)	7 (24)	12 (25)	1.0
Cognitive impairment	19 (100)	29 (100)	48 (100)	1.0
Pyramidal tract symptoms	13 (68)	6 (21)	19 (40)	0.002
Limb hypertonia	14 (74)	12 (41)	26 (54)	0.04
Dysarthria	10 (53)	14 (48)	24 (50)	1.0
Disconnection syndromes	8 (42)	19 (66)	27 (56)	0.14
Gait disturbance	10 (53)	22 (76)	32 (66)	0.12
Seizures	3 (16)	8 (28)	11 (23)	0.49
Death	4 (21)	0 (0)	4 (8)	0.02
Outcome MOHS ≤ 2	3 (n = 16) (19)	24 (n = 28) (86)	27 (n = 44) (61)	< 0.001
Generalized T2-signalabnormality	8 (n = 8) (100)	1 (n = 10) (10)	9 (n = 18) (50)	< 0.001
Extracallosal lesions	9 (47)	5 (17)	14 (29)	0.049
Callosal atrophy	11 (n = 14) (79)	5 (n = 19) (26)	16 (n = 33) (48)	0.005

[a] Presenting with coma or stupor
[b] Lacking major impairment of consciousness
[c] For comparison between type A and type B; p-values < 0.05 were considered as statistically significant
[d] Values are number (%) of patients, except for the category 'age'

Table 3 Residual symptoms in non-fatal cases of type A and type B

	Type A (non-fatal, n = 14)	Type B (n = 29)
Cognitive impairment	11 (79)	18 (62)
Disconnection syndromes	7 (50)	14 (48)
Pyramidal tract symptoms	5 (36)	1 (3)
Limb hypertonia	3 (21)	1 (3)
Dysarthria	8 (57)	5 (17)
Gait disturbance	5 (36)	5 (17)

Values are number (%) of patients

Clinical and radiological features in cases with no or minor impairment of consciousness

Twenty-nine cases (22 men, 7 women, mean age 44.8 years; range 33–61, median 43.5) running an acute to subacute course lacked major impairment of consciousness. The level of consciousness was described as normal in 18, while somnolence was reported in 11 cases. Frequent other clinical findings were cognitive impairment, gait disturbance, astasia-abasia, dysarthria, signs of interhemispheric disconnection and limb hypertonia, whereas seizures and pyramidal tract symptoms were noted less frequently (Table 2).

Rigidity and pyramidal tract syndromes generally improved greatly and were rarely described in the chronic stage; gait disturbance and dysarthria also resolved in a substantial proportion of patients, whereas disconnection syndromes and cognitive impairment were the most common residual findings (Table 3).

Outcome determined according to the Modified Oxford Handicap Scale in 28/29 patients was 1.5 on average (range 0–3, median 1.5) after a median period of 3 months. Outcome was favorable (MOHS ≤ 2) in 24/28 patients. There was no fatality.

CT in the early stage was reported in 21/29 cases of this group, showing normal findings in four, an isolated hypodense area either in the genu or splenium in ten cases, and hypodense lesions in both parts of the corpus callosum in seven cases.

Compared with MRI, which was performed in all 21 patients, callosal lesions were detected on early CT in 81 %.

Early T2-weighted MRI obtained after a mean period of 4.2 days (range 0–8, median 5, not specified in 2 cases) was provided in ten patients, including sagittal scans in six patients. Hyperintense swelling of the entire corpus callosum was reported in one patient, while the remaining patients had lesions of focal character affecting the splenium in three cases. The splenium and genu were involved in two cases. In a further three, lesions affected part of the body and the splenium. In one case, the lesion was confined to the body of the corpus callosum. Focal T2-shortening suggesting petechial callosal hemorrhage was seen in one patient [48].

T1-weighted MRI in the subacute to chronic stage was performed in 20 cases after a median of 60 days (range 14–300, not specified in 5), including sagittal scans in 18 cases. Most frequently reported patterns

were combined lesions in the splenium and genu, and isolated lesions in the splenium. Three patients had lesions throughout the entire corpus callosum, no lesions were detected in two patients.

Atrophy of the corpus callosum was evaluated in 19 cases by MRI performed in the chronic stage and was seen in 5 (26%).

Extracallosal lesions affecting the periventricular white matter were detected in five of 29 patients (17%). Reversibility of T2-hyperintense extracallosal lesions was demonstrated in three cases.

Statistical analysis

When compared with cases with at most slight consciousness impairment (which we summarized as type B), impairment of consciousness (type A) was found to be significantly associated with the following clinical features: pyramidal tract symptoms, limb hypertonia, death and poor outcome (MOHS ≥ 3; Table 2). T2-hyperintense signal abnormality of the entire corpus callosum in the early stage ($p < 0.001$), extracallosal lesions ($p < 0.05$) and callosal atrophy ($p = 0.005$) were associated radiological features.

"Chronic" cases

Two additional patients [27, 33] were admitted in a chronic condition because of neuropsychiatric symptoms without a known history of a preceding acute or subacute neurological illness accounting for the clinical condition. MRI on admission showed T1-hypointense lesions in the corpus callosum, limited to the splenium in one patient and extending from the genu to the body of the corpus callosum in the other patient. The clinical condition did not change in both patients.

Discussion

From the clinical point of view, two principal subtypes of MBD may be differentiated: coma or stupor is the predominant clinical feature in one – referred to as type A –, versus a normal or at most slightly impaired level of consciousness in the other, type B respectively. Some additional clinical symptoms differed between groups with a significantly higher prevalence of pyramidal tract symptoms and limb hypertonia in type A, whereas the remaining symptoms were found to a similar extent in the two forms.

Previous attempts to characterize subtypes of MBD date back to the autopsy era, when a classification was developed which, according to the rate of clinical progression, differentiated three subtypes of MBD [6]. The acute form, like type A, was characterized by coma, seizures, limb hypertonia and pyramidal tract symptoms, while rapid onset of dementia, limb hypertonia, dysarthria and astasia-abasia was considered typical for subacute forms, bearing analogies to type B. As a lethal course was assumed in acute and subacute forms within days to few months, sporadic reports on cases with a prolonged course over years [6, 9] prompted the description of a chronic form otherwise clinically resembling the subacute form [6].

In contrast, more recent data suggest an overall good prognosis of MBD (mean MOHS 2.4, range 0–6, median 2). Although a higher grade of disability (MOHS ≤ 2 19% vs. 86%, $p < 0.001$) and fatality (21% vs. 0%; $p < 0.02$) was significantly more frequent in patients with type A MBD, prognosis is still much less devastating than previously inferred [6]. This is even more true for the subtype without marked impairment of consciousness in the acute stage, which we found to be burdened with a rather low level of handicap (mean MOHS 1.5 (range 0–3, median 1.5) and no reported fatality. The most likely explanation for these discrepancies is selection bias related to autopsy as the only established pre-imaging diagnostic methodology, but considerable advances in survival of critically ill patients may also account for the reduction in fatality. However, evidence of a generally favorable prognosis in type B hampers justification for differentiating subacute and chronic forms, particularly since the reviewed data do not support the existence of a genuine chronic-progressive course; the reports of two cases lacking evidence of an acute stage appear most likely due to incomplete medical history. Therefore, a dichotomic classification, restricted to the differentiation of clinical syndroms may be more up-to-date. The terms "acute, subacute and chronic" should be used rather to describe a stage, not a subtype of MBD and may be used in relation both to type A and type B.

In type A, a prodromal stage with neuropsychiatric symptoms and gait disturbance has been reported in around 50% of cases before onset of coma. Although this phenomenon may be a direct result of aggravated alcohol consumption as proposed earlier [6], similarity to symptoms in type B suggests it may be the manifestation of beginning callosal demyelination. In fact, two well-documented cases [26, 35] in which stepwise deterioration in neuroimaging was associated with progressive disturbance of consciousness support the inference that type A may evolve from type B.

In the past decade, neuroimaging has proved to be a suitable tool for in-vivo diagnosis of MBD. The best method to assess callosal lesions is sagittal MRI offering the opportunity of visualizing the entire corpus callosum [45]. By contrast, accurate visualization of the body of the corpus callosum is difficult in axial planes, limiting the diagnostic yield of axial MRI and particularly CT.

Despite the relatively low number of cases providing early sagittal MRI, our extracted data provide some evidence that diffuse edema of the entire corpus callosum, showing as T2-hyperintense swelling, is the characteristic finding in the acute stage of forms presenting with impaired consciousness.

By contrast, partial T2-hyperintense lesions of the corpus callosum are the typical finding on MRI in the acute stage of type B. Rapid reversibility of these lesions demonstrated in some cases suggest underlying focal edema, while demyelination does not seem to contribute significantly to T2-signal abnormality [20, 46].

Compared with MRI, CT has several disadvantages in the diagnosis of MBD. Due to its inferior spatial resolution, sensitivity of CT in the detection of early callosal lesions appears to be limited. Moreover, as CT usually fails to visualize the body of the corpus callosum, differentiation of partial forms limited to the genu and splenium [8, 20] from diffuse forms [11, 23] is impossible.

In the chronic stage of MBD, T1-hypointense and T2-hyperintense lesions, consistent with areas of cystic necrosis, are typical findings on MRI. Involvement of major parts of the corpus callosum is common in type A [31, 32] whereas in type B, cystic lesions tend to be smaller and of more focal distribution [4, 43]. In both forms, the extension of callosal edema in the acute stage may markedly exceed areas of ultimate cystic necrosis, and, as indicated before, reversibility of T2-hyperintense lesions has been documented in cases lacking evidence of cystic-necrotic lesions by imaging in vivo [20, 46].

This phenomenon, demonstrated in the case reported above, may be explained by failure of conventional MRI to demonstrate areas of presumed pure demyelination leading to ostensibly complete radiologic restitution after resolution of edema. Observations in patients with multiple sclerosis support this hypothesis, showing that marked demyelination determined by magnetization transfer imaging may occur prior to T2-lesion demonstration [41]. In contrast, remyelination appears an unlikely explanation for recovery on MRI, given the short period of time in most cases. Marked atrophy of the corpus callosum is found much more frequently in the chronic stage of type A (79 % vs. 26 %; $p = 0.005$) paralleling the finding of diffuse callosal edema in the acute stage.

The prognostic relevance of extracallosal lesions has been discussed controversially and they have been repeatedly suggested as a marker for a poor prognosis [18, 35]. Our reviewed data show a trend towards a less favorable outcome in patients with extracallosal lesions (MOHS ≥ 3 54 % vs. 29 %; $p = 0.12$) not reaching statistical significance.

The relatively small number of cases providing early sagittal MRI, possible selection bias and the non-standardized manner of outcome determination, necessitating our attempt of deriving a more global outcome scale, are the most important shortcomings of this work.

Nevertheless, this review provides evidence that it may be more pertinent to clinical practice to differentiate two clinicoradiologic forms of MBD, both of which have a better prognosis in survival and functional impairment than traditionally conveyed from pre-imaging literature:

Type A is characterized by acute to subacute onset of impairment of consciousness and pyramidal tract syndromes. Early findings in neuroimaging include T2-hyperintense swelling (MRI) or ill-defined hypodensity (CT) of the corpus callosum consistent with diffuse callosal edema. Prognosis is less favorable with considerable disability and fatality.

Type B lacks major impairment of level of consciousness. It is characterized by acute to subacute onset of cognitive impairment, dysarthria, gait disturbance and signs of interhemispheric disconnection. Partial T2-hyperintense lesions are characteristic on early MRI. Prognosis is favorable, there seems to be no early fatality.

Further studies providing detailed prospective clinical and neuroimaging data are needed to confirm our results and to elucidate risk factors and predictors of clinical course and prognosis.

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