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ORIGINAL COMMUNICATION

MRI and clinical syndrome in dura mater-related Creutzfeldt-Jakob disease

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Abstract *Objective* Iatrogenic Creutzfeldt-Jakob disease (iCJD) is mainly associated with dura mater (DM) grafts and administration of human growth hormones (hGH). Data on disease course in DM-CJD are limited. We describe the clinical and diagnostic findings in this patient group with special emphasis on MRI signal alterations. *Methods* Ten DM-CJD patients were studied for their clinical symptoms and diagnostic findings. The MRIs were evaluated for signal increase of the cortical and subcortical structures. *Results* DM-CJD patients had a median incubation time of 18 years and median disease duration of 7 months. The majority of patients were MM homozygous at codon 129 of the prion protein gene (*PRNP*) and presented with gait ataxia and psychiatric symptoms. No correlation between the graft site and the initial disease course was found. The MRI showed cortical and basal ganglia signal increase each in eight out of ten patients and thalamic hyperintensity in five out of ten cases. Of interest, patients with thalamic signal increase were homozygous for methionine. *Conclusion* The MRI findings in DM-CJD largely resemble those seen in sporadic CJD, as the cortex and basal ganglia are mainly affected.

Key words CJD · MRI · dementia · cerebellar disorder · CNS infection

Introduction

Studies in iatrogenic CJD are extremely useful to understand some aspects of infections in humans, as the infectious agent may reach the brain via different routes: direct inoculation (EEG depth electrodes), oral infection (growth hormone therapy, vCJD), peripheral infection (blood transfusion) and superficial infection (dura mater and corneal transplant).

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The diagnosis of iCJD is based on the presence of typical symptoms (dementia, ataxia, extrapyramidal and pyramidal signs, myoclonus and akinetic mutism) and a history of iatrogenic exposure. The finding of 14-3-3 protein in the CSF may support the diagnosis (77 % sensitivity) [1, 2].

Dura mater grafts have been found as disease cause in 200 CJD patients worldwide [1]. Due to the long incubation periods ranging from 16 months to 31 years, DM-CJD cases are still detected nowadays [1, 3–9].

Increased rates of early ataxia have been reported in DM-CJD, hGH-CJD and vCJD [10–13]. In DM-CJD, a possible influence of the graft location on the clinical onset has been suggested [14, 15]. Only limited data were reported on paraclinical tests in iCJD, such as MRI. Since the MRI pattern of high signal abnormalities follows the lesion pattern of the brain as detected by pathology, the analysis of MRI in iCJD might be extremely useful.

The goals of our study were to describe MRI and clinical findings in a larger number of DM-CJD patients and to correlate them with the graft location and codon 129 genotype.

Methods

Patients with suspected CJD are reported to the CJD Surveillance Unit in Goettingen, (established in 1993) and examined by a study physician at the hospital reporting the case. A questionnaire about the patient's history (profession, habits, meat consumption) is filled out and copies are made of the medical charts (clinical findings, laboratory tests, EEG and MRI). The patients are classified as *possible*, *probable* or *no CJD* case according to established criteria [16]. One Croatian case (case 10) was included in this study because material was sent for genetic analysis and all clinical data were available.

Genetic analysis

Analysis of the prion protein gene (*PRNP*) was performed after isolation of genomic DNA from blood according to standard methods [17]. *PRNP* mutations were excluded in all but one patient by full *PRNP* sequencing (case 9).

Neuropathology

Histological examination was performed according to standard methods [18, 20].

Clinical examination

The patients were examined for the presence of typical CJD symptoms at onset (within first month) and during the disease course. Symptoms representing a residual state after surgery were not included in the analysis. Residual symptoms which progressed at the time of the disease onset were considered to be CJD signs and included in the study.

MRI

MRIs were available in nine out of ten patients. All MR examinations had been obtained from a 1.5 Tesla scanner (a total of 11 T2w, 9 FLAIR (fluid attenuated inversion recovery), 6 PDw (proton density weighted imaging) and 4 DWI (diffusion-weighted imaging), including serial MRIs in four patients) and were mainly available as hardcopy. Digital MRI data were available in four patients (cases 2, 3, 5 and 8). The MRI scans were reported independently and in consensus by two neuroradiologists (KK and MK) aware of the CJD diagnosis but not aware of the disease aetiology. The interobserver agreement was moderate for all the sequences (Concordance 80,. and $\kappa = 0.52$) and high for FLAIR (Concordance 83.6 and $\kappa = 0.57$), PDw (Concordance 83.3 and $\kappa = 0.67$) and DWI (Concordance 83.9 and $\kappa = 0.65$). The results of the consensus review were used for the study.

Using a standardized protocol, *seven cortical areas* (the frontal, parietal, temporal, occipital and insula cortex, as well as the cingulate gyrus and hippocampus), the *basal ganglia* (caudate nucleus, putamen, globus pallidus), the *thalamus* and the *cerebellum* were assessed for signal increase in relation to suspected normointense tissue.

Results

Patients with dura mater grafts

In the years 1993 to 2006, ten DM-CJD cases (four *definite* and six *probable*) were identified (nine in Germany, one in Croatia) (Table 1). All surgeries were performed between 1980 and 1987 (Fig. 1). The median age at onset was 55 years (range 25–70); the median disease duration was 8 months (range 2–30). Incubation periods ranged from 9 to 23 years (median 18 years) (Fig. 1).

The codon 129 genotype was available in all patients (8 MM, 1 VV and 1 MV). Codon 219 was not examined in any case. The type of pathological prion protein (PrP^{Sc} 1 or 2) was analyzed in three out of four autopsied cases (only formalin fixed brain tissue was available in one patient): Three patients displayed PrP^{Sc} type 1. In one further case, the PrP^{Sc} type could not be clearly identified as type one or two (case 7) (as previously discussed) [21] (Table 1).

Clinical presentation

The main symptoms at onset (within the first month) and during the course of the disease are displayed in Table 2. Seven out of ten patients presented with gait ataxia (in three cases in isolation). Psychiatric abnormalities (depression and aggression) occurred in four out of ten patients (in one case as the only presenting symptom). Visual signs (double vision) were found in three patients, pyramidal signs (hemiparesis) in two and extrapyramidal signs (rigidity and choreatic movements) in one out of ten patients.

Only one patient displayed early signs of dementia. As unspecific clinical signs, vertigo (five patients) and headaches (five patients, data not displayed) were found most frequently. Further symptoms observed in the

Table 1 Clinical and diagnostic data in ten dura-related iatrogenic CJD cases

Case	Sex/age (years)	Codon 129 genotype (PrP^{Sc} type)	Cause for surgery	CJD diagnosis (WHO criteria)	Incubation (years)	Disease duration (months)	EEG: PSWC	CSF: 14-3-3
1	m/38	MV	Brain trauma	Probable	10	4	+	+
2	m/44	MM (1)	Brain trauma	Definite	19	25	+	+
3	f/70	MM	Meningeoma	Probable	19	3	–	+
4	m/42	MM	AV-angioma	Probable	13	4	+	+
5	m/54	MM	Meningioma	Probable	18	11	–	+
6	f/56	MM (1)	Acousticus neurinoma	Definite	9	6	+	+
7	m/57	MM	Hemangioblastoma	Definite	20	10	–	+
8	f/65	MM	Trigeminal neuralgia	Probable	15	12	–	+
9	f/64	MM (1)	Pilocytic astrocytoma	Definite	23	2	+	+
10	f/25	VV	Pilocytic astrocytoma	Probable	17	30	(+)	(–)
	Median 55 years			**Median**	**18**	**8**	**5/9**	**9/9**

M male; *f* female; *PSWC* periodic sharp wave complexes
(+), (–) = assessed as positive or negative at the hospital reporting the case (not included in the present analysis)

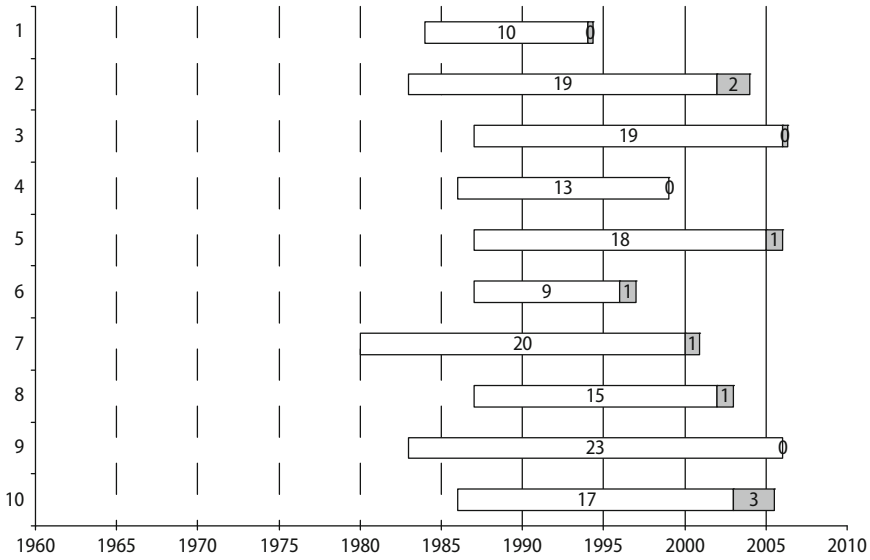

Fig. 1 Incubation periods (years) and disease duration (months) in patients with dura mater graft

early disease stage were dysaesthesias in three patients and loss of hearing, tinnitus, dysarthria, aphasia, abnormal sense of taste in one patient each.

Time course of symptoms

The median duration from the beginning of the disease to the onset of typical CJD symptoms is given in Fig. 2. Ataxia and psychiatric signs were among the earliest symptoms and followed by visual signs (median 1 month) and dementia (median 2 months). Myoclonus, extrapayramidal and pyramidal signs were typical signs of the advanced disease stage (median 3 to 4 months). Akinetic mutism was found in only two patients.

Dura graft location and initial clinical symptoms

Details on the graft placement and the clinical signs are shown in Table 2.

Early ataxia occurred most frequently in patients with suboccipital graft (four cases) but also in three patients with different graft location. Psychiatric signs were predominant in patients with frontal graft (three cases) but also found in one patient with suboccipital graft. Two patients with early pyramidal signs (hemiparesis) had a dura graft in the parietal area. Early rigidity was found in one patient with frontobasal graft. In four patients, the early disease course appeared to be monosymptomatic: three patients with suboccipital graft showed isolated ataxia for a time period of 4 weeks (case 9), 6 weeks (case 7) and 8 weeks (case 10). In one

Table 2 Dura graft location and clinical signs at onset and during course of the disease

Case	Dura graft location	Onset (1st month of the disease)						Course**					
		Dementia	Ataxia	Visual	EPM	Pyramidal*	Other	Dementia	Ataxia	Visual	EPM	Pyramidal*	Myoclonus
1	Fronto-basal	+	+	–	+	–	Psychiatric, dysarthria	+	+	–	+	+	+
2	Fronto-basal	–	–	–	–	–	Psychiatric	+	+	+	–	–	+
3	Fronto-parietal	–	–	+	–	+	Psychiatric, aphasia	–	+	–	–	+	+
4	Temporal	–	+	+	–	–	Dysaesthesias, vertigo	+	+	–	+	+	+
5	Parieto-occipital	–	+	–	–	+	Dysaesthesias, vertigo	+	+	–	–	–	+
6	Suboccipital	–	+	–	–	–	Psychiatric, dysaesthesias, loss of hearing and sense of taste	–	+	–	–	+	+
7	Suboccipital	–	+	–	–	–	Vertigo	+	+	+	+	+	+
8	Suboccipital	–	–	+	–	–	Vertigo, hyperhidrosis	+	+	+	+	+	+
9	Suboccipital	–	+	–	–	–	–	+	+	+	+	+	+
10	Suboccipital	–	+	–	–	–	Vertigo, tinnitus	+	+	–	+	–	+
	–	1/10	7/10	3/10	1/10	2/10		8/10	10/10	4/10	6/10	7/10	10/10

* corresponding to hemiparesis (two patients at onset) or spasticity (seven patients during the course)
** During the disease course all but one patient (case 5) developed psychiatric signs. Only two patients (cases 6 and 8) became akinetic and mute
EPM extrapyramidal signs

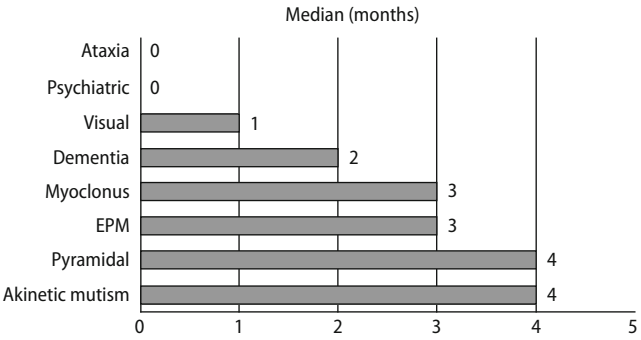

Fig. 2 Time course of symptoms in patients with dura mater graft

further patient with frontobasal graft, only psychiatric signs were present for a time period of 6 months (case 2).

MRI

A synopsis of the MRI findings and applied sequences is given in Table 3. The cingulate gyrus was the most frequently affected cortex region (eight out of ten), followed by the frontal, temporal and parietal lobes (six out of ten, each).The occipital cortex was least affected (three out of ten). Basal ganglia hyperintensity was found in eight out of ten patients (in one case only during follow-up), and thalamic hyperintensity in five (in three cases only on PDw). In one patient (MV type), no signal abnormalities were found (Fig. 3). The current criteria for a pulvinar- or hockey stick sign (pulvinar or dorsomedial thalamus brighter than the other grey matter) were not met in any of the patients [22, 23].

Two patients showed pronounced signal increase in the brain hemisphere containing the graft: In one patient with right temporal graft, the signal increase was more pronounced in the right temporal and parietal lobes (Case 4). In one patient with left suboccipital graft, the left frontal cortex appeared to be more hyperintense than on the right side (Case 10). In two other patients, the findings were reversed (signal more pronounced in the opposite brain hemisphere) (Cases 6 and 9).

Discussion

In a recent study on DM-CJD cases, MRI sensitivity was reported to be high but no details were given on the involved brain areas [24]. According to a literature review, basal ganglia signal increase was found in eight out of 27 patients [6, 8, 9, 21, 25, 26], additional cortical signal increase in three [9, 25, 26] and thalamic hyperintensity in one [9]. In a large number of further cases, only atrophy was reported, which is most likely due to the less com-

Table 3 MRI signal increase in eight iatrogenic CJD cases caused by dura mater transplant

Case	Dura graft location	Genotype	Frontal	Temporal	Parietal	Occipital	Insula	Gc	Hc	Bg	Thalamus	Cerebellum	MRI 1 (time point)*	MRI 2 (time point)*
1	Fronto-basal	MV	–	–	–	–	–	–	–	–	–	–	T2, FLAIR (1/3)	–
2	Fronto-basal	MM	+	–/+	–/+	–	–	+	–	–/+	–	–	FLAIR, DWI (2/3)	T2, FLAIR (2/3)
3	Fronto-parietal	MM	–	+	–	+	+	+	–	+	+	–	T2, FLAIR (1/3)	–
4	Temporal	MM	+	+	+	+/–	+	–/+	+	+	–	–	T2, FLAIR (1/3)	T2, FLAIR, DWI (3/3)
5	Parieto-occipital	MM	+	+	+	–	+	+	+	+	+	–/+	T2, PD, DWI (2/3)	T2, PD, FLAIR, DWI (2/3)
6	Suboccipital	MM	+	–/+	+	+/–	+	+	–/+	+	–/+	–	T2, PD (2/3)	T2, PD, FLAIR (3/3)
7	Suboccipital	MM	–	–	–	–	–	–	–	+	+	+	PD (2/3)	–
8	Suboccipital	MM	+	+	+	–	+	+	–	+	+	–	T2, PD, DWI (1/3)	–
9	Suboccipital	MM	–	–	–	–	–	+	–	+	–	–	T2, FLAIR (2/3)	–
10	Suboccipital	VV	+	–	+	–	–	+	–	–	–	–	T2, FLAIR (1/3)	–
		–	6/10	6/10	6/10	3/10	5/10	8/10	3/10	8/10	5/10	2/10		

–/+ = signal increase during follow-up; +/– = signal increase not visible on follow-up MRI; *Bg* Basal ganglia; *Gc* Cingulate gyrus; *Hc* Hippocampus; * Time point given in thirds of the disease course

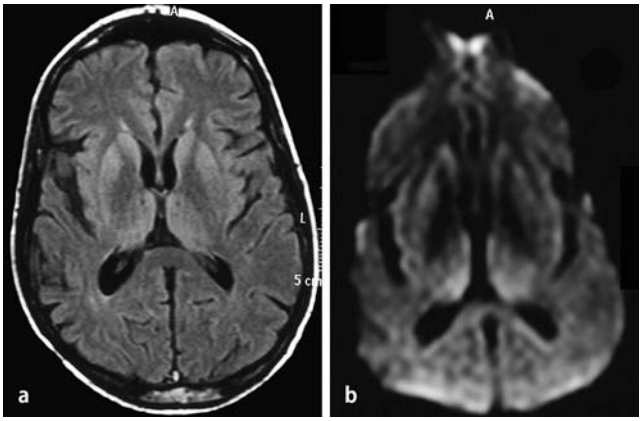

Fig. 3 Axial FLAIR (**a**) and diffusion-weighted (**b**) MRI of a 55-year old male patient (Case 5) six months after the disease onset showing signal increase in the basal ganglia, thalamus and cortex

mon use of FLAIR and DW images in the past (Table 4) [3, 5–9, 21, 25–41].

We studied the MRI findings in ten iatrogenic CJD patients after dura mater transplant by highly sensitive sequences. Cortex involvement was found in all but two patients. The basal ganglia were affected in eight, the thalamus in five and the cerebellum in two cases. The majority of our patients was MM homozygous at codon 129 of the *PRNP* and presented with gait ataxia.

At first sight, the MRI findings in our patients seem to largely resemble those seen in sporadic CJD. In sCJD, six molecular types (codon 129 genotype + PrP^{Sc} type 1 or 2; MM1, MM2, MV1, MV2, VV1, VV2) have been described with various clinical and diagnostic findings [42, 43]. Basal ganglia and cortical signal increase are most frequently found on the MRI [44–48]. Thalamic signal increase represents a comparatively rare finding, which seems to largely depend on the application of DW images [45–48].

Although the majority of our patients were not distinguishable from sporadic cases by means of MRI, the finding of thalamic hyperintensity in five out of eight MM homozygous patients is notable. According to previous literature reports, thalamic hyperintensity appears to be rather typical of MV2 type sporadic CJD and atypical of MM homozygous sCJD patients [49–51]. However, as only small patient groups have been studied so far with limited numbers of DW images, it remains to be confirmed that thalamic hyperintensity is rather not typical of MM homozygous sporadic CJD.

From the clinical point of view, sporadic CJD cases with MM homozygosity may present with rapidly progressive dementia (MM1 individuals), rather slowly developing cognitive signs (MM2-*cortical* individuals) or early ataxia (MM2-*thalamic* individuals with variable disease onset). The latter patients, who *clinically* most resemble our iatrogenic patients, are however well dis-

Table 4 Review of the literature: MRI findings and codon 129 genotype in dura-related iatrogenic CJD

Author	Gender/Age at onset (years)	Codon 129 genotype (PrP^{Sc} type)	Dura mater introduction	Incubation (years)	Disease Duration (months)	MRI signal increase	Atrophy (CT/MRI)	MRI sequence	MRI performed (m.a.o.)
Kopp et al. 1996 [31]	f/52	MM (1)	Left sylvian artery aneurism 1984	11	5	–	–	n.m.	n.m.
Hannah et al. 2001 [30]	f/39	MM (1)	Arnold Chiari I malformation 1992	6	4	–	–	n.m.	n.m.
Nishida et al. 2002 [34]	f/69	MM (1)	Hemifacial spasm 1984 (Janetta's operation)	14	6	–	–	n.m.	n.m.
Mochizuki et al. 2003 [7]	f/79	MM (1)	Parasaggital meningeoma 1982	15	18	–	+	T1, T2	n.m.
Wakisaka et al. 2006 [9]	f/19	MM (1)	Brain trauma 1985	17	10	Basal ganglia, pulvinar, left fronto-temporal cortex	–	T2, PD, DWI	1 week prior to death
Preusser et al. 2006 [8]	m/28	MM (2)	Brain trauma 1982	23	6	Basal ganglia	–	T2	n.m.
Delisle et al. 1993 [29]	m/18	MM	Craniopharyngeoma 1981, hGH 1982	8	12	–	+	n.m.	n.m.
Yamada et al. 1994 [41]	f/31	MM	Pituitary adenoma 1985	5	27	–	+	T1	12
Martinez-Lage et al. 1994 [33]	m/17	MM	Cerebellar astrocytoma 1983	7	3	–	+	T2	2nd week after admission or later
Martinez-Lage et al. 1994 [33]	m/25	MM	Arnold Chirai malformation 1983	9	15	–	+	T2	2nd week after admission or later
Yamada, et al. 1997 [40]	m/52	MM	Right frontal convexity meningeoma 1984	8	10	White matter	+	T2	9
Takashima at al. 1997 [37]	f/38	MM	Aneurysm of right middle cerebral artery 1985	9	17	–	–	n.d.	–
Shimizu et al. 1999 [34]	m/68	MM	Hemifacial spasm 1985	11	9	–	+	n.m.	1
Shimizu et al. 1999 [36]	f/68	MM	Right parasaggital meningeoma 1986	10	12	–	+	n.m.	n.m.
Kimura et al. 2001 [5]	m/42	MM	Pituitary adenoma 1984	14	13	–	–	DWI and other	n.m.
Croes et al. 2002 [28]	m/51	MM	Arteriovenous malformation 1983	14	6	–	–	n.m.	n.m.
Croes et al. 2002 [28]	m/44	MM	Hemangioblastoma 1988	10	4	–	–	n.m.	n.m.
Kobayashi et al. 2003 [25]	f/37	MM	Cerebellar astrocytoma (at the age of 14)	23	n.m.	Basal ganglia, Cortex	+	DWI	n.m.
Kretzschmar et al. 2003 [21]*	m/58	MM	Angioblastoma 1980	19	18	Basal ganglia	–	n.m.	n.m.
Pocchiari et al. 1992 [35]	f/32	VV	Ethmoidal meningocoele 1981	10	8	–	+	n.m.	n.m.
Liscic et al. 1999 [32]*	m/24	VV	Brain trauma 1986	12	10	–	+	T2	8
Boutoleau et al. 2003 [3]	m/35	VV	Brain trauma 1991	10	2	–	–	n.m.	n.m.
Antoine et al. 1997 [27]	m/25	MV	Dura mater embolization in the external carotid artery for a nasopharyngeal angiofibroma	8	8	–	–	n.m.	n.m.
Thadani et al. 1988 [39]	f/28	n.m.	Cholesteatoma 1985	1.6	3	–	–	n.m.	n.m.
Takayama et. al 1993 [38]	m/38	n.m.	Cranial nerve decompression for hemifacial spasm 1985	5	n.m.	–	+	n.m.	n.m.
Lang et al. 2001 [6]	m/57	n.m.	Cerebellar angioblastoma 1980	19	19	Basal ganglia	–	DWI	n.m.
Ukisu et al. 2005 [26]	f/57	n.m.	n.m.	n.m.	n.m.	Basal ganglia, Cortex	–	T2, DWI	2 and 3 months

– = no abnormalities reported; *n.m.* not mentioned; *m.a.o.* months after onset; *n.a.* not applicable; * patients included in our study

Table 5 Disease phenotypes in sporadic and iatrogenic CJD with MM genotype

	Sporadic CJD			Iatrogenic CJD	
	Classic variant	Atypical variants with MM genotype		Dura mater-associated	vCJD
Genotype + PrP^{Sc} type 1 or 2	MM1[a]	MM2 – cortical[b]	MM2 – thalamic[c]	MM1[d]	MM1[e]
Infectious mode	–	–	–	Superficial	Oral
Age (median)	68 years (31–89)	67 years (60–82)	61 years (30–71)	56 years (19–79)	30 years (mean) (15–52)
Clinical onset	Dementia	Dementia	Variable	Ataxia	Ataxia
MRI signal increase	Cortex and basal ganglia	Cortex	None	Cortex, basal ganglia, thalamus	Cortex, basal ganglia, thalamus

[a] [52] Collins et al. 2006; [b] [50] Krasnianski et al. 2006, [51] Hamaguchi et al. 2005; [c] 7 cases reported [51] Hamaguchi et al. 2005, [44] Shiga et al. 2004, [53] Yamashita et al. 2001; [d] 5 literature cases ([31] Kopp et al. 1996, [30] Hannah et al. 2001, [34] Nishida et al. 2002, [33] Mochizuki et al. 2003, [9] Wakisaka et al. 2006) and 3 own cases; [e] [54] Zeidler et al. 2000, [22] Collie et al. 2003

tinguished by MRI, as signal abnormalities are usually not observed in this particularly rare disease type. In MM2-*cortical* individuals, signal increase was mainly found in the cortex (Table 5) [7, 9, 22, 30, 31, 34, 44, 50–54].

Variant CJD patients, who may also present with early psychiatric signs and gait ataxia, may be differentiated from our cases by the presence of the *pulvinar sign* on the MRI. In the early disease stages, this finding may however be missing and follow-up exams should thus be performed [22]. Finally, a typical history of surgery may shift the diagnosis to iatrogenic CJD rather than sporadic or variant (Table 5) [7, 9, 22, 30, 31, 34, 44, 50–54].

Three of our MM homozygous patients did not show thalamic signal increase on the MRI. This might be explained by the MR examination time point and applied MR sequences, as thalamic signal changes were mainly seen in the later disease stages and on PDw images. Although the PDw sensitivity for thalamic hyperintensity has been reported to be high, it should be considered that information on the specificity of this sequence is very limited [22, 47].

Thalamic hyperintensity has also been reported in a Japanese dura recipient (MM type), four growth hormone recipients (two MV types, one VV type and one with unknown genotype) and one case of vCJD after blood transfusion (MM type) [9, 55, 56]. In conclusion, we have to consider the possibility that thalamic hyperintensity might be a peculiarity of acquired CJD forms.

In line with other studies, our patients were mainly MM homozygous at codon 129 of the *PRNP* [1, 11, 12, 26]. The prevalence of MM or VV homozygosity in iCJD has been discussed as due to increased susceptibility.

Methionine and valine homozygosity are associated with shorter incubation periods in iCJD [1, 57–59]. However, in DM-CJD cases, no such influence was found [60]. Compared to other reports, the incubation periods observed in our patients were significantly prolonged (mean 18 years vs. 8 years), which may be best explained by the fact that German CJD surveillance was only first established in 1993 [11]. Iatrogenic CJD cases with shorter incubation periods were thus probably missed.

No clear correlation between the original graft location, the clinical syndrome and the MRI signal alterations was found, which may be due to varying examination time points and techniques or may indicate the independence of MRI signal alterations in iatrogenic CJD. Another possibility to discuss is that the clinical syndrome and MRI changes might be functions of the infectious agent's characteristics rather than the site of inoculation.

DM-CJD cases have recently been divided into a *plaque type* and *non-plaque type* on the basis of clinicopathological findings. The plaque type usually presents with ataxia, whereas classic CJD features are found in the non-plaque type [24]. MRI hyperintensities were frequent in both types (not described in detail). In our study group, neuropathological data were limited and only one patient with florid plaques was found. This case presented with isolated ataxia, and the MRI showed hyperintensities of the cortex, basal ganglia and thalamus.

Summarizing, the MRI findings in DM-CJD are similar to sporadic CJD, showing frequent cortex and basal ganglia involvement. Thalamic hyperintensities in MM homozygotes might however be suggestive of an iatrogenic CJD form, rather than sporadic.

Conflict of interest The authors declare no conflict of interest.

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