Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2010;29:371–378
DOI: 10.1159/000278692

Accepted: January 19, 2010
Published online: May 5, 2010

Clinical Features of Rapidly Progressive Alzheimer's Disease

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Key Words
Alzheimer's disease, clinical characteristics · Apolipoprotein E · *PRNP* gene codon 129 · Alzheimer's disease, rapid progression

Abstract
Objective: To characterize clinical features, CSF biomarkers and genetic polymorphisms of patients suffering from a rapidly progressing subtype of Alzheimer's dementia (rpAD). ***Methods:*** Retrospective analyses of 32 neuropathologically confirmed cases differentially diagnosed as AD out of a group with rapidly progressive dementia. CSF biomarkers (14-3-3, tau, β-amyloid 1–42) and genetic markers (*PRNP* codon 129, apolipoprotein E, ApoE, polymorphism) were determined. ***Results:*** Median survival was 26 months, age at onset 73 years. Biomarkers: mean β-amyloid 1–42: 266 pg/ml, median tau: 491 pg/ml, 14-3-3 positive: 31%. Genetic polymorphisms showed a predominance of methionine homozygosity at *PRNP* codon 129 and a low frequency of ApoE4 (38%, no homozygous patients). Thirty-five symptoms were studied. Frequent symptoms were myoclonus (75%), disturbed gait (66%) and rigidity (50%). ***Discussion:*** rpAD is associated with a diversity of neurological signs even able to mimic Creutzfeldt-Jakob disease. Biomarkers and genetic profile differ from those seen in classical AD. The findings on biomarkers, symptomatology and genetics may aid the differential diagnostic process. Copyright © 2010 S. Karger AG, Basel

Introduction and Objectives

Alzheimer's disease (AD) is the most frequent cause of dementia [1]. In most cases, the progression of the disease is slow with a disease duration of approximately 10 years while rapid progression is observed in some cases [2–4]. Rapid progression can be defined by decline on psychometric tests such as the Mini Mental State Examination score, e.g. 5 points/year [3], or on a basis of survival time, e.g. less than 4 years [5]. At the moment no consensus on the term 'rapidly progressive dementia' exists. A need for a definition therefore becomes obvious and a discussion on that topic should be encouraged. Several patients with rapidly progressive dementia (very fast cognitive decline) and additional focal neurological symptoms consistent with prion disease such as Creutzfeldt-Jakob disease (CJD) often featuring a notably short time of survival were reported to the German National Surveillance Unit for Transmissible Spongiform Encephalopathies (TSE). As was discovered post mortem, these patients had actually been suffering from AD as the most frequent differential diagnosis [6–11]. Since these patients might represent a peculiar subgroup of AD patients, we performed a study with respect to clinical and genetic characteristics as well as cerebrospinal fluid (CSF) biomarkers.

Limited data are available on the frequency of focal neurological signs in AD. Rapidly progressive AD forms have been described, and early occurrence of focal signs was re-

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1420–8008/10/0294–0371$26.00/0

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ported to indicate poor prognosis [12, 13]. Our aim was to characterize the clinical features of our patients giving a descriptive overview of this highly selected group with rapidly progessing AD (rpAD). Considering contradictory data on genetic polymorphisms such as prion protein gene *(PRNP)* codon 129 or apolipoprotein (Apo) E type and the rate of AD progression [14–16], it was also an objective to determine these genetic markers in the rpAD group.

Methods

Patients who met the inclusion criteria as follow were included into the study:

1 having been reported to the German National CJD Surveillance Unit because of clinically suspected prion disease;
2 having been reported within a time period from 1993 to 2004;
3 post mortem neuropathological examination available;
4 neuropathological examination having revealed sufficient evidence of AD pathology while excluding prion disease as well as other relevant neurological disorders (e.g. significant brain infarction).

The number of patients selected was 32 (table 1). All patients had been examined by a study physician at the notifying hospital. Informed consent to participate in a study striving to monitor CJD epidemiology in Germany as well as to advance differential diagnostics of rapid dementias had been obtained. None of the patients had suffered from severe psychiatric or neurological diseases prior to the onset of the rapid dementia. CSF and blood samples had been taken, as well as copies of relevant diagnostic test results (MRI, EEG, laboratory tests) shortly after patients had been reported to the Surveillance Unit. A questionnaire concerning the patient's history had been filled out.

Clinical characteristics being the presence of 35 distinct neurological, psychiatric and autonomic symptoms as well as their time of occurrence were examined. Analysis of the symptoms' median time span from clinical onset of the disease to the disease's fatal end point was performed. The time point of the clinical onset was determined by means of semistructured interviews with family members, the treating physicians and persons having had regular contact with the patient. The disease duration was then divided into thirds. The proportions of the rpAD study population developing symptoms in one of these three thirds of the disease duration were evaluated, thereby gaining insight into whether a symptom emerged in an early, middle or late stage ('clinical profile').

If available, CSF parameters were examined. These included the proteins 14-3-3, tau and β-amyloid 1–42. Hyperphosphorylated tau protein and β-amyloid 1–40 had to be excluded because, due to the retrospective study design comprising cases from the years 1993 until 2004, these biomarkers had not been determined regularly. Therefore depiction of phosphorylated tau and β-amyloid 1–40 mean values of a group too small was not considered meaningful. Protein 14-3-3 analysis had been performed at least twice in each CSF sample as described previously [17]. Tau protein had been measured by Innotest hTau ELISA, and β-amyloid 1–42 by Innotest β-amyloid 1–42 ELISA (Innogenetics N.V., Ghent, Belgium).

Genetic features determined comprised ApoE and *PRNP* gene codon 129 polymorphisms. Analysis had been carried out by means of standard methods [18]. The prevalence of clinical signs stratified by *PRNP* codon 129 genotype was analyzed subsequently and compared by means of Fisher's exact test.

Results

The median disease duration (clinical onset to death) was 26.4 months, and the median age at clinical onset 73 years (table 1). The gender proportion appeared to be balanced almost equally. No significant difference in survival or age at onset could be seen when comparing patients being methionine-homozygous with non-methionine-homozygous patients at *PRNP* codon 129.

Pathological changes suggestive of proteinase-K-resistant or proteinase-K-sensitive [19] prion disease was absent while evidence of AD was seen in all cases. Retrospectively reviewing the results of the neuropathological examination, standard Braak and CERAD classification was performed in 28 cases, while 4 had not been available to our access. In the nonclassified cases, the pathological diagnosis was 'Alzheimer's dementia'. Of those classified, Braak and CERAD stages were distributed as given in table 1. Negligible Lewy body pathology could be found in 2 of the 32 cases, a meningioma in 1 case (right parietal convexity, diameter: 1.5 cm) and a subependymoma (9 × 4 × 5 mm frontal cornu of the left lateral ventricle) in another case, the latter two probably not being the cause of dementia or death. Diffuse white-matter lesions of vascular origin as expected considering the patients' age were commonly seen. Other significant pathology, e.g. infarction, inflammatory disease, hemorrhage or relevant tumor, was not present.

CSF tau values were determined in 29 patients with a median of 491 pg/ml (table 1). β-Amyloid 1–42 levels had been analyzed in the CSF of 18 patients resulting in a mean level of 266 pg/ml (table 1). Thirty-one percent of the entire rpAD study population (n = 32) were positive for CSF proteins 14-3-3 (table 1). *PRNP* gene codon 129 polymorphism (M = methionine, V = valine) was evaluated in 21 patients: 57% being homozygous for methionine (M/M), 29% being heterozygous (M/V) and 14% possessing 2 valine alleles (V/V) as is depicted in figure 1. Mutations were ruled out by sequencing of the entire *PRNP* gene as previously reported [18]. The ApoE status was studied in 16 patients revealing that no subject was homozygous for the type 4 allele (E4/E4), 6% possessed an E2/E4 combination, 31% were E3/E4 heterozygous, 6% were heterozygous for E2/E3, and E3/E3 homozygosity was seen in 56% (fig. 2).

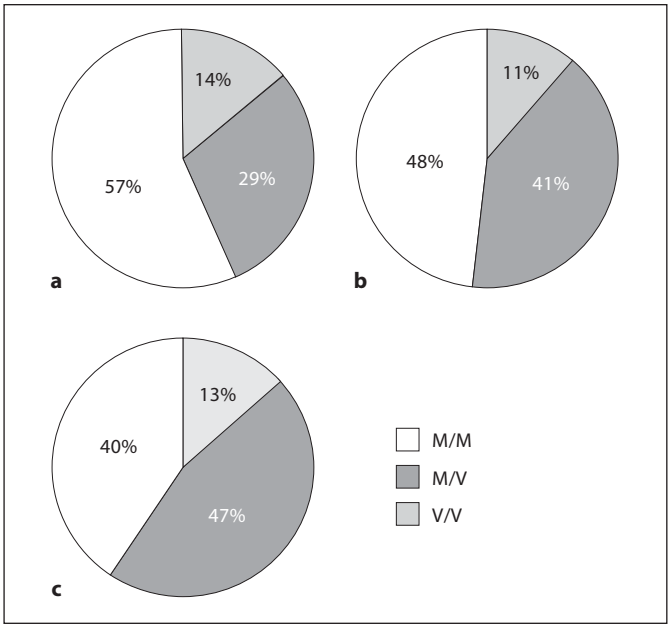

Fig. 1. Distribution of the codon 129 *(PRNP)* polymorphism in the rpAD study population (**a**, n = 21), a typical AD population (**b**, n = 482, modified from Riemenschneider et al. [32]) and healthy controls (**c**, n = 189, modified from Riemenschneider et al. [32]).

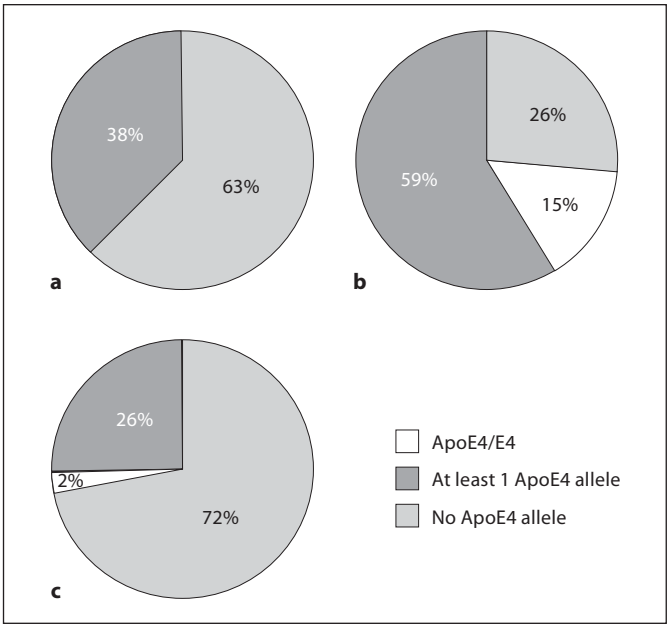

Fig. 2. Distribution of ApoE4 in the rpAD study population (**a**, n = 16), a typical AD population (**b**, modified from Farrer et al. [37]) and healthy controls (**c**, modified from Farrer et al. [37]).

Table 1. Properties of the rpAD study group including biomarkers

Category	Value	n
Median age at onset, years	73 (32, 60, 78, 89)	32
Median survival time, months	26.4 (1.3, 7.2, 45.4, 127.6)	32
Gender proportion (m:f), %	47:53	32
Clinical classification (CJD)	probable: 16%, possible: 40%, left unclassified or 'no CJD': 44%	32
MRI (CJD)	typical of CJD: 0, not typical: 53%, no MRI available: 47%	32
EEG (CJD)	typical of CJD: 6%, not typical: 81%, no EEG available: 13%	32
Median CSF tau, pg/ml	491 (207, 323, 911, 4,736)	29
Mean CSF β-amyloid 1–42 ± SD, pg/ml	266 ± 120	18
CSF 14-3-3 protein positive, %	31	29
Neuropathology Braak stage, %	III: 7, IV: 21, V: 39, VI: 32	28
Neuropathology CERAD stage, %	A: 8, B: 15, C: 77	26

Figures in parentheses indicate 1st, 25th, 75th and 100th percentiles. Clinical classification from Zerr and Poser [11], MRI from Zerr et al. [48] and EEG from Zerr and Poser [11].

The detailed clinical profile is given in figure 3. The most frequent signs were myoclonus (75%), gait disturbance (66%), positive Babinski's sign (66%), rigidity (50%), aphasia (66%), falls (50%) and hallucinations (44%). The least frequent symptoms were intention tremor (16%), disturbed vision (13%) and disinhibition (3%). Especially aphasia, myoclonus and rigidity were symptoms predominantly appearing in advanced disease stages, while depression, disturbed gait and impaired concentration occurred rather early in the disease course (fig. 3).

Category	Sign/symptom	Frequency (total), %	Clinical profile: symptoms' relative frequency within disease thirds Early (1st third): black Middle stage (2nd third): dark gray Late stage (3rd third): light gray	Median time to symptom onset, months
Cerebellar	ataxia	31		12.5
	dys/bradydiadochokinesia	25		15.0
	dysmetria	22		12.9
	dysarthria	22		4.0
	intention tremor	16		12.0
Extrapyramidal	rigidity	50		13.1
	tremor	38		9.0
Neurological (other)	myoclonus	75		13.0
	Babinski's sign	66		13.1
	disturbed gait	66		9.0
	aphasia	66		14.0
	recurrent falls	50		6.1
	hallucinations	44		13.0
	akinetic mutism	38		20.0
	primitive reflexes	34		14.0
	apraxia	31		19.5
	spasticity	25		31.1
	epileptic seizures	25		13.0
	palsies	22		10.0
	dysphagia	19		21.6
	diplopia	13		2.5
	cortically disturbed vision	13		17.0
Psychiatric	dementia	100		0.0
	disorientation	88		2.0
	depression	47		4.0
	apathy	38		17.5
	impaired concentration	31		4.5
	anxiety	28		6.0
	aggression	28		12.0
	delusion/paranoia	9		15.0
	disinhibition	3		51.1
Autonomic	incontinence	44		11.5
	disturbed sleep	41		16.0
	significant weight loss	28		20.0
	hyperhidrosis	16		13.1

Fig. 3. Clinical profile of the rpAD study group (n = 32). Frequency of signs and symptoms, total frequency, relative frequency (conditioned for disease thirds 'early, middle, late') and median time to symptom onset.

Differences in occurrence of clinical signs dependent on *PRNP* codon 129 polymorphism were seen e.g. for hallucinations, disturbed sleep and apraxia which were found to be especially frequent in M/M individuals. Epileptic seizures, primitive reflexes and akinetic mutism were particularly frequent in non-M/M individuals. Those differences were statistically significant for hallucinations and epileptic fits.

Discussion

As AD is a major challenge for the ageing society, it is of importance to advance the understanding of the underlying mechanisms. Identification of different AD subtypes using combinations of symptom patterns as well as biomarker constellations might have implications for developing appropriate management strategies. Typically, AD is a slowly progressive disease of the elderly. As Goldberg [20] states, the time from clinical onset to diagnosis is about 24 months; thenceforward, the time until admission to a nursing home is about 25 months, and after that the modal patient's survival time is approximately 44 additional months.

The patients examined in this study were those initially registered to the German National Study for the Surveillance of TSE but after neuropathological workup finally diagnosed as having AD. We found this special group worthy of further detailed description, because it seemed to differ from classical AD populations regarding the multitude of focal signs. Since 1993 more than 2,800 patients have been referred to the CJD Unit, one third of them suffered from clinically diagnosed AD [8]. Roughly 100–150 patients per year are diagnosed as having CJD, the sporadic form being predominant. Depending on the age group, 45–88% of them undergo autopsy [8]. In a very small proportion, only AD pathology mostly without any other significant neuropathology was seen instead of CJD. The true proportion of rpAD considering all referrals is not known due to the autopsy rate not being 100%.

All cases studied here suffered from rapid cognitive decline and featured a short median survival time of 26.4 months (table 1). In these cases, the differential diagnoses typically comprise a variety of diseases such as inflammatory, paraneoplastic, metabolic or prion disorders [8, 11, 21–23]. The rapidity of the decline and the clinical features may mislead the involved physician to suspect a prion disease such as CJD as a typical representative of rapidly progressive dementias. AD itself is the most frequent differential diagnosis of CJD [7–11]. It is important to mention that a clinical diagnosis of AD in this rpAD group is especially difficult as McKhann's criteria for the diagnosis of AD (NINCDS-ARDRA) exclude focal neurological signs, gait disturbances or impaired coordination in early stages [24].

Van Everbroeck et al. [22] analogously published findings on the clinical features of patients who were differentially diagnosed as having another dementia than CJD out of an initially CJD suspect population from Belgium. Their mean patients' age was 71 years at clinical onset, which is similar compared to this study. In both studies they were older than typical CJD patients. Regarding the clinical symptoms, we tried to differentiate more clinical signs and examine the time point of occurrence as well as analyze whether a symptom is an early-, middle- or late-stage symptom.

The CSF parameters determined (tau, β-amyloid 1–42; table 1) were at similar levels to those in the study of van Everbroeck et al. [22]. Mean CSF tau values of 803 ± 553 pg/ml and mean β-amyloid 1–42 values of 265 ± 156 pg/ml for 'typical' AD patients have been previously reported in the literature [25]. Cutoff values with good diagnostic sensitivity, specificity and predictive values have been suggested with total tau = 530 pg/ml and β-amyloid 1–42 = 400 pg/ml [26]. Considering those values, it is intriguing that, while β-amyloid 1–42 values were decreased as expected and as reported for slowly progressive AD, the median tau values of our study group appeared not to be elevated. Tau was even slightly decreased compared to patients whom van Everbroeck et al. [22] differentially diagnosed as having AD out of a group initially suspected to suffer from CJD. Gloeckner et al. [27] show that tau is a good marker differentiating AD from CJD. The presence of 14-3-3 proteins in the CSF, which are a marker for neuronal destruction [28], was different from the study of van Everbroeck et al. [22]. They found 4% to be positive whereas 31% of the patients were tested positive in this study (table 1). The detectability of 14-3-3 proteins in rpAD has been previously reported for 1 case [29]. This has important implications for TSE surveillance units and their interpretation of this biomarker. The 14-3-3 proteins are a substantial marker in the differential diagnostics of rapidly progressive dementia and prion diseases. Until now it has been supposed to be highly suggestive of prion disease if inflammation, ischemia, hemorrhage and epileptic seizures have been excluded.

Recent data point towards a possible link between the *PRNP*-gene-encoded prion protein and AD as the prion protein PRPc might be involved in the regulation of the β-secretase-mediated cleavage of amyloid precursor pro-

tein [30]. Single-nucleotide polymorphisms within the *PRNP* gene have been found that might be associated with AD [31]. In that context the distribution of *PRNP* gene polymorphism at codon 129 is fascinating. In our study 57% of the patients were found to be homozygous for methionine, while Riemenschneider et al. [32], who evaluated a 'typical' AD population and healthy controls, found 48% of the average AD population to be homozygous for methionine and only 40% of the healthy population. Some reports have demonstrated contradicting results on *PRNP* codon 129 polymorphism in various neurodegenerative conditions. Especially the influence on AD susceptibility, time of onset or patients' rate of decline was examined. The study of Poleggi et al. [33] does not support a role for *PRNP* gene polymorphism as a susceptibility factor for AD. Riemenschneider et al. [32] and Li et al. [34] draw a similar conclusion. In contrast, Del Bo et al. [35] found methionine homozygosity or the methionine allele at all to be a risk factor for AD as well as a correlation between the rate of cognitive decline and valine homozygosity.

The ApoE type 4 allele is a well-known and accepted risk factor for AD [1, 36, 37]. Contradicting data on the influence of ApoE type on disease progression rate are available in the literature. Martins et al. [16] demonstrate an influence, while Bracco et al. [14] or Kleiman et al. [15] rather disagree. Analysis of the ApoE type distribution in our study yields interesting results as well. We surprisingly found no patient to be homozygous for ApoE4. Only 38% possessed at least 1 ApoE4 allele compared to approximately 59% of a typical AD population examined by Farrer et al. [37] (fig. 2). Our findings are partially consistent with those of Giannattasio et al. [38] who claim that absence of the type 4 allele might be a predictor of short survival in some AD patients.

As a main objective of this study, we examined the clinical features in terms of symptom frequency, time span until onset and time point of onset relative to disease duration (fig. 3). The development of clinical signs in dependence on *PRNP* gene codon 129 polymorphism was evaluated as well.

Most of the patients experienced psychiatric symptoms apart from dementia (fig. 3). Regarding the psychiatric symptoms evaluated, interestingly, visual or acoustic hallucinations as well as anxiety were far less frequent in methionine-homozygous patients than in heterozygous ones. That difference is statistically significant ($p = 0.03$).

Motor signs and their frequency in AD patients have been described before [39–42]. Scarmeas et al. [41] report the frequency of motor signs in AD patients to increase during the course of the disease. Overall they showed tremor to be present in 11% of their AD population (38% in our study), rigidity in 26% (50% in our study) and posture instability/gait disturbance/falls in 29% (in our study: gait disturbance 66%, falls 50%). Motor signs also seem to be predictive of a poor outcome in AD [13]. The observed high frequency of motor signs in the examined population with rpAD compared to the typical AD population as described by Scarmeas et al. [41] would be consistent with the reported prognostic capability regarding a poor outcome.

Grubenbecher et al. [43] investigated the *PRNP* codon 129 polymorphism in Wilson's disease and revealed M/M status appearing to be a risk factor for severer neurological symptoms, especially for developing tremor. For tremor in particular there seems to be no predominance in M/M AD patients in this study (M/M vs. non-M/M = 33 vs. 40%). Interestingly we observed dysmetria to appear far less frequently in non-M/M individuals compared to methionine-homozygous patients.

Myoclonus and epileptic seizures are known to occur in a proportion of AD patients. Approximately three quarters of rpAD patients suffered from myoclonus (fig. 3). The large percentage may be one of the main reasons – apart from the celerity of decline – for suspecting CJD in the first place. Seizures were reported in 25%. Volicer et al. [44] report that 21% of the examined AD patients suffered from epileptic events. This finding was also associated with faster decline in language functions [44]. Occurrence of seizures seems to be significantly dependent on *PRNP* status (M/M vs. non-M/M = 50 vs. 10%, $p = 0.03$).

Vegetative features analyzed were weight loss, sleep disorders, incontinence and hyperhidrosis (fig. 3). As Johnson et al. [45] suggest, accelerated weight loss might be an indicator of AD. Almost a third of the observed rpAD patients experienced weight loss which they or their relatives felt to be abnormal and therefore significant. Sleep disturbances occurred in 41% of the rpAD patients. Plazzi et al. [46] suggest that the *PRNP* codon 129 polymorphism might affect sleep also in healthy individuals. The fact that approximately 25% of the methionine-homozygous patients versus 50% of the non-M/M patients in our study suffered from sleep disturbances might be another hint to support the hypothesis of Plazzi et al. [46]. Incontinence and the other autonomous signs evaluated were not seen to differ notably in dependence from *PRNP* codon 129 polymorphism.

Conclusion

With this paper we gave a descriptive overview of a special subtype of AD which is characterized by a very rapid course, short survival and a variety of focal neurological signs. A possible selection bias in this study has to be considered. Only cases having been reported to the German TSE Surveillance Unit were subject to this study. Cases were reported when CJD was suspected clinically. Therefore it is imaginable that rpAD forms which are characterized by fewer neurological symptoms might exist but were possibly not detected by this study.

The prevalence of such rapid AD forms with poor prognosis is not known. Thus, for the treating physician it is important to know that such a disease entity exists in order not to be misled in the diagnostic process and, in the worst case, to mistakenly suspect CJD with far-reaching consequences for the patient and affiliated persons. Dubois et al. [47] suggested modified diagnostic criteria derived from McKhann's criteria putting emphasis on imaging and biomarkers. Both however also exclude early neurological focal signs as it seems appropriate for most AD cases. It might be of help to mention such abnormal AD subtypes within potentially new criteria not strictly excluding early focal signs.

This small study serves as a basis for an ongoing longitudinal prospective study striving to elicit factors determining the course and the symptomatic appearance of rpAD in order to aid the diagnostic process. Those factors should comprise conventional as well as novel biomarkers, genetic characteristics and morphological as well as metabolic features discovered by means of neuroimaging. Another task being work in progress focuses on the clinical differences between rpAD and CJD to aid the discrimination of both illnesses by means of clinical signs and laboratory tests.

Acknowledgements

This study was supported by grants from the Federal Ministry of Education and Research (BMBF 01GI0301 and KZ 0312720), the Federal Ministry of Health (BMG Az325-4471-02/15) and the Robert Koch Institute through funds of the Federal Ministry of Health (grant No. 1369-341).

We thank the involved physicians for case notification and for providing clinical and pathological data as well as MRI scans to the National TSE Surveillance Unit, Göttingen, Germany. We hereby also express our appreciation and gratitude to B. Ciesielczyk and staff for performing the CSF and blood analyses.

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