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Diagnostic profiles of patients with late-onset Creutzfeldt-Jakob disease differ from those of younger Creutzfeldt-Jakob patients - a historical cohort study using data from the German national reference centre

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Abstract:

Background: In contrast to other neurodegenerative diseases sporadic Creutzfeldt-Jakob disease (sCJD) is rarely diagnosed in patients older than seventy-five years. However, data describing the characteristics of sCJD in the very old are rare and inconclusive. Therefore a historical cohort study was designed to evaluate clinical, CSF, EEG and MRI features of this group.

Methods: Patients older than 75 years identified via the German surveillance program from 2001 to 2012 (n=73) were compared to a random subsample of sCJD patients younger than 75 (n=73) from the same time period using an historical cohort design.

Results: Older patients showed a faster disease progression represented by an earlier point of diagnosis and a shorter survival time ($p<0.001$). In early stages of disease, older patients presented slightly more often with dementia ($p=0.127$) or dysarthria ($p=0.238$), whereas disorders of the extrapyramidal ($p=0.056$) and visual system ($p=0.015$) were more common in the younger group. Atypical MRI profiles such as MRI lesions restricted to one hemisphere ($p<0.001$) or cortical lesions only ($p=0.258$) were found more frequently in patients older than 75 years, whereas typical cortical and basal ganglia hyperintensities were more common in the younger group ($p=0.001$).

Conclusion: We demonstrated for the first time that patients with late-onset sCJD differ from younger sCJD patients with respect to MRI profiles and initial clinical presentation but not CSF markers. Misclassification of CJD cases older than 75 years seems likely due to atypical clinical and radiological presentation. This might contribute to lower sCJD incidence rates in this age group.

Keywords:

Creutzfeldt-Jakob disease, late-onset dementia, diagnostic criteria, misclassification, MRI

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare fatal prion disease typically associated with rapid-progressive dementia, ataxia, visual symptoms and myoclonus. According to the underlying cause of disease, it can further be divided into genetic, iatrogenic and sporadic CJD (sCJD). [7, 13]. Whereas a definite diagnosis is restricted to neuropathological examination, in vivo diagnosis of sCJD is based on clinical symptoms, cerebrospinal fluid (CSF) markers, MRI and EEG profiles [15, 17]. Six molecular subtypes (MM1, MM2, MV1, MV2, VV1, VV2) of sCJD have been identified [11]. Classification is based on the methionine-valine polymorphism at codon 129 of the Prion Protein gene (*PRNP)* and on two distinct types of prion protein (PrP^{Sc} type 1 and 2). Subtypes differ from each other with respect to disease course, survival time, CSF and MRI profiles [11, 13].

Although sCJD is transmissible from one patient to another by transfer of neuronal tissue and is thereby showing infectious features, it is primarily seen as a neurodegenerative disease [12]. Age-specific incidence rates increase with age in most neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease) [9]; however, sCJD incidence rates are highest between 60 and 75 years of age and drop down thereafter [1, 4, 5]. The drop was located at a cut-off of 75 years in a US-based study by Holman et al., whereas it seemed to be slightly higher in two European studies available. However, age is grouped in bands of 10 years in these studies and a re-analysis of the data from the study of Heinemann et al. could confirm a cut-off of 75 years in this study population at well.

Reasons for lower incidence rates in patients older than 75 years have proposed in recent years. While some researchers argued that this finding might support the hypothesis of the transmission of an infectious agent within a specific age frame and with a specific incubation period, others attributed the lower rates in the oldest age groups to surveillance problems based on atypical clinical presentation and misclassification as other types of dementia [1, 3]. The latter hypothesis is supported by the observation that age-specific sCJD incidence rates have been increasing in these age groups in those countries that started an active CJD surveillance program [2, 4, 14].

Despite this unsolved epidemiological peculiarity of sCJD, there are no data available describing the characteristics of CJD in the very old.

It was therefore, the aim of this study to investigate characteristics of patients with late-onset sCJD and to evaluate how these characteristics might contribute to decreasing incidence rates in individuals over 75 years of age.

Methods

Study design and study population

This is a historical cohort study using data from an ongoing surveillance study of the German national reference centre for Transmissible Spongiform Encephalopathies (NRZ-TSE). In Germany, all patients suspected to suffer from CJD are referred to the NRZ-TSE for expert opinion. These patients are then followed up until an alternative diagnosis can be established or until death. Patients are visited by a study physician at the point of diagnosis; regular phone calls with relatives and family doctors are performed thereafter.

Patients were considered for inclusion in this study, if they were diagnosed with probable or definite CJD between 2001 and 2012. All patients with familiar or iatrogenic CJD were excluded. In this time period 1,442 sCJD patients were identified via the German surveillance system. For inclusion in this study, patients must have been examined by a study physician of the NRZ-TSE according to standardized protocols. In addition, MRI scans of the patients must have been available to the study investigators.

An age older than 75 years at disease onset was defined as the exposure of interest. A total of 297 patients with definite or probable sCJD could be identified in this age range representing 20.6% of all patients with a probable or definite diagnosis between 2001 and 2012. After applying the inclusion criteria as stated above, 73 individuals older than 75 years (>75 years) were identified and included in this study. 121 (40.7%) of the 224 patients excluded from the study were not visited by a study physician, 28 (9.4%) did not provide a MRI scan to the study investigators and 75 (25.3%) of the 224 were neither visited nor did they provide a MRI scan. There were no significant differences between included and excluded patients in age, sex, duration of disease, autopsy rates and proportion of available subtypes.

Seventy-three (73) patients were selected as the non-exposed comparison group from all sCJD patients younger than 75 years (<75 years) at disease onset (diagnosed with sCJD between 2001 and

2012 and eligible to this study with respect to the above named inclusion and exclusion criteria) by using a random selection process. The selected patients were shown to be representative for the source population with respect to age, sex, duration of disease, autopsy rates and proportion of available subtypes

For use as a cohort study, first day of follow-up was defined as the date of first symptom; all patients were followed up until death.

Diagnostic tests

Clinical presentation

All patients enrolled in this study were examined by a study physician according to a standardized protocol including neurological examination and neuropsychological testing. Patient's history was taken from each patient using a) semi-structured interviews with close relatives, b) interviews with attending physicians and primary physicians, c) hospital records. Duration of disease (from date of first symptom until death) was split into three parts of equal length for each individual patient in order to provide a time frame which allows accounting for differences in disease progression (first, second and third part of disease).

CSF analyses

Protein 14-3-3 was analysed in all study participants by Western blot according to previously published protocols [6, 16]. Western blot results were classified in a binary way (negative= no band present, positive= band present). A positive and negative control was added to each blot for quality control. CSF Tau protein was quantitatively analysed using a commercially available ELISA according to the manufacturer's instructions (Innogenetics, Ghent, Belgium). A positive Tau-test was considered at a cut off level >1300pg/ml [10].

EEG analyses

EEGs were reviewed by a study physician (LR) according to WHO criteria for EEG profiles in CJD patients [15]. EEG profiles were reviewed by a second study physician (AK) in a random subsample of study participants to check for inter-reader reliability. Both investigators were blinded to the exposure status of the respective patient.

MRI analyses

MRI profiles of all study participants were assessed by a study physician (LR) according to a standardized protocol. The protocol used in this study included pathological findings in three different MRI weightings (DWI, FLAIR, T2) as well as brain atrophy and white matter lesions. Findings were classified as abnormal if present in at least one weighting. The term “hyperintensities” was used for describing typical sCJD findings (high signal abnormalities in DWI/FLAIR). MRI profiles were reviewed by a second study physician (DS) in a random subset of study participants to check for inter-reader reliability. Both investigators were blinded to the exposure status of the respective patient. In case of differing judgments for EEG or MRI, cases were discussed between reviewers and a consensus opinion was formed.

Statistical analyses

Data analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, USA). Categorical outcome variables were assessed using cross tabulation, Odds Ratios (OR) and chi-square or Fisher’s tests as appropriate. Continuous variables were described using means (with standard deviation [SD]) and medians (with interquartile range [IQR]) and were analysed using t-tests and Wilcoxon Rank sum tests as appropriate. Due to differences in time from first symptom to diagnosis, multivariable analyses were performed using logistic regression models and multiple linear regression models as appropriate. Survival analyses for time from first symptom to diagnosis and for time from first symptom to death were performed with Kaplan-Meier estimates and Cox regression models. For all multivariable analyses, exposure variables and potential confounders were initially tested individually for their effect on the outcome of interest. Potential confounders were then introduced in the model in the order of their univariable effect. A forward selection process was chosen to assess the influence of potential confounders on the effect of the exposure of interest. Variables were defined as confounders and kept in the model, if they were associated with the exposure of interest as well as with the outcome and if the effect size of the exposure was changed by at least 10%.

Sensitivity analyses

Several sensitivity analyses were performed in this study. At first, the main analyses of this study were repeated restricting the study population to definite sCJD cases only. A second sensitivity analysis

was then performed with a cut-off of 80 years in order to allow for potential uncertainties in previous incidence studies.

Ethics approval

This study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was given by all study participants or their legal next of kin. Ethics approval was obtained from the local Ethics Committee of the University of Göttingen (Study 11/11/93).

Results

73 patients older than 75 years and 73 patients younger than 75 years with probable or definite sCJD were included in this historical cohort study. Individuals older than 75 years were slightly more likely to be female (63.0% vs. 50.7%, p=0.133), but were less likely to get autopsied (45.2% vs. 58.9%, p=0.098) or to be investigated for molecular subtype (13.7% vs. 49.3%, p<0.001) than patients younger than 75 years (Table 1). The proportion of missing values for molecular subtype was high in both groups (86.3% vs. 50.7%), so that the observed pattern of molecular subtypes cannot be generalized to the respective groups. However, MM1 subtypes were more frequent in the older patient group, whereas atypical subtypes such as MM2 and VV1 were only found in the younger age group (Table 1). Older individuals had a faster course of disease represented by a shorter time from first symptom to diagnosis and by a shorter survival time when compared to the younger patient group (Hazard Ratio [95% Confidence Interval]: 2.36 [1.65-3.38] and 2.08 [1.48-2.94], Figure 1). When restricting the analysis to the initial clinical presentation (representing the first third of disease duration), the older study group showed slightly more often symptoms of dementia (p=0.127) and dysarthria (p=0.238), whereas visual disorders (p=0.015), extrapyramidal signs (p=0.056), vertigo (p=0.043) and myoclonus (p=0.028) were considerably more frequent in the younger group (Table 2).

When expanding this analysis to the entire duration of disease patients under 75 years were more likely to develop vertigo (p=0.007) and visual symptoms (p=0.010), whereas patients over 75 years had a higher risk of the presence of pyramidal signs (p=0.098, Table 2).

No differences could be shown in CSF biomarker profiles or EEG profiles between groups. This did not change after adjusting for time from first symptom to the date of the respective CSF or EEG investigation (Table 3).

MRI profiles of patients older than 75 years were significantly less frequently compatible with established MRI criteria for sCJD than MRI profiles of the younger group (Odds Ratio [OR], 95% Confidence Interval [CI]: 0.14 (0.04 – 0.43)). Typical DWI and FLAIR hyperintensities of the cortex and the basal ganglia could be shown in 36.1% and 58.3% respectively of the older patients, but in 61.6% and 83.6% of the younger patients (Table 4, $p<0.001$). Atypical presentations with pathological hyperintensities restricted to one hemisphere (12.3% vs 0.0%) or restricted to cortical regions only (15.1% vs. 9.6%) were found more often in patients older than 75 years. As expected, white matter lesions were found more often in the older (67.6% vs. 39.7%, $p<0.001$), whereas there was no difference in the frequency of brain atrophy between groups (19.2% vs. 26.0%, $p=0.322$, Table 4). Results could be confirmed in a multivariable analysis adjusted for sex, time from first symptom to MRI and level of diagnosis.

Sensitivity analyses restricted to definite sCJD cases only (n=33 in the older group vs. n=43 in the younger group) or patients above the age of 80 (n= 23) showed results consistent with the primary analyses of this study.

Discussion

The aim of this study was to compare characteristics of late-onset sCJD patients with those of younger sCJD patients in order to derive hypotheses for the reasons of low sCJD incidence rates in individuals older than 75 years. In this study we have demonstrated for the first time that sCJD patients older than 75 years differ from younger sCJD patients with respect to MRI profiles and initial clinical presentation, but not with respect to CSF markers or EEG profiles.

Symptoms typically associated with sCJD could be observed more frequently in the younger age group in both early and late disease (Table 2). However, dementia, dysarthria and pyramidal signs were seen more often in late-onset sCJD cases. Although all patients were systematically examined by trained study physicians, the first examination typically took place after the first third of disease duration so that differences in this time interval could be attributable to information bias e.g. since

younger patients are reviewed more thoroughly by primary care physicians. However, this can be excluded for differences observed thereafter.

We found no differences in CSF markers both when adjusted for the timing of lumbar puncture and when not. MRI profiles were available for all participants. Presentations compatible with established diagnostic criteria for sCJD were less frequently observed in older individuals. Interestingly, late-onset sCJD patients not only showed typical MRI profiles less frequently, but also exhibit atypical patterns like DWI and FLAIR hyperintensities restricted to one hemisphere or to cortical regions only more often.

One might assume that observed differences between older and younger sCJD patients are due to the faster course of disease in late-onset sCJD patients resulting in an earlier diagnosis and thereby also in a less typical clinical presentation and MRI pattern. However, multivariable analyses adjusted for differences in time to diagnosis confirmed the primary results of this study and showed that observed differences between both groups were independent of different disease progression rates.

This study included the largest sample of late-onset sCJD cases investigated so far. However, the present study was restricted to sCJD cases which were suspected to be a case pre-mortem and which were diagnosed in collaboration with the German National reference centre. Therefore, it must be kept in mind that features identified in this study do not necessarily apply to late-onset CJD patients who have not been identified correctly within the German surveillance system. However, in a sensitivity analysis restricted to definite sCJD cases only, the major results of this study could be confirmed.

Since only patients with available MRI scans were included in this study, the study might have been prone to selection bias by over-representing those patients in need of extensive diagnostic procedures and thereby those with an atypical course of disease. However, this would not have affected the older patients only, since the same inclusion criteria were applied for both older and younger patients. The exclusion of patients without an available MRI might have reduced the generalisability of our study, but has not affected the validity of the study results. In addition, we could confirm, that patients older than 75 years included in this study were representative for all patients older than 75 in our database with respect to age, sex, duration of disease, autopsy rates and proportion of available subtypes

A major limitation of our study is the low proportion of patients with identified subtypes within the study population. It is possible that observed differences between groups are at least partly due to

differences in subtypes. When looking only at patients with identified subtypes, late-onset sCJD cases harbored more often MM1 subtypes than younger CJD patients; there were no atypical subtypes in this patient group. This is consistent with existing evidence showing that isolated cortical hyperintensities are more common in patients with PrP^{Sc} Type 1 [8]. However, the observed differences in subtypes in our study must be evaluated in the light of the extremely high proportion of missing values. While there is no evidence that systematic differences in subtypes are responsible for the observed clinical and MRI differences, it cannot be ruled out due to the high proportion of missing subtypes. This limitation does not affect the clinical relevance of the study as the observed differences are important for the assessment of the clinical diagnosis independently of subtype distributions in the respective age groups. However, it will be interesting for future prospective studies to confirm the results of this study within a study population with high proportions of definite subtypes.

As a result of this study it can be concluded that patients older than 75 years detected by current diagnostic guidelines seem to display more commonly atypical features with respect to clinical and MRI characteristics. Some of these characteristics may be attributable to molecular subtypes that differ between the two groups. It must be kept in mind, that the conclusions drawn from this study are limited by the fact that the study is restricted to sCJD cases which have been diagnosed given our current ability to detect sCJD and might not be transferable to the cases we do not detect.

However, due to

(1) the rapid course of disease,
(2) a less impressive initial clinical presentation (frequently, as dementia)
(3) atypical MRI profiles

it seems likely, that a considerable proportion of late-onset sCJD cases are not identified correctly and are misdiagnosed as other forms of dementia. Awareness of this variation in clinical presentation and MRI findings in older patients could improve the detection of sCJD in the more elderly. This might be helpful for both correct diagnostic classification in future studies and the application of potential treatments.

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Conflict of interests

The authors declare that they have no conflict of interest.

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Tables:

Table 1: Baseline characteristics by age at onset

		Group older than 75 years (n=73)		Group younger than 75 years (n=73)		
		n=	in %	n=	in %	p-value
Sex	Male	27	37.0	36	49.3	0.133**
	Female	46	63.0	37	50.7	
Subtype	MM-1	7	9.6	15	20.5	-
	MM-2	0	0	4	5.5	
	MV-1	0	0	3	4.1	
	MV-2	1	1.4	3	4.1	
	VV-1	0	0	2	2.7	
	VV-2	2	2.7	9	12.3	
	Missing	63	86.3	37	50.7	<0.001*
Diagnosis	probable	40	54.8	30	41.1	0.098**
	definite	33	45.2	43	58.9	
		Median	IQR***	Median	IQR	p-value
Age (in years)		77.9	76.8 – 80.6	63.0	56.8 – 69.7	<0.001**

*Chi-square tests
**Wilcoxon Rank sum test
***Interquartile range

Table 2: Clinical signs and symptoms during first third of disease duration and during the total duration of disease (by age at disease onset)

	Present within first third of disease					**Present at any point of disease**				
Symptoms	Group older than 75 years (n=73)		Group younger than 75 years (n=73)			Group older than 75 years (n=73)		Group younger than 75 years (n=73)		
	Number (n=)	Percent (%)	Number (n=)	Percent (%)	p-value*	Number (n=)	Percent (%)	Number (n=)	Percent (%)	p-value*
Dementia	49	67.1	40	54.8	0.127	73	100	73	100	1.000
Visual disorders	13	17.8	26	35.6	0.015	19	26.0	34	46.6	0.010
Gait disturbance	44	60.3	42	57.5	0.737	69	94.5	70	95.9	0.757
Vertigo	15	20.5	26	35.6	0.043	15	20.5	30	41.1	0.007
Psychiatric symptoms	23	31.5	30	41.1	0.228	36	49.3	44	60.3	0.183
Aphasia	22	30.1	23	31.5	0.858	41	56.2	48	65.8	0.309
Dysarthria	13	17.8	8	11.0	0.238	35	47.9	41	56.2	0.320
Myoclonus	0	0.0	6	8.2	0.028	55	75.3	57	78.1	0.695
Akinetic mutism	0	0.0	3	4.1	0.245	73	100	73	100	1.000
Pyramidal signs	3	4.1	4	5.5	1.000	40	54.8	30	41.1	0.098
Extrapyramidal signs	4	5.5	11	15.1	0.056	46	63.0	48	65.8	0.730

*Chi square test or Fisher's exact test as appropriate

Table 3: CSF biomarkers and EEG characteristics by age at disease onset

Marker	**Group older than 75 years (n=73)**	**Group younger than 75 years (n=73)**	**p-value**
	Median (IQR)		
T-Tau (pg/ml)	5228 (3452 – 11418)	5003 (2630 – 10768)	0.733***
	Positive n= (%)		
Proteins 14-3-3	69 (94.5%)	70 (95.9%)	0.698****
T-Tau**	61 (85.9%)	64 (88.9%)	0.592****
EEG**			
normal	1 (1,4%)	1 (1,5%)	0.667*****
General alterations	32 (44,4%)	30 (44,8%)	
Triphasic waves, non-periodic	15 (20,8%)	10 (14,9%)	
Periodic triphasic waves	24 (33,3%)	27 (40,3%)	

**A positive T-Tau was estimated as >1300 pg/ml
***using multiple linear regression adjusted for sex and time from onset of symptoms
****Chi square tests
*****Fisher's exact test

Table 4: MRI characteristics by age at disease onset

	Group older than 75 years (n=73)	**Group younger than 75 years (n=73)**	**OR (95% CI)***	**p-value****
sCJD MRI criteria fulfilled	50 (68.5%)	68 (93.2%)	0.14 (0.04 – 0.43)	<0.001
Basal ganglia hyperintensities	42 (58.3%)	61 (83.6%)	0.26 (0.11 – 0.60)	0.001
Thalamic hyperintensities	9 (12.5%)	21 (28.8%)	0.28 (0.11 – 0.70)	0.016
Cortical hyperintensities	26 (36.1%)	45 (61.6%)	0.36 (0.18 – 0.74)	0.003
Cortical hyperintensities only	11 (15.1%)	7 (9.6%)	1.68 (0.51 – 4.89)	0.258
Unilateral hyperintensities	9 (12.3%)	0 (0,0%)	-	<0.001
Atrophy	14 (19.2%)	19 (26.0%)	0.85 (0.36 – 2.00)	0.322
White matter lesions	48 (67.6%)	29 (39.7%)	3.19 (1.54 – 6.59)	<0.001

*Odds Ratio (95% Confidence Intervall) adjusted for sex and time from onset of symptoms
**Wald test

Figure legends:

Fig. 1 Survival time (1a) and time to diagnosis (1b) by age at disease onset. Grey lines represent the group older than 75 years, black lines the group younger than 75 years at disease onset. Hazard Ratios and p values of Likelihood Ratio Tests are displayed in 1c (CI stands for confidence interval, LRT for Likelihood Ratio Test).