Psychiatric Symptoms in Patients With Sporadic Creutzfeldt-Jakob Disease in Germany

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ABSTRACT

Background: Psychiatric symptoms in sporadic Creutzfeldt-Jakob disease (sCJD) are still not sufficiently evaluated.

Aim: To describe psychiatric symptoms in sCJD with respect to molecular subtype.

Method: Patients in this retrospective study were classified according to established diagnostic criteria. 248 sCJD patients with known molecular subtype were recruited from January 1993 to December 2004 and investigated. Psychiatric symptoms were defined according to Möller and colleagues and the AMDP system (Study Group for Methods and Documentation in Psychiatry) and were collected by direct examination by study physicians or extracted from medical documentation. Our data were compared with published data on variant CJD (vCJD).

Results: Psychiatric symptoms were common in sCJD patients (90%) and mostly found already at the disease onset (agitation in 64% of the patients, hallucinations in 45%, anxiety in 50%, depression in 37%). All psychiatric symptoms but illusions were found early in the disease course. Psychiatric symptoms in sCJD were less frequent than in vCJD.

Conclusions: We provide the first detailed analysis of psychiatric symptoms in a large group of patients with sCJD with respect to differences concerning frequency and time point of occurrence of psychiatric symptoms between molecular subtypes. These data suggest that psychiatric symptoms occurring early in the disease course are common not only in vCJD but also in other CJD types.

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Human prion diseases are transmissible diseases caused by accumulation of pathological prion protein (PrPSc) in the central nervous system. About 85% of cases are sporadic.[1,2] The polymorphism at codon 129 of the prion protein gene (PRNP) and the PrPSc types 1 and 2 were the basis for a molecular classification of sporadic Creutzfeldt-Jakob disease (sCJD), which showed a good correlation with the clinical and pathological phenotype of sCJD.[3] M129 V polymorphism of the PRNP and PrPSc type were shown to influence the disease duration, clinical course, age at onset, and other disease features. However, while psychiatric symptoms are considered important and are well documented in new variant CJD (vCJD), and early psychiatric symptoms are even a part of diagnostic criteria of vCJD,[4] only few studies have investigated psychiatric symptoms in sCJD. Data on PrPSc type or M129 V polymorphism are constantly missing in these studies, the number of patients investigated is rather limited, patients with probable and not definite sCJD are also included, and the data acquisition and evaluation vary considerably and hamper the comparability of the data. Therefore, the aim of this study was to provide a detailed analysis of psychiatric symptoms in a large group of patients with probable and definite sCJD with respect to M129 V genotype and PrPSc type.

There are many difficulties in evaluation of psychiatric symptoms in CJD patents. Especially the classical sCJD subtype is rapidly progressive, and most patients are too ill at the time point of physician contact to undergo complex, stressful, and time-consuming tests. Communication with the patients is often hampered by aphasia and prominent dementia. Most CJD surveillance units are run by neuropathologists, neurologists, and epidemiologists and not by psychiatrists, and most notifications to the CJD surveillance units are also done by neurologists. Thus, the quality of the data and the number of the data are limited, although physicians treating sCJD patients are faced with psychiatric symptoms in increasingly demented patients. This article aims to describe the spectrum of psychiatric presentation in CJD to focus future clinical examination on this particular point and for more accurate diagnosis and early adequate treatment.

METHOD

Study Design

German patients with suspected CJD were reported to the CJD Surveillance Unit in Göttingen and examined on site. Cerebrospinal fluid, blood samples, and copies of the important diagnostic tests such as laboratory tests, electroencephalogram, and magnetic resonance imaging (MRI) were taken.[2] Detailed questionnaires were filled out with the relatives. After complete description of the study to the subjects, written informed consent was obtained. The patients were classified according to established diagnostic criteria.[5–7] Psychiatric symptoms were defined according to Möller et al[8] and the AMDP system (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie [German] = Study Group for Methods and Documentation in Psychiatry)[9] and were collected by direct examination by study physicians or extracted from medical documentation. A psychiatric symptom was counted as present if it was observed by study physicians during examination or mentioned in the medical documentation or clearly described in the medical documentation, independently from the extent of the symptom. The present study is a retrospective study.

Clinical Points

- Psychiatric symptoms occurring early in the disease course are common not only in variant Creutzfeldt-Jakob disease (CJD) but also in sporadic CJD.
- Sporadic CJD is not only a neurologic but a neuropsychiatric disorder.
- Although the clinical diagnosis of sporadic CJD has improved from several years ago, no specific treatment is currently available.

According to AMDP, *irritability* was defined as an undercurrent of anger or aggressiveness, *hallucinations* as perceptual experiences without a corresponding stimulus in the environment, *illusions* as misinterpretation of a real perception (the presence of a real object as differentiation from a hallucination). *Depression* (depressed mood) was defined as negatively tinged affective state characterized by lowered mood and experienced as sadness. Depression covers a wide spectrum of feelings, from sadness, uneasiness, being downcast, loss of pleasure, dullness, dejectedness, and loss of interest to feelings of grief, sorrow, despair, helplessness, and extreme inner torment. *Affective lability* was defined as rapid changes in affect or a kind of affect variability in which an affect persists for only a very short period and shows many ups and downs. *Anxiety* was defined as fearfulness or apprehensive feelings without specification or objective basis. *Delusions* were defined as a disease-induced failure in reality testing that is maintained on the basis of subjective belief and a priori evidence. A delusion is a contradiction of reality that is not supported by the collective beliefs and concepts of humankind. *Agitation* (or motor restlessness) was defined as aimless and purposeless motor activity. *Apathy* was defined as a lack of feeling, emotion, or interest. It is a state of indifference or the suppression of emotions such as concern, excitement, and motivation.

Neuropathological and Molecular Studies

Western blot analysis, analysis of the *PRNP*, and immunohistochemistry were performed by standard methods.[10–12] Patients with CJD without *PRNP* mutations or evidence of iatrogenic CJD with known PrP^{Sc} type recruited from January 1993 to December 2004 were included in this study.

Statistical Analysis

Significance values (*P*) were tested by the SAS software (version 9.3) (SAS Institute, Cary, North Carolina). Categorical parameters such as gender or psychiatric symptoms were described by absolute and relative frequencies. Continuous parameters such as age at onset were described by mean ± SD. All comparisons between molecular subtypes were done using a nonparametric rank-based procedure.[13] In case of global significance, pairwise comparisons between all subgroups were performed. The Bonferroni method was applied to control the type I error rate. A *P* value < .05 was considered statistically significant.

RESULTS

Study Collective

Two hundred forty-eight patients with definite sCJD, known M129 V polymorphism and PrP^{Sc} type who were registered at the CJD Surveillance Center in Göttingen in the time period from January 1993 to December 2003 were included in this study. A further 272 patients were excluded from the study, as M129 V polymorphism, PrP^{Sc} type, or both were unknown or no definite CJD could be diagnosed. Two methionine homozygous patients with pathological prion protein type 2 (MM2) were excluded from the study, for they were of thalamic type (very rare subtype of MM2 with distinct clinical features and therefore it did not occur often enough for any statistical analysis and would be a bias source if it were analyzed together with cortical subtype), whereas all other MM2 patients were of cortical type (MM2c). There were 140 female and 108 male patients (ratio = 1.3:1.0). There was significant difference concerning sex distribution between different sCJD subtypes. In valine homozygous sCJD patients with pathological prion protein type 1 (VV1), there were significantly more male patients compared to other subtypes (*P* adjusted by Bonferroni method [*P* adj] < .0001 in methionine homozygous sCJD patients with pathological prion protein type 1 [MM1], *P* adj = .0105 in methionine valine heterozygous patients with pathological prion protein type 2 [MV2], and *P* adj = .00225 in valine homozygous sCJD patients with pathological prion protein type 2 [VV2]). Data on age, sex, and disease duration stratified by molecular subtype are shown in Table 1. VV1 patients were at disease onset at a significantly younger age than other subtypes (*P* adj < .001 for all subtypes but methionine valine heterozygous sCJD patients with pathological prion protein type 1 [MV1] [here, *P* adj = .0004]). The shortest disease duration was found in MV1 (median = 4.5 months), and VV1 had the longest duration (median = 17.5 months; *P* adj < .0001). There were also significant differences concerning disease duration between VV1, MM1 (*P* adj < .0001), and VV2 (*P* adj = .0105), as well as between MM1, MM2c (*P* adj = .00133), MV2 (*P* adj < .0001), and VV2 (*P* adj = .0060). Furthermore, there were significant differences between MV2, MV1 (*P* adj < .002), and VV2 (*P* adj < .0001). The most frequently occurring subtype was MM1 (61%), and VV1 was the rarest (4%).

Frequency of Psychiatric Symptoms and Time Point of Occurrence

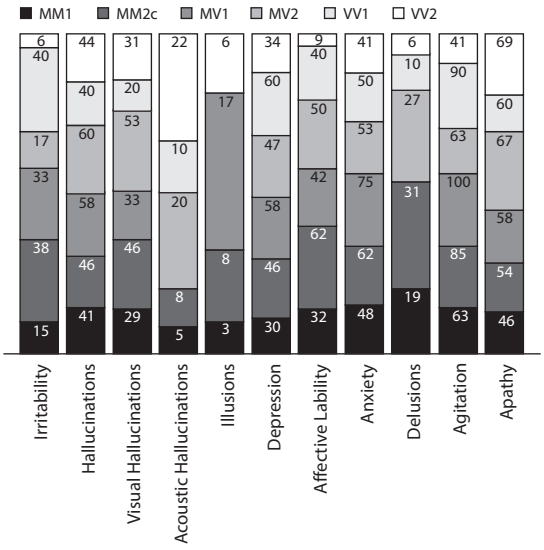
Frequency of psychiatric symptoms stratified by molecular subtype is shown in Figure 1. Psychiatric symptoms were common (90%) in all sCJD patients, with no significant differences between molecular subtypes. Agitation occurred in two-thirds of the patients, hallucinations and anxiety in about one-half of the patients, and depression in one-third.

Table 1. Data on Sex, Age at Onset, and Disease Duration Stratified by Molecular Subtypes in Patients With Sporadic Creutzfeldt-Jakob Disease (sCJD)

Variable	All Patients	MM1	MM2c	MV1	MV2	VV1	VV2
Patients, n (%)	248 (100)	151 (61)	13 (5)	12 (4.5)	30 (12)	10 (4)	32 (13.5)
Male patients, n (%)	108 (43.5)	58 (38.4)	7 (53.9)	6 (50)	13 (43.3)	9 (90)	15 (47)
Female patients, n (%)	140 (56.5)	93 (61.6)	6 (46.1)	6 (50)	17 (56.7)	1 (10)	17 (53)
Duration, mo							
Median	6	4.75	15	4.5	13	17.5	6.75
Range	1.5–50	1.5–38	4–24	3–21	4–32	8–50	3–15
Mean ± SD	8.7 ± 7.3	6.8 ± 6.2	13.1 ± 7.1	6.5 ± 5.2	14.8 ± 6.4	21.3 ± 11.7	7.4 ± 2.9
Age, y							
Median	64.5	67	68	62.5	63	42.5	65.5
Range	19–85	31–85	47–82	53–79	49–75	19–55	40–81
Mean ± SD	64.5 ± 9.9	66.5 ± 8.6	66.5 ± 9.0	61 ± 8.4	63.6 ± 6.5	37.9 ± 11.4	64.8 ± 9.6

Abbreviations: MM1 = methionine homozygous sCJD patients with pathological prion protein type 1; MM2c = methionine homozygous sCJD patients with pathological prion protein type 2, cortical subtype; MV1 = methionine valine heterozygous sCJD patients with pathological prion protein type 1; MV2 = methionine valine heterozygous sCJD patients with pathological prion protein type 2; VV1 = valine homozygous sCJD patients with pathological prion protein type 1; VV2 = valine homozygous sCJD patients with pathological prion protein type 2.

Figure 1. Frequency of Psychiatric Symptoms Stratified by Molecular Subtype



Abbreviations: MM1 = methionine homozygous sCJD patients with pathological prion protein type 1; MM2c = methionine homozygous sCJD patients with pathological prion protein type 2, cortical subtype; MV1 = methionine valine heterozygous sCJD patients with pathological prion protein type 1; MV2 = methionine valine heterozygous sCJD patients with pathological prion protein type 2; sCJD = sporadic Creutzfeldt-Jakob disease; VV1 = valine homozygous sCJD patients with pathological prion protein type 1; VV2 = valine homozygous sCJD patients with pathological prion protein type 2.

Visual hallucinations occurred significantly more often than acoustic hallucinations ($P < .001$). Psychiatric symptoms were found early in the disease course (median disease duration = 0 months). Sequence of occurrence of psychiatric symptoms stratified by molecular subtype and time period in disease course is shown in Table 2.

Irritability. Irritability was observed after a median disease duration of 1 month and occurred in 17% of the patients. It was most frequent in VV1 patients (40%) and rare in VV2 patients (6%). However, there was no significant difference concerning the frequency and the time point of occurrence (1 month in MM1 and VV1, 3 months in MM2c and MV1, 5 months in MV2 and VV2 patients) between the subtypes.

Hallucinations. Hallucinations were common (45%) in sCJD patients. They occurred after a median disease duration of 2 months. Visual hallucinations were significantly more common than acoustic ($P < .001$), tactile hallucinations were seen in only 1 patient (MV2 subtype), and no other types of hallucinations were reported. There were no significant differences concerning frequency and time of occurrence between the subtypes. However, in MM2c patients, hallucinations occurred as late as 6.5 months after disease onset; in MV2 patients, after 5 months; in MM1 patients, as early as in 1 month; in MV1 patients, in 2 months; and in VV2 patients, in 2.5 months.

Illusions. Illusions occurred after a median disease duration of 4 months and were rare (5%) in our patients. They did not occur in MV1 or VV1 patients. They were more rare and appeared significantly later in MV2 (17%) than in MM1 (3%) patients (P adj = .0169). In VV2 patients, they appeared after a median disease duration of 0.5 months; in MM1, after 2 months; in MV2, after 5 months; and in MM2c, as late as after 11 months.

Depression. Depression occurred in 37% of the patients after a median disease duration of 1 month. The frequency was between 31% (MM1 patients) and 60% (VV1 patients). However, there was no statistically significant difference between the subtypes concerning the frequency and the time point of occurrence (0 months in MV1; 1 month in MM1; 2 months in MM2c, MV2, and VV2 patients; 3.5 months in VV1 patients).

Affective lability. Affective lability occurred after a median disease duration of 2 months and was found in 34% of the patients, with the frequency of only 9% in VV2 patients, but up to 62% in MM2c patients. However, the difference between the subtypes concerning frequency (Figure 1) and time point of occurrence (1 month in MM1

Table 2. Comparison of Occurrence of Psychiatric Symptoms Stratified by Molecular Subtypes and Time Period in Disease Course (by thirds) in Patients With Sporadic Creutzfeld-Jakob Disease (sCJD)

	Disease Course		
Subtype	First Third	Second Third	Final Third
All subtypes	Irritability, hallucinations (visual/acoustic), depression, affective lability, anxiety, delusions/paranoia, agitation, apathy	Illusions	
MM1	Irritability, hallucinations (visual/acoustic), illusions, depression, affective lability, delusions/paranoia, agitation, apathy		
MM2c	Irritability, depression, affective lability, anxiety, agitation, apathy	Visual hallucinations, delusions/paranoia	Acoustic hallucinations, illusions
MV1	Depression, affective lability, agitation, apathy	Acoustic hallucinations, irritability, anxiety	Visual hallucinations
MV2	Depression, agitation, delusions/paranoia, apathy	Hallucinations (visual/acoustic), irritability, illusions, affective lability, anxiety	Tactile hallucinations
VV1	Irritability, depression, anxiety, agitation, delusions/paranoia, apathy	Hallucinations (visual/acoustic), affective lability	
VV2	Depression, anxiety, agitation, delusions/paranoia, acoustic hallucinations, illusions, apathy	Visual hallucinations	Irritability, affective lability

Abbreviations: MM1 = methionine homozygous sCJD patients with pathological prion protein type 1; MM2c = methionine homozygous sCJD patients with pathological prion protein type 2, cortical subtype; MV1 = methionine valine heterozygous sCJD patients with pathological prion protein type 1; MV2 = methionine valine heterozygous sCJD patients with pathological prion protein type 2; VV1 = valine homozygous sCJD patients with pathological prion protein type 1; VV2 = valine homozygous sCJD patients with pathological prion protein type 2.

and MV1, 3 months in MM2c, 5 months in VV2, 6 months in MV2, and 7 months in VV1 patients) was not statistically significant.

Anxiety. Anxiety was found in 50% of the patients and occurred after a median disease duration of 1.75 months. There were no significant differences concerning frequency (Figure 1) or time point of occurrence between different subtypes (median of 1 month in MM1; 2 months in MV1, VV1, and VV2; 3 months in MM2c; and 4.5 months in MV2 patients).

Delusions. Delusions occurred after a median disease duration of 1 month and were reported in 17% of the cases. They were not observed in MV1 patients and were rarer in VV2 (6%) than in MM2c (31%) and MV2 patients (27%); however, the difference was not statistically significant. Persecutory delusion was the most common delusion reported (77% of patients with delusions). In 8 cases (19%), there were other delusions (delusion of poisoning, delusion of guilt); in 3% the content of delusion was not reported. Delusions occurred in MM1 patients after a median disease duration of 1 month, in VV2 after 1.5 months, in VV1 after 2 months, in MV2 after 4 months, and in MM2 patients after 5.5 months, but there were no significant differences concerning time point of occurrence.

Agitation. Agitation occurred after a median disease duration of 1 month, was rather common in sCJD patients (64%), and was statistically significantly different between the subtypes ($P = .0021$). It was significantly more common in MM2c (85%, P adj = .0145) and VV1 (90%, P adj = .0027) than in VV2 patients (41%). There was no significant difference concerning the time point of occurrence, although it occurred after a median duration of 1 month in MM1 and MV1 patients, after 2 months in VV2, after 3 months in VV1, and after 4 months in MV2 patients.

Apathy. Apathy occurred in 53% of the patients, with the median time of occurrence of 1 month, and was more common in MM1 patients (46%) than in other subtypes. In MM1, apathy occurred earlier (after median disease duration of 1 month) than in VV2 (after median disease duration of 2 months). In MM2c (median = 0 months) and MV1 (median = 0 months), apathy occurred earlier than in MV2 (median = 2 months) and VV2 (median = 1.5 months); however, the differences were not significant.

Characterization of Molecular Subtypes

MM1 subtype. The MM1 patients showed all psychiatric symptoms evaluated already at the disease onset. Agitation (63%) and anxiety (48%) were the most frequent symptoms, followed by apathy.

MM2c subtype. All MM2c patients had psychiatric symptoms. Agitation (85%), anxiety (61.5%), and affective lability (62.5%) dominated the clinical picture. Although psychiatric symptoms usually did not occur at the disease onset (median = 3–4 months), they were already common in the first third of disease course. Agitation was significantly more common in MM2c (P adj = .0145) than in VV2 patients (41%). Hallucinations were found in MM2c patients significantly later than in MM1 patients (median = 6.5 months, P adj = .0053), while depression was frequent (58%) and occurred earlier in the disease course (median = 2 months).

MV1 subtype. The MV1 patients often showed psychiatric symptoms at disease onset. The most frequent symptoms were agitation (100%), anxiety (75%), depression (58%), and hallucinations (58%). While hallucinations were found in the second and final third of disease course, agitation and depression were seen early in the disease course and anxiety in the second third of disease course. Delusions did not occur in these patients.

MV2 subtype. MV2 patients showed a high frequency of agitation (63%), hallucinations (60%), and anxiety (53%). While agitation was seen already during the first third of disease course, hallucinations and anxiety did not occur before second third of disease course. Delusions were slightly

less common in MV2 than in MM2c patients, but they were more frequent than in other subtypes.

VV1 subtype. All VV1 patients had psychiatric symptoms, but these were mostly not present at the disease onset. Agitation (90%), depression (60%), and anxiety (50%) were the most common psychiatric symptoms. Agitation was significantly more common in VV1 (90%) than in VV2 (41%) patients (P adj = .0027). Hallucinations occurred in the second third of disease course and therefore later than agitation, depression, and anxiety. Frequency of all psychiatric symptoms investigated, except illusions and delusions, was at least 40%, rather high.

VV2 subtype. Although VV2 patients were less anxious and agitated than patients with other molecular subtypes, these symptoms (41% each) were only slightly less common than hallucinations (44%), which were the most frequently occurring psychiatric symptom. Agitation was significantly more common in MM2c (85%, P adj = .0145) and VV1 (90%, P adj = .0027) than in VV2 patients (41%). Interestingly, VV2 subtype was the only subtype in which irritability and affective lability were found as late as in the final third of disease course.

Patients With Psychiatric Presentation

Patients with isolated psychiatric presentation for at least 4 weeks were rare. Only 19 patients (10 MM1, 3 MV1, 1 VV1, 2 VV2, 0 MM2c, and 3 MV2) presented with psychiatric symptoms. There was no statistically significant difference in age, sex, subtype, or disease duration.

Comparison With vCJD

We compared our data on sCJD patients with those on vCJD by Zeidler et al.[14] Early psychiatric symptoms included in the vCJD criteria are anxiety, apathy, social withdrawal, delusions, and depression. As social withdrawal is rather nonspecific and may be, for example, part of depression or frontal lobe syndrome, we provide comparative data for apathy, anxiety, delusions, and depression. In addition, we also compared data on relevant noncriteria symptoms affective lability and visual and acoustic hallucinations with those from Zeidler et al.[14]

Anxiety in vCJD was significantly more common than in all sCJD patients (P adj = .0030). The differences to sCJD subtypes were not significant. Depression was significantly less frequent only in MM1 patients in comparison with vCJD. Apathy was also significantly more common in vCJD than in sCJD (P adj = .0030), with no difference between sCJD subtypes and vCJD. Delusions were significantly more frequent in vCJD than in all sCJD patients and in each molecular subtype, with P adj < .0001 for all subtypes but MM2c (P adj = .0149).

There was a statistically significant difference in affective lability between vCJD and all sCJD patients (P adj = .0420). It was also significantly more common in vCJD than in VV2 patients (P adj = .0032). Acoustic hallucinations were more often in vCJD than in sCJD; however, the difference was not statistically significant. For visual hallucinations, the differences were not statistically significant.

DISCUSSION

The main methodical limitation of this study is that no standardized, quantitative, prospective data evaluation was possible, so that the data acquisition and evaluation vary considerably and hamper the comparability of the data. However, sCJD is a rare and rapidly progressive disease, and study physicians are often involved late in the disease course so that aphasia or even akinetic mutism makes a systematic exploration of psychiatric symptoms very difficult. Furthermore, as there are no vCJD patients in Germany, we had to compare our data on sCJD with data on vCJD taken from the literature.

In this study, we have shown that certain symptoms and CJD subgroups are correlated. For future studies, it would be of great value to use symptoms in prediction models for CJD subgroups. Cluster analysis would be an adequate tool to illustrate that symptoms can be used to distinguish CJD subgroups. However, due to missing values, multivariate methods such as hierarchal clustering and principal component analysis would yield a biased view. In addition, we think that our study collective is too small to train a prediction model and make a sound validation of it. Nevertheless, our sCJD group is one of the largest studied so far and, to our knowledge, the largest one concerning the data on psychiatric symptoms. In this study, the detailed data on psychiatric symptoms in sCJD patients were evaluated in a representative group of patients from systematic surveillance, with consistent data collection in a single country. Moreover, only patients with definite sCJD, known M129 V polymorphism, and PrP^{Sc} type were included in the study allowing characterization of distinct molecular subtypes. We hope that our study gives important hints concerning characterization of sCJD subtypes.

In vCJD, psychiatric symptoms are well documented and a part of diagnostic criteria.[4,14] In contrast, most data on psychiatric features in sCJD are case reports or very small patient series,[15–19] and psychiatric symptoms are not a part of diagnostic criteria. The only larger study on psychiatric symptoms (126 patients) performed so far included 61% of patients with probable sCJD, and data on M129 V polymorphism or PrP^{Sc} type were not given.[20] Similar to our study, that study's retrospective nature and its use of chart review made it impossible to use a formal, objective, and standardized psychiatric assessment. Of course, this is a limitation of such studies. On the other hand, we can assume that real frequency of psychiatric symptoms may be even higher and spectrum of psychiatric features in sCJD may be even wider than spontaneously reported and noticed here.

A study by Wall et al[20] classified psychiatric symptoms in a different way than in our report. Data on anxiety, depression, agitation, and psychotic symptoms were available, but rather unspecific symptoms such as "sleep disturbance," which are not included in our study, have been also evaluated. Interestingly, disorganized thought process, speech, and behavior including confabulations and perseveration were classified as psychotic symptoms, although this attribution

is not common. Depressive symptoms included weight loss, although this symptom is unspecific, and common somatic causes, such as dysphagia, often found in CJD may also lead to weight loss.

The number of psychiatric symptoms in our study (90%) was similar to that found in a study by Wall et al (about 90%).[20] Thompson et al[21] observed behavioral and psychiatric symptoms in 79% of sCJD patients during the disease course. Our patients also showed psychiatric symptoms already at the disease onset (median = 0 months). Visual hallucinations were more common than auditory hallucinations, as usually seen in organic psychoses.[8] The frequency of hallucinations and delusions was similar to that in more common dementias such as multi-infarct dementia or Alzheimer's Disease.[22] Frequency of depression in patients in the study by Wall et al[20] was similar to that in our study, while anxiety and agitation were much more common in our patients.

Some psychiatric symptoms, such as hallucinations or anxiety, were found in all molecular subtypes, with nonsignificant differences in frequency; other symptoms, such as irritability, were rarely seen in some subtypes (VV2). It should be considered that absolute time data are not very meaningful, for disease duration highly varies by subtype, and a time period of 1 month has another relevance for median disease duration < 5 months (MV1) than for disease duration of 13.5 months (VV2). Therefore, we stratified time of occurrence of psychiatric symptoms by disease course thirds to achieve better comparability of the data (Table 2). In all sCJD patients together, all psychiatric symptoms but illusions were found already in the first third of disease course. However, this effect seems to be due to a high proportion of MM1 patients in sCJD, in whom all psychiatric symptoms are found already in the first third of disease course. In less-frequent subtypes, some psychiatric symptoms, such as hallucinations, occurred as rule in the second and final third of disease course.

Some studies have tried to find a relationship between psychiatric symptoms and imaging studies. Only few of them were focused on CJD. Kropp et al[23] reported a pronounced signal increase confined to the gray matter of the occipital and visual cortex on T2- and proton density–weighted images in patients with Heidenhain type CJD. However, not only visual hallucinations but also other visual symptoms were found in these patients. A case report by Tsivgoulis et al[24] reported an occipital cortical ribboning in diffusion-weighted (DWI) MRI in a CJD patient with prominent visual hallucinations initially mistaken for dementia with Lewy bodies (DLB). Patients with sCJD who met DLB criteria (including visual hallucinations) showed also cortical ribboning on DWI MRI.[25] In contrast, in patients with Parkinson's disease with visual hallucinations, ventral visual pathway showed abnormalities in 18F-fluordesoxyclucose positron emission tomography (FDG-PET) so that not only occipital lesions may occur in visual hallucinations.[26] In a patient with visual hallucinations in Charles Bonnet Syndrome, a hypermetabolism was found in FDG-PET in the visual association cortex, whereas hypometabolism in the same region was observed in DLB patients with visual hallucinations.[27] We did not find any data on correlation of MRI and PET findings associated with acoustic hallucinations or delusions in CJD, for there are large methodic difficulties (early aphasia in CJD, reduced compliance for investigations because of prominent dementia). However, there are some data on this topic in schizophrenia patients. According to Parellada et al,[28] schizophrenic patients with auditory verbal hallucinations showed a significant activation of the supplementary motor area, anterior cingulum medial superior frontal area and even cerebellum in FDG-PET. Schizophrenic patients with delusions showed in functional MRI significantly reduced accuracy in the imagined condition, with performance negatively associated with degree of delusions. This was accompanied with reduced activity in the left dorsolateral prefrontal cortex and left hippocampus in the patient group. The severity of delusions was negatively correlated with the blood-oxygenation-level dependent response in the left hippocampus. However, it remains unclear whether these data may be transferred to the symptoms of CJD patients. Moreover, retrospective correlation is almost impossible and only very short time period between symptom and cerebral imaging may allow a correlation.

Compared with vCJD,[14] sCJD had only some psychiatric symptoms, such as delusions, apathy, anxiety and affective lability, that were significantly less frequent. In contrast, frequency of depression and visual and acoustic hallucinations was not significantly different between vCJD and sCJD. A previous article from our research group[29] showed a much lower frequency of visual hallucinations in sCJD patients compared with the present study, but the data were obtained from a smaller group of only 25 patients.

In spite of the high frequency of psychiatric symptoms in sCJD, psychiatrist as first physician contacted was unusual in all subtypes, but this fact may also at least partly depend on prejudices concerning psychiatric contacts still broadly held in the German population. Nevertheless, 12% of the patients were initially seen by psychiatrists. Only 19 patients (7.7%) presented with isolated psychiatric symptoms, although psychiatric symptoms at onset combined with neurologic deficits were very common (Table 2). No significant differences between the cases with isolated psychiatric presentation and other cases investigated in this study could be found; however, they may be explained by the low number of cases with isolated psychiatric presentation compared to the total number of patients investigated.

Interestingly, early clinical diagnosis in vCJD was not possible in the great majority of cases because of nonspecific initial symptoms with a wide range of different psychiatric symptoms. Once neurologic signs develop, a diagnosis is usually made promptly, but this is often at a relatively advanced stage of illness.[30] As the disease duration in sCJD is often shorter than in vCJD, psychiatric symptoms occur often simultaneously to neurologic symptoms and signs so that the diagnosis is more simple, apart from atypical subtypes.

It has been already noticed that psychiatric symptoms are common in all types of prion disease, and there is significant heterogeneity both within and between disease types.[21]

In summary, we could disclose differences concerning frequency and time point of occurrence of psychiatric symptoms between molecular subtypes of sCJD. Although psychiatric symptoms in sCJD are common, some of them are still less frequent than in vCJD, and isolated psychiatric symptoms over a longer period of time are rare in sCJD. We suggest that sCJD should be considered as a neuropsychiatric disease, and evaluation of psychiatric symptoms should be performed as carefully as that of neurologic disturbances. We hope that detailed data on psychiatric symptoms in different molecular subtypes of sCJD may improve CJD diagnosis and treatment of these patients.

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