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RESEARCH PAPER

A proposal of new diagnostic pathway for fatal familial insomnia

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ABSTRACT

Background In absence of a positive family history, the diagnosis of fatal familial insomnia (FFI) might be difficult because of atypical clinical features and low sensitivity of diagnostic tests. FFI patients usually do not fulfil the established classification criteria for Creutzfeldt–Jakob disease (CJD); therefore, a prion disease is not always suspected.

Objective To propose an update of diagnostic pathway for the identification of patients for the analysis of D178-M129 mutation.

Design and methods Data on 41 German FFI patients were analysed. Clinical symptoms and signs, MRI, PET, SPECT, polysomnography, EEG and cerebrospinal fluid biomarkers were studied.

Results An algorithm was developed which correctly identified at least 81% of patients with the FFI diagnosis during early disease stages. It is based on the detection of organic sleep disturbances, either verified clinically or by a polysomnography, and a combination of vegetative and focal neurological signs and symptoms. Specificity of the approach was tested on three cohorts of patients (MM1 sporadic CJD patients, non-selected sporadic CJD and other neurodegenerative diseases).

Conclusions The proposed scheme may help to improve the clinical diagnosis of FFI. As the sensitivity of all diagnostic tests investigated but polysomnography is low in FFI, detailed clinical investigation is of special importance.

INTRODUCTION

The most common genetic form of prion disease worldwide is caused by a point mutation at codon 200 of the *PRNP*.¹ In contrast, in Germany, the most frequently occurring mutation is located at the codon 178 of the *PRNP* (D178N mutation in coupling with methionine at codon 129: (D178N, 129M))² and leads subsequently to fatal familial insomnia (FFI). Clinicopathological features compatible with FFI have been described as early as in 1939 and 1963.^{3–4} Lugaresi *et al*⁵ were the first to describe FFI in a patient with a family history of insomnia and autonomous disorders. Postmortem examination revealed marked atrophy of the anterior and dorsomedial thalamic nuclei. Later the disorder was classified as a prion disease and its transmissibility was confirmed in animal experiments.⁶ So far, a number of FFI patients with heterogeneous clinical phenotypes have been reported.⁷ The clinical phenotype in FFI seems also to depend on the M129V polymorphism.^{7–9} In most cases, the clinical diagnosis of FFI is hardly

possible on the basis of the criteria established for sporadic Creutzfeldt–Jakob disease (sCJD) or familial CJD.^{10–13} Disease duration in FFI is as rule prolonged and CJD typical signs such as myoclonus are either absent or seen only very late in the disease course. Laboratory tests and technical investigations which are frequently positive in other prion diseases (14-3-3 proteins in cerebrospinal fluid (CSF), EEG, MRI) are usually normal or non-specifically changed and so they do not provide any further clues to the diagnosis.^{7–14} Clinical criteria of FFI proposed several years ago are helpful in the diagnosis of FFI.^{15–16} However, sensitivity and specificity of these criteria have to be determined in a context of differential diagnosis of rapid progressive dementia. Moreover, some new data have been collected since publication of the criteria, and the role of the codon 129 genotype in FFI phenotype has been recently demonstrated.⁹ The aim of the present study was to develop a scheme to support the clinical diagnosis of possible FFI and to provide a basis for the selection of patients who should be subjected to a *PRNP* analysis in the absence of clear family history for FFI. In addition, such a scheme might be helpful when *PRNP* analysis is not available for various reasons.

DESIGN AND METHODS**Study design**

Patients with suspected prion disease were reported to the CJD Surveillance Unit in Göttingen and examined at the notifying hospital by the authors; the clinical data were collected as described previously.¹⁷ Data on sleep disturbances were obtained from anamnestic means (patients, their relatives, treating physicians), especially in the absence of polysomnography. CSF, blood samples and copies of the diagnostic tests (EEG, MRI, [¹⁸F]FDG positron emission tomography (PET), [¹²³I]-IMP single-photon emission CT (SPECT), polysomnography, laboratory tests) were taken. Because genetic testing was not available at the time as patients were enrolled into the study, they were classified according to established diagnostic criteria of sCJD.^{10–11}

MRI and EEG findings

The MRI images were classified as CJD-typical according to the established criteria.¹⁸ The EEGs were analysed according to established criteria.¹⁹

Polysomnography

Polysomnographic recordings were obtained at the notifying hospitals according to standard



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procedures;²⁰ however, no specific analysis with respect to FFI diagnosis was done since FFI was not specifically suspected in most patients.

PET and SPECT

PET and SPECT were performed at the notifying hospitals as described previously.^{14 21 22} Special attention was paid to thalamic hypometabolism.

Neuropathological and molecular studies

Western blot analysis and immunohistochemistry (in biopsied/autopsied patients) and the analysis of *PRNP* were performed using standard methods.^{23–25}

Biochemical CSF analysis

The 14-3-3 protein analysis was performed at least twice in each CSF sample as described previously.²⁶

Statistical analysis

Significances (p) were tested by the SIGMASTAT 3.1 software (Systat Software Inc., Point Richmond, USA) using Student t test/Mann-Whitney rank sum test or χ^2 test/Fisher exact test. A p value <0.05 was considered as statistically significant.

RESULTS

Study collective

From 1 June 1993 to 31 May 2005, 105 patients with a confirmed *PRNP* mutation were detected. Out of these patients, 32 were diagnosed with FFI. In addition, we included nine further FFI patients with available clinical data from the same families. Since in a few cases some data (eg, on the 14-3-3 test or MRI) were incomplete, some results were obtained on the basis of lower case numbers. In all, 28 patients were male and 13 were female (ratio 2.2 : 1). The median age at disease onset was 56 (range 23–73) years. The median disease duration was 11 (range 6–24) months. There were 20 MM (12 male, eight female) and eight MV (seven male, one female) patients. In 13 patients, no M129V genotype was available, but the diagnosis had been confirmed by autopsy, and family history for (genetically proven) FFI was positive. The median age at disease onset in MM patients was 55 years (range 27–70), and the median disease duration was 10 months (range 6–21). The median age at disease onset in MV patients was 60 years (range 23–69) and the median disease duration was 19 months (range 10–24).

Disease onset and duration varied by codon M129V genotype (table 1), with a non-significantly earlier onset and significantly shorter duration in methionine homozygous (MM) patients (p=0.007). Male gender was associated with an earlier age at

onset and a more rapid disease course. However, this association was not statistically significant.

Clinical findings

Data on the clinical findings have been previously published by the authors.⁹ The clinical features varied by M129V genotype (figure 1). The time of occurrence of symptoms and signs during disease course also varied depending on the M129V genotype (table 2).

Neuropathological studies

Autopsy was performed on 21 of our FFI patients. Overall, 20 of 21 patients showed FFI typical neuropathological findings with prominent thalamo-olivary pathology.²⁷ Severe astrocytic gliosis and nerve cell loss but weak spongiform changes were observed. Fine reticular PrP^{Sc} deposits in the thalamus were only detectable with the PET blot method.²⁵ This pattern resembles PrP^{Sc} type 1, although an electrophoretic mobility comparable with PrP^{Sc} type 2 was described in FFI patients.²⁸ Only one patient with confluent vacuoles (this without thalamo-olivary pathology) showed perivacuolar PrP^{Sc} deposits, which were detectable with conventional immunohistochemical staining methods.

Diagnostic tests

Detailed data on the diagnostic tests have been published previously.⁹ Almost all clinical and paraclinical tests revealed no or only slight non-specific changes. In FFI patients, the 14-3-3 test in the CSF, otherwise helpful in diagnosing prion diseases, was positive in two of 28 cases only. In one of them, inflammatory CSF changes (slight pleocytosis and oligoclonal bands) were detected.^{12 29}

Family history of FFI

Data on family history were available in 29 patients. Family history was negative in 10 of these patients (35%) and positive in 19 (65%).

Development of the diagnostic pathway for FFI

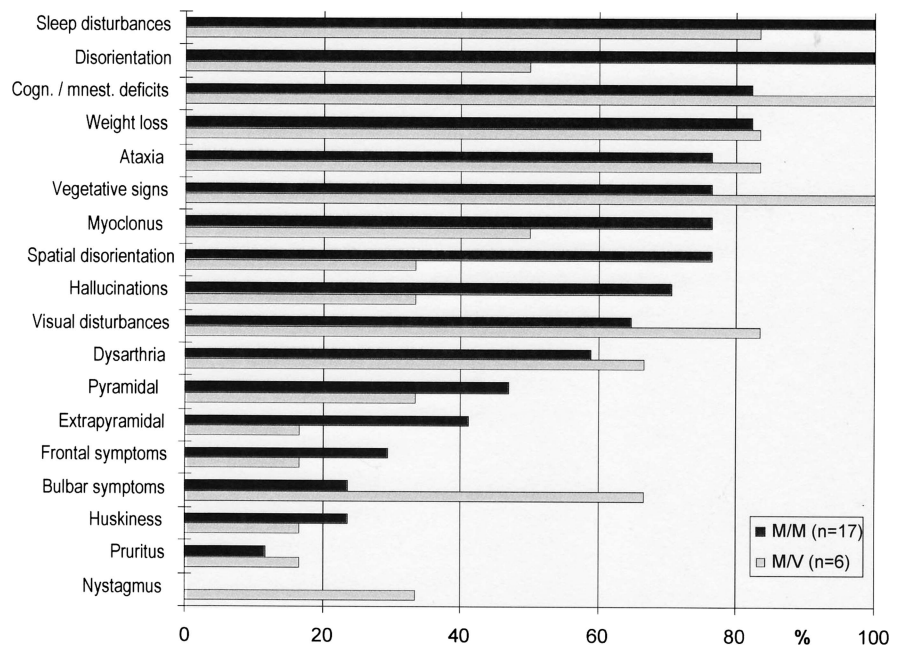
All possible combinations of symptoms and signs were tried and that with the highest sensitivity was selected. The weighting was performed by dividing the frequency of symptoms by week at appearance. The most common clinical symptoms and signs were grouped into three categories (A, B, C) (table 3). The first category comprises organic sleep disturbances (A), which were observed in almost all patients (96%). The second category (B) consists of symptoms and signs frequently occurring in sCJD, which is the major differential diagnosis of FFI (CJD-like symptoms).^{12 30} The third category (C) comprises symptoms and signs which are typical for FFI,^{7 31–34} and are not included in the diagnostic criteria of sCJD.¹⁰ To select the items required for the diagnosis of FFI, we weighted them in terms of their chronological occurrence (table 4). Some signs and symptoms were not evaluated either because they were observed in few cases only or, in most cases, because they could not be linked to a particular disease stage. In a second step, we divided the items into major and minor diagnostic parameters. The most important parameter was sleep disturbance, which occurred as the first symptom of FFI in all patients, except in one case. The minor parameters were selected and weighted according to their frequency and chronological occurrence (category C). Our aims were:

1. High sensitivity
2. High specificity

Table 1 Patient characteristics stratified by codon 129 genotype

Codon 129 polymorphism	Sex	n	Age at onset		n	Duration of illness (months)	
			Median	Range		Median	Range
MM	m	12	53	27–67	10	9	6–21
	f	8	57	50–70	5	13	9–17
	Σ	20	55	27–70	15	10	6–21
MV	m	7	61	23–69	5	15	10–24
	f	1	–	48	1	23	–
	Σ	8	60	23–69	6	19	10–24

f, female; m, male.

Figure 1 Frequency of clinical symptoms and signs stratified by codon 129 genotype (%).

- Reliable classification as FFI no later than in the middle of the disease course
- Easy applicability (analogously to the CJD criteria).

In accordance with this scheme, all patients must have organic sleep disturbances (clinically apparent or by polysomnography). In addition, at least one symptom typical for FFI and two CJD-like symptoms are required for diagnosis of suspected FFI (figure 2). In these patients, a *PRNP* analysis is required as the subsequent diagnostic step.

Verification of accuracy and applicability

The proposed scheme reached a sensitivity of 91% in our original patient group. Based on their use, it was possible to establish the diagnosis of FFI within a median of 17 weeks (4.4 months) after disease onset. While a sensitivity of 100% was found in our MV FFI patients, it was 88% in MM FFI patients. The median disease duration was 11 months, so the diagnosis based on the proposed criteria was established early in the disease course. We tested the applicability in an additional cohort of FFI patients who were seen in a prospective setting

since June 2005 and were not included in the dataset for the scheme development. In these patients (n=16), the proposed scheme correctly identified 13 of 16 (81.3%) of the patients. Major reasons for failure were lack of autonomic disturbances and no data on weight loss or no weight loss.

To test specificity of our diagnostic approach for differentiation of FFI and sCJD, we applied our scheme to 40 randomly selected MM1 sCJD patients (24 women, 16 men; age range 54–86, median 68 years; median disease duration 4, range 1–19 months) representing classical CJD. For randomisation, 40 subsequent MM1 patients diagnosed during the time period of the FFI recruitment for this study were taken. Only seven of these 40 sCJD patients fulfilled the criteria of FFI, so that the specificity within this group was high (83%). This control group was selected because it represents the most frequent classical CJD type.

Loss of weight with a cut-off point of more than 10 kg during the last 6 months was observed in 5% of sCJD patients in comparison with 83% in FFI ($p<0.001$). Vegetative signs were found in only 33% of MM1 patients compared with 83% in FFI ($p<0.001$). Husky voice was noticed in none of MM1 patients, but in 22% of FFI patients ($p=0.005$).

Table 2 Time of occurrence of symptoms/signs present both in codon 129 MM and codon 129 MV patients

Symptom/sign Genotype	N patients (%)		Mean±SD (weeks)		Median (weeks)	
	MM (n=17)	MV (n=6)	MM (n=17)	MV (n=6)	MM (n=17)	MV (n=6)
Vegetative	13 (77)	6 (100)	4±0	18.5±3	0	23
Sleeping disturbances	17 (100)	5 (83)	3±0	15±0	0	0
Bulbar	5 (29)	5 (83)	19±0.5	23±16	11	20
Visual	11 (65)	5 (83)	13±1	6±2	12	2
Cognitive/mnestic	14 (82)	6 (100)	13±0	16±0	12	20
Hallucinations	12 (71)	2 (33)	16±0	57.5±19	14	57.5
Spatial disorientation	13 (77)	2 (33)	20±2	38.5±1	16	38.5
Ataxia	13 (77)	6 (100)	21±4	9±2	20	4
Dysarthria	10 (59)	4 (67)	21±0	27±0.5	20	28.5
Myoclonus	13 (77)	3 (50)	16±1	32±3.5	21	32
Pyramidal	8 (47)	2 (33)	29.5±5	28±5	26	28

Table 3 Frequency of clinical symptoms and signs in fatal familial insomnia patients (n=23)

	Symptoms and signs	N	%
Category A	Organic sleep disturbances*	22	96
Category B	Cognitive/mnemonic deficits	20	87
	Spatial disorientation	15	65
	Psychiatric	20	87
	Hallucinations†	14	61
	Personality change	13	57
	Depression	5	22
	Anxiety	4	17
	Aggressiveness	2	9
	Disinhibition	2	9
	Listlessness	2	9
	Others‡, each	1	4
	Ataxia	19	83
	Myoclonus	16	70
	Visual	16	70
	Double vision	12	52
	Blurred vision	5	22
	Others§, each	1	4
	Dysarthria¶	14	61
	Pyramidal	10	43
	Extrapyramidal**	8	35
Category C	Loss of weight	19	83
	Vegetative signs	19	83
	Hyperhidrosis	13	57
	Newly diagnosed arterial hypertension	6	26
	Tachycardia	4	17
	Obstipation	3	13
	Hyperthermia	2	9
	Others††, each	1	4
	Bulbar symptoms	10	43
	Husky voice	5	22
	Dysphagia	3	13
	Bulbar speech	3	13
	Tongue fasciculation	1	4
	Pruritus	3	13

*Including polysomnography; insomnia, hypersomnia, restless sleep and sleep attacks.

†Optical in 14 patients, additionally acoustic in two of them.

‡Paranoia, fearfulness and rage to clean up.

§Seeing of flashes, poor vision, sliding field of vision and bad spatial vision.

¶Pseudobulbar and cerebellar.

**Nearly equally rigour, tremor and dystonia, mostly in combination.

††Tachypnoea, arterial hypotonia, intolerance of warmth, goose bumps, cardiac arrhythmia and abrogated day-night rhythm of blood pressure.

We also applied our algorithm to 40 randomly selected sCJD patients (23 MM, nine MV, eight VV genotype). There were 28 women, 12 men; age range was 41–81 years, median age was 73 years; and median disease duration was 10 months (range 2–28 months). For randomisation, 40 subsequent patients with excluded PRNP mutation diagnosed during the time period of the FFI recruitment for this study were taken. Only seven of these 40 sCJD patients fulfilled the criteria of FFI, and so the specificity within this group was high (83%).

Loss of weight with a cut-off point of more than 10 kg during the last 6 months was observed in 10% of these patients in comparison with 83% in FFI ($p < 0.001$). Vegetative signs were found in only 30% of non-selected sCJD patients compared with 83% in FFI ($p < 0.001$). Husky voice was noticed in none of non-selected sCJD patients, but in 22% of FFI patients ($p = 0.005$). Thus, the results in this group were very similar to those in MM1 patients.

Moreover, we established a further control group consisting of all German CJD surveillance patients with neuropathologically proved diagnosis other than prion disease referred ante mortem to the surveillance centre as a potential prion disease, which

Table 4 Symptoms in fatal familial insomnia patients (n=23) stratified by time of occurrence

Symptom/sign	Frequency*	Time of occurrence (d)	Frequency weighted by time
Loss of weight (<10 kg)	19	14	1.357
Husky voice	5	14	0.357
Psychiatric	20	84	0.238
Sleeping disturbances	22	107	0.206
Vegetative	19	124	0.153
Visual	16	157	0.102
Cognitive/mnemonic	20	207	0.097
Frontal lobe signs	2	22	0.091
Myoclonus	16	226	0.071
Ataxia	19	273	0.070
Bulbar	10	145	0.069
Extrapyramidal	5	78	0.064
Spatial disorientation	15	260	0.058
Dysarthria	14	259	0.054
Pyramidal	10	205	0.049

*Number of patients with positive symptom/sign.

included 30 patients (14 women, 16 men; age range 26–87, median 73.5 years; median disease duration 11.5, range 1–70.5 months). There were 15 patients with Alzheimer's disease (AD), four patients with inflammatory CNS diseases, two with both AD and Lewy body disease (DLB), two with DLB, and one each with AD and congophil amyloidopathy, AD and vascular dementia, AD and unclear tauopathy, congophil amyloidopathy, vascular dementia, autosomally dominant leukodystrophy, and metabolic CNS disease. In this patient group, only 20% were identified by the algorithm as potential FFI cases. Loss of weight with a cut-off point of more than 10 kg during the last 6 months was observed in 3% of neuropathologically confirmed non-prion disease patients compared with 83% in FFI ($p < 0.001$). Vegetative signs were found in only 30% of non-prion disease patients in comparison with 83% in FFI ($p < 0.001$). Husky voice was absent in non-prion disease patients, but reported in 22% of FFI patients ($p = 0.012$).

DISCUSSION

The aim of the present study was to develop a scheme for the clinical diagnosis of FFI. In addition, such a scheme might be also helpful when PRNP analysis is not available for various reasons.

As discussed previously and shown in table 2, there is a significant phenotypic variability between MM and MV genotypes. Myoclonus, spatial disorientation and hallucinations were more frequent in the MM patients.^{7–9} Bulbar disturbances and vegetative dysfunction were more common in MV FFI patients. Phenotypic differences between MV and MM FFI patients may be caused by different rates of PrP^c to PrP^{Sc} conversion.^{3,5}

Differently from our previous study,⁹ we analysed the clinical data in FFI patients in order to develop a scheme for early identification of patients who should be subjected to PRNP analysis. The rationale for this study is given in the Introduction section. To our knowledge, diagnostic criteria of FFI have been suggested twice.^{15–16} They are based on data from 24 FFI patients. No

Figure 2 Diagnostic algorithm for fatal familial insomnia.

- A) Obligatory **organic sleep disturbances**. If not yet clinically apparent, a polysomnography has to be performed.
- B) At least **two** of the following “**CJD-like symptoms/signs**”
1. Psychiatric*
 2. Ataxia
 3. Visual
 4. Myoclonus
 5. Cognitive/mnesic deficits
- C) At least **one** of the following “**relatively disease-specific symptoms/signs**”
1. Loss of weight with a cutoff point of > 10 kg during the last 6 months
 2. Vegetative**
 3. Husky voice

*Visual hallucinations, personality change, depression, anxiety, aggressiveness, disinhibition, listlessness

**Hyperhidrosis, newly diagnosed arterial hypertension, tachycardia, obstipation, hyperthermia

specificity or sensitivity of these criteria has been reported. They consist of six items and include clinical data, EEG and PET investigation. Since the availability of PET is limited, we intended to develop an easy and widely applicable scheme, which consists of three items and allows raising the suspicion of FFI by clinical means. The specificity of this approach was tested on two control groups with relevant differential diagnoses.

We attempted to establish an easily applicable scheme allowing reliable identification as a possible FFI no later than in the middle of the disease course. To make the attempt as precise as possible, we stratified the symptoms and signs of FFI by time of occurrence and their frequency. The scheme facilitates differentiation from the classical CJD, non-selected sCJD and non-CJD cases according to CJD criteria.^{10–11} However, differentiation from atypical sCJD subtypes may sometimes be more difficult.

A specificity of at least 80% could be reached for each of the groups. In contrast to FFI criteria (ICSD criteria and criteria proposed in the British Medical Bulletin¹⁵) which both require the presence of an autosomal dominant disease or a familial pattern, here we can select patients from families in which the FFI diagnosis is not established, as our studies showed that about a third of our patients did not fulfil this criterion.⁹ This fact might be explained by missing information about the presence of a neurodegenerative disorder by the family members or by occurrence of new mutations.

Interestingly, psychiatric symptoms were frequent in our FFI patients, and they are also common in sCJD.³⁶ However, they are not a part of sCJD criteria, while we found them an important part of our FFI criteria.

Although the diagnosis of atypical subtypes of sCJD using the established criteria may fail, some diagnostic tests, such as MRI in the MV2 subtype and detection of the 14-3-3 proteins in MM2 and VV1 subtypes, are helpful in the sCJD diagnosis.^{37–39} The clinical diagnosis of FFI, by contrast, is solely based on the careful observation of the clinical course, and only polysomnography and, to some extent, PET may contribute to the FFI diagnosis before genetic testing is performed and a *PRNP* mutation is detected.¹⁴ All reports on FFI have emphasised the diagnostic importance of polysomnography in FFI, and this is also confirmed in our study.^{7 20 34 40}

CONCLUSIONS

Summarizing, we attempted to establish an easily applicable scheme allowing reliable classification as FFI no later than in the middle of the disease course. This facilitates differentiation both from the classical CJD and non-CJD cases initially classified as possible CJD as the most frequent classification in FFI patients according to CJD criteria.^{10–11} Suspicion of FFI and consecutive order of appropriate genotyping by clinicians may be more frequent and could arise earlier, if updated, easily applicable clinical criteria are available. The scheme would also allow the clinical diagnosis in cases with no available genetic testing. A specificity of at least 80% and a sensitivity of 81.3%–91% could be reached. Early diagnosis of FFI might be important for early and sufficient counselling of patients and their relatives, also concerning the risk of inheritance, and potentially also for treatment studies. We hope that this attempt may improve the early recognition of this peculiar and rare prion disease.

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Ethics approval Any necessary ethics committee approval was secured for the study reported by the local ethic committee of the Medical University of Goettingen.

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