Characterization of Movement Disorders in Patients with Familial Creutzfeldt-Jakob Disease carrying the E200K Mutation

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ABSTRACT: **Background:** While myoclonus and ataxia are considered common in patients with familial Creutzfeld-Jakob disease (fCJD), other movement disorders are less prevalent.

Objectives: To systemically evaluate the frequency of extrapyramidal signs and movement disorders in patients with fCJD.

Methods: A detailed neurological examination, with special emphasis on movement disorders and extrapyramidal signs, was conducted in 43 consecutive symptomatic CJD patients (26 males and 17 females; mean age 58.7 ± 8.9 yrs, range 43–77 years) carrying the E200K mutation in the *PRNP* gene.

Results: Limb or gait ataxia was noted in 38 patients (88%) (37 patients, 86%, had ataxia at presentation). Myoclonus was evident in 25/43 patients (58%) (21 patients, 49%, at presentation). In 95% of the patients (41/43) (37/43, 86% at presentation) at least one extrapyramidal sign throughout the disease course was noted, the most prevalent being rigidity (28/43, 65% of the patients; and 22/43, 51% at presentation), followed by the glabellar sign (24/43, 56% of the patients; and 22/43, 51% at presentation), bradykinesia (19/43, 44%; and 15/43, 35% at presentation), dystonia (15/43, 35%; 12/43, 28% at presentation) and tremor (13/43, 30%; 12/43, 28% at presentation).

Conclusions: In this unique population of fCJD patients, myoclonus was less prevalent than previously reported while other extrapyramidal signs were common and occurred at a relatively early stage of the disease. The high prevalence of movement disorders can be added to other phenomena characteristic of this familial disorder among Libyan Jews. Whether this is attributable to the E200K mutation itself or to some other mechanism has still to be elucidated.

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KEY WORDS: Creutzfeld-Jakob disease (CJD), movement disorders, prion diseases, myoclonus, extrapyramidal signs

Creutzfeldt-Jakob disease is the most common human prion disease, characterized by a rapidly progressive multifocal neurological dysfunction, myoclonic jerks and a terminal state of severe cognitive impairment [1]. Its pathogenesis involves formation and deposition of the abnormal prion protein (PrP^{Sc}) in the central nervous system [2]. Neurodegeneration and prion protein deposition are mostly found in the cortex, basal ganglia, thalamus, and cerebellum [2]. CJD can be etiologically classified into familial, sporadic, and infectious forms [1]. The familial forms are caused by mutations in the gene encoding for the prion protein. The largest cluster of fCJD exists in Jews of Libyan and Tunisian ancestry carrying an E200K mutation (Glu to Lys substitution) in the prion protein gene (*PRNP*) [3,4].

Early symptoms of the disease are non-specific and include headache, anxiety, sleep disturbances and weight loss. Later, more diffuse neurological impairment emerges, including cognitive decline, cerebellar ataxia, myoclonus, pyramidal and extrapyramidal deficits, and impairments of vision [1]. The disease is invariably fatal, with survival rarely exceeding a few months to one year [1].

The prevalence of movement disorders in patients with sporadic CJD is very high, occurring in approximately 90% of patients during the disease course [5]. However, previous reports on patients with fCJD revealed a prevalence of 69–86% of myoclonic jerks but a lower prevalence (35–64%) of other extrapyramidal signs [6-9]. These studies were relatively small and sparse and the patients carried different mutations. We had the opportunity to evaluate a homogenous group of fCJD patients carrying the E200K mutation, as part of a longitudinal prospective study. We present here the results of that survey, which systematically evaluated the prevalence of extrapyramidal signs and movement disorders in this unique population.

CJD = Creutzfeldt-Jakob disease
fCJD = familial CJD

PATIENTS AND METHODS

The study group included consecutive CJD patients followed at the Sheba Medical Center, as part of a longitudinal prospective study during the period 2005–2010. The study was approved by the institutional review board and all patients (or first-degree relatives in cases where the patient was incapable) signed an informed consent prior to inclusion in the study. The clinical diagnosis of CJD was based on accepted diagnostic criteria [10] and required a relatively rapid decline of cognitive function together with subacute changes in behavior and neurological deficits with at least two of the following features: myoclonus, visual or cerebellar symptoms, pyramidal or extrapyramidal dysfunction, or akinetic mutism.

Diagnoses were confirmed by clinical follow-up until death, and were supported by typical magnetic resonance imaging [11], electroencephalographic findings [10], elevated cerebrospinal fluid tau protein levels [10], and genetic testing for the E200K mutation. Following demographic and clinical data collection the patients were examined by a neurologist trained in movement disorders. The presence of movement disorders was documented in the file and rated using a specific scale developed by us for the evaluation of neurological signs in CJD [12].

RESULTS

The study group included 43 patients (26 males and 17 females) with a mean age of 58.7 ± 8.9 years (range 43–77 years). All patients carried the E200K mutation in the *PRNP* gene. The mean duration from appearance of the first sign to the first evaluation (presentation) was 3.9 ± 2.4 months (range 2–9 months).

When they first presented at our clinic, 37 patients (86%) had at least one extrapyramidal sign, 27 (63%) had at least two signs and 19 (44%) had a well-established extrapyramidal syndrome with at least three signs. Twelve patients (28%) had at least two of the four cardinal signs required for the diagnosis of parkinsonism (UK Brain Bank criteria) [13]. Once the disease progressed, the number of patients with at least one extrapyramidal sign increased to 41 patients (95%). Thirty-two patients (74%) had at least two signs and 22 (51%) had at least three signs throughout the disease course. Eighteen patients (42%) had parkinsonism.

The spectrum of various movement disorders in our patients is presented in Table 1. As can be seen the most prevalent signs were rigidity and the glabellar sign, followed by bradykinesia, dystonia and tremor. Only one patient had choreoathetosis.

Table 1. Prevalence of various movement disorders in 43 patients with familial CJD carrying the E200K mutation

Sign	No. of patients at presentation	Percentage of patients at presentation	No. of patients during disease course	Percentage of patients during disease course
Ataxia (limb or trunk)	37	86%	38	88%
Rigidity	22	51%	28	65%
Glabellar sign	22	51%	24	56%
Myoclonus	21	49%	25	58%
Bradykinesia	15	35%	19	44%
Dystonia	12	28%	15	35%
Tremor	12	28%	13	30%
Choreoathetosis	0	0%	1	2%

DISCUSSION

Several movement disorders – including myoclonus, dystonia, tremor and parkinsonism – have been described in patients with sporadic, familial and new variant CJD [14,15]. The frequency of movement disorders increases with disease duration but they sometimes occur at an early stage [5]. While myoclonus is by far the most prevalent movement disorder in CJD, occurring in 82–100% of the patients with advanced disease [5,9] and considered one of the clinical criteria for the diagnosis of CJD [9], other movement disorders are less prevalent, reported in around two-thirds of patients with sCJD and in 35–64% of fCJD patients [6]. Our thorough prospective study of consecutive fCJD patients carrying the E200K mutation revealed a relatively low occurrence of myoclonus but a higher prevalence than previously reported of other extrapyramidal signs that were documented relatively early in the disease course.

The most prevalent movement disorders in our series were rigidity and glabellar signs. Bradykinesia was also frequent, presenting in more than one-third of our patients. Even more notable is that 42% of our patients had parkinsonism. Although parkinsonism is a classic characteristic of the terminal stage of sporadic and variant CJD [16,17], it is less frequently described in patients with the familial disorder [8]. The parkinsonism is usually atremulous and of the akinetic rigid form, although a few cases of atypical parkinsonism with corticobasal degeneration-like [18] or progressive supranuclear palsy-like [19] syndromes have been described. Tremor can occur early in the course of sCJD and is usually kinetic or postural in nature. Rest tremor is less frequent and is commonly associated with other movement disorders such as dystonia or myoclonus. In vCJD, tremor is common and is included in the diagnostic criteria [20] but only a few case reports of tremor in patients with fCJD have been published [6]. Since almost one-third of our patients had tremor, this is a much higher percentage than previously reported for patients with the familial disorder.

Dystonia as an early symptom in sCJD or fCJD is rare (only a few cases reported) but was documented in more than 50% of

sCJD = sporadic CJD
vCJD = variant CJD

patients in later stages of the disease [21]. In our series dystonia was present in about one-third of the patients.

Choreoathetosis is considered very rare (only a few cases reported) in sCJD but was reported in 20 of 35 patients with vCJD in a late stage of the disease [17]. In our series only one patient had choreiform movements, consistent with the frequency in previous reports. This clinical finding of a low prevalence of chorea is interesting in view of the prominent imaging changes in the caudate nucleus that are frequently seen in CJD [11].

The high prevalence of movement disorders in our E200K-positive fCJD patients can be added to other phenomena characteristic of the familial disorder among Libyan Jews, such as headache, aggravated startle responses, sleep disturbances, pruritus, and peripheral neuropathy [6,22]. Apparently, in fCJD patients carrying the E200K mutation, the contribution of myoclonus to the clinical diagnosis is less prominent than in sCJD, at least early in the disease course.

Several possible explanations can be proposed to interpret the high prevalence of movement disorders in fCJD patients with the E200K mutation:

- The spectrum of movement disorders observed in this special fCJD group may also be an intrinsic feature of the E200K mutation itself. This possibility is plausible in view of the various unique clinical features seen in patients with the E200K mutation [6,22] and is supported by reports that myoclonus develops earlier in patients with the methionine/methionine (M/M) or methionine/valine (M/V) polymorphism at codon 129 of the *PRNP* and that seizures occur more frequently in the MM1 and MV1 sporadic CJD genotypes [16].
- The brain areas involved in these patients may be slightly different from those involved in sCJD. We have carefully mapped the early diffusion changes in the thalamic-striatal network of fCJD patients [23]. Similar work has not yet been completed in sCJD.
- A third explanation may be attributed to the nature of the prion protein (PrP). Gabizon et al. [24] have shown that PrP(E200K) is different from wild-type PrP (wtPrP) concerning the rate of migration, glycosylation pattern, and rate of degradation. In addition, myoclonus was reported to occur earlier in the scrapie variant of the prion protein PrP^{sc} type 1 [25] and chorea was much more prevalent in patients with vCJD [17]. It is therefore possible that the difference between the characteristics and function of E200K PrP and the wtPrP accounts for the high prevalence of MD in patients with fCJD.

CONCLUSIONS

We report an early occurrence and high prevalence of movement disorders in a unique population of patients with fCJD carrying the E200K mutation. This unique feature can be added to other phenomena characteristic of the familial disorder in Libyan Jews. Genotype-phenotype correlations of this special fCJD form compared to other genetic forms and the mechanisms by which the E200K mutation contributes to the described clinical heterogeneity have yet to be elucidated.

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