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ORIGINAL COMMUNICATION

Familial Creutzfeldt–Jakob disease homozygous to the E200K mutation: clinical characteristics and disease course

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Abstract

Objective To characterize the demographic, clinical features and disease course of familial Creutzfeldt–Jakob disease (fCJD) patients homozygous to the E200K mutation.

Methods The Israeli National CJD Database was screened for patients homozygous to the E200K mutation. Patients' demographic data, clinical presentation and neurological findings, tau protein levels in the cerebrospinal fluid (CSF) and EEG, were assessed.

Results Ten homozygous E200K patients were identified (80% males). Average age of onset was 47.5 ± 6.1 years (range 40–56) and the average age of death was 49.3 ± 7. 7 years (range 42–63) with average disease duration of 27.7 ± 9.7 months (range 2–97). Initial clinical presentation included behavioral change in 4/10 patients, cognitive decline in 3/10 patients and focal neurological deficits in 2/10 patients. Throughout the disease course, the clinical signs in descending order of prevalence included cerebellar (70%), brainstem (60%), extrapyramidal (50%), pyramidal (50%), frontal lobe signs (30%), and disturbances of ocular motility (30%) Compared to the 228 heterozygous E200K fCJD patients, the 10 homozygous patients were significantly younger at disease onset (47.5 vs 59.7 years, $p < 0.001$), had a longer disease duration (27.7 vs 8.5 months, $p < 0.001$) and presented more frequently with behavioral changes as initial manifestation (4/10 vs. 34/228, $p = 0.05$).

Conclusions Homozygous E200K fCJD patients are characterized by a relatively younger age of onset and longer disease duration. Behavioral changes as a presenting symptom were more common in homozygous patients and cerebellar dysfunction was the most common neurological manifestation throughout the disease course.

Keywords Creutzfeldt–Jakob disease · Familial · E200K · Homozygous · Heterozygous · Prion · Genetics

Introduction

Creutzfeldt–Jacob disease (CJD) is the most common human prion disease, characterized by rapid cognitive decline, psychiatric and behavioral disturbances, cerebellar, pyramidal and extrapyramidal involvement, visual disturbances, myoclonus and epileptic seizures [1]. The disease is etiologically classified into sporadic, familial and acquired forms [2].

The largest cluster of familial CJD (fCJD) which is transmitted as an autosomal-dominant trait exists in Israel in Jews of Libyan ancestry carrying an E200K (Glu to Lys) mutation in the gene encoding for the prion protein (*PRNP*) [3, 4]. Most patients are heterozygoteus for the mutation, although homozygous cases have been described as well [5]. The disease course of homozygous patients with autosomal-dominant disorders is expected to be more aggressive compared with heterozygous patients due to dysfunction of both alleles,

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a phenomenon that has been demonstrated in several other autosomal-dominant disorders [6]. A well-known example is alpha thalassemia in which patients who are homozygous to the mutated allele die in utero ("Hydrops Fetalis") or soon after delivery, whereas heterozygous patients develop mild hypochromic microcytic anemia. Another example is familial hypercholestolemia where heterozygous patients usually develop mild disease, whereas homozygous patients are severely affected [7]. A more aggressive disease has been described in homozygous patients with dominant neurological disorders as well: Charcot-Marie-Tooth 1A homozygous trait leads to a more severe disorder [8] and homozygous Machado–Joseph disease is characterizes by early onset and more aggressive disease course [9]. On the other hand, homozygous and heterozygous patients with Huntington's disease are similarly affected [10]. There are limited data on CJD patients homozygous to the E200K mutation. Simon et al. [5] compared 5 patients homozygous to E200K mutation to 65 heterozygous patients. The homozygous patients had a younger age of onset but no differences were found in other clinical features. In the present study, we reviewed a larger population of E200K homozygous CJD patients to further characterize them.

Methods

The Israeli National CJD database consists of the medical records of patients diagnosed with CJD according to WHO criteria [11] in Israel since 1968 [12]. The database which includes demographic, clinical and laboratory data including genetic tests for mutations in the *PRNP* gene was screened for patients homozygous for the E200K mutation. Demographic data (age, gender), clinical presentation, neurological features, tau protein levels in the cerebrospinal fluid (CSF) and EEG reports were evaluated. Clinical presentation was defined as the first symptom related to the disease. Age of onset was defined as the patient's age at the time of clinical presentation. Based on the neurological examination, we calculated the CJD neurological status scale (CJD-NS) score [13]. In the CJD-NS score, each sign in the neurological examination is assigned to one of eight neurological systems (vision and ocular motility, brainstem, cerebellar, extrapyramidal, pyramidal, frontal releasing signs, peripheral neuropathy and cortical systems). The System-Involved Score (SIS) is the sum of affected systems. The SIS, therefore, ranges from 0 (no neurological system involved, apparently unaffected individual) to 8 (all systems involved). Data of homozygous patients were compared to those of heterozygous E200K patients. Parametric variables were compared using ANOVA and the non-parametric variables were compared using Fisher exact test.

Table 1 Demographic data of the ten homozygous patients with CJD

Patients number	Gender	Age of onset (years)	Disease duration (months)
1	M	40	4
2	M	51	10
3	M	56	74
4	M	49	17
5	F	41	15
6	M	51	97
7	M	53	4
8	M	42	4
9	F	40	2
10	M	49	30
Average ± SD		47.5 ± 6.1 years	27.7 ± 9.7 months

M male, *F* female

Table 2 Most common initial clinical presentation in homozygote and heterozygote patients

	Homozygous patients	Heterozygous patients	*P* value
Number of patients	10	228	
Cognitive decline	30%	31%	1
Behavioral changes	40%	15%	0.05
Cerebellar symptoms	0	14%	0.3
Focal neurologic deficits	20%	11%	0.3

Results

Among 238 fCJD patients with available genetic data, we identified 10 (80% males) homozygous and 228 (47% males) heterozygous to the E200K mutation. Homozygous patients (Table 1) had an average age of onset of 47.5 ± 6.1 years (range 40–56) and a median age of onset of 49 years. Average age of death was 49.3 ± 7. 7 years (range 42–63, median 51 years) and average disease duration was 27.7 ± 9.7 months (range 2–97, median 10 months). The most common presenting symptom was behavioral changes in homozygous patients and cognitive decline in heterozygous patients (Table 2). Throughout the course of the disease, the abnormal neurological signs in descending order included cerebellar (70%), brainstem (60%), extrapyramidal (50%), pyramidal (50%), frontal lobe (30%) signs, and disturbances of ocular motility (30%). In comparison with the 228 heterozygous patients, homozygous patients were significantly younger at disease onset (47.2 vs 59.1 years, $p < 0.001$) and had a longer disease duration (27.7 vs 8.5 months) ($p < 0.001$) (Table 3). Behavioral changes as a presenting symptom were more

Table 3 Demographic and clinical data of E200K homozygous vs. heterozygous CJD patients

	Homozygous E200K	Heterozygous E200K	*P* value
No. of patients	10	228	
Mean age of onset (years ± SD)	47.5 ± 6.1 (40–56)	59.7 ± 9.7 (33–84)	< 0.001
M:F	8:2 (4.0)	107:121 (0.9)	0.1
Average disease duration (months ± SD)	27.7 ± 9.7 (2–97)	8.5 ± 9.6 (0.7–82)	< 0.001
Average level of tau protein in the CSF (pg/ml)	1211 ± 292(1008–1550) ($n = 3$)	1216 ± 560(20–3495) ($n = 40$)	0.99
Behavioral changes as an initial symptom (percent)	40%	15%	0.05

CSF cerebrospinal fluid, *F* female, *M* male, *SD* standard deviation

common in the homozygous patients (Table 3). Mean SIS in the homozygous group was 3.6 ± 1.43 (range 1–6). Low SIS (< 4) was associated with normal EEG ($p = 0.02$). However, SIS was not associated with gender, age of onset, disease duration or distribution of symptoms. Tau protein levels were available in 40/228 heterozygous patients with an average level of 1211 pg/ml and in 3/10 homozygous patients with an average level of 1216 pg/ml with no significant difference between the groups (Table 3).

Discussion

Homozygous trait in some autosomal-dominant genetic disorders such as alpha thalassemia or Machado-Joseph disease [9] is characterized by younger age of onset and more aggressive disease course compared to the heterozygous trait. Our study shows that CJD patients homozygous to the E200K mutation are younger at disease onset but have longer disease duration than heterozygous patients (although in some homozygous patients, disease duration was similar to the heterozygous patients), with similar clinical features in both groups. In E200K fCJD patients, the PRNP mutated gene encodes a normal functioning Prp^{c} protein, but due to the substitution of Glu with Lys, there is a higher risk of conversion of Prp^{c} to the pathogenic isoform of Prp^{Sc}. The lifetime risk of this conversion is very high, reaching 96% after age 80 [14, 15]. The load of the susceptible Prp^{c} protein in homozygous carriers is double, carrying a higher risk of earlier conversion to the pathogenic Prp^{Sc} protein than in heterozygous subjects. This might explain the younger age of disease onset in homozygous patients. However, once the conversion occurred and the vicious cycle had started, the process is similar in homozygote and heterozygote patients leading to similar expression of the disease. Another interesting finding in our study is the longer duration of the disease in homozygous patients, as already described previously in a smaller cohort [5]. Actually, longer disease duration has been reported in patients with variant CJD which is characterized by younger age of onset [16], as well as in young-onset sporadic CJD patients [17]. Possible explanations include more dedicated palliative care in young people and the increased frailty of elderly people [16]. The effect of various age-related disease modulating factors that may lead to prolonged disease course at younger age is also a possibility. An alternative explanation is that the mutation in the PRNP gene exposes the patient to an increased tendency of spontaneous conversion to the pathologic form compared to the wild type one. Patients homozygous to the mutation have double load of the mutant Prp^{c} protein with higher risk for the spontaneous conversion to Prp^{Sc} than heterozygous patients, therefore, the age of onset is earlier in the homozygous patients. However, the infective process, in which the PrP^{Sc} interacts with Prp^{C} and converts it to the pathologic form of Prp^{Sc}, is less effective in the mutant Prp^{Sc}, therefore, disease duration is longer in the homozygous patients.

In summary, homozygous E200K patients present characteristic disease course with younger age of onset, prolonged disease duration and behavioral changes as the most common initial presenting symptom, but otherwise typical phenotype.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical standard This research was performed in accordance with the principles of the Declaration of Helsinki and by the standards of the local ethics committee.

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