Parkinsonism and Related Disorders 19 (2013) 192–197

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The influence of gender on phenotype and disease progression in patients with Huntington's disease

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ARTICLE INFO

Article history:
Received 23 July 2012
Received in revised form
25 September 2012
Accepted 26 September 2012

Keywords:
Gender
CAG repeats
Huntington's disease
UHDRS
Progression

ABSTRACT

Introduction: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. The aim of this study is to determine whether gender plays a role in the phenotypic expression and progression of HD.
Methods: 1267 patients with HD (636 women) from the Registry project of the EHDN were included. A cross-sectional analysis (ANCOVA) controlling for differences in age at onset, disease burden, disease duration, smoking status, alcohol abuse, depression and the number of years of education, was performed to evaluate if there were differences between men and women in UHDRS motor, function and cognitive scores. Additionally, analyses on follow-up data using linear mixed models with the same covariates were performed to test for gender-related differences in progression.
Results: Baseline features did not differ between genders, with the exception of a higher frequency of past and current depression among women, and a higher number of years of education as well as more frequent alcohol abuse and smoking among men. In the cross-sectional ANCOVA analyses of patients with a mid-age HD onset, women showed worse scores than men in the functional domain (TFC, $P = 0.001$; UHDRS functional, $P = 0.033$), UHDRS motor ($P = 0.033$). The longitudinal analyses showed a faster rate of progression in women in the functional assessment ($P = 0.025$), the motor assessment ($P = 0.032$) and the independence scale ($P = 0.008$).
Conclusions: These results suggest a complex gender effect on the phenotypical presentation and the rate of disease progression in HD, with slightly more severe phenotype and faster rate of progression in women in especially the motor and functional domains.

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1. Introduction

Huntington disease (HD) is a neurodegenerative autosomal dominant disorder, caused by a CAG repeat expansion mutation in the *HTT* gene on the short arm of chromosome 4 [1]. HD is clinically characterized by motor abnormalities, cognitive impairment and behavioural abnormalities [1]. The symptoms usually appear between 30 and 50 years of age (range 2–85 years) in both sexes, which are equally susceptible to HD [1]. Despite the monogenic nature of the disease patients show extensive variation both in presentation and progression. It is recognized that variations in CAG repeat size accounts for up to 73% of the variation in age at onset (AO) [2]. In addition, some features of the phenotypic expression of HD, as well as the rate of disease progression are influenced by the length of the CAG repeat expansion [3,4]. One recent report suggested some influence of gender on disease progression [5], but the relationship between rate of progression and gender has not yet been studied in a large cohort of HD. In the

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http://dx.doi.org/10.1016/j.parkreldis.2012.09.012

140 CAG knock-in HD mouse model, gender appears to play a role in shaping the phenotype and some aspects of brain metabolism [6]. The aim of the present study is to assess whether gender influences clinical phenotype and disease progression in patients with HD.

2. Methods

2.1. Participants

Up to June 2011 a total of 7676 participants were enrolled into REGISTRY, an observational study of the European Huntington's Disease Network (EHDN). Details of the study design, including data collection and pseudonymisation, have been reported elsewhere [7]. This study is based on data from all participants with a clinically and genetically proven diagnosis of HD with a Unified Huntington's Disease Rating Scale (UHDRS) motor scale score ≥6, and from whom the following data were available from at least one visit between 2004 and the end of 2008: date of birth, gender, age at onset (AO), CAG repeat of the larger allele, inheritance (maternal or paternal), as well as scores of the Total Functional Capacity (TFC) scale [8,9]. This information was available for 1267 participants (636 women and 631 men). In addition, information on the following measures was also retrieved from the database: functional score (available for 995 of the 1267 patients), cognition total score (available for 804), independence (available for 991) and behavioural score (available for 856). All participants gave informed written consent according to the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines (http://www.ich.org/LOB/media/MEDIA482.pdf). Ethical approval was obtained from the local ethics committee for each study site contributing to REGISTRY. The REGISTRY protocol was approved by the EHDN Scientific and Bioethics Advisory Committee.

To assess the patients for the purpose of REGISTRY the motor, functional, cognitive and independence scales of the UHDRS'99 were used [9], together with the total functional capacity (TFC) scale (Appendix 1).

2.2. Statistical analysis

Crude differences between men and women were analysed with the independent samples *t*-tests or Chi-square tests as appropriate. Information on the exact dates of the assessments was available; time of disease onset however, was recorded as the year in which the first symptoms presented. To calculate disease duration, onset was therefore assumed to have occurred at 1st July of that particular year. To compare disease severity between genders at the time of the first visit, an analysis of covariance (ANCOVA) was carried out with the separate UHDRS assessments (motor, functional, cognitive, independence, behavioural) and the TFC in turn entered as dependent variable, sex, smoking status and alcohol abuse (the latter two classified as never, past or current) entered as fixed factors, and disease burden (i.e. $(CAG_{n_{larger\ allele}} - 35.5) \times$ age at examination) [10], disease duration and AO entered as covariates in all analyses. Since the number of years of education and the presence of depression were significantly associated with worse cognitive and behaviour – but not motor, function or independence – scores, we entered these variables in all models in which the dependent variable involved a cognitive measure or the behavioural assessment. This was not done for the motor, function and independence scores, since no significant association with these measures was present and this would thus have resulted in unnecessary loss of power because information on depression was available for only 847 individuals and on education for only 1165 individuals. The presence or absence of depression was determined by the raters at the end of the behavioural assessment when all relevant information had been obtained. Although normality is one of the assumptions of ANCOVA, the procedure is quite robust against moderate deviations from normality if the sample sizes are large (i.e., >200) and relatively equal (as in the present case) [11], and we therefore made no attempts to transform the data. In addition, normality of the residuals was checked after each analysis. Frequency histograms and normal probability plots of all dependent variables showed no large deviations from normality.

To evaluate if potential differences between men and women at the first visit were in later years followed by differences in disease course, a linear mixed model (LMM) analysis was subsequently performed. The separate UHDRS scores (motor, functional, cognitive, independence, behavioural) and the TFC were again in turn entered as dependent variables, with sex, smoking status and alcohol abuse entered as fixed factors, and disease burden, baseline disease duration, age at onset and time between visits entered as covariates in all analyses. Depression and years of education were handled as in the ANCOVA procedure. For each scale separately, the rate of disease progression was calculated as an increase or decrease in scale units (i.e., scale points) in a particular scale per year, using data of all patients who had two or more visits. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and random slopes were used for the follow-up time in all models. A restricted maximum likelihood (REML) model with an unstructured covariance type was used in all LMM analyses. The LMM analyses were first performed on all patients, but our primary analysis involved patients with a mid-age onset and therefore the analyses were subsequently repeated without the young (<20 years) and late onset (>60 years) cases to avoid that non-typical cases would influence the results [12]. *P*-values ≤ 0.05 were considered significant. Missing data were not imputed and all analyses were performed on participants with complete data using SPSS version 17.0.

3. Results

Baseline characteristics of patients are shown in Table 1. There were no differences between men and women in age at the initial visit, AO, disease duration or the number of CAG triplets in the larger alleles. With respect to the dependent variables in this study,

Table 1
Baseline characteristics according to gender at first visit.

Characteristic	Men	Women	*P*
Number (percentage)	632 (49.9)	635 (50.1)	
Age at first visit in years (mean ± SD)[a]	51.1 ± 12.0	50.5 ± 12.1	0.320
Age at onset in years (mean ± SD)[a]	43.4 ± 12.0	43.0 ± 12.1	0.561
Disease duration (years, mean ± SD)[a]	7.8 ± 5.6	7.5 ± 5.4	0.298
CAG repeats large allele (mean ± SD)[a]	44.7 ± 4.8	45.0 ± 4.7	0.228
Disease burden (mean ± SD)[a]	428.0 ± 126.1	439.2 ± 131.7	0.122
Number of years of education	11.3 ± 7.3	10.4 ± 5.3	**0.010**
Depression at examination (*N*, %)[b]	124/424 (29.2%)	153/423 (36.2%)	**0.032**
History of depression (*N*, %)[b]	291/626 (46.5%)	382/634 (60.2%)	**<0.001**
History of psychotic symptoms (*N*, %)[b]	73/626 (11.7%)	69/634 (10.9%)	0.662
History of OCD (*N*, %)[b]	96/626 (15.3%)	90/634 (14.2%)	0.568
History of Suicidal ideation or attempts[b]	122/626 (19.5%)	127/634 (20.0%)	0.809
Alcohol abuse[b]			
Current abuse	41 (6.5)	23 (3.6)	**0.001**
Past abuse	53 (8.4)	30 (4.7)	
No abuse	538 (85.1)	582 (91.7)	
Drug abuse[b]			
Current abuse	2 (0.3)	4 (0.6)	0.719
Past abuse	10 (1.6)	10 (1.6)	
No abuse	620 (98.1)	621 (97.8)	
Smoking status[b]			
Current smoker	184 (29.2%)	161 (25.2%)	**0.004**
Past smoker	156 (24.6%)	211 (16.7%)	
No smoker	292 (46.2%)	263 (41.4%)	
Type of onset[b]			
Motor onset	353 (55.9%)	324 (51.0%)	0.201
Cognitive onset	55 (8.7%)	45 (7.1%)	
Psychiatric onset	130 (20.6%)	150 (23.6%)	
Oculomotor or other onset	5 (0.8%)	6 (0.9%)	
Mixed onset	89 (14.1%)	110 (17.3%)	
UHDRS motor (mean ± SD)[a]	37.1 ± 21.0	39.4 ± 21.2	**0.049**
UHDRS functional (mean ± SD)[a]	17.9 ± 6.9	16.9 ± 7.1	**0.012**
TFC (mean ± SD)[a]	8.0 ± 3.8	7.4 ± 3.7	**0.028**
UHDRS behavioural (mean ± SD)[a]	14.9 ± 12.5	15.3 ± 12.4	0.381
UHDRS independence (mean ± SD)[a]	77.6 ± 18.9	75.7 ± 18.9	0.127
UHDRS cognitive total (mean ± SD)[a]	148.4 ± 74.3	139.5 ± 69.8	0.083
Verbal fluency (mean ± SD)[a]	16.9 ± 11.4	15.7 ± 10.5	0.099
SDMT (mean ± SD)[a]	20.5 ± 12.4	18.2 ± 12.0	**0.010**
Stroop colours (mean ± SD)[a]	39.8 ± 19.2	38.1 ± 18.3	0.218
Stroop words (mean ± SD)[a]	53.9 ± 24.5	51.8 ± 23.2	0.232
Stroop interference (mean ± SD)[a]	21.6 ± 12.6	20.7 ± 12.3	0.345
Stage I[b]	211 (33.4)	170 (26.8)	0.101
Stage II	182 (28.8)	202 (31.8)	
Stage III	172 (27.2)	181 (28.5)	
Stage IV	55 (8.7)	71 (11.2)	
Stage V	12 (1.9)	11 (1.7)	

N = number; OCD = obsessive compulsive disorder.
[a] Independent samples *t*-test.
[b] Chi-square test. *P*-values < 0.05 are printed bold.

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