Huntington's disease: cognition and apathy

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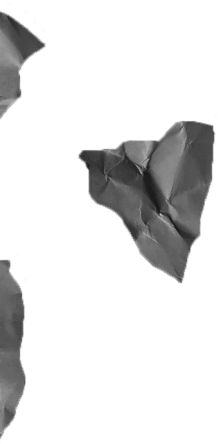

Chapter 2
Participants at the Leiden site of the REGISTRY study:a demographic approach

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Abstract

Background: REGISTRY is the largest European observational study of Huntington's disease (HD). The Leiden University Medical Center (LUMC) in The Netherlands is the largest recruiting site.

Objective: The aim of this paper is to give an overview of the baseline characteristics of all Leiden participants from the start of the study in 2005 until the close of REGISTRY at the LUMC in September 2014.

Methods: The Leiden cohort is described in two different ways: CAG repeat length and presence of motor signs.

Results: Division into groups based on prolonged CAG length revealed that the cohort consists of 4 intermediate - (27 – 35 CAG), 22 reduced penetrance - (36-39 CAG), 465 full penetrance - (> 39 CAG) and 60 control participants (< 27 CAG). The second way of dividing the participants based on present or absent of motor signs, showed that 170 pre-motormanifest - and 317 motormanifest participants were enrolled.

Conclusion: The Leiden REGISTRY cohort at baseline is mainly characterized by full penetrance gene expansion carriers who have been clinically diagnosed with HD but who remain relatively functionally independent. For the majority of these participants, disease onset was based on motor signs followed by psychiatric and cognitive signs.

Introduction

Huntington's disease (HD) is a devastating neurodegenerative disease with autosomal dominant inheritance, affecting approximately 10 per 100,000 people in Western countries[1, 2]. It is characterized by a triad of symptoms: progressive motor abnormalities, behavioral signs and cognitive deterioration[3]. HD is caused by an unstable trinucleotide repeat expansion which codes for mutant huntingtin on chromosome 4[4]. With the discovery of the expanded gene and its exact location[4] individuals who are at risk of developing this disorder can be tested for the expanded HD gene before any clinical signs become apparent. The fully penetrant nature with a CAG repeat of >39 means that a person will inevitably develop symptoms and signs of HD during their normal life span[5]. Over a course of, on average, 15 years, signs will gradually worsen, severely debilitate the patient, resulting in premature death[6]. Currently, symptomatic treatment is available, but as yet no cure or disease modification. Study of the expanded gene carriers over time provides valuable insights into disease progression which in turn might identify underlying disease mechanisms.

The relative rarity of HD poses challenges to the study of this disease. As substantial numbers of participants are needed to investigate the multimodal progression of HD, research relies heavily on international, multicenter studies, such as REGISTRY[7], COHORT[8], PREDICT-HD[9] and TRACK-HD[10].

The REGISTRY study is a European, multicenter, observational study coordinated by the European Huntington's Disease Network (EHDN)[7]. It was initiated in 2004 and 17 European countries have recruited or are still recruiting asymptomatic, symptomatic, at risk, and control participants. Assessments of motor, cognitive, behavior, and daily functioning are administered according to standard procedures and participants are asked to donate blood and urine samples annually. All data are rigorously monitored. At present, over 12,000 participants are included in the database with both cross-sectional and longitudinal data.

The Leiden University Medical Center (LUMC) in The Netherlands, with 589 participants enrolled, is the largest site in the REGISTRY followed by Madrid (Spain; 497 participants) and Münster (Germany; 464 participants). In Europe, the REGISTRY sites are being closed one by one in the transition to the worldwide, observational Enroll-HD study (for more information see www.enroll-hd.org). The REGISTRY site in Leiden was closed in September 2014, thus providing an opportunity to present an overview of the demographic and disease-specific characteristics of all enrolled REGISTRY participants at baseline visit.

In this paper, the Leiden population is described in two different ways. Clinical features are described according to CAG length categorization and presence of motor

signs. Using these classifications allows us to evaluate whether the most commonly used classification makes a useful distinction between participants and whether participants within these groups are homogeneous. Describing the large Leiden population thoroughly provides particularly useful information for designing future clinical trials and their target population. This paper can give guidance as to which variables should be taken into account for recruiting participants in order to answer specific research questions.

Methods

The Leiden University Medical Center (LUMC) is the largest national HD referral center in the Netherlands. Between 2005 and 2014, all individuals consulting the HD outpatient clinic were asked to participate in the REGISTRY study. About 2% did not participate for various reasons: non-Dutch speaking, refusal, attended outpatient clinic only once for second opinion. In Leiden, data from patients participating in other locally performed studies were also included in the REGISTRY database: CAPIT-HD[11], Riluzole[12], HD-project[13], PEP-HD[14], Track-HD[10], PADDINGTON[15], and local studies by the Department of Psychiatry[16]. Study assessments were administered by trained professionals and all data were monitored. All studies mentioned have been approved by the LUMC Medical Ethics Committee and all participants gave written informed consent.

Participants

The REGISTRY study included asymptomatic and symptomatic HD expansion mutation carriers, at risk participants and healthy controls (either negatively tested participants or community controls). The data extraction included first baseline visit on January 15th, 1998 (retrospective data) and last baseline visit on June 12th, 2014 (closing of REGISTRY), resulting in 589 baseline visits. In total, 42 participants were excluded from analysis because of missing CAG length (n=16), missing motor score on the UHDRS (n=9), at risk participant (n=10), juvenile HD (n=3) or intermediate CAG length (CAG repeats between 27 and 35; n=4). The intermediates were excluded because of the low number of participants and the lack of consensus about whether intermediate gene carriers develop HD or HD-like phenotype[17-19]. This resulted in 547 individuals taking part in the analysis, 60 of whom were controls.

First, the 487 HD expansion mutation carriers were divided according to the prolonged CAG allele. Participants with CAG repeats between 36 and 39 were classified as reduced penetrance and CAG repeats of ≥ 40 as full penetrance[20].

Second, the cohort was divided on the basis of the presence of motor signs according to the total motor score (TMS) of the Unified Huntington's Disease Rating Scale (UHDRS)[21] where a TMS of ≤ 5 was considered pre-motormanifest (PMHD) and TMS > 5 motormanifest (MHD)[10]. Other possible HD signs were not taken into consideration for this division.

Variables

General demographic data consisted of date of birth, gender, handedness, ethnicity, education (total years), employment, and marital status (partner: yes/no). HD-specific variables included number of CAG repeats of both the smaller and larger allele, information on family history (e.g. affected parent), and personal HD history. The personal history consisted of: age at onset, signs at onset, date of diagnosis and disease duration before baseline visit. These data were collected through an amnestic interview with participant and if possible partner/caregiver. Notably, age at onset is defined as age at which, for the first time, any HD related signs have occurred independent of a clinical diagnosis.

Clinical variables included items of the UHDRS: total motor score (TMS), total functional capacity (TFC), functional assessment score, independence score, total behavior score (TBS) and total cognitive score (TCS). The TCS consisted of the total correct score of the Stroop-Colour-Word-Interference test, the Symbol Digit Modalities test and verbal fluency test.

Statistical analysis

None of the reported variables proved to be normally distributed. Therefore, nonparametric tests were used to identify differences between groups: Mann-Whitney U test (U) or Kruskal-Wallis test (H). If multiple testing was performed, a conservative significance level was used: p=0.05 divided by the number of performed tests (i.e. either p= 0.03 or p= 0.02). Frequencies and median with ranges are reported in tables 1, 2, and 3.

Results

The results are presented according to the two divisions of the cohort: CAG repeat length and presence of motor signs.

Cohort divided based on CAG length

Division based on CAG length resulted in 22 reduced penetrance - and 465 full penetrance participants (table 1).

Demographic data

Age at baseline: The reduced penetrance group was significantly older (median age: 55years) than the full penetrance group (median age: 46years) at time of baseline visit (U=3736, z=-2.14, p=0.03). There was no significant age difference between the reduced penetrance group and controls (U=523, z=-1.44, p=0.15).

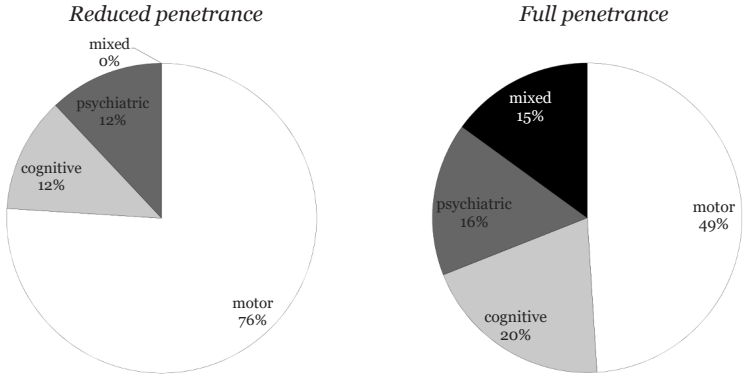
CAG smaller allele: The three groups did not differ significantly in the length of the smaller CAG allele (H(2)=3.26, p=0.2). Noteworthy is that one participant of the reduced penetrance group had an intermediate CAG length on the smaller allele (28/38). Seventeen participants of the full penetrance group had a smaller allele in the intermediate range, and one participant had a reduced penetrance CAG length on the smaller allele (36/46) and was considered to be homozygote.

Table 1: Division based on expanded CAG repeat length

		Reduced penetrance *N=22*	Full penetrance *N=465*	Control *N=60*	p-value
Full cohort *(N=547)*	Age in years[a]	55 (27-81)	46 (19-82)	49 (23-88)	$p < 0.05$
	Gender: male/female	11/11	191/274	26/34	$p > 0.05$
	CAG smaller allele[a]	17 (15-28)	17 (9-36)	17 [49] (16-18)	$p > 0.05$
	CAG larger allele[a]	39 (36-39)	43 (40-59)	18 [49] (17-24)	$p < 0.01$
		N=9	*N=317*	*N=0*	
Clinically diagnosed cohort *(N=335)*	Age at diagnosis in years[a]	67 (36-81)	48 (23-82)	NA	$p < 0.05$[b]
	Age at symptoms first noted by subject in years[a]	53 (36-74)	45 [4] (20-78)	NA	$p = 0.05$[b]
	Age at symptoms first noted by family in years[a]	53 (36-74)	44 [11] (20-75)	NA	$p < 0.05$[b]
	Rater's estimate of age at first symptoms in years[a]	53 (36-73)	44 [11] (20-72)	NA	$p < 0.05$[b]
	Disease duration before baseline visit in years[a]	3 (0-17)	5 [11] (0-24)	NA	$p > 0.05$[b]

Note: [a] median [number of missing data], (range); [b] testing only between reduced penetrance and full penetrance;
NA: Not applicable; N: Number.

Figure 1: First Huntington's disease sign judged by rater, for reduced and full penetrance groups



HD disease onset

In total, 335 participants were already diagnosed with HD at time of REGISTRY baseline visit: 9 reduced penetrance participants (41% of reduced penetrance group) and 317 full penetrance participants (68% of full penetrance group).

Age at diagnosis: The reduced penetrance group was significantly older (median age: 67) than the full penetrance group (median age: 48) at time of clinical HD diagnosis ($U=845$, $z=-2.09$, $p<0.03$).

Age at first HD sign: Within both the reduced penetrance and full penetrance groups, there was relative consensus between participant, family and professional rater about the age at which first HD signs occurred (table 1). Based on the rater's judgment, the reduced penetrance group was significantly older (median age: 53) than the full penetrance group (median age: 44) at time of first HD sign ($U=777.5$, $z=-2.23$, $p=0.03$).

First HD sign: For the reduced penetrance group, the rater judged that disease onset started with motor signs in about 76%, cognitive decline in about 12 % and psychiatric changes in about 12% (see figure 1).

For the full penetrance group, the rater judged that disease onset started with motor signs in about 49%, psychiatric changes in about 20%, cognitive decline in about 16% and mixed in about 15% (see figure 1).

Years between disease onset and baseline visit: There was no difference between the reduced and full penetrance group regarding the years between rater's estimate of disease onset and baseline REGISTRY visit ($U=1045.5$, $z=-1.24$, $p=0.21$).

Table 2: Division based on motor symptoms

	Pre-motormanifest *N=170*	Motormanifest *N=317*	Control *N=60*	p-value
Age in years [a]	38 (19-66)	51 (26-82)	49 (23-88)	p < 0.05
Gender: male / female	58 / 112	144 / 173	26 / 34	p = 0.05
Employment: employed / unemployed	127 / 43	76 / 241	41 / 19	p < 0.05
Marital status: partner / no partner	125 / 44 [1]	217 / 97 [3]	41 / 5 [14]	p < 0.05
Total Functional Capacity [a]	13 (8-13)	9 [1] (0-13)	13 [13] (10-13)	p < 0.05
Functional Assessment score [a]	25 [3] (20-25)	22 [2] (0-25)	25 [14] (24-25)	p < 0.05
Total Cognitive Score [a]	291 [34] (189-407)	178 [123] (45-341)	298 [3] (189-439)	p < 0.05
Total Behavioral Score [a]	0 [31] (0-23)	4 [14] (0-26)	1 [42] (0-15)	p < 0.05
Family history				
Affected parent: Mother/father/both	95 / 72 / 0 [3]	159 / 134 / 1 [25]	8 / 8 / 0 [44]	p > 0.05[b]
Age at onset mother in years [a]	45 [31] (25-71)	45 [54] (25-72)	50 [2] (44-57) [†]	p > 0.05[b]
Age at onset father in years [a]	46 [17] (27-75)	48 [51] (20-91)	55 [1] (41-75) [†]	p > 0.05[b]

Note: [a] median [number of missing data], (range); [b] testing only between pre-motormanifest and motormanifest;
[†] only participants from a confirmed HD family.

Cohort divided based on presence of motor signs

In total, 170 pre-motormanifest (PMHD) - and 317 motormanifest (MHD) participants were included (table 2).

General characteristics

Age at baseline: At time of baseline visit, the PMHD group (median age: 38 years) was significantly younger than the MHD group (median age: 51 years; U=11895.5, z=-10.17, p<0.01) and PMHD was also significantly younger than the control group (median age: 49 years; U=2497.5, z=-5.88, p<0.01).

Gender: There was a significant difference in the distribution of men and women between the three groups ($\chi^2(2)=5.9$, p=0.05). The PMHD had the highest percentage of female participants (about 66% compared to 55% in MHD and 57% in control).

TFC: The TFC score of the PMHD group was significantly higher than that of the MHD group (U=5809.5, z=-13.77, p<0.01), but significantly lower than the control group (U=2694.5, z=-3.56, p<0.01).

Table 3: Huntington's disease history for participants with clinical diagnosis

	Pre-motormanifest with clinical diagnosis N=35	Motormanifest with clinical diagnosis N=291	p-value
Age at diagnosis[a]	40 (28-65)	49 (23-82)	p < 0.05
Age at symptoms first noted by subject[a]	38 (28-63)	46 [4] (20-78)	p < 0.05
Age symptoms first noted by family[a]	38 [2] (28-63)	45 [9] (20-75)	p < 0.05
Rater's estimate of age at first symptoms[a]	38 [1] (28-63)	45 [10] (20-73)	p < 0.05
Disease duration[a,b]	3 [1] (0-11)	5 [10] (0-24)	p < 0.05

Note: [a] median in years [number of missing data], (range), [b] age at symptom onset by rater – age at baseline visit

On further classifying the MHD group into disease stages based on the TFC score by Shoulson and Fahn[22]: 126 (40%) participants were in stage 1, 94 (29%) in stage 2, 75 (24%) in stage 3, 19 (6%) in stage 4, and two (<1%) in stage 5; the data for one participant's baseline visit were missing.

HD disease onset for participants with clinical diagnosis

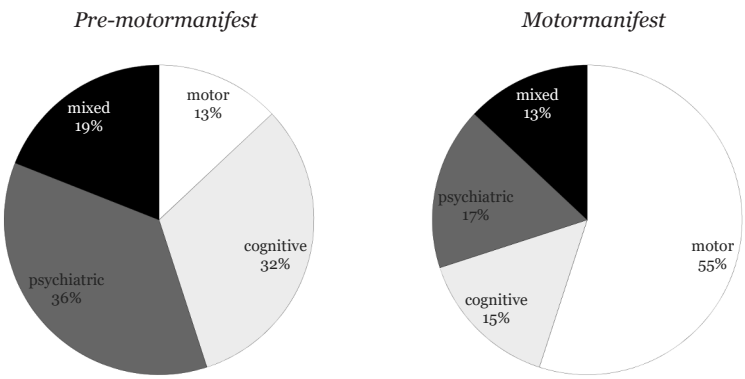
At time of REGISTRY baseline visit, 326 out of the 487 gene carriers were already clinically diagnosed with HD based on either motor, cognitive, psychiatric or mixed symptoms: 35 PMHD (21% of all PMHD participants), and 291 MHD (92% of all MHD participants) (see table 3).

Age at diagnosis: The PMHD group was significantly younger than the MHD group at time of clinical diagnosis ($U=3313$, $z=-3.38$, $p<0.01$).

Age at first HD sign: There was a relative consensus between participants, families and raters regarding the age at which first HD signs were noted within the PMHD group as well as within the MHD group (see table 3). According to the judgment of the rater, the first HD signs occurred significantly earlier in the PMHD group than the MHD group ($U=33337$, $z=-2.87$, $p<0.01$).

First HD sign: Within both the PMHD group and MHD groups, there was consensus between participants, families, and rater regarding the type of first noted HD sign. According to the rater's judgment in the PMHD group, the most frequently noted HD signs were psychiatric problems in 36%, followed by cognitive decline in 32%, motor signs in 13% and mixed first signs in 19%. For the MHD group, the rater judged that the first HD signs to be noted were motor signs in 55%, psychiatric problems in 17%, cognitive decline in 15%, and mixed in the remaining 13%[1] (see figure 2).

Figure 2: First Huntington's disease sign judged by rater, for pre-motormanifest and motormanifest gene carriers



1 Numbers are approximates

Years between disease onset and baseline visit: After disease onset, as judged by rater, the PMHD group attended their first REGISTRY visit after a median of 3 years, which was significantly lower than the MHD group (median of 5 years; U=3385, z= -2.79, p < 0.01).

Discussion

The present paper presents the descriptive data on demographics, clinical and HD-specific characteristics of the Leiden REGISTRY cohort. This is the largest REGISTRY cohort in Europe with primarily full penetrance participants. At baseline visit, the majority of participants were clinically diagnosed with HD and were in an early or mid-stage of the disease.

In the Leiden REGISTRY cohort, the percentage of participants with an allele in the reduced penetrance range (about 5%) was comparable to the percentage described in the literature[23, 24]. About 40% of these participants had already been clinically diagnosed with HD. As yet, little is known about disease progression for gene carriers in the reduced penetrance range. There are suggestions that these individuals have late HD onset[25-27] with chorea as primary disease sign[27, 28]. This supports the notion that gene carriers with a lower number of CAG repeats express a decreased phenotype variability compared to gene carriers with a high number of CAG repeats[29].

The majority of the Leiden REGISTRY participants were already clinically diagnosed with HD prior to the REGISTRY visit with a relatively high functional capacity (e.g. being able to travel to the outpatient clinic). For these participants, the rater judged that disease onset started most frequently with motor abnormalities. Nevertheless, for about one-third, disease onset started with cognitive and/or psychiatric signs as judged by the rater. Previous findings support that cognitive and psychiatric signs can precede motor signs by several years[10, 30-35]. This is even more stressed by the finding that about 21% of participants without any motor signs were already clinically diagnosed with HD based on psychiatric and/or cognitive problems. This implies that the TMS cut-off score of >5, as used in research, only distinguished between pre-motormanifest and motormanifest participants and ignores all other HD symptoms.

Unfortunately, no consensus has been achieved on when psychiatric and/or cognitive signs are disease-specific and which instruments should be used for making a distinction between purely premanifest and manifest participants. More studies are, therefore, needed to investigate thoroughly the progression of psychiatric and cognitive problems throughout the disease and to be able to advise which instrument is useful for identifying psychiatric and cognitive problems related to HD. Also the use of the TMS cut-off score of >5 for motor abnormalities is not always unambiguous as

shown in the Leiden cohort. Some participants were even clinically diagnosed with HD based on motor abnormalities without reaching the TMS threshold. This suggests that certain items on the motor UHDRS are more associated with HD signs than others, and a re-evaluation of the UHDRS might be useful. At this point in time, in designing research with purely premanifest HD, we can only advise that the clinical impression of the professional rater about whether any signs related to HD are present, should be taken into consideration. This could be implemented according to the newly proposed clinical diagnostic criteria which include and evaluate all HD signs[36].

Interestingly, the clinically diagnosed PMHD participants were enrolled in REGISTRY after a shorter period between estimated disease onset and baseline visit than the MHD group. This supports the findings that cognitive and/or psychiatric problems are more devastating for patients and caregivers[37, 38] and, therefore, they attend the outpatient clinic earlier. Moreover, patients who attend an outpatient clinic at a younger age and have regular follow-ups have a higher chance that HD signs will be identified by a professional at an early age.

Surprisingly, the occurrence of psychiatric symptoms was relatively low in the Leiden cohort compared to the estimates found in the literature[39]. One explanation could be that these patients are not recognized, under-diagnosed, referred directly to psychiatrists, or not willing to participate in studies.

In conclusion, the Leiden REGISTRY cohort is characterized by a majority of participants who already experienced symptoms related to HD but who were still relatively functionally independent at time of enrolment. For the majority of clinically diagnosed participants, disease onset was based on motor symptoms followed by psychiatric and/or cognitive symptoms. As this (Leiden) cohort consisted mainly of early HD patients, it is particularly interesting for future clinical trials with the focus on delaying disease onset and/or progression.

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