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# Clinical and genetic characteristics of late-onset Huntington's disease

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ABSTRACT

*Background:* The frequency of late-onset Huntington's disease (> 59 years) is assumed to be low and the clinical course milder. However, previous literature on late-onset disease is scarce and inconclusive.
*Objective:* Our aim is to study clinical characteristics of late-onset compared to common-onset HD patients in a large cohort of HD patients from the Registry database.
*Methods:* Participants with late- and common-onset (30–50 years)were compared for first clinical symptoms, disease progression, CAG repeat size and family history. Participants with a missing CAG repeat size, a repeat size of ≤35 or a UHDRS motor score of ≤5 were excluded.
*Results:* Of 6007 eligible participants, 687 had late-onset (11.4%) and 3216 (53.5%) common-onset HD. Late-onset (n = 577) had significantly more gait and balance problems as first symptom compared to common-onset (n = 2408) (P < .001). Overall motor and cognitive performance (P < .001) were worse, however only disease motor progression was slower (coefficient, −0.58; SE 0.16; P < .001) compared to the common-onset group. Repeat size was significantly lower in the late-onset (n = 40.8; SD 1.6) compared to common-onset (n = 44.4; SD 2.8) (P < .001). Fewer late-onset patients (n = 451) had a positive family history compared to common-onset (n = 2940) (P < .001).
*Conclusions:* Late-onset patients present more frequently with gait and balance problems as first symptom, and disease progression is not milder compared to common-onset HD patients apart from motor progression. The family history is likely to be negative, which might make diagnosing HD more difficult in this population. However, the balance and gait problems might be helpful in diagnosing HD in elderly patients.

## 1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by unwanted movements, psychiatric disorders, and cognitive deterioration [1]. HD results from an expanded CAG trinucleotide repeat in the Huntingtin (*HTT*) gene on chromosome 4 [2]. A CAG repeat size of 36 or more is invariably associated with HD. The common age of onset in HD is in the range of 30–50 years [1]. However, for a substantial part of HD patients symptoms and signs start after 59 years of age. It is believed that late-onset HD (LoHD) is not very common and usually very mild, although frequencies in literature vary between 4.4% and 25% in small cohorts [3–8]. These studies are not conclusive regards clinical presentation of LoHD or disease progression [3,6,9–11]. The proportion of LoHD patients in literature with a negative family history of HD ranges from 3 to 68% [5]. As late-onset chorea falls outside the common-age spectrum for HD, diagnosis might be more challenging [12]. Therefore, our aim is to provide an overview of this group of patients compared to HD patients with a common age of onset (30–50 years) in a large cohort of HD patients from the Registry database [13,14].

## 2. Patients and methods

Data were obtained from patients enrolled in the European Huntington's Disease Registry Database of the European Huntington's Disease Network (EHDN-Registry). This is a prospective monitored

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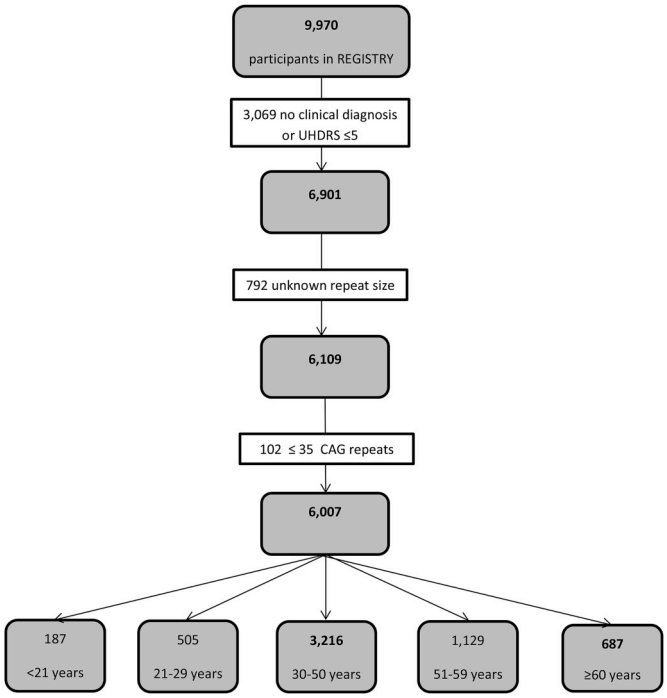


**Fig. 1.** Flowchart of inclusion by clinical diagnosis and repeat size. UHDRS presents for Unified Huntington Disease Rating Scale.

**Table 1**
Baseline characteristics of patients stratified by age of onset group.

| Characteristics | Late-onset (n = 687) | Normal-onset (n = 3216) | P-value for difference |
|---|---|---|---|
| Age of onset | 68.2 (5.6) | 44.7 (7.5) | – |
| Female | 364 (53.0%) | 1683 (52.3%) | 0.788 |
| CAG repeat size | | | |
| Allele 1 | 18.3 (3.6) | 18.6 (3.5) | 0.115 |
| Allele 2 | 40.8 (1.6) | 44.4 (2.8) | < 0.001 |
| CAG repeat size 36 - 39 | 95 (13.8%) | 75 (0.02%) | < 0.001 |
| Family history | 451 (76.1%) | 2940 (94.6%) | < 0.001 |
| Mother affected | 263 (43.6%) | 1467 (46.6%) | 0.190 |
| Age onset mother | 59.1 (11.1) | 43.9 (9.2) | < 0.001 |
| Father affected | 192 (32.2%) | 1477 (47.4%) | < 0.001 |
| Age onset father | 58.2 (10.8) | 47.2 (10.4) | < 0.001 |
| First clinical symptom | | | |
| Motor | 446 (65.5%) | 1574 (49.1%) | < 0.001 |
| Cognitive | 49 (7.2%) | 262 (8.2%) | 0.434 |
| Behavior | 94 (13.8%) | 760 (23.7%) | < 0.001 |
| Oculomotor | 0 (0.0%) | 6 (0.2%) | 0.599 |
| Mixed | 88 (12.9%) | 562 (17.5%) | 0.004 |
| Other | 4 (0.6%) | 39 (1.2%) | 0.220 |
| UHDRS | | | |
| Chorea | 652 (94.9%) | 3054 (95.0%) | 1.000 |
| Dystonia | 415 (60.4%) | 2052 (63.8%) | 0.102 |
| Rigidity | 409 (59.5%) | 1940 (60.3%) | 0.733 |
| Gait and balance problems | 577 (84.0%) | 2408 (74.9%) | < 0.001 |

Data are mean (SD) or n (%).
Abbreviations: UHDRS = Unified Huntington's Disease Rating Scale.

study recording the natural course, clinical spectrum, and management of HD in 140 centers in 17 European and 3 non-European countries [13,14]. Participants provided written informed consent for this observational study. Ethical approval was collected from the local ethics committee for each study site contributing to the EHDN Registry.

### 2.1. Participants and clinical assessments

Data from the EHDN-Registry database from 2004 to 2016 were used to compare participants with an age of onset of HD > 59 years (LoHD) with participants with an age of onset of 30–50 years (common-onset HD). Years of follow up varied between one and 11 years. The database includes repeated measurements of all HD patients that were seen in that period, but may have received their diagnosis well before being enrolled in the database. Patients who have a Unified Huntington's Disease Rating Scale (UHDRS) motor score of ≤5 do not meet the criteria of manifest HD and were therefore excluded [15,16]. Participants with a missing CAG repeat size or a repeat size of ≤35 were also excluded. Data collection adhered to a standard protocol including electronic case report forms and used identical study protocols for the assessment and sampling of biomaterials. At each center, participants were evaluated by specialists with experience in HD. Study site raters were trained, evaluated, and certified annually to minimize inter-rater and intra-rater variability. Data entry was reviewed online and on-site by monitors fluent in the language of the study site. The *HTT* CAG genotyping was carried out at each local genetic laboratory.

The onset of disease was estimated by the clinician, family members and participants themselves. The documented time of clinical diagnosis was available as well. When clinical information was lacking, the family's estimated time of onset was used, then the patient's estimation and finally the date of clinical diagnosis.

Motor and psychiatric signs were scored using the UHDRS [17]. Higher UHDRS motor scores indicated a higher degree of motor impairment (maximum score 124). For cognition, we used the cognitive UHDRS composite score (UHDRS total corrected for letter fluency, symbol digit modalities test, and Stroop sub-scores for word reading, colour naming, and interference), with lower scores indicating lower performance. The disease stage was obtained from total functional capacity (TFC) scores with a maximum score of 13, with lower scores indicating a lower functional status. HADS-SIS sub-scores were obtained for depression, anxiety and irritability combined. A sub-score ≥11 meant the participant had an anxiety or depression disorder. Patients were followed up on a yearly basis according to the EHDN Registry protocol.

Family history and estimated age of onset in parents were obtained from the participants and/or family members. Comorbidities were documented according to the ICD-10 code.

### 2.2. Statistical analysis

Baseline patient characteristics stratified by onset category were described using mean and standard deviation, or absolute number and percentage. Where continuous variables were highly skewed, their location and spread were described using median and interquartile range (IQR).

Baseline differences between age of onset, gender, CAG repeat size (both alleles), family history, parental inheritance, age of onset in parents, first clinical symptom according to patient and family (motor, cognitive, psychiatric, mixed, other), total motor scores on UHDRS, and first symptoms (chorea, dystonia, rigidity, gait and balance problems) were tested using the independent *t*-test or the Mann-Whitney *U* test for normally and non-normally distributed continuous variables, respectively, or the Chi-squared test for categorical variables. In case of expected cell counts of 5 or lower, we used Fisher's exact test.

Longitudinal differences between the groups regarding the total motor score, total function capacity scale (TFC) score, total of neuropsychological test scores (verbal fluency letter test, verbal fluency category test, Stroop colour naming test, Stroop word reading, Stroop interference test, symbol digit modality test) and HADS-SIS sub-scores were compared using linear mixed-effects regression. The mixed-effects regression models included age group, centered time since diagnosis and an interaction term between both as fixed effects, and an intercept and slope as random effects using an unstructured variance-covariance matrix. Covariances between within-patient measurements over time were modelled using an autoregressive covariance structure. Where the

**Table 2**
Results of the longitudinal linear mixed-effects regression on all outcome parameters.

| | Average difference | p-value for difference | Interaction of age group and time | P-value for interaction |
|---|---|---|---|---|
| Motor score | 2.59 (0.94) | 0.006 | −0.58 (0.16) | < 0.001 |
| Total function capacity scale | −1.06 (0.22) | < 0.001 | −0.01 (0.03) | 0.795 |
| Verbal fluency letter test | −2.37 (0.56) | < 0.001 | 0.17 (0.11) | 0.113 |
| Verbal fluency category test | −1.83 (0.27) | < 0.001 | −0.04 (0.05) | 0.460 |
| Stroop colour naming test | −5.26 (0.81) | < 0.001 | 0.23 (0.16) | 0.142 |
| Stroop word naming test | −5.65 (1.10) | < 0.001 | 0.07 (0.22) | 0.751 |
| Symbol digit modality test | −5.18 (0.61) | < 0.001 | 0.28 (0.12) | 0.016 |
| Anxiety score | −0.19 (0.22) | 0.436 | 0.03 (0.05) | 0.541 |
| Depression score | 0.50 (0.26) | 0.049 | 0.06 (0.06) | 0.263 |
| Irritability score | −1.17 (0.49) | 0.017 | 0.05 (0.06) | 0.382 |

Data are presented as regression coefficient (standard error).
Note: a positive interaction indicates that the slope of the late-onset group over time is higher compared to the slope of the common-onset group.

model with the autoregressive covariance structure did not lead to a decrease in the Akaike Information Criterion (AIC), this covariance structure was subsequently omitted from the model, and only variances were estimated. In cases of a violation of heteroscedasticity, a variance function was added to the model.

For statistical analysis we used R, version 3.3.3.

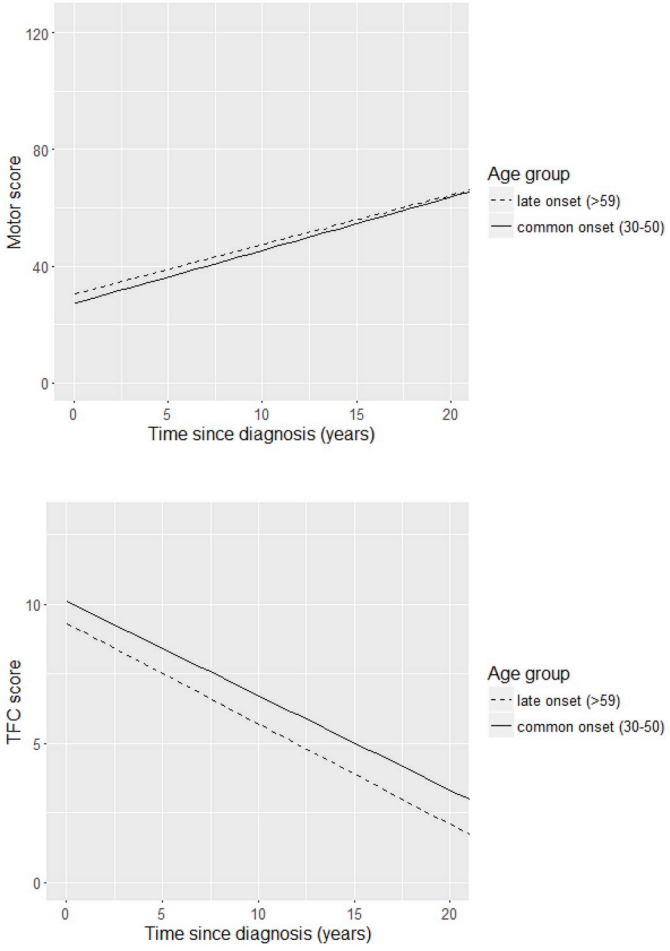


**Fig. 2.** Unified Huntington Disease Rating Scale - motor score (A) and Total Function Capacity (B) in time
UHDRS = Unified Huntington's Disease Rating Scale[2].

## 3. Results

### 3.1. Baseline analysis

9970 participants were included in the EHDN Registry, of which a total of 3069 participants without a clinical diagnosis of HD or a UHDRS motor score ≤5 were identified. Participants with a missing CAG repeat size (n = 792) and a repeat size of ≤35 (n = 102) were excluded. Of the remaining 6007 participants, 687 patients had an estimated age of onset > 59 years (11.4%) and 3216 (53.5%) an onset of age between 30 and 50 years (Fig. 1). Retrieving an estimation of the age of onset by rater was possible for 3020 (93.9%) participants with common-onset HD and for 630 (91.7%) participants with LoHD. The age of onset for the remaining part was retrieved from family members, the participant or time of diagnosis. Table 1 shows the baseline characteristics of all patients, stratified by age-of-onset group. The number of patients with motor symptoms as the first symptom was significantly higher in the LoHD group (n = 446) compared to the common-onset group (n = 1574) (p < 0.001), whereas the number of patients with behavioral symptoms was significantly higher in the common-onset group (n = 262) compared to the LoHD group (n = 49) (P < .001). Gait and balance problems were significantly higher as first symptom in LoHD (n = 577) compared to common-onset HD (n = 2408) (P < .001).

CAG repeat size in the affected allele was lower in the LoHD group (mean 40.8; SD 1.6) compared to the common-onset group (mean 44.4; SD 2.8) (P < .001). Also the number of patients with a CAG repeat in the reduced penetrance range in the LoHD group (n = 95) was significant higher in comparison with the common-onset group (n = 75) (P < .001). Fewer LoHD patients had a positive family history (n = 451) compared to common-onset patients (n = 2940) (P < .001). In case of a positive family history, the age of onset in parents was significantly higher in LoHD patients, with a mean age of onset of 59.1 (SD 11.1) in affected mothers and 58.2 (SD 10.8) in affected fathers, compared to a mean age of onset of in common-onset patient parents of respectively 43.9 (SD 9.2) and 47.2 (SD 10.4) (P < .001).

### 3.2. Longitudinal analyses

On average, patients with LoHD scored worse from the start as well as over the course of time compared to patients with common-onset HD (Table 2). There was a significant interaction (regression coefficient −0.58; SE 0.16; P < .001) between age of onset and the effect of time since diagnosis, showing a decrease in progression of the motor score for the LoHD group compared to common-onset group (Fig. 2A). We

observed statistically significant lower scores in the LoHD group compared to the common-onset group regarding the total function capacity scale (regression coefficient −1.06; SE 0.22; P < .001), but no significant interaction between age group and time (regression coefficient −0.01; SE 0.03; P = .795) (Fig. 2B). In addition, all neuropsychological tests (i.e. the verbal fluency tests, both Stroop tests, and the symbol digit modalities test) yielded significantly worse results for the LoHD group (Table 2). The two HADS sub-scores for anxiety and depression did not differ significantly between both age of onset groups (regression coefficient −0.19; SE 0.22; P = .049 and 0.50; SE 0.26; P = .049 respectively). The anxiety score in the late-onset group decreased over time, whereas for the common-onset group anxiety increased over time. However, there is no significant interaction (regression coefficient 0.03; SE 0.05; P = .543). The irritability sub-score, on the other hand, was significantly worse for LoHD patients (regression coefficient −1.17; SE 0.49; P = .017).

Compared to LoHD patients (10.5%), common-onset HD patients (14.4%) were found to be significant more prone to other neurological and/or musculoskeletal disorders (P = .012).

## 4. Discussion

We analyzed characteristics of LoHD patients in a large European HD cohort. The proportion of LoHD patients in the REGISTRY database is 11.4%. Previous studies that used small cohorts (all fewer than 50 patients) reported estimations of LoHD between 4.4 and 25% [3,4,6,7,18,19]. This study, however, represents the largest cohort study in literature describing the pheno- and genotype of LoHD patients and is therefore statistically more reliable. LoHD was thought to be rare for a long time. Possible explanations for the increase in prevalence include more accurate diagnostics, genetic testing, and better and more readily available symptomatic therapies, certainly in combination with an overall longer life expectancy [20].

In concordance with Koutsis and Lipe, we found that LoHD patients had significantly more balance and gait problems as a first clinical symptom compared to common-onset patients [6,10]. Gait and balance disturbances may be caused by other age related diseases, such as arthritis or polyneuropathy. However, the number of patients who suffered from neurological and/or musculoskeletal disease was significantly lower in the LoHD group compared to the common-onset group, so this provided no explanation for the gait and balance disturbances.

Entering the database, LoHD patients scored worse on motor, cognitive and behavioral domains and through-out the course of the disease, although differences in the behavioral symptoms of depression and anxiety did not reach statistical significance. Only progression of the motor score tended to be significantly slower compared to common-onset.

Furthermore, there was a significant difference in family history between the two groups: the LoHD group more frequently had a negative family history. Previous articles already mentioned this [5,10]. There are some hypotheses that might explain this phenomenon. First, one might consider that for those who had parents with a late onset of symptoms were more likely to have a negative family history as well and (prior to genetic testing) were misdiagnosed or not diagnosed at all. The fact that the parents of LoHD patients with a positive family history in this study also had a higher age of onset (average 58–59 years), supports this hypothesis. A second explanation might be that parents had an intermediate allele (27–35 CAG repeats). Intermediate alleles are not considered to cause HD, but have the potential to expand into the disease range within one or more generations. Another explanation is that parents had a reduced penetrance repeat length (36–39 CAG repeats). A CAG repeat of 36–39 might lead to reduced penetrance, which means that the clinical symptoms are milder and/or symptoms start later in life. Parents of 1–3% of HD patients are reported to have a repeat size < 36 [21]. Ramos-Arroyo et al. found this to be the case for four LoHD patients in Spain with a negative family history [18]. The fact that we found that reduced penetrance alleles were more frequent in the LoHD group supports this idea. Their ancestors might have had a reduced penetrance allele as well, or an intermediate repeat. Unfortunately, we do not have data for the participants' parents.

The CAG repeat length for LoHD was significantly lower than for common-onset HD. This is not a surprise, as we already know that CAG repeat length negatively correlates with age of onset and accounts for almost 50–70% of the variation in age of onset [22].

There are some limitations to this study. The REGISTRY data, unfortunately, contains multiple instances of missing data, which made it necessary to modify our statistical model accordingly. For many participants, age of onset is a crude estimation. The estimation of age of onset by the rater is likely to be the most reliable estimation. This was available for 92–94% of participants in both groups. Since there is no marker to establish the date of disease onset, this is the most accurate method currently available. By choosing two well-defined age groups we hoped to avoid any overlap in age of onset. Furthermore, the common age of onset for HD is in the range of 30–50 years. We chose to compare the common age of onset with an age of onset > 59. Ideally, all patients would have been tracked from the moment their first symptoms started, but this was not possible. As a result, some patients were already more affected than others when they were enrolled in this database.

Furthermore, the REGISTRY data provide no information on diagnostic delay in LoHD patients. This means that, especially, for those with a negative family history the estimated time of onset of disease remains a crude estimation, as mentioned above. It is likely, that disease onset might have been earlier, but not recognized as such by patient, family and/or healthcare professionals, because of a negative family history.

We conclude that LoHD patients present more frequently with motor symptoms and less frequently with behavioral problems compared to common-onset HD patients. They have significantly more balance and gait problems as first symptom compared to common-onset patients. In contrast to previous studies, we found that disease progression is not milder in LoHD as has been suggested before, however motor progression tends to be slower [5]. The family history is likely to be negative, which might make diagnosing HD more difficult in this population. However, the balance and gait problems as first symptom might be helpful in diagnosing HD in elderly patients with a clear chorea, mild or no behavioral problems and a negative family history.

## Financial disclosure/conflict of interest concerning the research related to the manuscript

The authors declare they have no conflict of interest concerning the research related to this manuscript.

## Financial disclosures of all authors

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## Ethical compliance statement

Participants provided written informed consent for this observational study. Ethical approval was collected from the local ethics committee for each study site contributing to the EHDN Registry.

We confirm that we have read the Journal's position on issues involved by each publication and affirm that this work is consistent with those guidelines.

## Authors' roles

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2. Manuscript: Writing of the first draft

Emilia Bijlsma

1. Research project: Conception
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1. Statistical analysis: A. Design, B. Execution, C Review and Critique

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2. Statistical analysis: Execution

Raymund Roos.

1. Research project: Conception
2. Manuscript: Review and critique

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