Clinical and genetic characteristics of late-onset Huntington's disease in a large European cohort

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Abstract

Background and purpose: Huntington's disease (HD) is an autosomal dominant condition caused by CAG-triplet repeat expansions. CAG-triplet repeat expansion is inversely correlated with age of onset in HD and largely determines the clinical features. The aim of this study was to examine the phenotypic and genotypic correlates of late-onset HD (LoHD) and to determine whether LoHD is a more benign expression of HD.

Methods: This was a retrospective observational study of 5053 White European HD patients from the ENROLL-HD database. Sociodemographic, genetic and phenotypic variables at baseline evaluation of subjects with LoHD, common-onset HD (CoHD) and young-onset HD (YoHD) were compared. LoHD subjects were compared with healthy subjects (HS) aged ≥60 years. Differences between the CoHD and LoHD groups were also explored in subjects with 41 CAG triplets, a repeat number in the lower pathological expansion range associated with wide variability in age at onset.

Results: Late-onset HD presented predominantly as motor-onset disease, with a lower prevalence of both psychiatric history and current symptomatology. Absent/unknown HD family history was significantly more common in the LoHD group (31.2%) than in the other groups. The LoHD group had more severe motor and cognitive deficits than the HS group. Subjects with LoHD and CoHD with 41 triplets in the larger allele were comparable with regard to cognitive impairment, but those with LoHD had more severe motor disorders, less problematic behaviors and more often an unknown HD family history.

Conclusions: It is likely that cognitive disorders and motor symptoms of LoHD are at least partly age-related and not a direct expression of the disease. In addition to CAG-triplet repeat expansion, future studies should investigate the role of other genetic and environmental factors in determining age of onset.

Keywords

41 CAG triplets, age of onset, allele expansion, Enroll-HD, late-onset Huntington's disease
INTRODUCTION

Huntington's disease (HD) is a rare heredo-neurodegenerative autosomal dominant disorder that is characterized by abnormal involuntary movements (most characteristically chorea), loss of motor control, progressive cognitive impairment and psychiatric disorders. HD is caused by cytosine-adenine-guanine (CAG) triplet-repeat expansions in exon 1 of the huntingtin gene (IT15), which is located on chromosome 4p16.3 [1,2]. CAG is the genetic code for the amino acid glutamine; the mutant alleles produce a sequence of 36 or more glutamines in the N-terminus of the Huntingtin protein (Htt), which results in selective neural cell death in the basal ganglia and cerebral cortex [3]. There is international agreement that disease onset should be defined as the time when motor signs occur, although the disease may manifest years earlier with psycho-cognitive symptoms. The age of onset of HD varies greatly. It usually occurs in middle adulthood, that is, between 35 and 55 years of age, but the disease can manifest at any age from 1 to 80 years. In a smaller percentage (approximately 10%–25%), patients experience initial symptoms after the age of 50 years; onset at the age of over 80 years has also been reported [4,5]. Current studies typically set a threshold at 60 years of age to define late-onset HD [6–13]. However, this age limit is arbitrary; in fact, "biological age" has more relevance than chronological age because the continuum of change between extremes of good health and loss of independence occurs in a wide time frame. Recent approaches have been exploring the overlap between the hallmarks of biological aging (i.e., genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction) and neurodegenerative disorders such as HD, and the subject of how aging may contribute to HD onset and progression is currently under debate [14,15].

Before the advent of genetic testing, epidemiological studies estimated that late-onset HD (LoHD) was present in 10%–25% of subjects [16,17]. In recent studies conducted in a larger European cohort, the percentage of tardive onset has been estimated at approximately 11% [11]. The clinical features of LoHD largely overlap with those of the common-onset phenotype (CoHD). The clinical characteristics of LoHD are slower disease progression, mild choreic symptoms [11] and less severe and slower cognitive decline [9,16–21]. Preponderant maternal transmission and attenuated chorea have also been hypothesized by some authors [20,22] but not confirmed by others [8,23,24]. However, it is common belief that disease progression is generally slower and less disabling because it is probably associated with a lower number of CAG repeats in the expanded allele [7,25]. As in other triplet diseases, age of onset correlates inversely with CAG-repeat length, which accounts for approximately 50% to 70% of the variability [26], with the higher variability being observed for 40–42 repeats [27,28]. Other genetic and environmental factors have been found to modulate the onset and the course of the disease [18,26,27,29,30]. In particular, in 2015, an initial combination of three genome-wide association studies (GWAS) carried out by the GeM-HD Consortium identified genome-wide significant loci on chromosomes 8 and 15 [31]. The modifier gene on chromosome 15 has been confirmed recently as FAN1 [32], involved in the repair of DNA damage, while the responsible gene on chromosome 8 is RRM2B, which encodes the small subunit of a heterotetrameric ribonucleotide reductase. A third GWAS locus suggested to be significant on chromosome 3 was confirmed in targeted follow-up of the original study [33]. Furthermore, a smaller GWAS of the TRACK-HD study participants identified MSH3, another mismatch repair gene, as an HD modifier [34] and three more DNA repair loci (PMS1, PMS2 and LIG1) have recently been identified as modifiers of onset in HD in a large cohort [35]. Taken together, these findings show that DNA repair/maintenance mechanisms play an important role in HD pathogenesis [35,36].

In conclusion, to date there is no definitive description of the genetic and phenotypical characteristics of tardive HD patients and the factors determining age of onset. In particular, it is not yet completely clear whether LoHD is characterized by an overall more benign disease expression.

The present study aimed to define the genetic and phenotypical profile of subjects with LoHD. Subjects were selected from a large cohort of HD patients and studied comprehensively with standardized tools (the ENROLL-HD database). We focused on subjects who were over 60 years of age at disease onset.

Consistent with the study aims, the following analyses were carried out:

(i) The clinical, behavioral and cognitive characteristics of White European subjects with LoHD were compared with those of subjects with onset in other age ranges;
(ii) The subgroup of LoHD patients in the initial stage of the disease (i.e., Shoulson Stage I, based on a Unified Huntington’s Disease Rating Scale [UHDRS] total functional score of 11–13) [37] was compared to the group of healthy subjects (HS) enrolled as non-consanguineous family controls aged >60 years;
(iii) The phenotypic characteristics of patients with the same number (41) of CAG triplets (low-range CAG triplet repeats associated with wide variability in age of onset) [28] divided on the basis of age at motor onset into two groups, LoHD and CoHD, were compared with the aim of determining which factors in addition to CAG triplet repeats influence the onset of the disease. This information is of great clinical relevance because it suggests the possibility of intervention with the aim of postponing the onset of symptoms for as long as possible.

MATERIALS AND METHODS

Participants

Study subjects were enrolled from the participants in the multicentric, global, longitudinal, observational study of HD families, Enroll-HD [https://enroll-hd.org/] [38].
We used baseline data obtained from the Enroll-HD database (July 2012–October 2018) in the Fourth Periodic Data Set (PDS4) released on December 31, 2018.

Eligible participants were White European motor-manifest adults with CAG ≥ 36 and motor signs compatible with clinically definite disease diagnosis (UHDRS, Motor Diagnostic Confidence Level = 4). Data were collected from 123 study sites located in 13 European countries.

Patients with HD were divided by age of onset into four groups based on the most recent classifications [10–12]: LoHD (≥60 years); common/typical adult-onset (CoHD: 30–59 years, CoHD), young adult-onset (YoHD: 20–29 years,) and juvenile/pediatric-onset (JHD: <20 years, excluding minors, we included subjects aged 18–19 years at the baseline visit). We preferred age at motor onset to age at diagnosis, as the latter is usually postponed from one to a few years compared to the actual onset. The identification of age of motor onset was retrieved from the HD Clinical Characteristics Questionnaire (HDCCQ), which was administered at baseline by a healthcare professional and which collects retrospective information about the prevalence and onset of eight symptoms commonly observed in HD [39], asking whether the participant has ever had the symptom (yes or no) and, if yes, the age at which the symptom was first experienced. Symptoms included were as follows: motor, cognitive impairment, apathy, depression, perseverative/obsessive behavior, irritability, violent or aggressive behavior, psychosis.

For further analysis, a subgroup of subjects with LoHD at early stage (Shoulson stage I) [37] was selected and compared to a group of ≥60 years HS from nonconsanguineous family controls (i.e. spouse) who were not blood related to HD patients.

Finally, for phenotypical comparisons, HD patients with 41 CAG repeats were extracted from the dataset and clustered into two groups, namely, a CoHD and an LoHD group, on the basis of age at onset.

**Outcome measures**

We analyzed the genetic, sociodemographic, clinical, neuropsychological and behavioral variables of HD patients that were reported at the enrollment baseline visit in the Enroll-HD database (for further details, see Table S1). We also analyzed the Burden of Pathology (BOP) score, an index of lifelong exposure to mutant Huntingtin, calculated using the formula based on age and CAG repeat length: age × (CAG-35.5) [40].

**Statistical analyses**

Statistical analyses were carried out using the Statistical Package for Social Science (SPSS) version 24.0 and R Studio version 1.4.1106. Summary statistics are expressed as means and standard deviations or percentages for categorical variables. Categorical variables were compared with chi-squared statistics and continuous variables with independent samples Mann–Whitney U-tests, depending on data distribution. Neuropsychological data were analyzed using analysis of covariance (ANCOVA) by inserting age, education level (according to the International Standard Classification of Education, ISCED) and disease duration as covariates or education level (ISCED) and BOP score as covariates.

To prevent false-positive significant results, we set the statistical significance threshold at a p value <0.005 in the analysis performed on the whole sample of adult HD motor-manifest subjects, whereas a p value <0.05 was set for the analyses conducted on subsamples. In post hoc analyses, Bonferroni’s correction was adopted to adjust p values when comparing more than two groups.

**RESULTS**

**Phenotypic and genetic characteristics of the four patient groups**

The complete original dataset included 15,301 participants. We excluded non-European, non-White European subjects, non-motor-manifest patients (or presenting prodromal non-specific neurological signs with a diagnostic confidence level <4), gene-negative subjects, family control subjects and minors (age <18 years at baseline). The final sample included 5053 adult motor-manifest subjects: 663 in the LoHD, 3960 in the CoHD, 368 in the YoHD and 62 in the JHD group. Due to the small number of juvenile/pediatric-onset subjects aged >18 years at baseline, the JHD group was not included in further analyses (Figure 1).

Table 1 summarizes the descriptive data of the three HD subgroups and the between-group comparisons.

The LoHD presented significantly fewer CAG triplets in the expanded allele and a lower BOP score than the other two HD groups. Regarding the UHDRS, despite the significantly shorter disease duration, the LoHD group presented comparable severity of motor symptoms and functional impairment (total motor score [TMS]; total functional capacity [TFC]) with respect to CoHD and YoHD.

Absence/unknown HD family history was significantly more common in LoHD patients (31.2%) than in the other groups (CoHD = 10%; YoHD = 3.2%) and paternal inheritance was significantly less common in that group than in any other group (Figure 2a). Expansion of the non-pathological allele was not different among the groups.

According to the rater’s opinion, the initial major symptom was primarily motor in all groups, with a higher frequency in the LoHD group compared to the CoHD and YoHD groups; the frequency of cognitive disorders at onset was slightly lower in those with LoHD compared to CoHD, but was similar to that in the YoHD group. Psychiatric/behavioral disorders at onset did not differentiate the subgroups in the rater’s opinion (Figure 2b).

In the psychiatric anamnesis, however, subjects with LoHD reported significantly less frequent history of alcohol/substance abuse, suicidal behavior/ideation, apathy, depression and irritability and obsessive/compulsive disorders than those with CoHD; alcohol/
substance abuse, suicidal behavior/ideation were also reported significantly less frequently in the LoHD compared to the YoHD group. With respect to the behavioral and psychiatric disorders in the last month before baseline, the Problem Behaviors Assessment questionnaire short version (PBA-s) [39,41,42] showed a lower irritability subscore in the LoHD than the CoHD group.

In the neuropsychological assessment, the LoHD group performed worse than the CoHD group on the Mini-Mental State Examination (MMSE) and the Symbol Digit Modality Test after controlling for confounding factors (Table 1). When BOP score was also introduced into the analysis, subjects with LoHD had the lowest scores on almost all tasks (except for the Trail-Making Test [TMT] part A, correct number of answers) compared to the other two groups and the CoHD group performed worse than the YoHD group (Table 1).

Demographic, cognitive and behavioral differences between subjects with LoHD in early stages and subjects with normal aging

The subgroup of subjects with early-stage LoHD with a TFC score in the range of 11–13 (Shoulson’s stage I) [37] and aged ≥60 years (N = 161) were compared with HS aged ≥60 years (N = 220). Sociodemographic, clinical and genetic characteristics are detailed in Table 2. Subjects with LoHD were older and had a lower body mass index than controls. As expected, those with LoHD presented with lower motor performance (TMS-UHDRS) and residual functional capacity scores (TFC-UHDRS) than the HS group and had a higher number of CAG repeats. No differences were observed between the two groups with respect to psychiatric history in terms of alcohol and drug abuse. On the PBA-s, the LoHD group had a higher apathy, irritability and executive (perseverative/obsessive symptoms) domain score than the HS group.

With respect to the neuropsychological examination, the LoHD group performed worse on all tasks.

Comparison between CoHD and LoHD subjects with 41 CAG triplets

It is known that, in HD, CAG-repeat length is inversely correlated with age of onset but does not fully account for age of onset variability. In order to investigate other factors potentially able to shape this variable, subjects (N = 593) with the same number of
| HD groups based on motor-onset age | Pairwise comparisons |   |   |   |
|-----------------------------------|---------------------|---|---|---|
| LoHD (n = 663) | CoHD (n = 3960) | YoHD (n = 368) | LoHD vs CoHD | LoHD vs YoHD |
| Female, % | 50.7 | 51.2 | 51.4 | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Age, years | 71.6 (5.6) | 52.7 (9.1) | 33.2 (6.4) | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| Age at motor onset, years | 65.1 (4.7) | 45.4 (7.8) | 25.4 (2.6) | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| Educational level (ISCED) | 2.9 (1.4) | 3.2 (1.2) | 3.1 (1.1) | <0.001<sup>c</sup> | Ns<sup>c</sup> |
| CAG larger allele (n repeats) | 40.8 (1.2) | 43.7 (2.5) | 50.7 (4.3) | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| CAG normal allele (n repeats) | 18.2 (3.1) | 18.2 (2.9) | 18.1 (3.0) | Ns<sup>b</sup> | Ns<sup>b</sup> |
| Penney BOP score | 375.8 (78.7) | 418.9 (91.7) | 493.5 (128.4) | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| BMI, kg/m<sup>2</sup> | 24.6 (4.1) | 24.5 (4.7) | 23.4 (4.8) | Ns<sup>b</sup> | <0.001<sup>b</sup> |
| UHDRS TMS | 41.2 (18.7) | 41.2 (22.8) | 44.6 (25.9) | Ns<sup>b</sup> | Ns<sup>b</sup> |
| UHDRS TFC score | 7.4 (3.7) | 7.7 (3.9) | 7.3 (4.2) | Ns<sup>b</sup> | Ns<sup>b</sup> |
| Disease duration, years | 6.5 (4.1) | 7.3 (5.2) | 7.7 (6.0) | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| Inheritance, % |   |   |   |   |
| Maternal | 38.8 | 45.4 | 46.2 | 0.001<sup>a</sup> | Ns<sup>a</sup> |
| Paternal | 30.0 | 44.6 | 48.6 | <0.001<sup>b</sup> | <0.001<sup>b</sup> |
| Absent/Unknown | 31.2 | 10.0 | 5.2 | <0.001<sup>a</sup> | <0.001<sup>a</sup> |
| Initial major symptom in rater's opinion, % |   |   |   |   |
| Motor | 60.0 | 50.8 | 50.9 | <0.001<sup>a</sup> | 0.004<sup>a</sup> |
| Cognitive | 3.5 | 6.0 | 5.4 | 0.009<sup>a</sup> | Ns<sup>a</sup> |
| Psychiatric/behavioral | 18.4 | 21.4 | 19.6 | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Other/Unknown | 0.4 | 1.1 | 1.6 | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Mixed (motor plus other) | 17.7 | 20.7 | 22.5 | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Psychiatric anamnesis presence, % |   |   |   |   |
| Alcohol abuse history | 4.2 | 8.1 | 9.2 | 0.001<sup>a</sup> | 0.001<sup>a</sup> |
| Drug use/abuse history | 1.2 | 5.2 | 13.0 | <0.001<sup>a</sup> | <0.001<sup>a</sup> |
| Suicidal behaviour/ideation | 21.5 | 32.2 | 31.7 | <0.001<sup>a</sup> | <0.001<sup>a</sup> |
| Apathy | 64.6 | 71.2 | 66.0 | 0.001<sup>a</sup> | Ns<sup>a</sup> |
| Depression | 63.5 | 76.0 | 67.7 | <0.001<sup>a</sup> | Ns<sup>a</sup> |
| Irritability | 64.7 | 73.3 | 67.7 | <0.001<sup>a</sup> | Ns<sup>a</sup> |
| Psychosis | 13.1% | 14.3% | 16.9% | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Obsessions/Compulsions | 51.6 | 57.6 | 55.0 | 0.004<sup>a</sup> | Ns<sup>a</sup> |
| PBA-s baseline domain score |   |   |   |   |
| Depression | 4.8 (6.0) | 5.5 (6.5) | 5.1 (6.2) | Ns<sup>a</sup> | Ns<sup>a</sup> |
| Irritability/aggression | 2.9 (4.3) | 3.7 (5.2) | 3.7 (5.4) | <0.001<sup>b</sup> | Ns<sup>b</sup> |
| Psychosis | 0.3 (1.5) | 0.4 (1.9) | 0.6 (2.8) | Ns<sup>b</sup> | Ns<sup>b</sup> |
| Apathy | 4.1 (4.9) | 4.3 (4.8) | 3.9 (4.8) | Ns<sup>b</sup> | Ns<sup>b</sup> |
| Obsessions/compulsions | 3.4 (5.3) | 4.1 (5.9) | 4.2 (6.4) | 0.002<sup>b</sup> | Ns<sup>b</sup> |
| Neuropsychological tests, estimated marginal means (SE) |   |   |   |   |
| Age, ISCED and disease duration as covariate |   |   |   |   |
| MMSE (0–30) | 23.3 (0.3) | 24.3 (0.1) | 24.2 (0.4) | 0.002<sup>d</sup> | Ns<sup>d</sup> |
| Symbol Digit Modality Test (0–110) | 18.3 (0.6) | 20.6 (0.2) | 20.7 (0.8) | 0.001<sup>d</sup> | Ns<sup>d</sup> |
| Categorial fluency (animals) | 10.8 (0.3) | 11.3 (0.1) | 10.9 (0.3) | Ns<sup>d</sup> | Ns<sup>d</sup> |
triplet repeats (41 CAG triplets) were split into two subgroups: 233 LoHD 41CAG vs. 360 CoHD 41CAG. Sociodemographic, clinical and neuropsychological variables were compared in subjects with a potentially comparable genetic status but different ages of onset (Table 3). As expected, at the baseline visit, subjects in the LoHD 41CAG subgroup were older than those in the CoHD 41CAG subgroup, and their age at motor onset was higher. Subjects in the LoHD 41CAG subgroup had worse motor performance (TMS) and functional capacity (TFC) and shorter disease duration. Pure motor onset was slightly significantly more frequent in those with LoHD 41CAG (Figure 2b). Despite the same number of CAG repeats, absent or unknown family history was more frequent in LoHD 41CAG, but maternal or paternal inheritance did not differentiate the groups (Figure 2b). The length of the non-pathological allele was not different between the two groups.

Furthermore, according to the psychiatric anamnesis, subjects in the LoHD 41CAG subgroup reported a history of depression and suicidality ideation/behavior less often than those in the CoHD 41CAG subgroup and less severe current depression and anxiety symptoms on the PBA-s. In the neuropsychological assessment significant differences emerged only on the Stroop Interference Test and the TMT part B (correct responses), with worse performance in the LoHD 41CAG subgroup when correcting for confounding factors.

**DISCUSSION**

This study focused on the LoHD population and was aimed at dissecting the correlated genotype–phenotype complexity in this subpopulation. Out of 5053 White adults with motor-manifest HD, 13%...
had late-onset HD, which was consistent both with previous reports, showing that in 4.4%–12.5% of HD subjects the disease manifests at the age of over 60 years [10] and with the percentage (11%) reported in the Registry cohort, which comprised European subjects (including non-White subjects) [11].

A negative correlation between CAG expansion and age of onset accounts for 50%–70% of the age variation [43]. As expected, our LoHD group showed fewer triplet repeats than the CoHD and YoHD groups, in line with data from other studies conducted in same-age groups [7,10]. Furthermore, the significantly shorter disease duration in subjects with LoHD compared to the other groups corroborates what has already been observed [7,8,44].

Late-onset HD significantly differed from CoHD and YoHD regarding absent /unknown family history (31.2% vs. 10% and 5.2%, respectively), confirming data reported in previous studies [9–11]. It has been proposed that a possible explanation for missing HD history is that these subjects may have had a parent with a mild phenotype caused by reduced penetrance allelic copy or a parent with a non-pathogenetic permuted allele that further expanded in successive generations [11].

Late-onset HD significantly differed from CoHD and YoHD regarding absent /unknown family history (31.2% vs. 10% and 5.2%, respectively), confirming data reported in previous studies [9–11]. It has been proposed that a possible explanation for missing HD history is that these subjects may have had a parent with a mild phenotype caused by reduced penetrance allelic copy or a parent with a non-pathogenetic permuted allele that further expanded in successive generations [11].

It is noteworthy that we did not find any difference between the LoHD and CoHD groups, either in the whole sample of patients or in the subsample of those with CAG41 triplets, in the expansion of the non-pathological allele. In agreement with our data, no difference was documented between the CoHD and LoHD groups in a large European cohort from Registry [11,39].

Subjects with LoHD presented with motor onset more frequently than the other groups [7,8,11] and with cognitive onset slightly less frequently than the CoHD group. At the baseline visit, TMS and TFC did not differentiate the groups despite different disease duration (shorter in the LoHD group), further suggesting that motor symptoms are characteristic of this group. While our data are consistent with those reported in previous studies showing more severe motor disorders in individuals with LoHD [11,12], they are in contrast with others that report lower severity of motor symptoms, particularly chorea [11]. This is coherent with clinical observations of patients with longer disease duration in which chorea is replaced by a rigid- akinetic phenotype.

In line with recent data [12,13], the anamnestic presence of psychiatric and behavioral disorders was less significant in the LoHD group compared to the other groups as was the detection of current psychiatric symptoms at baseline.

Regarding cognitive impairment, the global measure (MMSE) and a few executive tasks were more impaired in subjects with LoHD than in those with CoHD and were overall comparable in the LoHD and YoHD groups. However, it is likely that the origin of the cognitive impairment is different in LoHD and YoHD, that is, correlated to aging in LoHD [45] and to the disease in YoHD. Consistent with this, introducing BOP score as a covariate in the statistical comparisons, that is, controlling for general effects of the disease, performance on the cognitive tasks clearly reflected the age of the subjects, with lower scores in older subjects (LoHD) and higher scores in younger subjects (YoHD).

Thus, the hypothesis that LoHD might correspond to less severe disease expression [7,21] is at least partially supported. However, subjects with early-stage LoHD (Shoulson stage I) already showed clear signs of a widespread cognitive disorder compared to HS aged ≥60 years, as well as behavioral manifestations...
TABLE 2 Sociodemographic and clinical variables of subjects with late-onset Huntington’s disease in the early stage of disease (Shoulson stage I) and family non-blood-related healthy subjects, aged ≥ 60 years (total subjects = 381)

|                        | Early-stage (Shoulson stage I) LoHD | Healthy subjects |
|------------------------|-------------------------------------|------------------|
|                        | ≥60 (n = 161)                       | ≥60 (n = 220)    |
| Female, %              | 42.9                                | 56.4             |
| Age, years             | 69.3 (5.3)                          | 66.5 (5.2)       |
| Educational level (ISCED) | 3.4 (1.4)                        | 3.1 (1.3)       |
| Age at motor onset, years | 64.8 (4.4)                         |                 |
| CAG larger allele (n repeats) | 40.6 (1.0)                        | 19.5 (3.1)      |
| CAG normal allele (n repeats) | 18.3 (2.8)                         | 16.6 (2.1)      |
| Penney BOP score       | 352.0 (66.8)                        |                 |
| BMI, kg/m²             | 24.9 (4.0)                          | 28.0 (4.4)      |
| UHDRS total motor score | 24.9 (10.9)                        | 1.9 (2.7)       |
| UHDRS total functional capacity | 12.0 (0.8)                        | 12.7 (0.7)      |
| Disease duration, years | 4.4 (3.5)                          |                 |
| Psychiatric anamnesis, % |                                      |                 |
| Alcohol abuse history | 0.6                                | 2.3             |
| Drug use/ abuse history | 0                                  | 0.9             |
| PBA-s baseline domain score |                                    |                 |
| Depression             | 4.1 (5.8)                          | 4.2 (5.1)       |
| Irritability/ Aggression | 2.5 (3.8)                         | 1.3 (2.8)       |
| Psychosis              | 0.2 (1.2)                          | 0 (0)           |
| Apathy                 | 1.4 (2.9)                          | 0.7 (2.0)       |
| Executive              | 1.5 (2.9)                          | 0.7 (2.0)       |
| Neuropsychological Tests estimated marginal means (standard error) | | |
| MMSE (0–30)            | 26.9 (0.2)                         | 29.0 (0.2)      |
| Symbol Digit Modality Test (0–110) | 26.6 (0.8)                        | 38.0 (0.6)      |
| Categorial fluency (animals) | 14.5 (0.4)                        | 20.0 (0.3)      |
| Phonological fluency (letters) | 26.3 (1.1)                        | 34.7 (0.8)      |
| Stroop Color Naming Test (0–100) | 48.8 (1.0)                        | 64.8 (0.8)      |
| Stroop Word Reading Test (0–100) | 68.4(1.3)                         | 87.3(1.1)       |
| Stroop Interference Test (0–100) | 23.6(0.8)                          | 33.2(0.6)       |

TABLE 2 (Continued)

|                        | Early-stage (Shoulson stage I) LoHD | Healthy subjects |
|------------------------|-------------------------------------|------------------|
|                        | ≥60 (n = 161)                       | ≥60 (n = 220)    |
| TMT – part A (time, 0–240s) | 66.1(2.7)                         | 42.1(2.1)       |
| TMT – part A (correct, 0–25) | 24.9(0.2)                          | 24.6(0.2)       |
| TMT – part B (time, 0–240s) | 138.6(5.1)                         | 95.9(3.8)       |
| TMT – part B (correct, 0–25) | 22.6(0.5)                          | 23.5(0.4)       |

Note: Mean and standard deviation are reported unless otherwise specified. Between-group comparisons are also reported (significant p < 0.05 in bold).

Abbreviations: BMI, body mass index; BOP, Burden of Pathology; ISCED, International Standard Classification of Education; MMSE, Mini-Mental State Examination; PBA-s, Problem Behaviors Assessment questionnaire short version; TMT, Trail-Making Test.

aChi-squared test.
bIndependent samples t-test.
cIndependent samples Mann–Whitney U-test.
dANCOVA including age, sex and ISCED as covariates.

differences in phenotypic expression between LoHD and CoHD are cancelled out when subjects with the same low number of triplets are considered, in our population, some elements of diversity remain, namely, greater behavioral impairment in those with CoHD and cognitive impairment in LoHD, respectively. More frequent motor onset was also confirmed in the LoHD group.

It is quite interesting to note that despite the same allele expansion, greater difficulty in identifying positive family history in LoHD was confirmed, with a consistently greater presence of cases with absent or unknown inheritance (28.3 vs. 16.1) in this group. Thus, our data on subjects with an equal number of triplets differ in some respects from the data reported in a recent work [28]. In conclusion, what we see in the phenotypical expression of LoHD is probably the combined effects of disease- and age-related factors [46]. As recently investigated, genetic modifiers independent of CAG length contribute to age of onset [36]; furthermore, the intervention of epigenetic and environmental factors cannot be excluded. Cognitive impairment in LoHD is only partly determined by the disease; in fact, there may also be age-related factors [46]. There is evidence of an age-related decline at a more rapid rate in HD, with aging exacerbating cerebral damage in HD. In some brain regions, HD seems to be associated with an accelerated epigenetic age and an overlap between the cellular mechanism of aging and
**TABLE 3** Sociodemographic, clinical and neuropsychological variables of subjects with common-onset Huntington’s disease (HD) with 41 CAG triplets and subject with late-onset HD with 41 CAG triplets (total subjects with 41CAG = 593)

| Variable                                      | LoHD Onset ≥ 60 years (n = 233) | CoHD Onset 30–59 years (n = 360) | p-value |
|-----------------------------------------------|---------------------------------|---------------------------------|---------|
| Female, %                                     | 54.1%                           | 53.3%                           | Ns^a    |
| Age, years                                    | 70.6 (4.7)                      | 60.1 (7.6)                      | <0.001^b|
| Age at motor onset, years                     | 64.2 (3.5)                      | 52.0 (6.1)                      | <0.001^b|
| Educational level (ISCED)                     | 3.0 (1.4)                       | 3.3 (1.3)                       | 0.009^c |
| CAG normal allele (n repeats)                 | 18.2 (3.1)                      | 17.9 (2.8)                      | Ns^b    |
| Penney BOP score                              | 388.3 (25.8)                    | 330.7 (41.8)                    | <0.001^b|
| BMI, kg/m^2                                    | 24.7 (3.9)                      | 25.4 (4.7)                      | Ns^b    |
| UHDRS total motor score                       | 42.7 (19.1)                     | 33.6 (19.4)                     | <0.001^b|
| UHDRS total functional capacity               | 7.4 (3.7)                       | 8.7 (3.6)                       | <0.001^b|
| Disease duration, years                        | 6.4 (3.8)                       | 8.1 (5.8)                       | <0.001^b|
| Inheritance, %                                |                                 |                                 |         |
| Maternal                                      | 42.1                            | 48.3                            | Ns^a    |
| Paternal                                      | 29.6                            | 35.6                            | Ns^a    |
| Absent/Unknown                                | 28.3                            | 16.1                            | <0.001  |
| Initial major symptom in rater’s opinion, %   |                                 |                                 |         |
| Motor                                         | 59.3                            | 51.2                            | Ns^a    |
| Cognitive                                     | 3.4                             | 4.4                             | Ns^a    |
| Psychiatric/behavioural                       | 18.8                            | 23.9                            | Ns^a    |
| Other/Unknown                                 | 0.9                             | 1.1                             | Ns^a    |
| Mixed (motor plus other)                      | 17.6                            | 19.4                            | Ns^a    |
| Psychiatric anamnesis presence, %             |                                 |                                 |         |
| Alcohol abuse history                         | 4.8                             | 5.3                             | Ns^a    |
| Drug use/abuse history                        | 0.9                             | 3.6                             | 0.038^a |
| Suicidal behaviour/ideation                   | 23.7                            | 36.7                            | 0.001^a |
| Depression                                    | 69.5                            | 79.7                            | 0.005^a |
| Irritability                                  | 66.5                            | 71.7                            | Ns^a    |
| Psychosis                                     | 13.3                            | 17.5                            | Ns^a    |
| Apathy                                        | 66.1                            | 67.8                            | Ns^a    |
| Executive                                     | 51.9                            | 53.9                            | Ns^a    |
| PBA-s baseline domain score                   |                                 |                                 |         |
| Depression                                    | 4.4 (5.4)                       | 5.9 (6.9)                       | 0.005^b |
| Irritability/ aggression                      | 2.9 (4.3)                       | 3.2 (4.6)                       | Ns^b    |
| Psychosis                                     | 0.2 (1.2)                       | 0.3 (1.8)                       | Ns^b    |
| Apathy                                        | 4.3 (5.1)                       | 4.0 (4.8)                       | Ns^b    |
| Obsessive/compulsive symptoms                 | 3.1 (4.9)                       | 3.6 (5.6)                       | Ns^b    |
| Neuropsychological tests estimated marginal means (standard error) | | | |
| MMSE (0–30)                                   | 24.1 (0.5)                      | 25.3 (0.3)                      | Ns^d    |
| Symbol Digit Modality Test (0–110)            | 21.3 (0.9)                      | 22.4 (0.7)                      | Ns^d    |
| Categorial fluency (animals)                  | 11.7 (0.5)                      | 12.2 (0.3)                      | Ns^d    |
| Phonological fluency (letters)                | 21.2 (1.2)                      | 22.1 (0.8)                      | Ns^d    |
| Stroop Color Naming Test (0–100)              | 38.2 (1.4)                      | 41.6 (1.1)                      | Ns^d    |
| Stroop Word Reading Test (0–100)              | 53.3 (1.9)                      | 56.5 (1.4)                      | Ns^d    |
the pathogenesis of HD has been widely described [47]. Therefore, it is possible that, in the elderly, the effects of brain damage interact with age-related fragility, contributing to a greater impact on cognitive dysfunction. Similar considerations can be taken into account with regard to motor and functional impairment. From this point of view, it is possible to conclude that the late-onset disease is more benign, as some of the symptoms can be attributed to the "age factor". In this regard, it is also significant that some of the clinical manifestations persist in those with LoHD, even when they are compared to subjects with CoHD but the same allele expansion, supporting the hypothesis that additional factors concur in the phenotypical expression. In 2018, Morrison and Delatycki [48] suggested that, out of the 30% of factors not related to triplet size, 10% are environmental, providing a possible chance for intervention to postpone the age of onset of HD and slow its progression. Lifestyle interventional treatments, including diet, physical exercise, maintaining/improving social relationships, psychobehavioral support to minimize stress impact and enhance coping strategies, will possibly postpone the age of onset of HD and slow its progression. Lifestyle interventional treatments, including diet, physical exercise, maintaining/improving social relationships, psychobehavioral support to minimize stress impact and enhance coping strategies, will possibly impact healthspan and phenotypical expression of the disease in HD subjects [49,50].

The strength of our study is the large number of subjects and variables considered. However, we also acknowledge some limitations. First, this was a cross-sectional observational study that focused on the baseline visit but did not cover disease progression, which could be an important driver of diversity between LoHD and CoHD [8]. In fact, many other useful observations can be drawn from the longitudinal observation of the evolution of symptoms to answer the questions we have posed. A longitudinal approach will be followed in future studies. Experimental designs constructed to disentangle age-related from disease-derived factors could also help to better define clinical pictures in patients with late-onset disease, as well as in the search for genetic and familial factors not expressed by the triplet repeat expansions in exon 1 of the huntingtin gene (IT15).

Finally, identification of any environmental factors with a role in modulating age of onset would have great clinical importance; in fact, this could suggest important strategies and interventions for delaying disease onset as much as possible, increasing the healthspan of HD mutation carriers.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Martina Petracca: Data curation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). Sonia Di Tella: Data curation (equal); Formal analysis (equal); Methodology (equal); Software (lead); Writing – original draft (equal); Writing – review and editing (equal). Marcella Solito: Conceptualization (equal); Data curation (equal); Methodology (equal). Paola Zinzi: Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal). Maria Rita Lo Monaco: Conceptualization (equal); Data curation (equal); Formal
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INFORMED CONSENT
This study did not require institutional review board (IRB) approval because it utilized pre-collected, deidentified data from the Enroll-HD database. Each study site that collected data received its own approval for the study from the local or national coordinator. Site IRB and all participants, or their authorized representative in case of inability, gave their written informed consent for participation in the study and the distribution of de-identified data for research purposes.

DATA AVAILABILITY STATEMENT
Details regarding Enroll-HD are accessible at website https://enroll-hd.org/Enroll-HD. Dataset access can be requested by qualified researchers at https://enroll-hd.org/or-researchers/

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ENDNOTE
1 ISCED: Educational Levels coded internationally as: 0, preprimary; 1, primary; 2, lower secondary; 3, upper secondary, 4, postsecondary, 5, first-stage tertiary, 6, second-stage tertiary.

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