Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis

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Summary

Background Huntington's disease is a rare, neurodegenerative disease caused by an expanded CAG repeat mutation in the huntingtin gene. Compared with adult-onset Huntington's disease, juvenile Huntington's disease (onset ≤20 years) is even rarer and has not been studied extensively. We aimed to further characterise juvenile Huntington's disease by examining the effect of CAG repeat size on disease presentation, progression, and survival.

Methods We did a retrospective analysis of patients with juvenile Huntington's disease aged 20 years or younger, according to the length of their CAG repeat and who had disabling psychiatric symptoms (with motor symptoms) or motor symptoms alone, and of patients with adult-onset Huntington's disease manifesting aged 30–60 years with 40 or more CAG repeats, from the REGISTRY and ENROLL-HD platforms and from two institutional databases (Lega Italiana Ricerca Huntington Foundation and the Instituto Neurociencias de Buenos Aires and the Sanatorio de la Trinidad Mitre). Patients with psychiatric but no motor symptoms were excluded. We compared symptoms at onset and longitudinally in patients with juvenile Huntington's disease with highly expanded (HE subgroup) or low expansion (LE subgroup) mutations, grouped by hierarchical clustering analysis. We also compared disease progression (longitudinal change in Unified Huntington's Disease Rating Scale–Total Motor Score) and survival of patients with juvenile and adult-onset Huntington's disease.

Findings We extracted medical records from 580 patients entered into the studies or databases between June 23, 2004, and March 31, 2018, of whom 36 patients met our definition of juvenile Huntington's disease and 197 for adult-onset Huntington's disease. According to caregiver reports, gait disturbance was more often a first presenting symptom in the HE subgroup (eight [80%] of 10 patients) than in the LE subgroup (seven [27%] of 26 patients; p=0·0071), whereas loss of hand dexterity was more common in the LE subgroup (11 [42%] of 26 patients) than in the HE subgroup (0 [0%] of 10 patients; p=0·0160). Compared with the LE subgroup, development delay (0 [0%] in the LE subgroup *vs* nine [90%] in the HE subgroup; p<0·0001), severe gait impairment (nine [35%] in the LE subgroup *vs* nine [90%] in the HE subgroup; p=0·0072), and seizures (three [11%] in the LE subgroup *vs* eight [80%] in the HE subgroup; p<0·0001) prevailed over time in the HE subgroup. Disease progression was more rapid in juvenile Huntington's disease (n=14) than in adult-onset Huntington's disease (n=52; generalised estimating equation model, p=0·0003). Of 121 deceased patients, median survival was shorter in the juvenile Huntington's disease (n=17) cohort than in adult-onset Huntington's disease (n=104) cohort (hazard ratio 2·18 [95% CI 1·08–4·40]; p=0·002).

Interpretation Patients with HE juvenile Huntington's disease differ clinically from patients with LE juvenile Huntington's disease or adult-onset Huntington's disease, suggesting reclassification of this particularly aggressive form of Huntington's disease might be required.

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Introduction

Large CAG expansions (>60 CAG repeats) in the huntingtin gene, caused by increases in CAG length during intergenerational unstable transmission,[1] are associated with juvenile Huntington's disease, which is typically defined as being symptomatic at age 20 years or younger.[2] Although juvenile Huntington's disease is a rare variant of Huntington disease, accounting for only about 4–10% of all cases,[3] its prevalence might be underestimated, owing to the atypical motor and psychiatric presentation.[4] Its rarity can also cause challenges in the identification and recruitment of patients with juvenile Huntington's disease for long-term observational and longitudinal studies.[5–7]

Compared with adult-onset Huntington's disease, there are major gaps in the understanding of several important issues relating to juvenile Huntington's disease, including symptomatology, which specific brain regions are preferentially affected, how the disease progresses, and overall life expectancy. Furthermore, an absence of validated juvenile Huntington's disease assessment tools makes it challenging to track disease progression in these patients over time.

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Research in context

Evidence before this study

We searched PubMed for human studies in English language using the search terms, "Huntington's disease AND (prospective OR prospectively)" and "Huntington's disease AND (prospective OR prospectively) AND juvenile" published between Aug 18, 1979, and March 31, 2018. The search revealed that although several hundred prospective trials have been done in adult-onset Huntington's disease, such studies are scarce for the much rarer juvenile variant. The extent to which findings in adult populations might be applicable to juvenile Huntington's disease is unknown. Some cross-sectional studies done in patients with Huntington's disease have noted the aggressiveness of this juvenile variant relative to the adult-onset form (in terms of a much earlier age of onset). However, the reasons why the juvenile Huntington's disease variant is so aggressive remains unknown, and longitudinal studies tracking disease symptomatology, disease progression, brain pathology, and survival have not been done.

Added value of this study

To our knowledge, this study provides, for the first time, a detailed description of the presenting features of juvenile Huntington's disease, how its symptoms evolve over time, and the mutation effect it has on survival in these patients. This study also reports how these features compare with those of adult-onset Huntington's disease. In a small subset of patients, the effect of juvenile Huntington's disease was also assessed. A unique set of clinical and pathological features can clearly distinguish patients with juvenile Huntington's disease who had large CAG expansions (>80 CAG repeats) from those with smaller CAG expansions and from those with adult-onset Huntington's disease. Patients with these large CAG expansions experienced different motor and non-motor symptoms at disease onset and throughout the disease course, showed a faster rate of disease progression and had reduced survival not previously reported in patients with Huntington's disease.

Implications of all the available evidence

The results from our study add to the existing evidence by confirming that the juvenile variant of Huntington's disease is particularly aggressive and associated with an early symptom onset. Furthermore, our results also suggest that the current classification of juvenile Huntington's disease might need to be revised. Specifically, juvenile patients who have large CAG expansions (>80 CAG repeats) could be regarded as having a more severe form of Huntington's disease than juvenile patients with smaller expanded repeat regions and from those with adult-onset Huntington's disease.

Cases of childhood-onset (<10 years) or adolescent-onset (<18 years) juvenile Huntington's disease are rarely reported in the literature. Very few observational, retrospective reports have been published to date, although early global developmental delays have been reported in one patient (18 months old).[8] Previous studies investigated symptom presentation only (but not disease progression and further development of symptoms) and did not correlate symptoms to CAG repeat length. Thus, whether early developmental delays (motor, cognitive, or behavioural) and learning difficulties might be associated with substantially increased CAG repeat length and whether this increased CAG repeat length might predispose the individual to a more severe disease course is unknown.[9,10]

We retrospectively analysed data from two prospective observational studies done in patients with juvenile Huntington's disease and adult-onset Huntington's disease and from two databases held by authors' institutions in Italy and Argentina. The goals of the study were to gain insights into how CAG expansion length and triplet instability affect symptom presentation in juvenile Huntington's disease, whether disease progression and survival vary between juvenile Huntington's disease and adult-onset Huntington's disease, and examine the patterns of brain abnormalities in very young (age range 5·5–8 years) patients with juvenile Huntington's disease who have large CAG expansions (>80 repeats).

For **REGISTRY study protocol** see https://www.enroll-hd.org/enrollhd_documents/2016-10-R1/registry-protocol-3.0.pdf

For **ENROLL-HD study protocol** see https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf

Methods

Study design and populations

We did a retrospective study involving patients with Huntington's disease who were either enrolled in the large international REGISTRY (NCT01590589; start date June, 2004, no longer active) or ENROLL-HD (NCT01574053; start date July, 2012, still active), or entered into institutional databases held by the Italian League for Research on Huntington and related diseases (LIRH) Foundation, Rome, Italy (start date March, 2001, still active)[11] and the Instituto Neurociencias de Buenos Aires and the Sanatorio de la Trinidad Mitre, Buenos Aires, Argentina (start date October, 2010, still active).[12]

Briefly, REGISTRY and ENROLL-HD recruited carriers of the Huntington's disease gene mutation (regardless of whether they displayed clinical symptoms and signs of Huntington's disease), their family members (at-risk or confirmed non-mutation carriers), and individuals without a family history of Huntington's disease (controls). Participants were assessed at enrolment (baseline) and annually thereafter. At each visit, participants had a broad range of clinical, motor, cognitive, behavioural, and quality-of-life assessments, and donated blood samples. Full details can be found online in the REGISTRY and ENROLL-HD study protocols. Baseline and follow-up data for a similar range of assessments from mutation carriers were collected and entered into two institutional databases.

Outcome measures in REGISTRY, ENROLL-HD, and the institutional databases included the Unified Huntington's Disease Rating Scale–Total Motor Score (UHDRS–TMS),[13] an internationally validated scale, which was assessed at baseline (year 0) and annually thereafter.

We extracted medical records entered in the REGISTRY and ENROLL-HD platforms and institutional databases between June 23, 2004, and March 31, 2018. We used an established definition of juvenile Huntington's disease. Four patients were eligible for inclusion if they had an age of onset of 20 years or younger and disabling psychiatric symptoms (with motor symptoms) or motor symptoms alone. We excluded patients with psychiatric but no motor symptoms to avoid comorbidity bias. Patients were excluded from longitudinal analysis if they had fewer than 15 years follow-up. We required complete medical records for inclusion in the retrospective analyses of symptoms at onset (cross-sectional) and over time (longitudinal). Patients who also had four or more consecutive annual UHDRS–TMS assessments were eligible for inclusion in the retrospective longitudinal analysis of change in UHDRS–TMS.

Patients eligible for inclusion in the adult-onset Huntington's disease analyses had to be carriers of the Huntington's disease gene mutation at baseline, had to meet a specific definition of adult-onset Huntington's disease devised for this study, namely an age of onset of motor symptoms of 30–60 years (ie, far enough away from the juvenile Huntington's disease cohort age to avoid potential bias of a young adult-onset Huntington's disease population and far enough away from the age for late-onset adult-onset Huntington's disease, which might be associated with milder disease course), and had a CAG length of 40 or more repeats to ensure full penetrance of the mutation.[14] As with the juvenile Huntington's disease cohort, we required the additional eligibility criteria of four or more consecutive annual UHDRS–TMS assessments and more than 15 years follow-up for inclusion in the retrospective longitudinal analysis of change in UHDRS–TMS.

Neurological and behavioural manifestations were assessed in eligible patients by two expert neurologists, FS (juvenile Huntington's disease and adult-onset Huntington's disease) and EMG (juvenile Huntington's disease) using the UHDRS–TMS. FS and EMG also obtained medical records during annual follow-up assessments and interviews with these patients and their family members or caregivers, which took place between June 23, 2004, and March 31, 2018. Written informed consent was obtained from patients, caregivers, and relatives according to the Declaration of Helsinki before study or database entry.

Procedures

We retrospectively analysed the source databases, medical records, and notes from historical caregiver interviews and experienced hospital specialists to generate a detailed picture of neurological, behavioural, and non-motor symptoms, including those uncommon in adult-onset Huntington's disease (eg, autistic spectrum disorders and seizures),[6,7,9,10,14,15] that occurred in patients with juvenile Huntington's disease at disease onset (cross-sectional) and during the disease course (longitudinal). We reassessed CAG mutation length in the REGISTRY and ENROLL-HD platforms and in the two institutional databases according to the described method.[16] We defined highly expanded (HE) and low expansion (LE) subgroups through hierarchical clustering analysis[17] based on the CAG repeat length, baseline UHDRS–TMS score, and patient's age. We quantified the CAG repeat mosaicism (ie, different CAG repeat lengths within the same tissue), an indicator of triplet instability, in patients' blood DNA by obtaining a weighted-max peak (W_{mp}), according to the following formula:

$$W_{mp}=w\times M_{ph}$$

where w is the proportion of the peaks at the right side of the maximum peak (appendix).[18] HE and LE subgroups were compared to each other for difference in W_{mp}.

From the patients identified in these analyses, we then selected those who had four or more consecutive annual UHDRS–TMS assessments to compare the rate of disease progression (as indicated by change in UHDRS–TMS) in patients with juvenile Huntington's disease and adult-onset Huntington's disease. We also identified any deceased patients from the LIRH Foundation institutional database and compared survival between those patients with juvenile Huntington's disease and adult-onset Huntington's disease. Finally, we retrospectively reviewed all available coronal and sagittal MRI scans (1·5 Tesla) that had been done at diagnosis in patients with childhood Huntington's disease (two boys, two girls; age range 5·5–8·0 years) and from a single post-mortem brain of a fifth female patient (aged 8 years) diagnosed with childhood Huntington's disease to identify potential early brain abnormalities (appendix).

See Online for appendix

Statistical analysis

We used Student's t test to compare differences in UHDRS–TMS at baseline and year three between juvenile Huntington's disease HE and LE subgroups and the adult-onset Huntington's disease cohort. By this method, we used both CAG repeat length and the ratio between UHDRS–TMS at baseline and age at onset (appendix). We compared differences in clinical presentation between patients with juvenile Huntington's disease in the HE and LE subgroups using the χ^2 or Fisher's exact tests for categorical variables, as appropriate. For continuous variables, we verified the normal distribution of data using normality QQ plots. When data were normally distributed, we used Student's t test, otherwise we applied the Mann-Whitney U test. We used Kaplan-Meier analysis

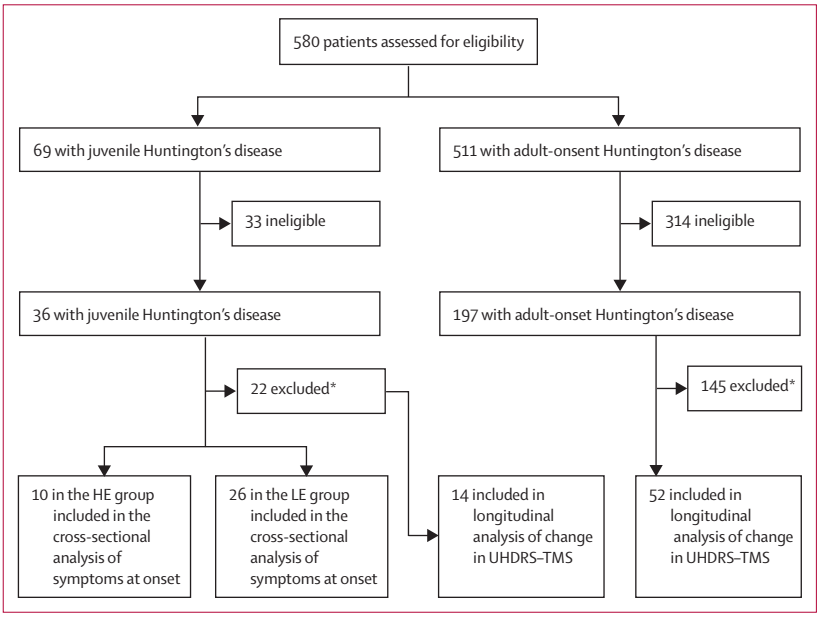

Figure 1: **Study profile**
*Patients were excluded if they had <15 years follow-up and <4 consecutive annual assessments of UHDRS–TMS.

	Patients with juvenile Huntington's disease in the HE subgroup (n=10)	Patients with juvenile Huntington's disease in the LE subgroup (n=26)	Patients with adult-onset Huntington's disease (n=197)
Female gender	3 (30%)	14 (54%)	95 (48%)
Male gender	7 (70%)	12 (46%)	102 (52%)
Maternal inheritance	0 (0%)	6 (23·08%)	108 (55%)
Paternal inheritance	10 (100%)	20 (77%)	89 (45%)
Mixed onset*	5 (50%)	5 (19%)	63 (32%)
Motor onset	1 (10%)	11 (42%)	95 (48%)
Non-motor onset	4 (40%)	10 (38%)	39 (20%)
Median age at onset, years (IQR)	4 (3–6)	16·5 (13–20)	44 (39–51)
Median number of CAG repeats (IQR)	86 (83–104)	60·5 (54–65)	44 (42–45)
Median length of follow-up, years (IQR)	5·25 (4–6)	8·5 (6–15)	6·8 (1–37)

Data are n (%), unless otherwise specified. HE=highly expanded. LE=low expansion. *Refers to combined motor and psychiatric symptoms, according to REGISTRY and ENROLL-HD protocols.

Table: **Demographics and clinical characteristics of patients with juvenile Huntington's disease and adult-onset Huntington's disease**

and log-rank tests to analyse the overall survival of patients with juvenile Huntington's disease and adult-onset Huntington's disease. We modelled longitudinal changes in UHDRS–TMS between juvenile Huntington's disease and adult-onset Huntington's disease cohorts over time using the generalised estimating equation model with exchangeable correlation structure (appendix). We calculated CAG-age product (CAP) as product of CAG repeat length and age at diagnosis, a variable of the form age×(CAG–35·5). We tested the difference in baseline CAP scores between patients with juvenile Huntington's disease and adult-onset Huntington's disease using a Mann-Whitney *U* test. All statistical analyses were done with R software (version 3.4.0). For all tests, we considered a p value of <0·05 as significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

This retrospective study included 580 patients with data entered in the source databases between June 23, 2004, and March 31, 2018. 69 patients had juvenile Huntington's disease, median age of onset was 16 (IQR 8–19) years and median CAG expansion length was 60 (50–68) repeats. 36 (52%) of 69 patients (girls, n=17; boys, n=19) were eligible for inclusion. Of 511 patients with adult-onset Huntington's disease, 197 (38%; women, n=95; men, n=102) were eligible for inclusion (figure 1; table).

Of 36 patients with juvenile Huntington's disease, hierarchical clustering analysis identified two subgroups, which we defined as HE (n=10) or LE (n=26; appendix). The LE subgroup had a median CAG length of 61 (IQR 54–65) repeats compared with 86 (83–104) repeats in the HE subgroup. The minimum CAG repeat length in the HE subgroup was 80 whereas the maximum in the LE subgroup was 73 (appendix).

The HE subgroup had a significantly lower median age of onset of motor and non-motor symptoms than the LE subgroup (4 [IQR 3–6] years *vs* 16·5 [13–20] years; p<0·0001; table) and increased mean CAG instability (29·3 [SD 49·4] *vs* 98·8 [100·6]; p=0·00053; appendix). Median follow-up was shorter in the HE subgroup than in the LE subgroup (5·25 [IQR 4–6] years *vs* 8·5 [6–15] years; p=0·0403; table), possibly owing to the higher mortality and disability in these patients. According to caregiver reports, gait disturbance was the first presenting symptom in significantly more patients in the HE subgroup than in the LE subgroup (eight [80%] of 10 patients *vs* seven [27%] of 26 patients; p=0·0071; appendix), whereas loss of hand dexterity (ie, clumsiness) was reported as the first presenting symptom in significantly more patients in the LE subgroup (11 [42%] of 26 patients *vs* 0 [0%] of 10 patients; p=0·0160; appendix). According to patients' medical records, subgroups did not differ in the mean frequency of presenting motor phenotypes (p=0·052; appendix). However, in both subgroups, dystonia and parkinsonism (nine [90%] of 10 patients in the HE subgroup; 17 [65%] of 26 patients in the LE subgroup) were the predominant neurological motor symptoms at onset, whereas ataxia was only reported in a small proportion of patients (one [10%] of 10 patients in the HE subgroup; three [12%] of 26 patients in the LE subgroup; appendix).

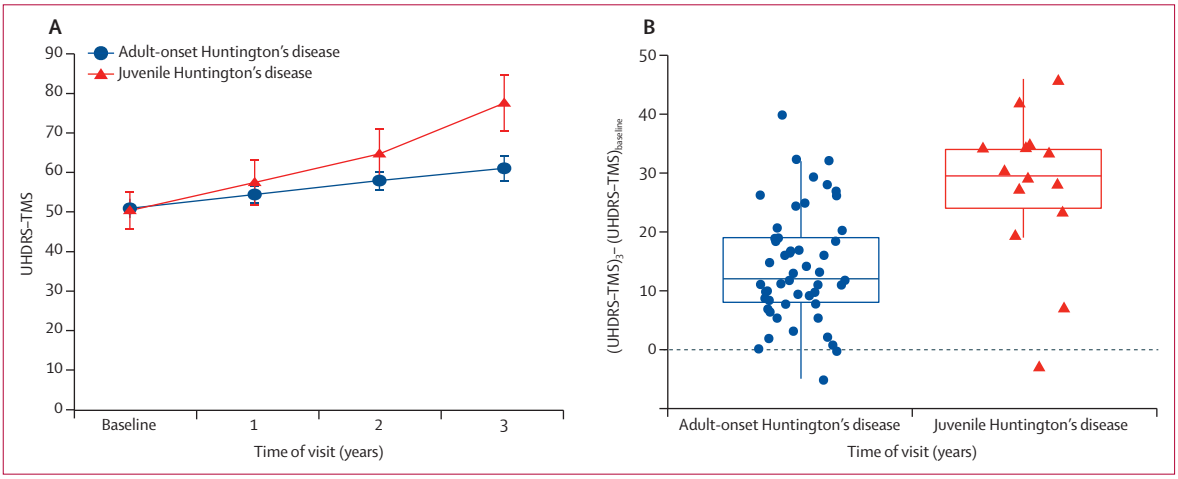

Figure 2: **Longitudinal changes in UHDRS–TMS in the juvenile Huntington's disease and adult-onset Huntington's disease cohorts**
(A) Change in mean UHDRS–TMS from baseline (year 0) to year 3 in the juvenile Huntington's and adult-onset Huntington's disease cohorts. (B) Rate of deterioration in UHDRS–TMS between baseline (year 0) and year 3 in the juvenile Huntington's disease and adult-onset Huntington's disease cohorts. UHDRS–TMS=Unified Huntington Disease Rating Scale–Total Motor Score.

Choreic movements at symptom onset occurred only in patients in the LE subgroup (six [23%] of 26 patients *vs* n=0 [0%] in the HE subgroup; appendix). At symptom onset, dyskinesias affecting the oral region occurred in significantly more patients in the HE subgroup than in the LE subgroup (six [60%] of 10 patients *vs* two [8%] of 26 patients; p=0·0024; appendix).

The main differences in clinical phenotype between the HE and LE subgroups occurred as the disease progressed. Severe gait impairment prevailed over time, affecting more patients in the HE subgroup than those in the LE subgroup (nine [90%] of 10 patients vs nine [35%] of 26 patients; p=0·0072; appendix). Conversely, chorea developed only in patients in the LE subgroup (nine [35%] of 26 patients *vs* 0 [0%] of 10 patients; p=0·0394; appendix). Differences in non-motor symptoms were also reported between subgroups: developmental delays, such as delayed achievement of normal speech and gait, occurred in nine (90%) of 10 patients in the HE subgroup, but in no patients in the LE subgroup (p<0·0001; appendix). Conversely, increased obsessional behaviour was significantly more common in patients in the LE subgroup compared with those of the HE subgroup (two [20%] of 10 patients *vs* 19 [73%] of 26 patients; p=0·0071; appendix). Finally, 11 (31%) out of 36 patients in the juvenile Huntington's disease cohort experienced seizures, which were significantly more common in HE patients than in LE patients (eight [80%] of 10 patients *vs* three [12%] of 26 patients; p<0·0001; appendix).

14 (39%) of 36 patients from the juvenile Huntington's disease cohort and 52 (26%) of 197 patients from the adult-onset Huntington's disease cohort had undergone up to at least four or more consecutive annual UHDRS–TMS assessments (figure 1). Among these patients, median CAG repeat length was 65 (IQR 55–70) repeats and age at onset was 14 (11–18) years in the juvenile Huntington's disease cohort and 43·5 (42–45) repeats and 45 (40–52) years in the adult-onset Huntington's disease cohort. The difference in baseline CAP between the juvenile Huntington's disease cohort (median of 525·8 [IQR 234·1]) and adult-onset Huntington's disease cohorts (417·1 [100·5]) was significant (p=0·0005).

A significant effect of time (ie, the period between the baseline assessment and the assessments at years 1, 2, and 3) on UHDRS–TMS progression was reported for the interaction between the juvenile Huntington's disease and adult-onset Huntington's disease cohorts, at all timepoints (p=0·0003; figure 2A; appendix). The rate of UHDRS–TMS deterioration was also significantly higher in the juvenile Huntington's disease cohort than in the adult-onset Huntington's disease cohort, with a mean increase of 27·43 (SD 12·9) units versus 13·52 (10·1) units over 3 years (p=0·0016; figure 2B).

From a total of 216 eligible patients listed in the LIRH Foundation institutional database, 121 deceased patients with an available age at death were identified (juvenile Huntington's disease, n=17 [censored, n=2]; adult-onset Huntington's disease, n=104 [censored n=93]; figure 3; appendix). Median survival was significantly shorter in the juvenile Huntington's disease cohort than in the adult-onset Huntington's disease cohort (hazard ratio [HR] 2·18 [95% CI 1·08–4·40]; p=0·002). Median survival in the HE subgroup was also significantly shorter than both the LE subgroup (HR 4·35 [95% CI 0·82–23·11]; p<0·0001) and the adult-onset Huntington's disease cohort (5·62 [1·25–25·22]; p<0·0001; figure 3). Survival was similar between patients with adult-onset Huntington's disease and those in the LE subgroup (HR 0·77 [95% CI 0·35–1·66]; p=0·467).

In all four patients with childhood Huntington's disease and imaging data available, MRI and magnetic

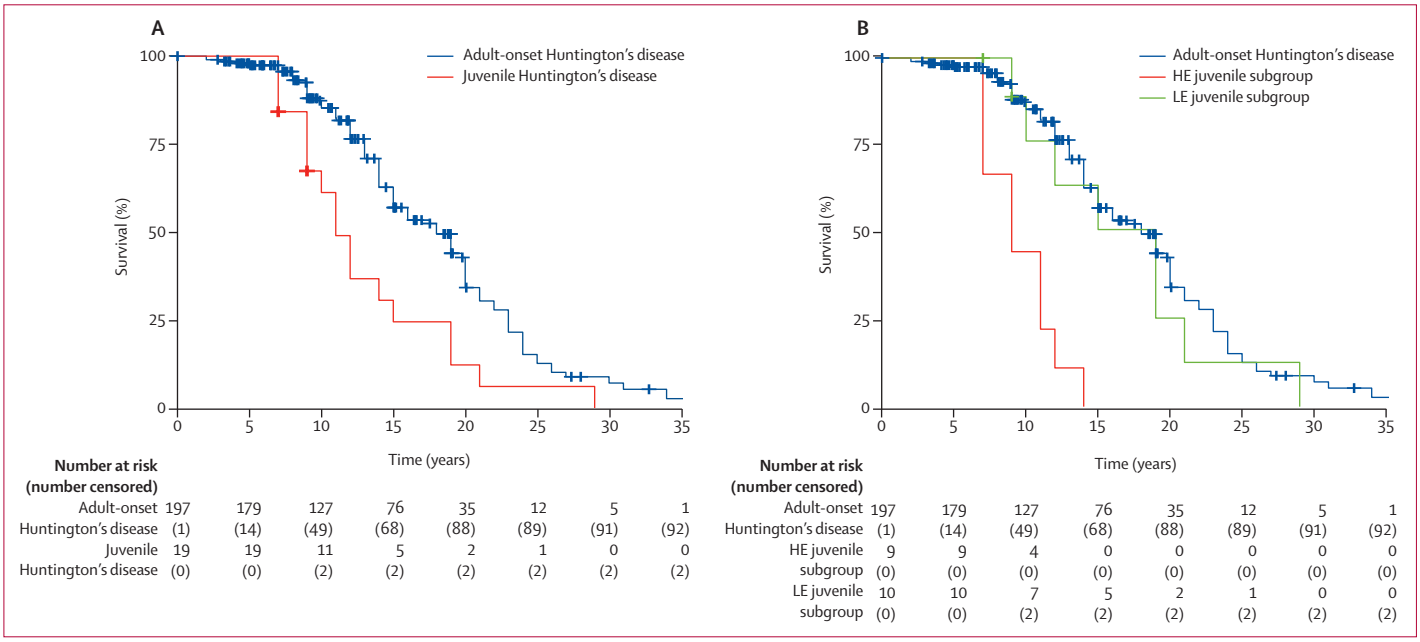

Figure 3: **Survival from enrolment according to Huntington's disease cohorts**
HE=highly expanded. LE=low expansion.

resonance spectroscopy revealed early, selective, bilateral, and global pathological involvement of both striatal nuclei, with marked volume loss in the caudate nucleus and putamen, but no substantial cortical or white matter involvement. These findings were associated with reduced neuronal density and changes in neuronal membrane markers (appendix). The post-mortem brain sample obtained from a fifth patient revealed severe striatal damage with preserved cortical and white matter tissues in line with the MRI brain scan obtained from the other four patients (appendix). All five patients had more than 80 CAG repeats (appendix).

Discussion

Much that has been learned from adult populations could, in theory, be examined in juvenile patients. For example, international observational studies have generated important insights into how disease progression in adult-onset Huntington's disease is influenced by CAG repeat length, age of onset, symptomatology, and other modifiers.[19–22] With this theory in mind, we also examined how CAG repeat length and age of symptom onset affects clinical manifestations and progression of juvenile Huntington's disease. We report a unique set of clinical and pathological features that can distinguish a subgroup of patients with juvenile Huntington's disease who have large CAG expansions (≥80 repeats) from those who have smaller CAG expansions (median of about 60 repeats) or from patients with adult-onset Huntington's disease. Compared with these two populations, patients with juvenile Huntington's disease exhibited an earlier age of onset of symptoms and increased mutation instability, presented with different motor and non-motor symptoms throughout the disease, experienced a faster rate of symptom progression, had reduced survival, and displayed specific brain abnormalities not previously reported in any patient with Huntington's disease.

Our retrospective longitudinal analyses revealed aggressive disease progression in patients with juvenile Huntington's disease carrying large-sized and unstable CAG expansions at baseline. These patients showed a larger baseline CAP (a predictor of Huntington's disease pathology severity),[23] and experienced a more rapid rate of deterioration in UHDRS–TMS (ie, accelerated progression of motor abnormalities) over time than the patients with adult-onset Huntington's disease or those from other studies.[20,24] The survival analysis, based on both CAG repeat length and age at onset, confirmed previous findings reporting a reduced lifespan in patients with juvenile Huntington's disease compared with those with adult-onset Huntington's disease, particularly in juvenile patients carrying large size mutations over 80 CAG repeats.[25] These patients also showed a significantly increased mosaicism of the expanded mutation (ie, genetically diverse tissues that differed in CAG expansion length), which might theoretically result in highly expanded CAG repeats in some parts of the brain, specifically in the striatum.[26] Such differences raise the question of whether the pathological effect of the CAG repeat mutation influences the phenotype according to the age at which the disease starts. For example, impaired gait or hand dexterity might develop differently in a young child (aged 2–10 years) compared

with that of an adolescent or an adult patient who has already acquired this ability.

Striatal damage progresses from birth as a linear function of CAG repeat lenght[23] and MRI from living patients and post-mortem brain images showed early severe striatal volume loss despite the preserved white matter and cortex in our five patients with childhood Huntington's disease, all of whom had more than 80 CAG repeats. Conversely, brain abnormalities in patients with adult-onset Huntington's disease include reductions in striatal volume associated with a loss of white and grey matter that starts before symptom onset.[20,27]

Our findings suggest the current classification of juvenile Huntington's disease might need to be revised. Specifically, we believe that patients with juvenile Huntington's disease who have large and particularly unstable expansions (HE juvenile Huntington's disease, ≥80 CAG repeats) should be regarded as having a pathogenic process that is more severe than that of patients with LE juvenile Huntington's disease or adult-onset Huntington's disease. This more severe form of juvenile Huntington's disease is coupled with a distinct clinical course, symptomatology, and neurodegenerative and brain development process, potentially influenced by the length and instability of the mutation. Notably, the HE juvenile Huntington's disease CAG mutation length shows remarkable mosaicism and determines age at onset and disease progression much more strongly than it does in adult-onset Huntington's disease, in which other factors (eg, genetic variations in chromosomal loci, which can hasten or delay disease onset and progression) are likely to contribute to the penetrance of the mutation and play an important part in disease development.[14,22,28] Future studies should clarify whether genetic factors influencing Huntington's disease progression in patients with adult-onset Huntington's disease also have a role in influencing the degree of CAG instability and mosaicism in juvenile Huntington's disease.[28]

Our work has several limitations. First, this study is a preliminary study based only on retrospective data. Inherent challenges are associated with comparing the clinical manifestation of the disease in patients who have HE juvenile Huntington's disease and patients who have LE juvenile Huntington's disease, given the differences in age of onset. Unlike in adult-onset Huntington's disease, disease processes in juvenile Huntington's disease are overlaid on the natural process of brain development, complicating the interpretation of how symptoms manifest and change over time. Therefore, whether differences in presenting symptoms represent a difference in disease pathophysiology or are a consequence of the developmental processes is unknown. For example, a patient who develops juvenile Huntington's disease as early as 2–4 years old might be more likely to experience gait difficulties than a patient who develops juvenile Huntington's disease at an older age, when stable walking might be better established. Similarly, issues with hand dexterity might be reported more often in adolescent-onset juvenile Huntington's disease, when hand coordination is fully established, than in younger-onset patients who might not have learned to write at the time of disease onset. Second, the survival analysis consisted only of patients who were identified as deceased in the source database (ie, no censored observations were available for patients with juvenile Huntington's disease or adult-onset Huntington's disease who did not die during the follow-up period), which might have resulted in a biased estimate of adult-onset Huntington's disease survival. Finally, the number of patients included in the brain imaging and neuropathological analyses was very small and the analyses were made retrospectively and were of a qualitative nature only. Ideally, the brain imaging would also have been performed in patients who were of the same age because the brain is still undergoing developmental changes during childhood, thus variability in brain morphology independent of disease is likely to be considerable.

To conclude, our findings show for the first time that in juvenile Huntington's disease, different disease mechanisms dependent on CAG length can translate into distinct phenotypic alterations and different rates of progression. This result suggests that a reclassification of juvenile Huntington's disease might be needed to account for these differences in clinical and biological manifestations of the disease.

Contributors

US, GBL, and FS designed the study. CF designed the statistical analysis. FC set the DNA genetic test for juvenile Huntington's disease and assessed mutation length. ADL set the DNA genetic test on Huntington's disease and analysed CAG mosaicism. SA-H set the DNA genetic test for Huntington's disease in Oman. SM, MM, and FS collected data. SA-H and QA-S collected data from Omani patients. AC, MC, JLE, and VP collected clinical data from Argentinian patients. AC and VP collected genetic data from Argentinian patients. AC, EMG, and MC collected MRI data from Argentinian patients. J-PGV collected neuropathological brain images from a patient with juvenile Huntington's disease with large mutation size. MA-O collected clinical and imaging data from the youngest juvenile Omani patients with the largest expansion. EMG and FS clinically assessed patients. CF, SM, TM, US, GBL, and FS analysed the data. SA-H analysed data from Omani patients. EMG, MC, JLE, and VP analysed and interpreted data of Argentinian patients. J-PGV, US, GBL, and FS interpreted the data. GB interpreted MRI and MRS data. SM interpreted behavioural changes. QA-S provided logistical support. CF and MM prepared artworks. FS wrote the manuscript. All authors provided a critical review and approval of the manuscript.

Declaration of interests

MM reports grants and personal fees from the Italian League for Research on Huntington and related diseases (LIRH) Foundation for this project. EMG provided consulting services and advisory board functions to Teva, Bago, Union Chimique Belge, Sanofi-Genzyme, Janssen-Biotoscana. GBL has received consulting fees from AOP Orphan Pharmaceuticals, Desitin GmbH, Hoffmann-La Roche, and Siena Biotech, consulting fees and travel support from Teva Pharmaceuticals, personal fees for participation on an Advisory Board from Hoffmann-La Roche, Pfizer, and Prana Biotechnology, and grant support from the Cure Huntington's Disease Initiative Foundation, and received other support from Ionis Pharmaceuticals, Raptor Pharmaceuticals, and Bayer Pharma. FS provided consulting services and advisory board functions to Teva, Pfizer, Hoffmann-La Roche, Oman

Ministry of Health—Sultanate of Oman, Istituto per la Sicurezza Sociale—San Marino Republic, and is co-founder, scientific officer, and consultant of the not-for-profit LIRH Foundation. CF, SM, TM, FC, ADL, GB, AC, MC, JLE, VP, MA-O, SA-H, QA-S, J-PVG, and US declare no competing interests.

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