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ORIGINAL COMMUNICATION

Comparison of mid-age-onset and late-onset Huntington's disease in Finnish patients

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Abstract The phenotype of juvenile Huntington's disease (HD) differs clearly from that of adult-onset HD, but information about differences between mid-age-onset HD and late-onset HD (LOHD) is scarce. A national cohort of 206 patients with adult-onset HD was identified using national registries and patient records. LOHD was defined as age ≥60 years at HD diagnosis. Genetic disease burden was assessed using CAG age product (CAP) score. LOHD comprised 25% of the adult-onset HD cohort giving a point prevalence of 2.38/100,000 in the Finnish population at least 60 years of age. The proportion of LOHD out of new HD diagnoses increased from 21% in 1991–2000 to 33% in 2001–2010. At the time of diagnosis, patients with LOHD had 10.4 units (95% CI 4.8–15.9; $p = 0.0003$) higher CAP scores, more severe motor impairment and slightly more severe functional impairment than that in patients with mid-age-onset HD. There was no difference in the rate of disease progression or survival between LOHD and mid-age-onset patients. The lifespans of deceased patients were shorter in mid-age-onset HD ($p < 0.001$) and LOHD ($p = 0.002$) than their life expectancies. Causes of death differed between the two patient groups ($p = 0.025$). LOHD comprises a quarter of Finnish HD patients and the proportion appears to be increasing. Our results did not reveal differences in the phenotype between mid-age-onset HD and LOHD, but prospective studies are needed.

Keywords Age of onset · Disease progression · Neurodegenerative disorders · Neuroepidemiology · Phenotype · Prevalence

Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder that is caused by CAG trinucleotide repeat expansion in the *HTT* gene [1]. The age of onset is inversely correlated with the length of the affected, but not the wild-type, trinucleotide repeat and is most commonly between the ages of 30 and 50 years, but may vary between 1 and 80 years [2, 3]. Clinically manifest disease is preceded by a prodromal phase characterized by subtle cognitive and motor signs [4] which, however, may be clinically very challenging to distinguish. The clinical phenotype of manifest HD differs distinctly between patients with an adult-onset HD and those with a juvenile-onset HD that has an onset before 20 years of age. The adult-onset disease is usually heralded by chorea, dystonia, and dysexecutive symptoms, while the juvenile form is often characterized primarily by cognitive deterioration, rigidity, and hypokinesia [5]. Younger age of onset is also associated with a faster clinical progression [6].

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Late-onset HD (LOHD) has previously been defined by age at onset of 50 years or later [7–9] and more recently by onset later than 60 years [10–15]. It has been considered rare encompassing only 4.7% of clinical HD cases [10], but proportions in the range of 9.4–19.6% have been reported after the introduction of genetic testing for HD [11–15]. However, only few studies have examined the phenotype of LOHD or compared LOHD with the mid-age-onset phenotype and the results have been inconsistent [13–15].

Progression of HD is affected by aging [16–18] and patients with LOHD enter the severe stage of the disease 2.8 years earlier than patients with mid-age-onset HD [13]. Compared to HD, the inverse correlation between CAG repeat length and age of onset has been suggested to be weaker [5, 13–15] or even absent [19] in LOHD. However, this proposition is not supported by recent prospective data [20]. It is, therefore, possible that the genetic disease burden at the time of diagnosis differs between patients with LOHD and patients with mid-age-onset HD which, in turn, might explain some of the differences between late-onset and mid-age-onset phenotypes. The question of possible phenotypic differences is important, as recent reports have suggested that the mean age at diagnosis is increasing [12, 21] and the prevalence of HD is rising at least in Caucasian populations [22]. Furthermore, patients with LOHD often die of diseases related to old age [14] and it is not known if LOHD itself affects survival. Therefore, we compared phenotypes in a nationwide cohort of patients with mid-age-onset and late-onset HD.

Methods

We have recently ascertained a comprehensive cohort of Finnish HD patients [21]. National registries were searched to identify the patients and patient charts were then reviewed to collect clinical data. Age at diagnosis was used instead of age at disease onset to ensure that all patients had HD with motor manifestations at the time of baseline assessment. Patients were defined to have mid-age-onset HD ($N = 154$) if they had received the diagnosis between the ages of 20 and 59 years and LOHD ($N = 52$) and if they had received the diagnosis at the age of 60 years or later. Genetic diagnosis had been made for 117 mid-age-onset patients and for 47 LOHD patients. CAG age product (CAP) score was used to measure genetic disease burden. The equation used to derive the score $\{CAP = 100 \times AGE \times [(CAG\text{-}30)/627]\}$ is indexed, so that the score would be approximately 100 at the time of expected disease onset [4].

Clinical data on motor, cognitive, and psychiatric symptoms and signs as well as on functional disability were gathered at the time of diagnosis and at 1-, 2-, 3-, and 5-year visits of follow-up according to a pre-defined, standardized protocol. The date and cause of death were obtained from Statistics Finland, the national authority that archives death certificates provided by healthcare.

The observed lifespans of the deceased subjects were compared with their life expectancies. For mid-age-onset patients, life expectancy at the age of 20 years was used for comparison and for LOHD patients, life expectancy at the age of 60 years. Ages of the patients at death were obtained from Statistics Finland as well as population life expectancies stratified according to sex and year of birth.

Statistical analysis

Normality of the continuous variables was tested using Kolmogorov–Smirnov test. Based on the test result, continuous variables were described in terms of mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were described as frequencies and proportions (percentages).

Differences in demographic factors between mid-age-onset HD and LOHD were tested using Student's t test, Mann–Whitney U test, or Fisher's z transformation on Spearman's correlation coefficients. Differences in survival between mid-age-onset HD and LOHD were tested using log-rank test. Generalized linear models were fitted for each symptom to investigate absolute progression and rate of progression between mid-age-onset HD and LOHD adjusting for demographic factors. Results are expressed in terms of odds ratios (OR) with their corresponding 95% confidence intervals. Cox survival regression models were fitted to investigate the differences in survival after the diagnosis between mid-age-onset HD and LOHD. Results are expressed in terms of hazard ratios (HR) with their corresponding 95% confidence intervals.

All analyses were conducted using the SAS System for Windows, V.9.4TS1M1 (SAS Institute Inc., Cary, NC, USA). p values less than 0.05 were considered statistically significant.

Results

We ascertained 52 patients with LOHD (Table 1) giving a prevalence of 2.38/100,000 (95% CI 1.56–3.20) in the Finnish population older than 60 years on 31 December 2010. LOHD comprised 25% of the adult-onset HD cohort, and interestingly, the proportion of LOHD among new diagnoses had increased from 21% in the years 1991–2000 to 33% in the years 2001–2010. CAG repeat lengths of mid-age-onset patients were greater than those of LOHD patients ($p < 0.001$, Table 1). At the time of diagnosis, the CAP score of the LOHD patients was 10.4 units (95% CI 4.8–15.9) higher than that of the mid-age-onset HD

Table 1 Basic characteristics of patients with mid-age-onset HD and late-onset HD

	Mid-age-onset HD ($N = 154$)	LOHD ($N = 52$)
Women [*n* (%)]	82 (53)	27 (52)
Age at diagnosis (years)	49.2 (43.9–55.0)	67.2 (64.6–72.7)
CAG repeat length in affected allele	44 (42–45)	41 (40–42)
CAP at diagnosis	105.3 (95.7–118.0)	117.5 (107.0–129.8)
Correlation of CAG repeat length and age at diagnosis	$r = -0.55$, $p < 0.0001$	$r = -0.34$, $p = 0.019$

Continuous variables are medians (interquartile ranges)

HD Huntington´s disease, *LOHD* late-onset HD, *CAP* CAG age product, *r* Spearman correlation coefficient

Table 2 Comparison of phenotype and functional status between LOHD and mid-age-onset HD at the time of diagnosis

	Difference between LOHD and mid-age-onset HD	
	OR	*p*
Chorea	1.65	0.0008
Dysarthria	3.08	0.0063
Disturbance of eye movements	1.62	0.25
Gait impairment	3.72	0.0002
Balance impairment	5.95	0.0003
Frequency of falls	3.10	0.50
Psychiatric or behavioral impairment	0.24	0.52
Handling domestic chores	2.20	0.04
Managing finances	1.59	0.29
Activities of daily living (ADL)	1.75	0.15
Level of care needed	1.03	0.93
Disease stage	1.61	0.21

OR Odds ratio, the likelihood of LOHD patients having more severe features compared to mid-age-onset patients, *HD* Huntington's disease, *LOHD* late-onset Huntington's disease

patients ($p = 0.0003$, Table 1). The CAP score at diagnosis in the LOHD group decreased from 126.4 ± 12.5 units in 1995–2002–112.5 ± 16.2 units in 2003–2010 ($p = 0.003$). The correlation between the repeat length and age at diagnosis was similar in LOHD and mid-age-onset HD patients ($p = 0.13$).

Motor impairment at the time of diagnosis was more severe in the patients with LOHD than that in patients with mid-age-onset HD. The difference in functional impairment was minor, and no difference was found in psychiatric and behavioral symptoms (Table 2). All clinical variables, except chorea, progressed during the 5 years of follow-up, but no difference was found in the rate of progression between patients with mid-age-onset HD or LOHD.

Survival after the diagnosis was similar between patients with mid-age-onset HD and LOHD ($p = 0.18$, log-rank statistics). Between genders, there was no difference in the survival in patients with LOHD ($p = 0.23$), while the median survival of women with mid-age-onset HD was 14.4 years and that of men was 10.5 years (HR 2.69, $p = 0.0012$). Multivariate analyses showed that male gender predicted shorter survival in mid-age-onset HD (Table 3).

Table 3 Predictors of survival in mid-age-onset HD and LOHD

	Mid-age-onset HD		LOHD	
	OR[a]	*p*	OR	*p*
Male gender	2.84	0.0008	1.50	0.39
Age at diagnosis[b]	1.04	0.16	1.14	0.005
CAG repeat length in affected allele	1.12	0.07	0.95	0.76

LOHD late-onset Huntington's disease

[a]OR predicting shorter survival

[b]OR of a 1-year increase in the age at diagnosis predicting shorter survival

The median lifespan of deceased patients with mid-age-onset HD was 57.1 years, while the median life expectancy at age 20 years was 71.4 years ($p < 0.001$ for difference) in a population matched with respect to sex and year of birth. Among the deceased patients with LOHD, the median lifespan was 75.0 years being shorter than the median life expectancy of 78.4 years at age 60 years in the general population ($p = 0.002$). Five (6%) patients with mid-age-onset HD and seven (28%) patients with LOHD outlived their life expectancy. Causes of death were available for 71 patients (90%) with mid-age-onset HD and for 19 patients (80%) with LOHD (Fig. 1). The frequency of the causes differed between the two groups ($p = 0.025$).

Discussion

We ascertained 52 patients with LOHD that comprised 25% of the entire national HD cohort. This proportion is clearly higher than those of 4.7–19.6% reported elsewhere [9, 11–13, 15]. The patients with LOHD had more motor signs and their functional disability was slightly more advanced at the time of diagnosis than patients with

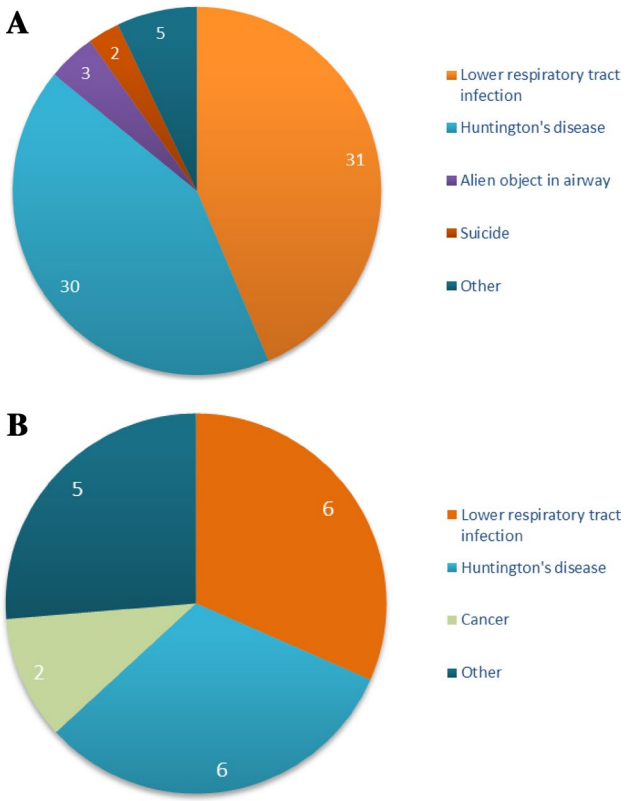

Fig. 1 Frequency of causes of death among patients with mid-age-onset HD (**a**) and LOHD (**b**). Death was attributed to the immediate cause of death if that had been defined. An exception was made in one case in which the cancer had been recorded as the basic cause of death and pneumonia as the immediate cause of death. For this case, death was attributed to cancer. The group "*Other*" includes Pulmonary embolism, Asthma, Bed Sores, Rheumatoid Arthritis (**a**) and Mania, Erysipelas, Obstructive ileus (**b**). *HD* Huntington's disease, *LOHD* late-onset Huntington's disease

mid-age-onset HD. There was no difference, however, in disease progression or survival and the more advanced presentation could be accounted for by a delay in the diagnosis HD in the elderly patients.

The prevalence of HD is lower in the Finns compared to that in other Caucasian populations [21, 22]. Furthermore, only 0.5% of the cases are juvenile compared to 4.8% in other countries [21, 23]. Here we found that the proportion of LOHD is higher than elsewhere. Interestingly, the proportion of LOHD has been reported to be as high as 40% in the island of Crete [24]. However, this concerns a subset of HD families that do not exhibit anticipation and that show shrinkage of the repeat expansion in successive generations [25]. Pedigrees of the Finnish HD patients do not suggest lack of anticipation nor do they suggest any missed cases of juvenile HD (data not shown). The high proportion of LOHD and low number of juvenile cases may be explained by genetic characteristics specific to the Finnish population. It remains to be examined if genetic factors modifying HD phenotype are present in the Finnish population.

At the time of HD diagnosis, the genetic disease burden was higher among patients with LOHD than that among patients with mid-age-onset HD. The disease burden is a function of age and higher values may be explained by factors that tend to delay the diagnosis, such as the assumed rarity of LOHD [10], mild manifestations at onset [14], and negative family history for HD in late-onset patients [13–15]. Furthermore, the motor signs essential for diagnostics of HD [4, 5] may be confused with normal age-related decline of motor abilities [26]. Similar to a previous report [13], we found that the motor phenotype was more severe at the time of diagnosis in patients with LOHD compared to that in patients with mid-age-onset HD, which may be a consequence of diagnostic delay and disease progression. Indeed, had the mean age at diagnosis been 7 years lower in the patients with LOHD, the mean CAP score would have been similar to that in patients with mid-age-onset HD. The difference in CAP scores is not caused by a weak or absent correlation between age of onset and CAG repeat length in LOHD patients [5, 13–15, 19], as this correlation was similar in mid-age-onset and LOHD patients. We found that the CAG repeat length in the affected allele of LOHD patients was similar to those in LOHD patients in two other populations [13, 14], suggesting that the age of onset should be grossly similar between these three cohorts, whereas a considerably higher mean CAG length has been reported in Peruvian LOHD patients [15].

We found no difference between LOHD and mid-age-onset HD in the rate of disease progression. Our finding is in conflict with a previous report, where patients with LOHD reached severe disease stage earlier than patients with mid-age-onset HD [13]. In that study, the age of disease onset was estimated from retrospective information on symptoms, including non-motor ones, and the time until the patients attained severe disease stage was measured [13]. On the other hand, we employed unequivocal motors signs as diagnostic criteria according to current consensus [4, 5, 27], estimated possible diagnostic delay by means of disease burden at the time of diagnosis and determined disease progression by comparing disease burdens at the time of diagnosis and after a 5-year follow-up. Methodological matters may thus explain the difference in the results on disease progression between the studies.

We found that male gender and higher age at diagnosis were predictors of shorter survival. The two factors have been reported to be associated with shorter survival in patients with HD [28–30] and male gender has been reported to be associated with shorter survival in the general population [31, 32]. In line with previous research [33], our study found no correlation between CAG repeat length and survival. These findings strongly suggest that factors unrelated

to HD pathology influence survival in HD. Indeed, we found that causes of death differed between patients with mid-age-onset HD and LOHD. A considerable proportion of deaths of LOHD patients were attributed to causes related to old age, such as cancer and myocardial infarction. Therefore, it is possible that ailments and functional compromises accumulating in aging might mask slower clinical HD progression in LOHD. Indeed, both CAG repeat length [16, 17, 34] and aging [16–18] have independent effects on disease progression. Prospective studies using robust biomarkers [4, 35] are needed to resolve the question on biological differences between the two types of adult-onset HD.

A retrospective study relies on everyday clinical assessments and clinical notes that may be incomplete. We sought to attenuate these limitations by adhering to a protocol designed in advance and to a strict assessment of data by a single expert. The most detrimental error would be inclusion of patients with mid-age-onset HD into the group of LOHD. To attenuate this error, it was required that all patients had unequivocal motor signs consistent with HD. Many of the previous studies have employed behavioral and psychiatric symptoms in the assessment of disease onset [10, 12–15], but these symptoms are not included in the core diagnostic features and are only incompletely related to disease progression [4, 5, 27].

In conclusion, we found that the proportion of LOHD is high among Finnish patients with HD and that the proportion has increased in two decades. Although LOHD is diagnosed later in relation with genetic disease burden than mid-age-onset HD, the clinical phenotype and the rate of progression do not seem to differ between these two forms of adult-onset HD. Nevertheless, prospective large studies on possible differences between mid-age-onset HD and LOHD are needed.

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Compliance with ethical standards

Conflicts of interest Jussi O.T. Sipilä has received honoraria (Merck, Pfizer), has received a consultancy fee (Rinnekoti Foundation), has received travel grants and congress sponsorship (Orion Pharma, Merck Serono, Sanquin, Lundbeck, Novartis), and holds shares (Orion Corporation). Tommi Kauko: Nothing to report. Markku Päivärinta has received honoraria (Lundbeck, Orion Pharma). Kari Majamaa has received travel grants (TEVA, MSD, Orion Pharma) and honoraria (Genzyme).

Ethical standards The study has been approved by the Ethics Committee of Hospital District of Southwestern Finland (Dnro ETMK 19/180/2010) and received the national study permit from the National Institute for Health and Welfare (Dnro THL/1456/5.05.00/2010). The study involved no contact with patients. Hence, no informed consent was stipulated.

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