Genetic Correlates and Clinical Characteristics of Huntington's disease Patients Followed Over the Lifespan at the HDSA Center of Excellence at UC Davis

Ryotaro Fukuda MS[1]; Ferheen Abbasi MS[1], Alexandra Duffy DO[1,2], Eleonora Napoli PhD[1,2], and Vicki Wheelock MD[1,2]
1. UC Davis School of Medicine, 2.Department of Neurology and HDSA Center of Excellence at UC Davis

Background

- Huntington's disease (HD) is an autosomal dominant degenerative neuropsychiatric disease.
- Currently no existing disease-modifying therapies, leading to death in an estimated 15 –20 years after diagnosis.[1,2]
- HD is caused by a CAG triplet expansion in the huntingtin gene (HTT), with CAGn greater than 36 causing HD.[2] There is a very strong inverse correlation between CAGn and age at onset.
- Prior HD registry or population-based studies of survival in the US, Denmark and Norway have been limited by the lack of genetic information and clinical features of HD. [3-6].

Objectives

Our objectives were to describe clinical and genetic characteristics of a cohort of patients prospectively followed until death at the HDSA Center of Excellence at UC Davis multidisciplinary clinic, and to determine the relationship between CAGn and age at death.

Methods

- Retrospective chart review was conducted for patients with HD followed until death at the HDSA Center of Excellence at UC Davis between 2007 – 2022.
- Data collected included gender, age at symptom onset, age at HD diagnosis, CAG repeat length, parental inheritance if known, baseline and last collected clinical measures including Unified Huntington's Disease Rating Scale Total Motor and Total Functional Capacity scores[7], BMI, MMSE or MOCA score, age at death, significant co-morbid conditions, history of hospice referral, causes of death and care setting at the time of death.
- Statistical analysis was performed with GraphPad Prism 9.4.1.

Results

- At the time of data collection, of the 518 identified patients with Huntington's disease 149 had died.
- The mean age at HD diagnosis was 49.4 ± 15.5 years (range, 5-77 years), with mean CAGn on the expanded allele 45.5 ± 8.8 (37-95).
- The mean age at death was 60.9 ± 14.4 years (range 23-87 years).
- Most patients (63%) were residing at home at the time of death, with 55% enrolled in hospice.
- Nineteen percent had elected to have feeding tubes for dysphagia and weight loss.
- Age at death showed a strong inverse correlation with CAGn (Pearson r=-0.8262; p < 0.0001, **Figure 2**).
- Median survival time after onset was 15 years (95% CI, 13-16 years, **Figure 3**).

Figure 1. Range of survival after symptom onset, years

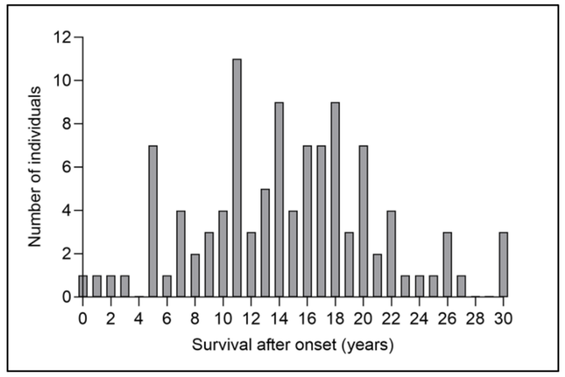

Figure 2. Age at death vs. CAGn of expanded allele

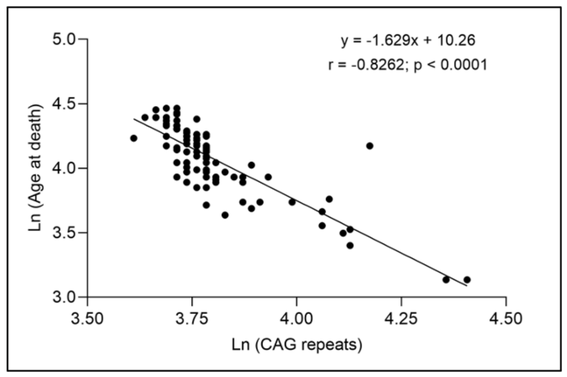

Figure 3. Survival Analysis

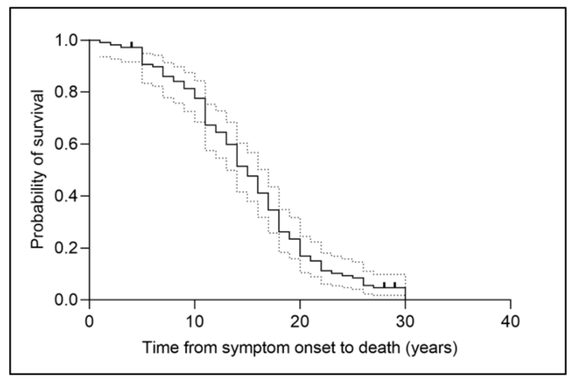

Table 1. Characteristics of the individuals with HD

Patients (n)	109
Female (n)	51
Male (n)	58
Age of HD onset	45.8 ± 14.9 years (5-73)
Age at HD diagnosis	49.4 ± 15.5 years (5-77)
Age at death	60.9 ± 14.4 years (23-87
Years of survival after symptom onset	14.7 ± 6.4 years (0-30)
Expanded CAG repeat size	45.5 ± 8.8 (37-95)
Wild type CAG repeat size	18.5 ± 3.4 (13-33)
UHDRS total functional capacity score (first visit)	7.8 ± 3.6 (0-13)
UHDRS total functional capacity score (last visit)	3.2 ± 2.9 (0-13)
UHDRS total motor score (last visit)	59.7 ± 21.1 (5-100)
Shoulson and Fahn Stage (first visit)	2.2 ± 1.1 (1-5)
Shoulson and Fahn Stage (last visit)	3.5 ± 1.0 (1-5)
Baseline BMI	24.3 ± 5.0 (14.9-39.0)
Last BMI prior to death	22.2 ± 5.2 (12.9-40.4)
Elected to have gastrostomy tube (n)	20
Residing at home at time of death (n)	66
Residing in assisted living at time of death (n)	9
Residing in skilled nursing at time of death (n)	28
Enrolled in hospice at time of death (n)	58

*Data are indicated as mean ± SD (range)
BMI = body mass index; CAGn = cytosine-adenine-guanine repeat length; HD = Huntington's disease, UHDRS = Unified Huntington's disease Rating Scale.

Table 2. Causes of death

Cause	No. (%)
Complications of advanced Huntington's disease	88 (80.7)
Suicide associated with HD	7 (6.4)
Sudden death, other cause	5 (4.6)
Trauma	2 (1.8)
Cerebrovascular event	2 (1.8)
Pulmonary embolism	1 (0.9)
Cardiovascular	1 (0.9)
Cancer	1 (0.9)
Pneumonia	1 (0.9)
Unknown	1 (0.9)

Conclusions

- The demographics and mean age at death were similar to those seen in prior population-based studies.[3-7]
- Similar to age at onset, age at death was strongly inversely correlated with CAGn.
- Mean survival after symptom onset was 15 years, shorter than that described by prior studies in European cohorts, possibly due to variability in identifying symptom onset.[6,8]
- The most common cause of death was complications of advanced HD, with half of patients referred to hospice care prior to dying.
- Most patients followed in our cohort received their care at home until end of life, highlighting the need to support their families in this long caregiving journey.
- Only 55 % of this cohort was enrolled in hospice at the end of life, suggesting that this is a gap in care.
- Further analysis of these data will be performed to determine if there are clinical correlates of disease progression that would suggest consideration of hospice referral in patients with advanced HD.

References

1. Caron NS, Wright GE, Hayden MR. Huntington Disease. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed July 14, 2022.
2. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *European Journal of Neurology*. 2018;25(1):24-34.
3. Lanska DJ, Lavine L, Lanska MJ, Schoenberg BS. Huntington's disease mortality in the United States. *Neurology*. 1988;38(5):769-769.
4. Sorensen SA, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. *J Med Genet*. 1992;29:911-4
5. Solberg OK, Filkuková P, Frich JC, Feragen KJB. Age at Death and Causes of Death in Patients with Huntington Disease in Norway in 1986–2015. *Journal of Huntington's Disease*. 2018;7(1):77-86.
6. Brogueira-Rodriges F et al. Survival, Mortality, Causes and Places of Death in a European Huntington's Disease Prospective Cohort. *Mov Disord Clin Pract*. 2017 Sep-Oct; 4(5): 737–742.
7. Huntington Study Group. Unified Huntington's disease rating scale: reliability and consistency. *Mov Disord*. 1996 Mar;11(2):136-42.
8. Rinaldi C, Salvatore E, Giordano I, et al. Predictors of survival in a Huntington's disease population from southern Italy. *Can J Neurol Sci*. 2012;39(1):48-51.

Acknowledgements

We thank patients with HD and their families for their contributions to this project. This work was support by the UC Davis School of Medicine Medical Student Research Fellowship program, the HD Society of America Center of Excellence grant, the Joseph P Roberson Foundation and the Les and Margaret Pue Foundation. Special thanks to Dan Schwarz and Keith Schwarz for their support.