Two centuries of mortality in ten large families with Huntington's disease: a rising impact of gene carriership

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Two Centuries of Mortality in Ten Large Families with Huntington Disease: A Rising Impact of Gene Carriership

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To estimate the impact of the Huntington gene on mortality, we studied ten families with Huntington disease, whose records started before 1800. We investigated mortality from 1800 to 1997 in 257 carriers of the Huntington gene and 474 potential carriers. Follow-up extended from age 20 years to the date of death or end-of-study date. The observed deaths were compared with those expected on the basis of the general population, adjusted for sex, age, and calendar time. To study the influence of the family and parental transmission, we calculated hazard ratios adjusted for sex, probability of carrying the gene, and year of birth. In 25,013 person-years, 420 deaths occurred, whereas 278 deaths were expected [standardized mortality ratio = 1.5; 95% confidence interval (CI) = 1.4–1.7]. Excess mortality was confined to ages 40–70 years (standardized mortality ratio = 2.2; 95% CI = 1.9–2.4). To study the evolution of mortality over time in this age group, we calculated absolute mortality rates per calendar period. From 1800 onward, mortality rates in the general population continuously declined, but among the families with Huntington disease this decline was absent. There were only small differences in risk between families, and the relative risk for paternal over maternal transmission was 1.2 (95% CI = 0.9–1.5). Our main finding is that persons who carry the Huntington gene and reach middle age have not benefited from advances in medical care and overall increase in life expectancy. (Epidemiology 1999;10:706–710)

Keywords: Huntington disease, SMR, life expectancy, mortality, pedigree.

Huntington disease (HD) is a slowly progressive autosomal dominant neurodegenerative disease with complete penetrance.[1] Clinical manifestation consists of gradually evolving involuntary movements (chorea), progressive dementia, and psychiatric disturbances, especially mood disorders and personality changes. HD affects between 3 and 7 per 100,000 individuals in white populations, but it has been described in populations of many different ancestries.[1] Onset occurs at about 40 years of age, although extremes of 2 and 80 years have been reported.[1–4] The mean duration of the disease is 16 years and is independent of the age at onset.[1,3,5,6] There is no treatment to prevent the onset or to delay the fatal course of the disease. Approximately 80% of juvenile patients inherit the HD gene from their father,[2,4,5,7–10] whereas a preponderance of maternal transmission has been noted in late-onset disease.[11–13] In Dutch late-onset patients, the sex of the affected parent was nearly equally distributed.[4,8] In addition it has been reported that, although the mean age at onset between affected mothers and their offspring did not differ greatly, affected children of affected fathers had a lower mean age at onset than their fathers.[14] This anticipation phenomenon was already reported in the 1970s as a difference in age at death between offspring of men and their fathers.[15,16]

In 1993, the HD gene was identified as an expansion and instability of a specific CAG trinucleotide repeat on chromosome 4p16.3.[17] In HD patients, this highly polymorphic CAG repeat is expanded to a range of 36 to 121 copies. Age at onset of the disorder is inversely correlated with the number of CAG repeats,[18–20] but there was a wide range of age at onset for any specific repeat number.[21] The repeat length accounts for approximately 50% of the variation in the age at onset.[20] During meioses, the HD repeat is unstable, showing both increases and decreases in size with the largest expansions in alleles of paternal origin. This finding could be an explanation for the anticipation phenomenon.[18–20]

Because anticipation may be observed as a consequence of ascertainment bias, the unbiased impact of the HD gene and its variation between families and line of inheritance can best be studied during long-term follow-up. We developed a method to study the survival of

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family members retrospectively by extending the follow-up to the past.[22] The aim of the present study was to compare mortality from 1800 through 1997 in members of HD families with that in the general Dutch population using the Family Tree Mortality Ratio method. The amount of excess mortality in the HD families provides an estimate of the impact of gene carriership on life expectancy. In addition, in these ten families we determined the influence of transmission of the HD gene from either maternal or paternal origin on mortality ratios.

Subjects and Methods

Study Population

Since the mid-1930s, clinical and genealogical data of the great majority of HD patients and their families in the Netherlands have been compiled in the Leiden Roster.[4,6,8,23] The pedigree information is obtained via the families and is verified and extended using municipal registers and national archives, in which all births and deaths have been reported since 1811, and using parish records for the period before 1811. The Leiden Roster is in compliance with Dutch legislation regarding privacy and protection of medical data. From these files, ten large HD pedigrees, between seven and nine successive generations, have been selected with patients in at least two branches and with a clear inheritance pattern. All proven, obligate, and potential carriers of the HD gene were included in this study. In the present generations the diagnosis of HD was confirmed by DNA analysis. In the previous generations, we used pathologic records and Mendelian reasoning to identify persons with a 50% or 100% probability of carrying the HD gene. Obligate carriers were family members who had passed on the HD gene from common ancestors to their affected offspring. Potential carriers were defined as all first-degree relatives of carriers (that is, children and siblings). Thus, Mendelian probabilities can be assigned to all individuals in the pedigree. Using parish records, municipal registers, and national archives, we verified and completed the dates of birth and death for all proven, obligate, and potential HD carriers. Follow-up for all individuals extended from 20 years after the date of birth to the date of death or to June 30, 1997. The reason for ignoring the first 20 years of life was that the obligate carriers, who have passed on the HD gene to their affected offspring, had to be alive at the start of the reproductive period. Moreover, we did not expect an impact of the HD gene before the procreation period. This approach of constructing pedigrees to extend the number of carriers into the previous generations has been described in former reports on mortality in hereditary diseases and is called the Family Tree Mortality Ratio method.[22,24–26]

Statistical Analysis

The overall mortality of the study population (observed) was compared with that of the Dutch general population (expected) adjusted for age, sex, and calendar period. The ratio of observed to expected number of deaths is the standardized mortality ratio (SMR), a rate ratio measure. The expected mortality was calculated by multiplying the total number of years lived by the study population with the sex-, age-, and calendar period-specific population mortality rates from the annual reports of the Netherlands Central Bureau of Statistics, using the computer program Person-Years.[27] Confidence limits for the SMR are based on a Poisson distribution for the observed number of deaths.[28] The calendar periods were divided into a 50-year interval from 1800 to 1849, 20-year intervals from 1850 to 1889, a 15-year interval from 1890 to 1904, and 10-year intervals from 1905 to 1997. To each of these periods we applied the population mortality rates of the midinterval year, subdivided by sex and into 5-year age groups.

Because of distinctions in structure of person-years over the calendar and age groups, one SMR cannot be compared with another SMR. Therefore, to study the influence of the family or of line of inheritance, we performed Cox regression analysis. In the two oldest generations it was, by definition, not known which parent transmitted the HD gene. The multivariate analysis calculated hazard ratios for the ten families and for parental transmission adjusted for sex, probability of carrying the HD gene, and year of birth.

Results

After removal of spouses and family members with less than 50% probability of carrying the HD gene, 849 persons from ten HD families had at least a 50% probability of carrying the HD gene. Of these, 731 individuals were 20 years of age and older and contributed person-years to the analysis. From these ten families, 143 affected men and 114 affected women were identified with certainty, with respectively 123 and 88 persons dying during the study period; 241 men and 233 women were potential HD gene carriers, with respectively 119 and 90 dying in the study period. The mean life expectancy in men was 63 years [95% confidence interval (CI) = 61–65 years], and that in women was 68 years (95% CI = 65–70 years). The mean life expectancy in proven and obligate HD carriers was 59 years (95% CI = 57–61 years), and that in potential HD carriers was 73 years (95% CI = 71–75 years).

Of a total of 25,013 person-years, 420 deaths were counted (242 in men and 178 in women) (Table 1). The expected number of deaths was 278 (154 in men and 124 in women), leading to an overall SMR of 1.5 (95% CI = 1.4–1.7) in both men and women. Table 1 shows the characteristics and relative mortality for the ten HD families separately. In all families there was excess mortality, although there were differences in the magnitude of the SMR.

The excess mortality was limited to the age group 40–70 years (SMR 249/115 = 2.2; 95% CI = 1.9–2.4) and was strongest in the age group 45–60 years (SMR 137/51 = 2.7; 95% CI = 2.3–3.2). To determine the evolution of mortality in this particular age group, in which the HD gene expresses its major impact, we

TABLE 1. Characteristics and Relative Mortality in the Ten Huntington Disease Families, from 20 Years of Age Onward

HD Family	No. Subjects			Person-Years	No. Deaths		SMR	95% CI
	Total	(Obligate) Carriers	Potential Carriers		Observed	Expected		
1	91	36	55	2,924	48	32.21	1.5	1.1–2.0
2	63	28	35	2,442	45	27.88	1.6	1.2–2.2
3	167	44	123	5,807	91	64.53	1.4	1.1–1.7
4	12	5	7	281	7	1.23	5.7	2.3–12
5	30	8	22	812	15	6.99	2.2	1.2–3.5
6	46	18	28	1,848	34	26.71	1.3	0.9–1.8
7	188	70	118	6,805	106	81.05	1.3	1.1–1.6
8	56	23	33	1,643	31	12.72	2.4	1.7–3.5
9	49	19	30	1,351	28	13.88	2.0	1.3–2.9
10	29	6	23	1,100	15	10.72	1.4	0.8–2.3
	731	257	474	25,013	420	277.91	1.5	1.4–1.7

HD = Huntington disease; SMR = standardized mortality ratio.

calculated the absolute mortality rates per 1,000 person-years in the HD families and in the general Dutch population per calendar period, adjusted for the age structure of the HD families over the whole time period (Figure 1). During the past 2 centuries, the absolute mortality rates of the general Dutch population continuously declined, but among the HD family members this decline was absent. Because of this phenomenon, the relative risk increased from 1.3 in the 19th century to 3.7 in the period 1975–1997 for the age group 40–70 years.

Using Cox regression analysis, we studied the influence of the family and the line of inheritance. The differences in risk among the HD families were small (Table 2), given that the smallest family (family 4) had the highest hazard ratio. Furthermore, the year of birth did not influence the mortality rate (as was already shown in Figure 1 by the fact that the absolute mortality rate remained stable over 2 centuries in the HD family members). The risk of dying was 1.4 times greater for men than for women, and proven and obligate carriers had a higher mortality rate than potential carriers (Table 2). The SMR for both paternal and maternal inheritance was 1.7 (95% CI = 1.5–1.9), but the SMR for unknown transmission (meaning the first and second generations) was equal to unity. In a Cox regression model adjusted for family, sex, probability of carrying the HD gene, and year of birth, individuals who inherited the HD gene from their father had an 18% higher risk of dying than family members who inherited the HD gene from their mother (Table 2). This effect was apparent in four families, but in three families the risk of dying might be lower for paternal than for maternal transmission (Table 3). In most families both paternal and maternal inheritance were present, although in families 4 and 5 most individuals inherited the HD gene from their mother, and in families 2, 6, and 10 there were more individuals who inherited the HD gene from their father (Table 3).

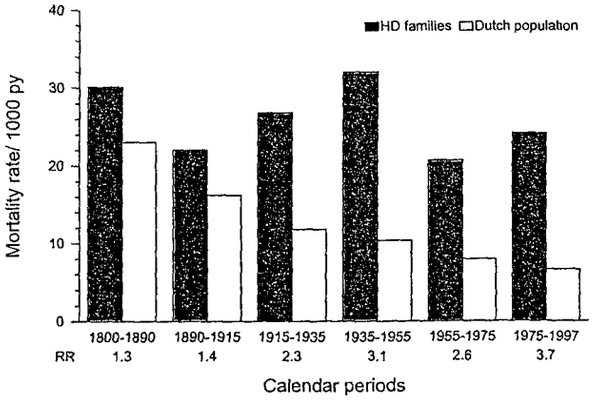

FIGURE 1. Absolute mortality rate per 1,000 person-years (py) in the HD families and in the general Dutch population according to calendar periods in the age group 40–70 years, adjusted for the age structure of the HD families over the whole time period. RR = rate ratio, the adjusted mortality rate of the HD families to the adjusted mortality rate of the general Dutch population per calendar period.

TABLE 2. Adjusted Hazard Ratio (HR) and 95% CI for Mortality from 20 Years of Age Onward Using Cox Regression Analysis

Covariates	No. Subjects	HR	95% CI
Family			
1	91	1	
2	63	0.85	0.56–1.30
3	167	0.96	0.68–1.38
4	12	3.69	1.64–8.30
5	30	1.55	0.86–2.81
6	46	0.72	0.45–1.13
7	188	0.74	0.53–1.05
8	56	1.25	0.79–1.98
9	49	1.67	1.03–2.70
10	29	1.00	0.55–1.83
Year of birth	731	1.00	1.00–1.00
Sex			
Men	384	1.43	1.17–1.75
Women	347	1	
Probability of HD gene			
Obligate carrier	257	2.55	2.06–3.15
Potential carrier	474	1	
Line of inheritance			
Paternal transmission	403	1.18	0.94–1.49
Maternal transmission	267	1	
Unknown transmission	61	0.96	0.81–1.13

TABLE 3. Hazard Ratio (HR) and 95% CI of Paternal *vs* Maternal Inheritance for Mortality from 20 Years of Age Onward, Using Cox Regression Analysis Adjusted for Sex, Probability of Carrying the HD Gene, and Year of Birth

Family	No. Offspring Paternal/Maternal	HR (Paternal *vs* Maternal)	95% CI
1	44/38	1.28	0.64–2.53
2	51/10	0.84	0.32–2.17
3	90/68	1.34	0.83–2 17
4	2/6	0	0–∞
5	5/21	0	0–∞
6	35/4	1.48	0 30–7.27
7	107/75	1.42	0.92–2.13
8	27/22	0.63	0.18–2.26
9	21/20	0.92	0.30–2.84
10	18/3	∞	0–∞

Discussion

We found a secular increase of relative mortality in the HD families, mainly because of decreasing mortality rates in the general Dutch population over the past 2 centuries. This means that the impact of the HD gene is rising: in comparison with the general Dutch population it becomes more disadvantageous to carry this gene. The fact that the mortality rates in the HD family members remained stable over calendar time implies that the duration of the disease has not changed (around 16 years), and it reflects the absence of medical therapy to delay the disease progression.[1]

According to the literature, in some families, HD follows a milder course, with longer survival.[1] In our study, all HD families showed excess mortality, and the SMR varied between 1.3 and 5.7. The most important factor associated with differences in mortality rate was the number of individuals contributed to the analysis by a specific family: the smallest family (family 4) had the highest risk. Taking the family size into account, these HD families might have a homogeneous genetic background (Table 2).

In the literature, the mean age at death is around 60 years, but it differs between the studies on the basis of the interval of observation.[1,15,16,29,30] In our study, the mean life expectancy (corrected for surviving individuals) for affected family members and their first-degree relatives was 65 years of age. Comparing the mean life expectancy of men and women (difference of 5 years) with the adjusted hazard ratio for men *vs* women (43% increase) and the mean life expectancy of certain (proven and obligate) carriers and potential carriers (difference of 14 years) with the mortality risk for certain *vs* potential carriers (155% increase; Table 2), it becomes clear that an increase of approximately 10% in risk might be equated with a decrease of 1 year in mean life expectancy. Thus, an adjusted hazard ratio of 1.2 for paternal over maternal transmission might imply that all offspring of affected fathers will, on average, live 2 years shorter than offspring of affected mothers. Bird et al[15] and Vegter-van der Vlis et al[16] have presented this finding although the purpose of these studies was to determine anticipation between generations. In the literature, there has been discussion of why and how paternal transmission can lead to earlier disease onset in their offspring.[5,7,9,10,13,14,31,32] After the identification of the HD gene,[17] the mechanism of expansion and instability of the CAG trinucleotide repeat length has partly clarified the discussion.[18–21,33,34]

The mortality rate for an individual was slightly higher if the HD gene was transmitted through the father, but this was not true for all families. In at least three of the studied HD families (families 2, 8, and 9), the line of inheritance had no influence on the mortality rate, and might even have had a reverse effect. In addition, if paternal transmission leads to earlier age at onset and therefore to higher mortality, one would expect a higher mortality rate in families with mainly paternal transmission as compared with families with mainly maternal transmission. Nevertheless, in the families under investigation this was not the case: the two families with preponderantly maternal inheritance had slightly higher mortality rates than the referent family, whereas the families with primarily paternal inheritance all had slightly lower mortality rates than the referent family. Because this phenomenon was most prominent in smaller families, this may be a chance finding. Our main finding is that persons who carry the HD gene and reach middle age have benefited less from any advance in medical care and overall expansion in life expectancy than have individuals of the general Dutch population. HD carriership has become progressively more disadvantageous.

References

1. Hayden MR, Kremer B. Huntington disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York: McGraw-Hill, 1995;4483–4510.
2. Adams P, Falek A, Arnold J. Huntington disease in Georgia. age at onset. Am J Hum Genet 1988;43:695–704.
3. Conneally PM. Huntington disease: genetics and epidemiology. Am J Hum Genet 1984;36:506–526.
4. Roos RAC, Vegter-van der Vlis M, Hermans J, Elshove HM, Moll AC, Kamp van de JJP, Bruyn GW. Age at onset in Huntington's disease: effect of line of inheritance and patient's sex. J Med Genet 1991;28:515–519.
5. Newcombe RG, Walker DA, Harper PS. Factors influencing age at onset and duration of survival in Huntington's chorea. Ann Hum Genet 1981;45: 387–396.
6. Roos RAC, Hermans J, Vegter-van der Vlis M, Ommen van GJB, Bruyn GW. Duration of illness in Huntington's disease is not related to age at onset. J Neurol Neurosurg Psychiatry 1993;56:98–100.
7. Myers RH, Madden JJ, Teague JL, Falek A. Factors related to onset of Huntington disease. Am J Hum Genet 1982;34:481–488.
8. Went LN, Vegter-van der Vlis M. Parental transmission in Huntington's disease. Lancet 1984;i:1100–1102.
9. Ridley RM, Frith CD, Farrer LA, Conneally PM. Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting. J Med Genet 1991;28:224–231.
10. Farrer LA, Cupples LA, Kiely DK, Conneally PM, Myers RH. Inverse relationship between age at onset of Huntington disease and paternal age suggests involvement of genetic imprinting. Am J Hum Genet 1992;50:528–535.
11. Myers RH, Goldman D, Bird ED, Sax DS, Merril CR, Schoenfeld M, Wolf PA. Maternal transmission in Huntington's disease. Lancet 1983;i:208–210.
12. Myers RH, Sax DS, Schoenfeld M, Bird ED, Wolf PA, Vonsattel JP, White RF, Martin JB. Late onset of Huntington's disease. J Neurol Neurosurg Psychiatry 1985;48:530–534.
13. Farrer LA, Conneally PM. A genetic model for age at onset in Huntington disease Am J Hum Genet 1985;37:350–357.
14. Ridley RM, Frith CD, Crow TJ, Conneally PM. Anticipation in Huntington's disease is inherited through the male line but may originate in the

female J Med Genet 1988 25 589–595
15 Bird ED Caro AJ, Pilling JB A sex related factor in the inheritance of Huntington s chorea Ann Hum Genet 1974,37 255–260
16 Vegter van der Vlis M, Volkers WS, Went LN Ages of death of children with Huntington's chorea and their affected parents Ann Hum Genet 1976,39 329–334
17 The Huntington s Disease Collaborative Research Group A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes Cell 1993,72 971–983
18 Duyao MP, Ambrose CM Myers RH, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbott M, Gray J, Conneally PM, Young A, Penney J, Hollingsworth Z, Shoulson I, Lazzarini AM, Falek A, Koroshetz WJ, Sax DS, Bird ED, Vonsattel JP, Bonilla E, Alvir J, Bickham Conde J, Cha JH, Dure L, Gomez F, Ramos M, Sanchez Ramos J, Snodgrass S, Young de M, Wexler N, Moscowitz C, Penchaszadeh G, MacFarlane H, Anderson M, Jenkins B, Srinidhi J, Barnes G Gusella JF, MacDonald ME Trinucleotide repeat length instability and age of onset in Huntington's disease Nat Genet 1993 4 387–392
19 Snell RG, MacMillan JC, Cheadle JP, Fenton I, Lazarou LP Davies P, MacDonald ME, Gusella JF, Harper PS, Shaw DJ Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease Nat Genet 1993,4 393–397
20 Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Starr E, Squitieri F, Lin B, Kalchman MA, Graham RK, Hayden MR The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease Nat Genet 1993,4 398–403
21 MacMillan JC, Snell RG, Tyler A, Houlihan GD, Fenton I, Cheadle JP, Lazarou LP, Shaw DJ, Harper PS Molecular analysis and clinical correlations of the Huntington's disease mutation Lancet 1993,342 954–958
22 Rosendaal FR, Heyboer H, Briet E, Buller HR, Brandjes DPM, Bruin de K, Hommes DW, Vandenbroucke JP Mortality in hereditary antithrombin-III deficiency 1830 to 1989 Lancet 1991,337 260–262
23 Went LN, Vegter-van der Vlis M, Bruyn GW, Volkers WS Huntington's chorea in the Netherlands the problem of genetic heterogeneity Ann Hum Genet 1983,47 205–214
24 Hille ETM, Westendorp RGJ, Vandenbroucke JP, Rosendaal FR Mortality and causes of death in families with the factor V Leiden mutation (resistance to activated protein C) Blood 1997,89 1963–1967
25 Boven van HH, Vandenbroucke JP Westendorp RGJ, Rosendaal FR Mortality and causes of death in inherited antithrombin deficiency Thromb Haemost 1997,77 452–455
26 Hille ETM, Duijn van E, Gruis NA, Rosendaal FR, Bergman W Vandenbroucke JP Excess cancer mortality in six Dutch pedigrees with the familial atypical multiple mole melanoma syndrome from 1830 to 1994 J Invest Dermatol 1998 110 185–189
27 Coleman M, Douglas A, Hermon C, Peto J Cohort study analysis with a FORTRAN computer program Int J Epidemiol 1986,15 134–137
28 Breslow NE, Day NE Rates and Rate Standardization In Breslow NE, Day NE, Heseltine E, eds Statistical Methods in Cancer Research vol II The Design and Analysis of Cohort Studies Oxford Oxford University Press, 1987 48–79
29 Lanska DJ, Lavine L, Lanska MJ, Schoenberg BS Huntington's disease mortality in the United States Neurology 1988,38 769–772
30 Pridmore SA Age of death and duration in Huntington's disease in Tasmania Med J Aust 1990,153 137–139
31 Boehnke M, Conneally PM, Lange K Two models for a maternal factor in the inheritance of Huntington disease Am J Hum Genet 1983,35 845–860
32 Reik W Genomic imprinting a possible mechanism for the parental origin effect in Huntington's chorea J Med Genet 1988,25 805–808
33 Myers RH, MacDonald ME, Koroshetz WJ, Duyao MP, Ambrose CM, Taylor SAM, Barnes G, Srinidhi J, Lin CS, Whaley WL, Lazzarini AM, Schwarz M, Wolff G, Bird ED, Vonsattel JPG, Gusella JF *De novo* expansion of a (CAG)n repeat in sporadic Huntington's disease Nat Genet 1993,5 168–173
34 Goldberg YP, Kremer B, Andrew SE, Theilmann J, Graham RK, Squitieri F, Telenius H, Adam S, Sajoo A, Starr E, Heiberg A, Wolff G, Hayden MR Molecular analysis of new mutations for Huntington's disease intermediate alleles and sex of origin effects Nat Genet 1993,5 174–179