

SHORT REPORT

Duration of illness in Huntington's disease is not related to age at onset

R A C Roos, J Hermans, M Vegter-van der Vlis, G J B van Ommen, G W Bruyn

Abstract

The age at onset and duration of illness were studied in patients with Huntington's disease in the Leiden Roster which at 1 July 1990 contained 2787 patients. Of 1106 patients, 800 deceased and 306 alive, the age at onset was known. The median duration was 16.2 (range 2-45) years. In contrast to the current opinion, the median duration was independent of the age of onset. The median duration in juvenile Huntington's disease was 17.1 years, which is much longer than reported in the literature, and comparable with the categories for the age of onset of 20-34 and 35-49 years. Only in the group where onset was over 50 years of age was the median duration somewhat shorter (15.6 years), which can be ascribed to unrelated causes of death. As age of onset and duration of illness are not related, at least two mechanisms to determine the clinical course have to be postulated: one for age of onset and another for duration of illness. Duration was shorter for males, especially for those with an affected father.

(*J Neurol Neurosurg Psychiatry* 1993;56:98-100)

Introduction

Huntington's disease is an autosomal dominant disorder, characterised by chorea, dementia, personality changes and emaciation. The mean age at onset is 40 years (SD 12.1), although extremes have been reported of 2 and 80 years.¹ The mean duration of illness is between 10.6 and 17.1 years.² The duration has been reported to be dependent on age of onset. In juvenile Huntington's disease, with an age of onset in the first decade, a mean duration of 8.3-11.9 years was found,² whereas Newcombe, Walker and Harper³ reported, in only five patients, no differences in duration compared with the other age-of-onset classes. They found a shorter duration in the group with age of onset over 55 years. Myers *et al*⁴ reported that patients with an age of onset up to 50 years had a longer period of illness. Currier, Jackson and Meydrech⁵ reported a more rapid course in patients with early onset. On the other hand, a shorter duration was found in patients with a later age of onset.² Myers *et al*⁶ found the shortest duration in the

oldest group of patients with onset over 50 years of age.

To gain more insight in the influence of age of onset on duration of illness in Huntington's disease, we reviewed our continuously updated database. The duration was calculated for all deceased patients with a known age of onset. For patients still alive, the duration was noted at 1 July 1990. Considering the status of the patient at last follow-up (deceased or alive) we used survival analysis to address the following questions: is there a relationship between age of onset and duration of illness? Does the sex of the patient or the affected (grand)parent, or both, affect the duration?

Patients and Methods

Sex, year of birth, year of death, age at onset and the lineage of inheritance of all affected patients of 201 pedigrees known on 1 July 1990 at the Leiden Roster, reaching back to the middle of the last century and containing 2787 patients from 201 families from the Netherlands.

Diagnoses were confirmed by experienced neurologists or psychiatrists for all older cases. All clinical information and postmortem reports were reviewed for confirmation of the diagnosis. Age of onset was taken as the age at which choreatic movements became manifest. Although some patients had been reported to have manifested affective disorders or cognitive dysfunction before the occurrence of involuntary movements, motor impairment was used because family circumstances determined by the disease may influence behaviour in patients at risk as well as induce observer bias in the assessment of behaviour. Year of birth and death data were verified in the community registries. The year of the last follow up was noted and verified. The duration was defined for the deceased patients as the length of

Table 1 The 80, 50 (median) and 20 percentiles of duration of illness of 1106 patients (800 deceased and 306 alive) with Huntington's disease in relation to age at onset

Age of onset (years)	N	Duration of illness (years)			p* overall
		80%	50%	20%	
<20	1106	11.0	16.2	23.2	
20-34	65	10.5	17.1	27.1	
35-49	274	12.3	17.0	25.0	
≥50	510	10.9	16.3	22.4	
	257	10.3	15.6	21.5	0.013

*Log-rank test.

Department of
Neurology, Academic
Hospital, Leiden, The
Netherlands

R A C Roos
G W Bruyn

Department of
Medical Statistics,
State University,
Leiden, The
Netherlands
J Hermans

Department of
Clinical Genetics
M Vegter-van der Vlis

Department of Human
Genetics
G J B van Ommen

Correspondence to:
Dr Raymund AC Roos,
Department of Neurology,
Academic Hospital Leiden,
PO Box 9600, 2300 RC
Leiden, The Netherlands.

Received 15 January 1992
and in revised form
27 April 1992.

Accepted for publication
14 May 1992.

Table 2 The 80, 50 (median) and 20 percentiles of duration of illness of 1106 patients (800 deceased and 306 alive) with Huntington's disease in relation to sex and lineage of inheritance

	N	Duration of illness (years)			p
		80%	50%	20%	
Overall	1106	11.0	16.2	23.2	
Female	532	11.2	17.1	23.3	
Male	574	10.5	15.5	22.5	0.008*
Affected mother	511	10.9	16.7	23.5	
Affected father	529	11.0	15.9	22.5	0.206*
Female with affected mother	244	10.8	17.1	23.5	
Female with affected father	260	11.9	17.3	23.3	
Male with affected mother	267	11.0	16.5	23.5	
Male with affected father	269	9.9	14.4	21.5	0.003*
MM	208	11.4	17.4	23.5	
MP	216	12.0	17.6	23.2	
PM	222	10.8	16.6	22.0	
PP	202	10.5	15.0	21.5	0.056*

*Log-rank test. **Stratified log-rank test. Lineage of inheritance: MM = grandmother-mother; MP = grandmother-father; PM = grandfather-mother; PP = grandfather-father.

survival after onset. For patients still alive at last follow-up, the duration was noted at 1 July 1990. Inference about the duration was made with the statistical techniques appropriate for the data.

As the precise duration is known for the deceased patients and deduced for the living patients, the life table technique was used to create survival curves. The descriptive statistics derived from these curves in our data are on the 80th, 50th (median), and 20th percentiles. The statistical comparison of the survival curves was done with the log-rank test. To adjust for pedigree effects, the analysis was also performed with stratification according to family (PHGLM procedure of the SAS package).

Results

Age at onset and duration of illness for the whole group

Of the 2787 patients, information about onset was available in 1106 patients as a result of the retrospective nature of the study. Reliable information on former cases was lacking. The mean age of onset in these 1106 patients was

40.0 years (SD 12.4 years). At the time of the study 800 patients had died. Their mean ages at onset and duration of illness were 55.8 years (SD 13.5 years) and 15.6 years respectively. The life table analysis for all living and dead patients gave a median duration of 16.2 years. Twenty per cent of the patients can be expected to have the illness for 23.2 years. The range of duration observed in our cohort was from two to 45 years.

Relation between age at onset and duration of illness (table 1)

We subdivided all cases into four classes according to age of onset: under 20; 20-34; 35-49; 50 years or over. Juvenile patients had the longest duration with the highest median of 17.1 years, and were comparable to the two middle groups, whereas patients with onset over 50 years had a slightly, but significantly, lower median duration (15.6 years) compared with each of the other classes (log-rank test: $p = 0.013$).

Relation between sex and lineage of inheritance and duration of illness (table 2, fig)

Males had a significantly lower median duration (15.5 years) compared with females (17.1 years; $p = 0.008$). This difference was observed in particular by males with a paternal line of inheritance. We also found that cases of both sexes with an affected father and grandfather had a small, but significantly shorter duration ($p = 0.056$) compared with those with other lineages of inheritance.

Adjustment for pedigree (table 2)

The effects studied above can be adjusted for pedigree effects by stratifying the log-rank analysis. This will, in general, not affect the median duration but gives larger standard errors and consequently less significant results. With this strategy, the effect of sex on duration changed to 0.07. When combining the effects of sex and lineage of inheritance, this analysis still showed a clearly significant difference ($p = 0.02$). Taking the four groups separately, probability was $p = 0.11$.

Discussion

We found a median duration of 16.2 years in 1106 patients with a range from two years up to 45. Almost 20% of the patients survived the onset of choreatic movements for more than 23 years. Five patients survived longer than 40 years. Such high values for duration have never been reported before. It underlines the importance of the continuous collection of clinical data in Leiden over many decades by a few neurologists with a special interest in Huntington's disease.

The prevailing hypothesis is that the clinical course of the juvenile disease is more rapid than in the older patients and therefore leads to a shorter duration. Recently, Myers *et al*⁷ reported that a slower disease progression was correlated with a later age of onset and a heavier weight at first examination. The duration in juveniles in our study was much longer

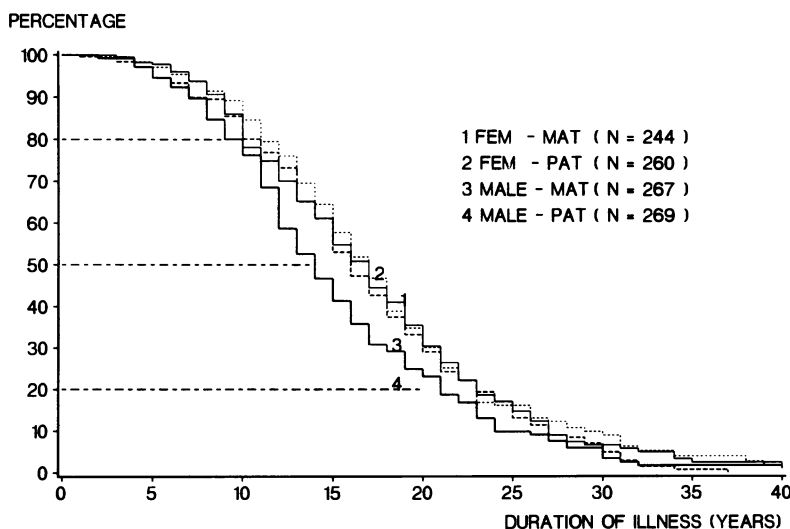


Figure 1 Duration of illness for 1040 patients with Huntington's disease with known age at onset, sex and parental inheritance. 1 = female maternal; 2 = female paternal; 3 = male maternal; 4 = male paternal.

than previously reported, however, and comparable with the other age groups, even exceeding that of the group with late onset.² Within the reported literature, a relation between age of onset and duration was found in juvenile cases, but it was not present for the choreatic patients.⁸

Farrer, Conneally and Yu⁹ postulated that a longer duration of illness could be expected in patients with 'superior aging genes' and therefore in patients with a later onset. In the model of Myers *et al*,⁶ a single mechanism, the accumulation of an unknown genetically determined factor, is proposed which determines both the age of onset and the rate of progression. Other possible explanations are sought in more complex genetic mechanisms as suggested by Ridley *et al* (1991),¹⁰ who proposed that the age of onset is determined by the state of methylation of genomic DNA as a result of imprinting.

The rather constant median duration in all age classes, as established in the present study, may indicate that the time span of symptomatic illness is determined by a different factor or factors. At the moment a certain stage of neuronal loss is reached, involuntary movements start and further clinical course seems to be controlled by one mechanism different from that determining the age of onset, and leading to further progression with a similar range for all age groups, suggesting a different effect of the same gene. The shorter duration in the group with late onset can be explained by the shorter life expectancy inherent in older age. The natural course of their disease is probably cut short by other, unpredicted disorders causing death. Another explanation might be a higher age at diagnosis in older and former cases, because of less medical attention, thereby overestimating the age of onset.

We confirmed earlier findings² that male

patients with paternal transmission had a shorter duration than females and those with a maternal line of transmission.

Closer observation of patients at risk after presymptomatic DNA analysis will lead to a more precise determination of the age of manifestation. In most studies, choreatic movements reported by the patients are used to determine the age of onset, but as it becomes possible to determine personality changes, psychiatric reactions and very subtle choreatic movements in a very early stage, it will become apparent that duration of illness has been underestimated.

We are grateful to Dr A R Wintzen, Professor P J Van Der Maas and Dr S van de Vathorst for their critical comments and to Mr Franken for his technical assistance. The medical students Miss A C Moll, Miss H M Elshove, and Mr M Sosef are thanked for their help with data accumulation.

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