Differences in duration of Huntington's disease based on age at onset

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Abstract

***Objectives*—Data from a sample of 2494 patients affected with Huntington's disease (HD), collected as part of the National Research Roster for Huntington Disease Patients and Families, were examined to determine if there was a relation between age at onset and duration of illness.**

***Methods*—Sufficient data for inclusion in analysis was available from 2068 patients, of whom 828 were deceased and 1240 were living. The median duration of disease was 21.4 years with a range of 1.2 to 40.8 years. Patients were categorised into one of four groups based on their age at onset.**

***Results*—Significant differences in duration based on the age at onset were found ($p<0.025$), with juvenile and late onset patients with HD having shorter duration of illness compared with those with an onset between 20–49 years.**

***Conclusions*—Duration of disease is influenced by the age at symptom onset with juvenile and late onset patients having the shortest duration.**

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Keywords: Huntington's disease; duration; age at onset

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Huntington's disease (HD) is a progressive, autosomal dominant, neurodegenerative disorder characterised by cognitive decline, psychiatric manifestations, and motor disturbance. Initially, the symptoms of HD are subtle with mild cognitive changes including memory decline and forgetfulness; behavioural changes including depression, irritability, impulsiveness, and apathy; and motor changes including minor difficulties in coordination, balance, and onset of slight adventitious movements of the trunk, limbs, and fingers.[1] As the cognitive and behavioural changes are mild and often attributable to various other causes, many patients define age at onset based on the manifestation of chorea. However, a significant proportion of patients clearly have onset of cognitive or emotional changes before the development of chorea. Unfortunately, until the molecular defect in HD was found, most clinicians relied on the onset of chorea before assigning a diagnosis of HD.

The symptoms of HD are associated with the presence of an excess number of CAG repeats in the HD gene.[2] A negative correlation has been found between the number of CAG repeats and the age at disease onset.[3 4] Patients with juvenile HD, defined as having disease onset before age 20, typically have a very large number of CAG repeats, usually greater than 55; whereas those with adult onset HD have a more modest number of CAG repeats, usually in the range of 40–50.[3 4] Transmission of the HD gene through an affected male usually results in a larger increase in the number of CAG repeats compared with transmission through an affected female.[3] Because most patients with juvenile HD have very many CAG repeats, it is not surprising that over 80% of such patients have an affected father.[5] There have been no reports of a significant correlation between duration of illness and the number of CAG repeats.

Conflicting reports in the literature have arisen regarding the relation between age at onset and the progression and duration of illness in patients with HD. Juvenile onset patients have been reported to have shorter[6] or similar[7 8] disease duration than patients with adult onset. Disease duration among those with onset beyond the age of 50 has been shown in some studies to be longer[9] than other patients with adult onset; however, other reports have found a shorter[6 10] duration among late onset patients. Earlier onset patients have been found to have a faster rate of basal ganglia atrophy than those with late onset[11]; however, studies of disease progression have not consistently identified an association between either age at onset[12–14] or the number of trinucleotide repeats[15–17] and the rate of clinical decline.

We have examined the relation between age at onset and duration of disease in a large sample of families collected through the National Research Roster for Huntington Disease Patients and Families (HD Roster).

Methods

The HD Roster, located at Indiana University, has been collecting data from HD families for nearly 2 decades. Detailed information on presenting symptoms, age at onset, diagnosis, and death are collected using the affected questionnaire (AQ). Information regarding cause of death is collected and coded according to the International Classification of Diseases (ICD) criteria.[18] The AQ is typically completed by the patient's parent, spouse, or child (~75%), increasing the reliability of the questionnaire data. Information on the AQ is verified, when possible, using medical records and certificates of birth and death.

The AQ collects data on initial symptoms of HD through two sources. The source person is asked to list the patient's first symptoms of HD. A maximum of three symptoms are accepted. In addition, a chart listing common physical, mental, and emotional signs of HD is included

Table 1 First symptoms of Huntington's disease

Symptom	*No of patients**	*% all observed symptoms †*
Chorea	877	28
Trouble walking	262	9
Unsteadiness/imbalance	260	8
Difficult to get along with	167	5
Depression	165	5
Clumsiness	154	5
Speech difficulty	149	5
Memory loss	93	3
Trouble holding an object	62	2
Lack of motivation	53	2
Suspicions/paranoia	48	2
Intellectual decline	44	1
Changes in sleep	30	1
Hallucinations	23	1
Weight loss	20	0.6
Sexual problems	7	0.2
Sadness	7	0.2
Other mental	363	12
Other physical	297	10

*The number of patients is reported from a total of 1901 patients with initial symptom information.
† The per cent of all observed symptoms from a total of 3086 reported symptoms. Patients could report up to three initial symptoms.

(table 1). The chart elicits simple presence or absence of each symptom, as well as a list of years after onset at which each symptom began. Collection of the initial symptom data through two AQ sections allows for verification and determination of data reliability.

Age at onset was defined by the family and verified, when possible, using medical records and therefore did not always consider chorea as the initial presenting symptom. Patients were classified into one of the following four groups based on their age at symptom onset: < 20, 20–34, 35–49, and ⩾ 50. The sex of the affected patient was used to determine if age at onset or duration were significantly different in males and females. In addition, parent of origin effects on these variables were also examined.

The duration of disease was known with certainty only for those patients (60% of sample) who were already deceased; however, inference about duration can be made with survival analysis techniques appropriate for data with censoring. In this case, the censored patients are those who are still alive and, therefore, whose eventual disease duration is not known. Duration of illness was defined for deceased patients as the duration of survival from onset to death; for the patients still alive, duration was measured from the age at onset until December 1997.

Survival data analysis presented a way to analyse censored data and to assess the effect of covariate information such as age of onset, sex, parent of origin, and lineage of inheritance on disease duration. We used the most common product limit estimate of survival distribution due to Kaplan-Meier implemented by the S-PLUS software package. Descriptive statistics derived from the survival distributions include the 75th, 50th (median), and 25th percentiles, mean, standard error of the mean, and 95% confidence intervals for the mean based on the log survival scale. The statistical comparison of the survival curves was performed with the log-rank test. Graphically, the Kaplan-Meier survival curves appear as a step function with a drop at each death.

Table 2 Distribution of age at onset

Effect	*No of patients*	*Age at onset (y)*		*t Test p Value*
		Mean	*(SD)*	
Overall	2068	40.0	(12.0)	
Sex effect				
Female	1074	39.8	(12.1)	
Male	994	40.1	(11.9)	0.5
Parent of origin effect (includes juvenile HD patients):				
Affected mother	934	40.7	(11.0)	
Affected father	939	37.9	(12.4)	0.0001
Parent of origin effect (excludes juvenile HD patients):				
Affected mother	919	41.0	(10.6)	
Affected father	861	40.1	(10.3)	0.06

Results

The AQ was completed by 2494 patients during the past two decades. Of these, age of onset was unknown for 157 patients and date of birth was missing for five patients. On review of the cause of deaths recorded in the AQ questionnaire, patients whose cause of death was due to neoplasia, accident, suicide, or heart problems, which might significantly shorten life span, were eliminated from further analyses (n=264). This resulted in a sample of 2068 patients to be used in the final analyses.

The average age at onset in the analysis sample was 40.0 (SD 12.0) years with a range from 2 to 75 years. A maximum of three presenting symptoms of HD could be listed for each patient. A total of 997 patients listed only one initial symptom, 623 gave two symptoms, and 281 had three initial symptoms. When all listed symptoms were analysed as one variable, the most common initial symptoms in the data set were chorea (877/3086, 28.4%), trouble with walking (262/3086, 8.5%), and unsteadiness (260/3086, 8.4%). A significant number of patients listed non-specific physical (297/3086, 9.6%) or mental (363/3086, 11.8%) difficulties. The distribution of initial symptoms is shown in table 1.

In this sample, females (n=1074) had an earlier age at onset (39.8 (SD 12.1)) than males (40.1 (SD 11.9) (n=994) (p=0.5; table 2). Unambiguous data regarding the affected parent were available for 1873 of the 2068 patients used in the analyses. Of these, 934 had an affected father and 939 had an affected mother. Not surprisingly, the mean age at onset for offspring of affected fathers was younger than offspring of affected mothers (37.9 *v* 40.7,

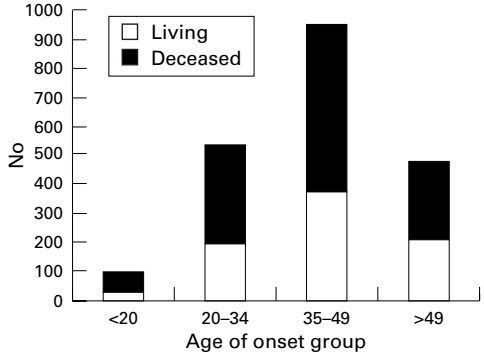

Figure 1 Proportion of subjects living and deceased

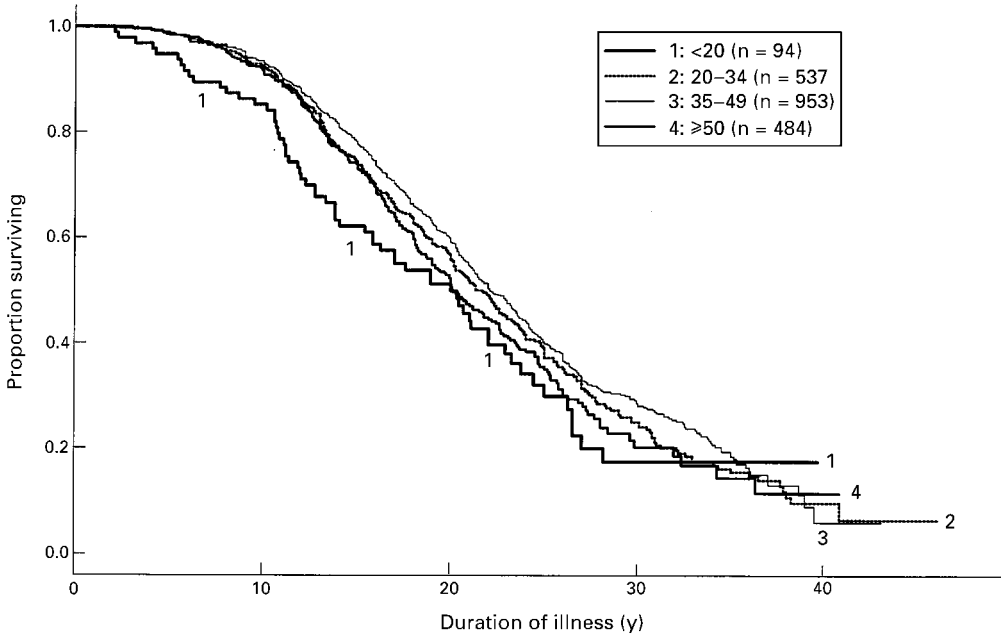

Figure 2 Comparison of survival curves.

p=0.0001). The lower mean age at onset in offspring of affected males was attributable to the patients with juvenile HD, of whom 78 of 93 were offspring of affected fathers. When the patients with juvenile HD were removed from the analysis, there was no significant parent of origin effect on age at onset (40.1 *v* 41.0, p=0.06).

Using data from the entire sample, the median duration of disease was 21.4 years. The minimum duration was 1.2 years and the maximum duration was 40.8 years. The sample of patients were then classified into one of four groups based on their age at onset. There were 94 patients with age at onset under 20 years, 537 with onset between the ages of 20 and 34, 953 with onset between 35 and 49, and 484 patients with late onset HD (onset⩾50) (fig 1). Comparison of the duration of illness among the four groups found significantly shorter duration among the juvenile and late onset patients with HD (p=0.025; fig 2[2], table 3). Patients with juvenile HD had a median duration of 20.0 years and the two mid-adult onset groups had median disease duration of 21.3 and 22.1 years respectively. The late onset group with onset at the age of 50 or later had a median duration similar to that in the juvenile onset group, with disease duration of 20.1 years.

Comparison of duration between male and female patients suggests that females have longer duration of disease than males (table 3). Females had a median duration of disease of 22.0 years and males had a duration of only 20.8 years (p<0.005). There was no significant difference in disease duration based on the parent of disease origin (p=0.66). However, when patient and parent sex were considered simultaneously, males with an affected father had significantly shorter duration of disease than the other three groups (p<0.006; table 3).

Table 3 Duration of illness

		Duration of illnesss (in years)			
Effect	*No of patients*	*75%*	*50%*	*25%*	*p Value*
Overall	2068	15.0	21.4	30.1	
Age of onset effect					
<20 years	94	11.3	20.0	26.5	
20–34 years	537	14.8	21.3	29.7	
35–49 years	953	15.8	22.1	32.1	
⩾50 years	484	14.5	20.1	28.0	0.025
Sex effect					
Female	1074	15.3	22.0	31.8	
Male	994	14.8	20.8	29.0	0.005
Parent of origin effect					
Affected mother	934	15.5	22.2	30.8	
Affected father	939	15.0	21.2	31.4	0.66
Sex and lineage effect					
Female with affected father	484	15.8	23.2	35.0	
Male with affected father	455	14.2	20.3	28.6	
Female with affected mother	491	15.6	22.0	31.7	
Male with affected mother	443	15.2	23.0	31.9	0.006

Discussion

The HD Roster is the largest collection of families with HD available in the world. By collecting detailed questionnaire data on the affected patients in each family, it is possible to characterise early findings of disease as well as to consider the relation between age at onset and duration of illness in a large sample. In addition, as the questionnaire is completed by a close family member, an assessment of the patient's disease progression is possible.

Unlike several other studies, we have collected detailed clinical data on early symptoms of HD. As a result, we have not defined age at onset of disease as age at onset of chorea. This is an important distinction, as many patients report, retrospectively, early findings of HD that do not include chorea. In fact, in this sample only 28% of patients reported chorea as one of their first symptoms of disease. A sizable number of patients (22%) reported nonspecific physical or mental difficulties as early

symptoms of HD. By allowing patients to define retrospectively, after disease has been confirmed, what the early findings of disease were, a more accurate age at onset is possible. This may, in part, account for some of the quite lengthy years of disease duration reported for some of the roster participants. However, this is unlikely to be the sole cause of long duration of illness, as Roos *et al*,[8] who considered age at onset only to be the onset of chorea, also found patients with quite lengthy duration of illness (>40 years).

Patients with either juvenile or late onset HD had significantly shorter disease duration than those who had onset in mid-life (onset 20–49). The course of HD is probably shorter in the older onset patients, in part, due to other unrelated conditions which shorten life expectancy. This result is similar to that found by other researchers.[8 12] Unfortunately, the most commonly listed cause of death on the AQ and death certificates was HD; in reality, such patients may have other comorbid causes of death. Our results also support the hypothesis that patients with juvenile HD have a shorter duration of illness than adult onset patients. Patients with juvenile HD had a 1 to 2 year shorter duration of illness than patients with onset between 20 and 49 years. This finding would support the contention that patients with juvenile HD have a different clinical presentation with more rapid onset and progression of symptoms.

Whereas the mutant gene resulting in HD has been identified, the normal role of its protein product, huntingtin, has not been well elucidated. The gene is widely expressed and its product is expressed at similar levels in both patients and controls.[19 20] It has been proposed that HD may result from a gain of protein function, caused by abnormal interactions between cellular proteins and the region of expanded polyglutamine residues encoded by the CAG nucleotides in the huntingtin protein.[21] Several proteins including huntingtin associated protein 1 (HAP-1[21]) and huntingtin interacting protein 1 (HIP-1[22]), have been identified the binding of which to the huntingtin protein is enhanced by the expanded number of glutamine residues found in the mutant protein. Animal studies have recently shown that mice transgenic for exon 1 of the human HD gene with many CAG repeats develop pronounced neuronal intranuclear inclusions consisting of the huntingtin and ubiquitin proteins.[23] Additional human studies have verified that the huntingtin protein forms insoluble high molecular weight protein aggregates only when the number of CAG repeats is within the pathogenic range.[24]

Our results support the model of a single mechanism determining both age at onset and rate of progression.[10] According to this hypothesis, the product of the HD gene accumulates, reaching a critical threshold, which then results in clinical features of disease. If there is rapid accumulation of the toxic product, then there would be earlier age at onset and a more rapid disease course. Under this model, it might be that patients with juvenile HD have tighter binding of HAP-1 and HIP-1 (or another unidentified huntingtin binding protein) than adult onset patients. This in turn might result in a more rapid accumulation of detrimental neuronal effects and a shorter disease duration. This conclusion would be supported by the association of longer trinucleotide repeat length, and hence earlier age at onset, with a faster rate of deterioration and greater pathological severity of disease.[25] Although the shortened disease duration of the late onset group would seem to contradict this model, it is very likely that patients with late onset have earlier mortality due to advanced age related comorbid conditions, not specified on the death certificate or reported by family members.

Further studies are necessary to better understand the progression of HD in juvenile and adult onset patients. Better characterisation of disease onset, including the variability in symptom onset is needed and likely will confirm our findings that symptoms other than chorea often mark the onset of disease. Estimating disease duration based on a more accurate estimate of symptom onset may support our findings that disease duration is actually longer than previously estimated.

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HISTORICAL NOTES

Convolutions and asymmetries of the brain

The "coils" of the brain are considered to have been first noted by Praxagoras of Cos c300 BC, and by Erasistratus c260 BC, who noted a resemblance to the coils of the intestines. Vesalius likened them to clouds and noted their presence and their rough similarity in the ass, horse, and ox.[1] Thomas Willis attempted to correlate the organisation of the convolutions with intelligence, and believed that: "movement is initiated in the cerebrum, convolutions and gyrations provide a more commodious area for (expansion of the animal spirits) in the use of memory and phantasy."[2] He also stressed that the brain's workings were mediated by the brain parenchyma and not, as previously held, by the ventricles. This was a fundamentally new idea, escaping the vague notions of the brain as affected by the humours and functioning by means of defined animal forces or *spiritus animalis*. Francois Leuret, 1797–1851, born in Nancy, France, was an impecunious "scrawny" boy who enlisted in the army to pursue his studies; he then trained with Esquirol at Salpêtrière and published a remarkable text[3] on the comparative cerebral anatomy with his pupil and friend Pierre Gratiolet (who named the central fissure as the fissure of Rolando). Leuret thought that intelligence related to the number of convolutions with their increasing complexity in primates. In England, Gall realised that convolutions "were an expansion of fibre bundles"; he put forward the idea that:

> "different phenomena suppose different apparatus; consequently, the various functions of the brain likewise suppose different organs" (local areas).

However, he went too far in extending this to surface contours of the skull, a concept that led to the bogus "art" of phrenology.

In 1889, Henry Maudsley, father of the Bethlem and Maudsley Hospitals, asked:

> "Is the brain which is notably double in structure, a double organ, seeming parted, but yet a union in partition?"

This provocative enquiry reflected long-standing arguments about the greater asymmetry of the human brain convolutions than that seen in lower mammals. Vicq d'Azyr, a physician and a considerable artist, had described the convolutions in 1786 noting the differences in morphology in other animals. Magendie similarly had written:

> "The number, the volume, the disposition of the circumconvolutions are variable; in some brains they are very large; in others they are less and more numerous. They are differently disposed in every individual; those of the right side are not disposed like those of the left. It would be an interesting research to endeavour to discover if there exists any relation between the number of circumconvolutions and the perfection, or imperfection, of the intellectual faculties—between the modifications of the mind and the individual disposition of the cerebral circumconvolutions".[4]

In England, in 1839, Henry Holland, physician to the Royal household, had considered the same problems:

> ". . . these deviations [are] more frequent in man than in many other mammalia most nearly approaching him in structure . . .in the brain and spinal marrow, the external parts on the two sides are less frequently symmetrical than those within; . . ."[5]

In 1854 Gratiolet[6] deduced that the two sides of the brain controlled movement of the opposite side of the body. He claimed that the frontal convolutions on the left side were in advance of those on the right in their development in the foetus. Jackson extended the notion saying that "if this be so, the left side of the brain is sooner ready for learning. It is the elder brother."[7] Paul Broca[8] showed that expressive speech was "localised" to the third left frontal convolution. However, it was preceded by Marc Dax's unpublished thesis submitted to Montpelier University in 1836 who had observed that the left hemisphere was damaged in aphasiacs (the source of the Broca-Dax controversy). The idea gradually evolved, partly owing to Broca, that the various areas of the brain were informed or "educated" by the functions they performed; it took many decades for it to be challenged.

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