Age at onset in Huntington’s disease: effect of line of inheritance and patient’s sex

Raymund A C Roos, Maria Vegter-van der Vlis, Jo Hermans, Hester M Elshove, Annet C Moll, Jaques J P van de Kamp, George W Bruyn

Abstract
The Leiden Roster for Huntington’s disease (HD) contained data on 2617 cases up to July 1988. The age at onset (AO) was known in 1084 cases and in 1020 of these both their AO and the sex of the affected parent was known. The mean AO was higher for females than for males and higher for maternal than for paternal cases. However, in the group born before 1925 only females with maternal inheritance had a higher mean AO. Data on influence of sex and line of inheritance were present for the grandparents as well as for the great grandparents. Influence of the line of inheritance from the grandparents was particularly present for the grandmother–father (MP) lineage; regarding the great grandparents a significant difference was found between the MPM and PMP lineage.

The results obtained for juvenile HD cases were comparable to those previously published. In late onset cases (over 50 years) no maternal preponderance in inheritance was found.

Huntington’s disease (HD) is an autosomal dominant disease, characterised by chorea, dementia, personality changes, and ultimate emaciation. The age at onset (AO) is usually between 30 and 50 years, although onset at 2 and 80 years has been reported.1,2 Although autosomal dominant genes are inherited in equal proportion from the father and the mother, differences in phenotypic expression in relation to line of inheritance are known to occur in myotonic dystrophy and Huntington’s disease. Juvenile patients (AO before the age of 20 years) inherit the gene much more often from an affected father (70%) than from an affected mother.2–4 The trend towards earlier AO in offspring of affected fathers has been confirmed by others.5–9 This anticipation was reported by Bird et al.10 who found that affected offspring of males with HD die at an earlier age than their fathers; however, this difference does not exist between affected offspring and their mothers.

Myers et al11,12 found that approximately 28% of patients (68 out of 238) show their first symptoms after the age of 50 years. In these late onset cases, 71% (32 out of 45) inherited the gene from the affected father. The sex ratio among the late onset cases was equal. In the study of Went et al,13 the preponderance of maternal descent in late onset cases was not confirmed; however, a much larger population was studied and the ages at death instead of onset were used.

In the study of Bird et al10 the sex of the affected grandparents was not correlated with the AO, but the influence of the great grandparents on the AO was not studied.

We reviewed our data on all known HD patients in the Leiden Roster, with the aim of examining the influence on the AO of the line of inheritance for up to three generations and of the sex of the patient. Studying the distribution of AO in a cohort of cases leads to biased information about the mean AO. This is caused by the fact that sibs at risk, in whom the clinical symptoms have not yet appeared, cannot contribute their AO to such a cohort of cases. If attention is focused on the mean AO itself, two methods are available to arrive at unbiased results. One method is to use life table techniques on complete pedigrees, including affected and at risk family members. The other method is to restrict the cases to a cohort born at least 60 to 70 years ago.14 Because complete pedigree information was not available for all 201 families, we had to rely on an age restricted group for unbiased conclusions about AO. However, for the comparison of female versus male and maternal versus paternal we used the total cohort. The bias present in the AO of the total cohort may not
necessarily invalidate these comparisons particularly if the distribution of the censoring variables (age at death or at the prevalence date) is similar in these groups. The second aim was to study more specifically factors influencing juvenile onset (JHD) and late onset HD.

Patients and methods
Relevant information was noted for sex, year of birth, year of death, age at onset, and the line of inheritance for all affected patients in 201 HD pedigrees known to the Leiden Roster on 1 July 1988. The information on sex, year of birth, death, and age at onset of patients of preceding generations was available because the pedigree, generation, and sib identification details had been noted in all cases. Diagnostic notes from neurologists and psychiatrists were available for all older (<1935) cases admitted to the analysis. All clinical notes and necropsy reports were reviewed for confirmation of the diagnosis. In any case in which the AO could not be retrieved with certainty from the notes the case was excluded from the material to be studied. The AO was taken as the age at which choreic movements were first noted. Although some patients reported earlier affective disorders or cognitive dysfunction, motor impairment was used because family circumstances can influence behaviour in at risk patients. Because the age of death (AD) is unequivocal, AD was compared to AO when both were known. It could be argued that our method of family sampling leads to selection of families with an evident proband, while families without such a proband had a lower chance of being selected. Because we did not have information about which member was the proband we had no means of checking this assumption.

Statistical comparisons of groups were performed using analysis of variance for quantitative variables and $\chi^2$ tests for qualitative variables. The AO distributions were symmetrical in all group, so the application of analysis of variance is justified. Correlations are given in Pearson’s correlation coefficients.

Results
A total of 2617 HD patients from 201 pedigrees comprised 1354 men (51.8%) and 1263 women (48.2%). The AO was known in 1084 patients and in 1020 cases the affected parent was also known. Because factors were studied that presumably influence AO, all further data stem from this group, unless specifically indicated. The number of patients in the four generations (the proband’s generation plus the three preceding generations), the number with known AO, and the number of females are shown in fig 1. The cumulative onset curve for all patients (n=1084) is shown in fig 2. The mean AO for the whole group was 40.0 (SD 12.1) years. Restricting the analysis to persons born before 1925 avoids the bias present in the AO distribution of the whole cohort. The mean AO of this restricted group of 689 patients

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**Figure 1** Total number of Huntington’s disease patients in four generations, the number of patients with known age at onset and affected parent, and the number of females among the latter.
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was 43.3 (SD 11.4). The mean AO broken down by the sex of the patient and by the sex of the affected parent is given in table 1. For the whole group, differences of about 2.5 years are found in mean AO between maternal and paternal descent, as well as between females and males. According to an analysis of variance these results do not indicate a statistically significant interaction between the sex of the patient and the line of inheritance; however, significant influence of sex exists (female higher than male, p=0.006), as well as of the affected parent (mother higher than father, p=0.001), on the AO. The results obtained for AO in patients born before 1925 are given in table 1B. The analysis of variance showed no significant interaction or significant effects of sex of the patient and line of inheritance (table 1B). Both effects are reduced from about 2.5 years (table 1A) to about 1 year (table 1B). This, together with the reduction in the number of subjects, leads to a loss of significance. The confidence intervals for the effect of sex (−0.8 to 2.8) and line of inheritance (−0.6 to 3.0) in table 1B do not contradict the effects found in table 1A, but also include 0, so do not confirm the effects.

The mean AO of the 822 cases with known line of inheritance from the grandparents for the whole group showed no interaction with sex and line of inheritance. The sex difference was statistically significant according to the analysis of variance (overall: females 39.9 years, males 37.5 years, p=0.003) (table 2A). Moreover, a significant difference in line of inheritance was found (p=0.02), pointing to a lower mean AO in the MP line.

With respect to the generation of the great grandparents (n=550) (table 2B), significant differences

### Table 1 Number of patients and mean (SD) of age at onset in years for females and males in relation to maternal (M) or paternal (P) inheritance of the gene for the whole group (A) and for those born before 1925 (B).

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Mean (SD)</td>
<td>No</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>A. Whole group (n=1020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>250</td>
<td>41.8 (10.5)</td>
<td>257</td>
<td>39.7 (11.4)</td>
</tr>
<tr>
<td>P</td>
<td>255</td>
<td>39.2 (11.9)</td>
<td>258</td>
<td>37.2 (14.0)</td>
</tr>
<tr>
<td>Total</td>
<td>505</td>
<td>40.5 (11.2)</td>
<td>515</td>
<td>38.4 (10.0)</td>
</tr>
<tr>
<td>B. Born before 1925 (n=632)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>168</td>
<td>44.8 (10.2)</td>
<td>163</td>
<td>42.5 (11.0)</td>
</tr>
<tr>
<td>P</td>
<td>159</td>
<td>42.4 (10.9)</td>
<td>142</td>
<td>42.6 (13.5)</td>
</tr>
<tr>
<td>Total</td>
<td>327</td>
<td>43.6 (10.9)</td>
<td>305</td>
<td>42.6 (12.2)</td>
</tr>
</tbody>
</table>

Analysis of variance results (p values): A B
Interaction (sex x inheritance) 0.93 0.17
Sex of the patient 0.006 0.23
Line of inheritance 0.001 0.17

### Table 2 Number of patients and mean (SD) of age at onset in years for females and males given for the grandparents (A) and great grandparents (B).

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Mean (SD)</td>
<td>No</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td>91</td>
<td>41.5 (9.2)</td>
<td>113</td>
<td>38.9 (11.6)</td>
</tr>
<tr>
<td>PM</td>
<td>116</td>
<td>40.6 (11.1)</td>
<td>103</td>
<td>38.1 (11.4)</td>
</tr>
<tr>
<td>MP</td>
<td>113</td>
<td>37.4 (12.2)</td>
<td>97</td>
<td>36.2 (13.6)</td>
</tr>
<tr>
<td>PP</td>
<td>82</td>
<td>40.6 (11.2)</td>
<td>107</td>
<td>36.6 (14.8)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMM</td>
<td>34</td>
<td>41.6 (7.3)</td>
<td>43</td>
<td>37.7 (13.1)</td>
</tr>
<tr>
<td>PMM</td>
<td>32</td>
<td>40.7 (10.6)</td>
<td>42</td>
<td>38.3 (9.9)</td>
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<tr>
<td>MMP</td>
<td>36</td>
<td>42.8 (10.8)</td>
<td>43</td>
<td>39.5 (10.9)</td>
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<tr>
<td>PPM</td>
<td>35</td>
<td>38.2 (10.7)</td>
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<td>35</td>
<td>38.5 (12.0)</td>
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<td>35.6 (11.9)</td>
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<tr>
<td>PMP</td>
<td>40</td>
<td>33.5 (12.2)</td>
<td>28</td>
<td>32.2 (16.4)</td>
</tr>
<tr>
<td>MMP</td>
<td>23</td>
<td>36.8 (11.0)</td>
<td>33</td>
<td>36.5 (11.4)</td>
</tr>
<tr>
<td>PPM</td>
<td>29</td>
<td>39.5 (10.5)</td>
<td>34</td>
<td>36.4 (17.1)</td>
</tr>
</tbody>
</table>

Analysis of variance results (p values): A B
Interaction (sex x inheritance) 0.76 0.98
Sex of the patient 0.003 0.005
Line of inheritance 0.02 0.001
between the mean AO of females and males were again found (p=0.005). The analysis of variance showed a significant difference between the eight lines of inheritance (p=0.001). Subsequent analysis (Scheffe procedures) showed only differences between the two extremes, that is, MPM and PMP. The clinical significance of this is not clear.

AO is often divided into four classes: AO under 20 years (juvenile HD), 20 to 34 years, 35 to 49 years, and over 50 years (late onset). Table 3 gives the results of the relation between the AO classes and the sex and line of inheritance. There are differences in sex (p=0.03) and line of inheritance (p<0.001). In the juvenile HD (JHD) group, males predominate with 66%. Late onset HD occurred in 23% (n=232) of the cases. In all the AO classes over 20 years, an equal distribution in both sexes was found. In the JHD group, 74% inherited the gene from the father, but in the other AO groups the sex of the affected parent has an equal distribution.

### Discussion

Despite the limitations of a retrospective study of AO in Huntington's disease patients, it should be emphasised that the data were gathered by only a very small number of interested neurologists over the last century. Exact determination of the AO at present is neither easier nor more difficult than a century ago. The distribution of the AO of all patients is indeed closely comparable to that previously published.

The mean AO of the whole group did not differ much from that reported elsewhere. For the group born before 1925, the mean AO increased to the same level as reported by Adams et al. and supports the findings of the life table method. Contrary to other reports we found an influence on the mean AO of the sex and the line of inheritance for the whole group. The mean AO of the females was consistently higher compared to the males and independent of the line of inheritance. The same pattern was found for the maternal line, but not for the paternal line within the group born before 1925. One explanation could be the underreporting of the paternal juvenile cases, who are males in 75% of the cases. Although juvenile Huntington's disease was reported in 1863 by Lyon, this entity only became well known after the second world war. In our restricted group born before 1925, only 2% showed an AO before the age of 20 years compared to 6% in the total group. The lack (12 out of 632 (2%) vs 58 out of 1020 (6%)) of paternal male JHD cases in the restricted group will lead to a higher mean AO for this group. One other explanation could be underreporting of the paternal female late onset cases leading to a lower mean AO in this restricted group. This was not supported by our findings, because we found 211 out of 632 (33%) vs 232 out of 1020 (23%) late onset cases in the restricted and total groups, respectively. The lower mean AO for males in our whole group has also been found in other studies. This can probably be explained by overrepresentation of male juvenile patients.

The mean AO of cases with affected fathers was significantly lower than the mean AO of those who inherited the gene from the mother, independent of the sex of the patient. This influence of paternal inheritance with a strongly expressed paternal anticipation has been reported several times. Brackenridge reported the same findings, but considered them to be artefacts. The fact that these differences disappear in the group born before 1925 could support this view.

That the sex of the affected case is of influence on the AO, as was found in our group, has not been reported before, and the effect of paternal transmission seemed not to be restricted to the JHD, as has also been reported. This could be explained by the reported anticipation in which AO is progressively earlier in the successive generation. Myers et al. found no effect of sex of the grandparents on the AO in 125 cases and found this compatible with a single generation hypothesis for the explanation of the paternal predominance in JHD and for the maternal predominance in late onset cases. In our much larger sample of 822 cases, the sex of the affected patient did influence the AO, whereas the AO was not influenced by the MM, PM, and PP lines. The mean AO of the female cases with MP inheritance showed a significantly lower mean AO compared to the other lines (p<0.05). Therefore, the sex of the affected grandparent seems to influence the AO when the gene is inherited through the paternal line and not when the gene is transmitted through the maternal line. The paternal genetic load preceded by maternal transmission seems to have an influence on the AO, leading to an earlier onset. This is also stated by Ridley et al., who showed that the AO of probands with a PP lineage was 4.3 years earlier than in those with an MP lineage. The single generation hypothesis, therefore, is not supported by these findings. Multiple modifying genes or epigenetic changes in methylation of the nucleic acid of the genome are much more likely causes of the expression of the parental influence on the AO.
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The percentage of 5·5% of JHD is comparable to that previously published. In our cases the gene for JHD was inherited from the father in 74% of cases, which is also in agreement with previous studies.

In the late onset group of 259 cases (23·8%), in 232 (22·7%) instances the sex of the affected parent was known, which is a much larger group than the one reported by Myers et al.11 (66 late onset cases = 27·7% of total) and the group of Farrer and Conneally.22 (91 late onset cases = 16% of total). As Myers et al.11 found the mother to be the affected parent in 32 of the 45 (71%) late onset cases and Farrer and Conneally22 in 56 out of 91 patients (61·5%), our data very convincingly showed that 50% (n = 116) inherited the gene from the mother. Clearly, maternal influence in the late onset AO group could not be shown. The methods were also retrospective and the same interpretation of AO (involuntary movements) was used by Myers et al.11 Farrer and Conneally22 included psychiatric symptoms for determination of AO. The data from the living and dead patients of 65 years and older, as was studied by Went et al.13 on part of our material showed the same results. Again no difference in parental inheritance was present and the maternal/paternal ratio was 120:112 (data not shown). Husquinet et al.23 found no maternal preponderance in the AD groups in a very heterogeneous group of Dutch, Belgian, and French cases (n = 173) of 66 years and older. Therefore, the hypothesis based on a maternal transmittable factor in combination with genetic modifiers for control of ageing has to be modified.22 Still, one might suggest a maternal protecting or delaying transmittable factor to explain the paternal preponderance in JHD, but an aggressive and genetically determined paternal factor has to be considered too.

We thank Mr H Franken for his technical assistance.

1 Hayden MR. Huntington’s chorea. Berlin: Springer Verlag, 1981.
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doi: 10.1136/jmg.28.8.515

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