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Which factors influence age at onset and rate of progression in Huntington's disease?

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SUMMARY

Fifty-one families of patients affected with Huntington's chorea were interviewed with respect to age at onset, symptoms at onset and course of the disease. The interview further comprised questions pertinent to line of transmission, socio-economic status, housing, previous illnesses and pregnancy and stillbirth. Since the study was set up as a fishing expedition detailed quantitative information was gathered on many life-style factors including eating, drinking and smoking habits.

In adult age onset cases earlier age at onset correlated with lower rate of progression. Line of transmission was of no influence on age at onset in cases with onset above 20 years. No statistically significant relationship was found between any factor studied and age at onset, except for the intake of milk. Higher previous milk intake was associated with earlier ages at onset. This finding is critically discussed. No difference was found between the respective ages at onset of conduct disorders and affective disorders. This suggests that they are both associated with the Huntington gene.

Key words: Huntington's disease; Age of onset; Rate of progression

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INTRODUCTION

Huntington's disease (HD) is an autosomal dominantly inherited disease with age dependent penetrance. Age at onset is something different from age at recognition. Within well informed families the interval between age at onset and age at recognition will be shorter than in less informed or less coherent families. Age at onset in HD varies widely between individuals even within one and the same kindred. Indeed, it varies much more widely than errors of recognition would explain. This makes one wonder what factor(s) might possibly influence age at onset. Hypotheses mentioned in this respect include modifying superior and inferior aging genes (Farrer et al. 1984), genetic heterogeneity (Went et al. 1983) and the autoimmune paradigm (Burch 1968). The influence of factors such as sex and line of transmission upon age at onset has been assessed in several recent studies (Newcombe et al. 1981; Meyers et al. 1983; Went et al. 1984). An influence of climate has been tentatively proposed (Brackenridge 1974). The only study on the influence of somatic and psychological stress (Korenyi et al. 1972) showed negative results. The possible influence of environmental factors such as previous trauma, drugs, eating, drinking and smoking habits, has not been studied systematically (Sanberg et al. 1981). The small geographical distances in the Netherlands, the moderate sea climate prevailing uniformely over the region of the study and the presence of a central family file on Huntington's disease at Leiden University, prompted us to set out a fishing expedition to study the potential influence of a number of "environmental" factors upon age at onset in HD.

PATIENTS AND METHODS

From the Leiden roster of HD, 60 ascertained patients were selected according to the following criteria:

(i) full detailed knowledge on parents and offspring;
(ii) the presence of more than one adequate, first-degree relative informant (parents, sibs) and spouses;
(iii) residence less than 100 km from our centre (Fig. 1)

After informed consent had been obtained from 51 individuals (response rate 85%), these families were visited at home by two of us (O.B. and W.v.d.K. or E.B.), and detailed information was gathered on age at onset, symptoms at onset and course of illness by a structured personal interview. In general, consensus was reached between the relatives present; if not, we selected the apparently most reliable information. All patients (30 males, 21 females, mean age of 53 years (range 26–78 years) were graded according to the Shoulson and Fahn scale (SF) (Shoulson et al. 1979). Two patients were graded SF1, 14 SF2, 7 SF3, 14 patients SF4, and 14 SF5. Psychological or psychiatric symptoms were defined according to the DSM III and broadly divided into affective disorders, conduct disorders and dementia.

Structured questions were posed pertinent to socio-economic status and housing, as well as to previous illnesses, cerebral trauma, pregnancy and stillbirth, use of drugs and hospital admittances prior to the onset of symptoms. Detailed quantitative inquiries

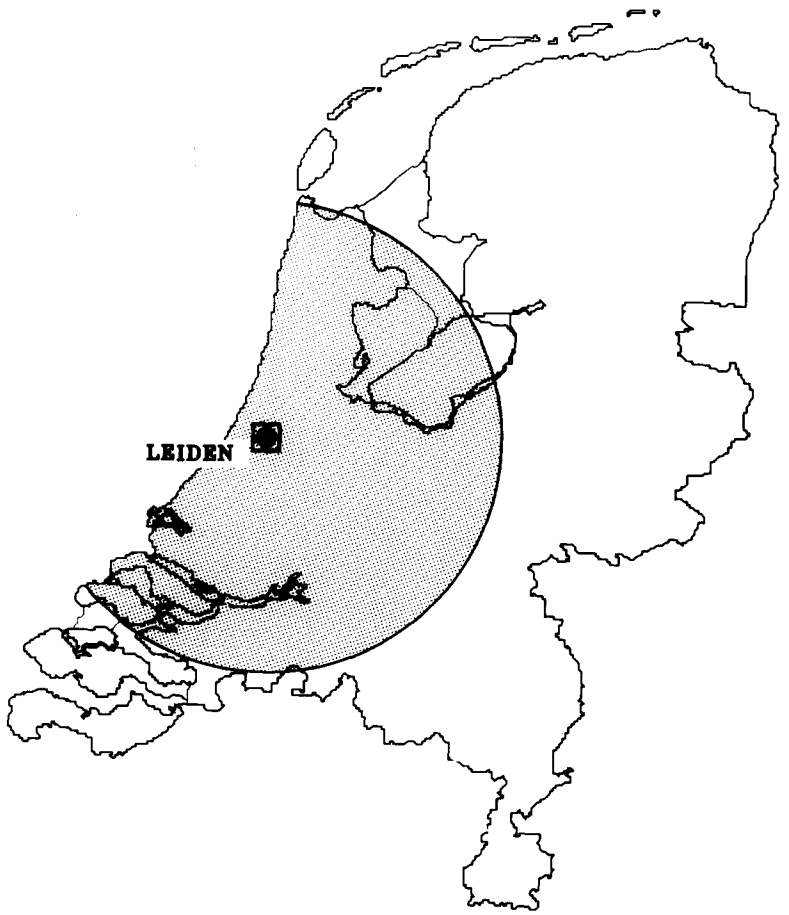

Fig. 1. The Netherlands and the area within a radius of 100 km around the Huntington Research Centre at Leiden.

were made with respect to eating, drinking and smoking habits over the 10 years prior to age at onset. Over these 10 years information was obtained about daily fish consumption and the intake of coffee, tea, milk products, fruit juices etc. was estimated. With respect to alcohol and tobacco all estimates were coded into grams. The associations between the factors mentioned and the age at onset were analysed using Spearman's rank correlation test.

RESULTS

Contrary to previous studies which showed an average duration of approximately 1.5 years per SF stage (Shoulson and Fahn 1979), we found an average duration (= rate of progression (RP)) of 5.1 years. The average age at onset of the involuntary movements (AOIM) was 38.6 $\pm$ 11.0 years (range 15–60) and the average age at onset of unequivocal psychological or psychiatric changes (AOPC) 38.1 $\pm$ 12.0 years (range 16–65). No

TABLE 1

P VALUES AND CORRELATION COEFFICIENTS OF SPEARMANS RANK CORRELATION TEST RESULTS FOR THE FACTORS STUDIED IN RELATION TO OVERALL AGE AT ONSET (AOAS), AGE AT ONSET OF PSYCHOLOGICAL CHANGES (AOPC), AGE AT ONSET OF INVOLUNTARY MOVEMENTS (AOIM) AND RATE OF PROGRESSION (RP)

	AOAS		AOPC		AOIM		RP	
	P	*r*	*P*	*r*	*P*	*r*	*P*	*r*
Sex	0.87	0.02	0.93	0.01	0.96	−0.08	0.97	0.01
Line of transmission	0.15	0.20	0.24	0.17	0.18	0.19	0.07	−0.26
Degree of urbanisation	0.32	−0.14	0.11	−0.23	0.75	−0.05	0.14	0.21
Number of concussions	0.82	−0.13	0.81	−0.13	0.80	−0.13	0.56	0.35
Previous hospitalisation	0.32	−0.14	0.27	−0.16	0.27	−0.16	0.49	0.10
Number of abortions	0.85	−0.09	0.85	0.09	0.70	−0.18	0.85	−0.10
Number of attacks of common cold per annum	0.09	−0.24	0.04*	−0.29	0.09	−0.24	0.67	−0.06
Alcohol consumption	0.52	0.09	0.47	0.11	0.49	0.10	0.52	−0.09
Tobacco	0.44	0.11	0.41	0.12	0.43	0.11	0.52	−0.09
Milk	0.03*	−0.30	0.05*	−0.29	0.04*	−0.29	0.19	0.19
Coffee	0.61	0.07	0.98	0.00	0.75	−0.04	0.99	0.00
Fruit juice	0.50	−0.10	0.28	−0.16	0.79	−0.04	0.92	−0.02
Tea	0.52	−0.09	0.09	−0.25	0.72	−0.05	0.03*	0.31
Cheese	0.32	0.14	0.42	0.12	0.17	0.20	0.24	0.17
Fish	0.94	0.01	0.80	−0.04	0.47	0.10	0.42	0.12

* $P \leqslant 0.05$.

significant differences were observed between affective disorders and conduct disorders with respect to the mean age at onset and its standard deviation. Suicidal attemps were not reported, but cases of successful suicide would, of course, not be included in our study. When age at onset for any symptom connected to HD (AOAS) was considered, the average was 36.5 ± 11.5 years (range 15–60). Early AOAS tended to result in a slower progression of the disease ($P = 0.04$). The line of transmission, i.e. whether the disease was inherited from the father or the mother did not influence AOAS. Sex of the patients was of no significant influence on the AOAS ($P = 0.15$). No statistically significant relationship could be established between AOAS, AOIM, AOPC and RP and the previous amount of consumption of a number of beverages (Table 1).

The patients consumed an average of 7.2 cups of coffee per day prior to onset of their disease as well as during their illness. This is remarkable when compared to the 4 cups a day of the average Dutch adult. The daily intake of alcohol prior to as well as after the onset of the disease did not differ from the average Dutch intake. With respect to smoking, the smokers/non-smokers ratio did not differ from the Dutch population and the use of tobacco in the smokers group did not differ significantly from the average in Dutch smokers.

A negative correlation coefficient was found between AOAS, AOIM, AOPC and the amount of daily milk and milk product consumption which tended to be statistically significant ($P = 0.05$) (Table 1). The estimated amounts of protein from other sources and fish were unrelated to the age at onset.

The socio-economic status of HD patients is likely to be influenced by the disease and therefore possibly lower than average. Only 4 patients belonged to the two highest classes on a 5-point scale. Only 2 divorces were mentioned on a total of 48 married patients. Married couples had an average of 2.7 children. Being brought up in either a big town or a small village had no influence on the parameters studied. With respect to the possible influence of diseases prior to the onset, concussion with brief loss of consciousness was found in 6 patients. This appeared not to influence AOAS, AOIM, AOPC and RP. No other previous affliction except for "common cold" occurred frequently enough in our patients to allow any statistical evaluation as to its effect on AOAS and RP. "Common cold" was defined as a period of nasal drip and/or sore throat. The frequency of occurrence of "common cold" in the 10 years previous to AOAS was rated by inquiring into the average total occurrences per annum over those years. The frequency of "common cold" did not correlate significantly with AOAS ($P = 0.09$).

The number of pregnancies did not relate to AOAS or any of the other parameters studied. This, of course, is in agreement with the absence of a correlation between sex and age at onset.

Stillbirth was reported in 6 of the 21 female patients. These 6 patients did not differ from the other 15 with respect to the AOAS and RP. The same holds true for the use of oral contraceptives in 5 female patients.

Spearman's rank correlation test results for most factors studied in relation to age at onset and rate of progression are presented in the table.

DISCUSSION

A crucial point in retrospective studies on the influence of any factor on age at onset is the accuracy with which the latter can be established. We used the method of personal interview with a group of relatives that could be expected to produce relevant and reliable information. Still, the results have to be handled with reservation. The same obtains for the data on life style factors during a period 10–20 years ago. Since prospective studies, covering many decades of repeated follow-up, clearly are not feasible, one has to settle for the present type of study.

Changes in behaviour are said to be early signs of HD (Dewhurst et al. 1970) and major affective disorders often precede the manifestation of movements by many years (Folstein et al. 1981). Our results do not bear this out.

There was no significant difference between the age at onset of conduct disorders and major affective symptoms in our study, which therefore does not support the conclusion of Folstein et al. (1983) that conduct disorders, in contrast with the major affective symptoms, are associated with disruption of families, rather than with the HD gene. The fact that early age at onset appeared to be associated with a slower rate of

progression was also observed by Newcombe et al. (1981). As they pointed out, an inverse correlation between age at onset and survival time (or progression rate) is inevitable, because overestimation of the first leads to underestimation of the second. Other possible explanations for such an inverse relationship, e.g. a declining resistance with age and decreased life expectancy in the elderly (Burch 1979) or a selection bias due to exclusion of patients with early age at onset and a high rate of progression, may contribute as well.

The fact that no influence could be established of line of transmission on age at onset in our patients with ages at onset above 20 years agrees with the observations of Went et al. (1984). In fact, the possibility that our results in this respect agree with those of Myers et al. (1983) is unlikely ($P = 0.02$), but only 3 of our patients showed an AOAS below 20 years and 2 of them inherited the disease from the father.

None of the socio-economical factors, housing factors, living area, or profession (toxic factors) did correlate with the age at onset. The fact that only 4 patients ranked up into the 2 highest social classes on a 5-point scale appears to be in agreement with the report of Reed et al. (1958) who established that affected men attain a lower socio-economical status than their unaffected brothers. Affected women again tend to marry men from lower social classes than their unaffected sisters.

With the exception of milk and milk products, life style factors did not consistently correlate with the age at onset. Milk and milk products tended to correlate negatively with age at onset (the higher the intake of milk products, the earlier the age at onset). One should keep in mind that the probability of finding significant relationships just by chance (type I error) is considerable in this kind of "fishing expedition" and a second type of error may result from a common confounder (e.g. milk consumption may depend upon age in the Dutch population). Relationships found should therefore preferably be biologically understandable. The biological relevance of this correlation is doubtful, although it may imply that some aspects of nutrition may influence the age at onset.

The absence of a correlation between alcohol consumption and age at onset needs further comment. Excessive alcohol intake has been reported to be associated with Parkinsonism (Black et al. 1980; Lang et al. 1982) and alcohol withdrawal with dyskinesia (Mullin et al. 1970). Since abuse of alcohol was reported in none of the patients, the effect of alcohol withdrawal cannot be inferred from our data. The absence of an effect of "social" alcohol intake on the involuntary movements in our patients suggests that alcohol is not an important factor in HD.

The use of tobacco in Huntington's disease has not been studied previously though one frequently encounters the opinion that HD patients are excessive smokers. The opposite has been observed in Parkinson's disease (Baumann et al. 1980) showing a highly significant difference compared with matched neighbours. Hemidystonia has been reported to be relieved by nicotine (Lees 1984). In our study no differences in smoking habits could be found between HD patients and the age matched average in the Dutch population. None of the patients reported a beneficial effect of smoking on involuntary movements.

No statistically significant relationship between age at onset and "somatic stress' was found. Korenyi et al. (1972) established a temporal relationship between a number of medical and surgical types of "stress" and the moment of onset of the disease or

aggravation of the disease. Their personal observations were few, however, and such a temporal relationship might well be due to the common need for causality in the patients' minds. In Parkinson's disease, patients appear to catch common cold less frequently before the onset of the disease (Nomoto and Igata 1983) compared with their neighbours. They are even less often afflicted by common cold after the onset of the disease (Lees 1984). One may hypothesize an association between the dopaminergic status of the striatum and the liability of suffering from common cold. Our study did not verify this hypothesis, although an increased frequency of common cold tended to be associated with earlier age at onset ($P = 0.09$). In summary, no correlations were found between age at onset and line of transmission, sex, pregnancies, stillbirth, contraception, a number of somatic stress factors, socio-economical factors and a number of life style factors with the possible exception of the intake of milk and milk products.

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