Journal of Medical Genetics (1975). **12**, 64.

Estimation of the age at onset of Huntington's disease from factors associated with the affected parent

C. J. BRACKENRIDGE and BETTY TELTSCHER

From the Department of Psychiatry, University of Melbourne, Victoria, Australia

Summary. In an attempt to relate the age at onset of Huntington's disease to parental factors, the effects of parental onset-age (P_o) and the age of the transmitting parent at the birth of a subsequently affected child (P_c) have been examined in a sample of cases ascertained from Victorian kindreds. There was a significant positive linear regression of onset-age on the variable $P_o - P_c$; the result was independent of the sex of affected parent or child. It is suggested that the pathogenetic process is activated in individuals at a fixed time before their genetically determined onset-ages and need not commence at birth. Somatic gene mutations accumulating with age may interact with modifiers activated at initiation of pathogenesis and favour the transmission of genes determining early onset. An important conclusion for genetic counselling is the desirability of parents at risk who intend to have children to plan their families early in life so that the illness will tend to appear in late adulthood in their affected children. The regression equation may also be applied to estimate the risk of inheritance of the disorder and, by taking interfamilial variation into account, appears to have an advantage over the existing method based on the distribution of onsettages.

An understanding of the factors associated with the manifestation of Huntington's disease at an age specific to each sufferer is important for several reasons. Firstly, it is desirable to identify the genetic and environmental effects which operate, determine their relative strengths and study the manner in which they interact. Second, it may be possible to manipulate external variables so as to favour late onset. Climatic temperature has been shown to affect the time when symptoms appear: on average, persons living in cold regions develop signs of the illness about a decade after those living in the tropics (Brackenridge, 1974a). It is not known whether this result can be exploited in a practical way. Third, if genetic factors affecting onset could be measured, it might be feasible to predict the time of manifestation from the relevant data. Such an approach would be useful for counselling subjects at risk by providing a more accurate probability of inheritance than is now possible. Attempts could also be made to promote the selection of genes predisposing to late onset of symptoms.

Previous work has demonstrated a correlation between the onset-ages of affected parents and children (Bell, 1941/1942; Panse, 1942; Cameron and Venters, 1967; Brackenridge, 1972a, 1972b). In addition, the proportion of cases displaying muscular rigidity has been shown to depend on the age of the affected parent at the time of their birth (Brackenridge, 1974b). Rigidity is associated with an earlier mean onset of the disorder than when chorea is the predominant sign (Bittenbender and Quadfasel, 1962; Brackenridge, 1973). The parental onset-age and the age of the affected parent at the time of birth of an affected offspring are therefore putative genetic factors influencing the onset-age of Huntington's disease.

Parental onset-age may precede, coincide with, or follow the times at which offspring bearing the deleterious gene are born. If, particularly in small sibships, the time of parental onset is an approximate estimate of the years of birth of affected

Received 5 March 1974.

offspring, it is plausible to suggest that interclass onset-age correlation is actually due to an intrinsic dependence of onset-age on parental age. Two hypotheses arise from considerations such as these.

Hypothesis I. Subject to environmental modification, the age at onset of symptoms is postulated to be directly proportional to the age of the transmitting parent when the gene-bearing child was born.

Hypothesis II. Onset-age may be regarded as a threshold parameter representing the time at which subclinical signs or symptoms dating from pathogenesis become overt. (Strictly speaking, age at manifestation is a preferable term to age at onset in this context, but the latter can be retained if it is remembered that onset relates to the frank appearance of neurological or psychiatric symptoms and not to the beginning of the pathological process.) Suppose that the time elapsing between the initiation of pathogenesis and the manifestation of Huntington's disease does not vary greatly among sufferers. This is synonymous with the idea that the pathogenetic process need not begin at birth, so that initiation may not commence until adulthood if onset is late. According to the second hypothesis, onset-age in a child is determined by the duration of the process in a parent at the time the child was born. The frame of reference for parental age therefore shifts from the time of birth of the parent to the time of manifestation of symptoms. It is envisaged that subsequently affected children conceived at successive stages of the unfolding of the disease become increasingly susceptible to an early expression of the gene. The hypothesis may be formulated as follows: subject to environmental modification, the age at onset of symptoms in a gene-bearing child is directly proportional to the period between the birth of the child and the parental onset-age. If C_o is the onset-age of a child, P_o is the onset-age of the parent and P_c is the age of the parent when the child was born, then if a, b, A, and B are constants, the mathematical models are:

$$\text{Hypothesis I}—C_o = a + b\ P_c, \text{ and}$$
$$\text{Hypothesis II}—C_o = A + B\ (P_o - P_c).$$

The present study reports the application of data collected during an ascertainment of Australian cases to tests of these hypotheses.

Material and methods

Persons affected with Huntington's disease were ascertained from kindreds in the State of Victoria if the sex, year of birth, and age at onset of symptoms were known for parent and child. The great majority of subjects lived in the Melbourne metropolitan area. Details of the 73 offspring are found in the Appendix; 31 kindreds and 42 sibships are represented. There were 38 males and 35 females; these were descended from 23 affected fathers and 19 affected mothers.

The hypotheses were tested using linear regression analyses in which C_o was the dependent variable and P_c or $P_o - P_c$ was the independent variable. The magnitudes of the regression coefficients were estimated and their significance from zero slope were assessed. Statistical procedures were carried out as described by Sokal and Rohlf (1969).

Results

Onset-ages. Tests were carried out to determine whether two requirements of the dependent variable in the regression model—normality of distribution and homogeneity of variances—were met by the 73 onset-ages. A Kolmogorov–Smirnov test afforded no basis to reject the null hypothesis that the ages was normally distributed ($D = 0{\cdot}084$, $p > 0{\cdot}6$). The mean and standard deviation of the 73 ages was $32{\cdot}5 \pm 12{\cdot}7$ years. When onset-ages of subjects were grouped according to the age of the affected parent at the times of their birth, no evidence of heterogeneity of their variances was obtained from Bartlett's test (corrected $\chi^2 = 19{\cdot}17$ with 17 df, $p > 0{\cdot}3$). Similarly, when grouped according to the time between the birth of an affected child and parental onset, variances of onset-ages were relatively uniform (corrected $\chi^2 = 22{\cdot}30$ with 21 df, $p > 0{\cdot}3$).

Hypothesis I. Examination of the effects of sex of the affected parent and child on the slopes obtained by regressing onset-age of persons on parental ages at their birth failed to disclose any significant results. The linear regression coefficients for offspring of transmitting fathers ($0{\cdot}094 \pm 0{\cdot}428$) and of mothers ($-0{\cdot}015 \pm 0{\cdot}455$) as well as for males ($-0{\cdot}110 \pm 0{\cdot}500$) and for females ($0{\cdot}005 \pm 0{\cdot}389$) were indistinguishable and of negligible magnitude. As would be expected, the result when sexes were combined ($-0{\cdot}012 \pm 0{\cdot}308$) also provided no evidence of a relation between the two variables.

Hypothesis II. The possibility of sex dependence was investigated in the linear regression of C_o on $P_o - P_c$. The slopes were $0{\cdot}781 \pm 0{\cdot}118$ for males and $0{\cdot}605 \pm 0{\cdot}160$ for females. These values were indistinguishable and significant in magnitude. When the sex of the affected parent was considered, the slopes obtained were $0{\cdot}730 \pm 0{\cdot}111$ for fathers and $0{\cdot}774 \pm 0{\cdot}123$ for mothers. Again these values were indistinguishable and individually significant. Pooling the data for each sex was therefore indicated.

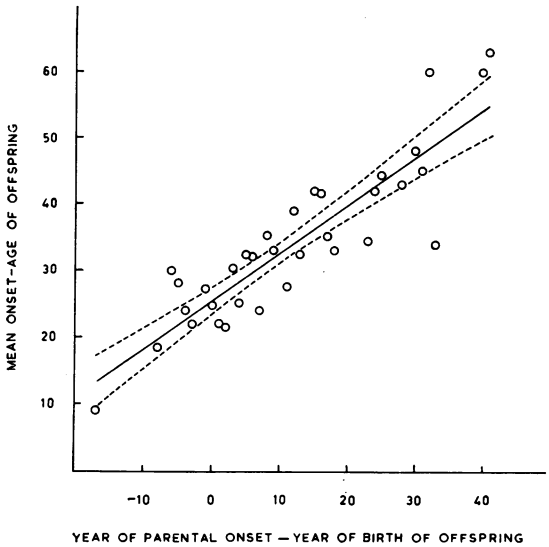

FIG. 1. The regression of onset-age of offspring in years on the difference between the year of parental onset and the year of birth of subsequently affected offspring. Points represent mean onset-ages at particular values of the independent variable.

Mean values of C_o at particular values of the independent variable are shown in Fig. 1 together with the regression line and its 95% confidence limits. The regression accounted for 77·5% of the total variation and the estimate and standard error of the coefficient were $0{\cdot}716 \pm 0{\cdot}068$. The high significance of this result is reflected in the analysis of variance in Table I. Although the differences between onset-ages at the 34 values of the independent variable fell short of significance, their variation was successfully accounted for by the regression line and deviations were relatively slight.

The regression equation obtained was

$$C_o = 25{\cdot}6 + 0{\cdot}716\ (P_o - P_c).$$

This means that when the year of parental onset exceeds the year of birth of a child possessing the Huntington gene, the predicted onset-age for the child exceeds 25·6 years. It becomes 25·6 years when parental onset coincides with the year of childbirth and falls progressively lower as children are born during the time parental symptoms are apparent.

Assessment of Risk. To determine the effectiveness of the equation as a predictor of onset-age, an examination was made of the differences between the fitted values and the means of the observed values. A plot of these residuals showed them to be normally distributed as required by regression theory. There was no trend when they were plotted against the dependent and independent variables, so that the variance (and hence the error of prediction) was essentially constant over the ranges studied. The standard deviation of the residuals was 3·2 years.

The predicted onset-age for a new single value of $P_o - P_c$ can be calculated from the results already obtained. Table II lists mean onset-ages, standard errors, and 80%, 90%, and 95% confidence limits predicted for particular values of $P_o - P_c$. Appropriate ages at intermediate values of $P_o - P_c$ can be determined by interpolation. The relative probability of inheritance of Huntington's disease can also be calculated. Suppose a person at risk, now aged 45 years, was born five years before the onset of parental symptoms. If such a person carries the abnormal gene, the predicted onset-age is $25{\cdot}6 + (5 \times 0{\cdot}716) = 29$ years. The number of standard deviations between the predicted and present age is $(45 - 29)/11{\cdot}2 = 1{\cdot}43$. Reference to the standard normal density function shows that the probability of an observation exceeding 1·43 standard deviations from the mean is 0·076/0·5. The conditional probability of inheritance is therefore 15·2%. Since the prior probability is 50%, the joint probability is 7·6% and the total probability is estimated to be 7·6%/(7·6% + 50%) or 13%.

Discussion

The first hypothesis that the age of the transmitting parent at the time of the birth of a child

TABLE I

ANALYSIS OF VARIANCE OF ONSET-AGES OF OFFSPRING IN RELATION TO THE PERIODS BETWEEN PARENTAL ONSET AND THEIR YEAR OF BIRTH

Source of Variation	Sum of Squares	DF	Mean Squares	Variance Ratio
Between periods	6788·8	33	205·7	1·65*
Due to linear regression	5261·6	1	5261·6	110·25†
Deviations from regression	1527·2	32	47·7	0·38‡
Within periods	4875·1	39	125·0	
Total	11,663·9	72		

* $p > 0{\cdot}05$; † $p < 0{\cdot}001$; ‡ $p > 0{\cdot}8$.

TABLE II

PREDICTED MEAN ONSET-AGES AND CONFIDENCE LIMITS OF OFFSPRING FOR SELECTED PERIODS BETWEEN PARENTAL ONSET AND THEIR YEAR OF BIRTH (P_o–P_c)

P_o–P_c	Predicted Mean Onset-age	Standard Error	Upper Confidence Limits		
			80%	90%	95%
−20	11·3	11·4	14·7	19·0	22·7
−10	18·5	11·3	14·6	18·8	22·5
0	25·6	11·2	14·5	18·7	22·4
10	32·8	11·2	14·5	18·7	22·4
20	39·9	11·2	14·5	18·7	22·4
30	47·1	11·3	14·6	18·8	22·5
40	54·2	11·4	14·8	19·0	22·7

All values are measured in years.

possessing the deleterious gene determines the onset-age of the disease in that child can be discarded in view of the results obtained. No evidence of a functional relationship was obtained either in the material as a whole or when divisions according to sex of child and affected parent were made. On the other hand, strong evidence in favour of the second hypothesis was found. The age at manifestation of Huntington's disease is determined to a considerable degree by the difference between the time of parental onset and the time of birth of the gene-bearing child.

If, as is usually the case, parental onset occurs after the birth of a given child, symptoms should appear in the child later than 26 years of age. If the parent shows signs of the disorder when a child is conceived, onset in the offspring is likely to occur before the age of 26 years. Considering that such environmental factors as trauma, infection, and climatic temperature (Korenyi, Whittier, and Conchado, 1972; Brackenridge, 1974a) may modify the inheritance of onset-age, the variation about the regression line is acceptably small. The greatest source of error involved in testing the hypothesis is probably the estimation of onset-age by close relatives of affected persons. It will be of interest to determine whether the regression equation derived in Victoria holds elsewhere, but with different constants, or whether the linearity of the relationship is disturbed.

When the differences between the fitted and observed onset-ages were plotted as a function of the independent variable, the absence of any trend suggests that the postulated constancy of the interval between initiation of pathogenesis and onset-age is a reasonable approximation. The results obtained are also consistent with the other underlying supposition that pathogenesis need not commence at birth but may be activated some years later. If this is so, a plausible mechanism which would account for the present findings is that induction of pathogenesis is programmed at a genetically determined age in a person possessing the abnormal gene. A regulator may operate on a number of modifying genes responsible for onset-age by 'switching' them on some time before symptoms become manifest. Regardless of parental sex, it is proposed that somatic gene-mutations accumulating with age interact with the modifiers activated at initiation and favour the transmission to the child of those genes determining early onset. The critical factor affecting the inheritance of onset-age is therefore parental age after initiation. If the period between initiation and onset is relatively constant among affected individuals, the year of onset minus the year of birth of each gene-bearing child is a convenient measure of the times of gene expression in the next generation. Somatic gene-mutations have also been invoked to explain the relation of parental age to the presence of rigidity in the symptomatology (Brackenridge, 1974b). The findings were explicable in terms of the theory of Burch (1968) and evidence was obtained that mutation rates were of comparable magnitude, but of opposite effect, in affected fathers and mothers.

A general conclusion of importance in genetic counselling is the desirability of persons at risk who intend to have children to plan their families at an early age. Should the prospective parent inherit the disorder, maximizing the periods between the birth of children and their own onset age will tend to delay the appearance of symptoms in children to whom the abnormal gene has been transmitted. This seems to be a promising approach to select for onset in late adulthood.

The regression equation should also find practical application in the estimation of the risk of inheriting Huntington's disease. So far the only method of assessing risk more accurately than the theoretical Mendelian ratio lies in using the onset-age distri-

bution; the chance of being affected is then an inverse function of age. The use of this approach in counselling persons at risk has been described by Cameron and Venters (1967), Murphy (1968), Emery (1969), and Murphy and Mutalik (1969). It has the drawback, however, of not taking variations in onset-age between families into account. Use of the equation presented here may yield a low estimate of risk at an age when most bearers of the gene begin to show signs of the illness. The disadvantage of the present method is that persons at risk will not always have the necessary parental details. Our experience in Victoria suggests that the proportion of such cases is quite low. Although the information may appear to be lacking in the first instance, it may be subsequently obtainable from relatives or records with sufficient accuracy for a reasonable assessment to be made.

This work was supported by a grant from the National Health and Medical Research Council of Australia.

References

Bell, J. (1941/1942). On the age of onset and age at death in hereditary muscular dystrophy with some observations bearing on the question of antedating. *Annals of Eugenics*, **11**, 272–289.

Bittenbender, J. B. and Quadfasel, F. A. (1962). Rigid and akinetic forms of Huntington's chorea. *Archives of Neurology*, **7**, 275–288.

Brackenridge, C. J. (1972a). Familial correlations for age at onset and age at death in Huntington's disease. *Journal of Medical Genetics*, **9**, 23–32.

Brackenridge, C. J. (1972b). The relation of some features of Huntington's disease to the age at onset of symptoms in parents. *Clinical Genetics*, **3**, 477–482.

Brackenridge, C. J. (1973). The relation of sex of affected parent to the age at onset of Huntington's disease. *Journal of Medical Genetics*, **10**, 333–336.

Brackenridge, C. J. (1974a). Effect of climatic temperature on the age of onset of Huntington's chorea. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 297–301.

Brackenridge, C. J. (1974b). Relation of parental age to rigidity in Huntington's disease. *Journal of Medical Genetics*, **11**, 136–140.

Burch, P. R. J. (1968). *An Inquiry Concerning Growth, Disease and Ageing*. Oliver and Boyd, Edinburgh.

Cameron, D. and Venters, G. A. (1967). Some problems in Huntington's chorea. *Scottish Medical Journal*, **12**, 152–156.

Emery, A. E. H. (1969). Genetic counselling. *Scottish Medical Journal*, **14**, 335–347.

Korenyi, C., Whittier, J. R., and Conchado, D. (1972). Stress in Huntington's disease (chorea). *Diseases of the Nervous System*, **33**, 339–344.

Murphy, E. A. (1968). The rationale of genetic counseling. *Journal of Pediatrics*, **72**, 121–130.

Murphy, E. A. and Mutalik, G. S. (1969). The application of Bayesian methods in genetic counselling. *Human Heredity*, **19**, 126–151.

Panse, F. (1942). Der Erbchorea: eine Klinisch-genetische Studie. In *Sammlung Psychiatrischer und Neurologischer Einzeldarstellung*, vol. 18, ed. by A. Bostroem, K. Berlinger, and G. Schaltenbrand, Thieme, Berlin.

Sokal, R. R. and Rohlf, F. J. (1969). *Biometry*. Freeman and Company, San Francisco.

Appendix

Details of Parents and Offspring

Kindred No.	Affected Parent				Affected Offspring		
	Case No.	Sex	Year of Birth	Year of Onset	Sex	Year of Birth	Age at Onset
1	6	F	1907	1941	F F F	1932 1936 1938	36 27 37
3	2	F	1899	1933	M F	1922 1925	31 29
4	1	M	1903	1960	F	1930	34
6	3	F	1895	1927	F F M	1918 1924 1926	30 34 26
	4	F	1918	1948	F F	1937 1941	24 20
9	1	M	1903	1960	M	1937	34
10	1	F	1864	1904	M F M	1891 1896 1902	40 35 40
	3	F	1896	1931	M	1926	38
	4	M	1902	1942	F	1939	30
14	1	M	1872	1912	M	1912	30
	2	M	1914	1944	M F	1944 1945	18 11

Appendix—*continued*

Kindred No.	Affected Parent				Affected Offspring		
	Case No.	Sex	Year of Birth	Year of Onset	Sex	Year of Birth	Age at Onset
15	7	M	1885	1937	M F	1912 1914	48 35
	8	F	1889	1926	F	1909	52
19	1	M	1856	1919	M	1879	60
	2	M	1879	1939	M F F	1906 1908 1914	34 45 41
20	1	M	1892	1927	F M	1923 1933	35 32
28	2	M	1902	1930	M M M F F	1930 1931 1933 1935 1938	23 30 30 28 19
31	1	F	1900	1918	F F F M	1922 1924 1926 1935	24 28 18 9
34	1	F	1887	1930	M F M	1912 1914 1924	33 50 47
35	1	M	1918	1947	F M	1943 1950	13 14
44	2	M	1911	1937	M	1934	21
46	1	F	1889	1929	M F	1918 1921	28 42
	2	M	1918	1946	M	1946	6
47	1	F	1890	1930	M M	1914 1926	30 30
	2	M	1914	1944	M	1942	3
50	6	M	1892	1952	M	1928	42
51	1	M	1894	1933	F M	1921 1921	45 42
54	1	F	1871	1911	M	1912	43
60	5	M	1900	1935	F	1934	18
63	1	M	1886	1935	F	1931	30
	2	F	1931	1961	F	1955	17
79	5	M	1892	1940	M	1923	25
83	2	F	1876	1938	M	1897	63
	3	M	1878	1941	M M	1909 1911	60 62
85	4	F	1879	1921	M M	1906 1908	42 45
	5	M	1890	1925	M F F	1913 1917 1925	30 35 45
87	11	F	1895	1930	F	1926	18
92	1	M	1901	1956	M	1939	29
98	2	M	1901	1932	F	1925	28
113	1	F	1892	1920	M F	1920 1921	27 25
120	1	F	1904	1951	F	1923	43
126	1	F	1877	1940	M	1924	45