Parental factors associated with rigidity in Huntington's disease

C J BRACKENRIDGE

From the National Research Institute of Gerontology and Geriatric Medicine, Mount Royal Hospital, Victoria, Australia

SUMMARY The discriminatory power of ten factors has been explored in relation to the presence or absence of muscular rigidity in patients with Huntington's disease. The sex and neurological sign of an affected parent were the only two significant determinants of rigidity or choreoathetosis in offspring. It was shown, using the Mantel-Haenszel method of adjusting for confounding variables, that the risk of a patient displaying rigidity (and thereby having a graver prognosis) is five times as great for those with rigid parents as it is for those with non-rigid parents. Additionally, the risk of a patient displaying rigidity is more than three times as great for those with affected fathers as it is for those with affected mothers. Some implications of these findings are discussed.

A minority of patients with Huntington's disease display muscular rigidity during the course of their illness. In association with hypokinesia and tremor, the sign may precede or follow the more usual picture of choreoathetoid and hypertonic movements or, particularly in young subjects, replace them as the sole presenting feature. Any attempt to understand the relation between the rigid and choreic forms of the disorder must reckon with the following observations.

- (1) Their neuropathological changes are indistinguishable,¹ though cytometric variation of putaminal neurone populations is suggestive.²
- (2) Monozygotic twin sisters discordant for neurological sign have been reported.³
- (3) Rigid cases have a different form of age of onset distribution and are more frequently of affected paternal descent than choreic cases.⁴

With respect to the sex of the transmitting parent, the proportion of rigid cases has been shown to decrease linearly with advancing paternal age and to increase linearly with advancing maternal age.⁵ Such unusual effects underline the need to explore further the role of the affected parent in predisposing offspring with the abnormal gene to the triad of rigidity, hypokinesia, and tremor. A multivariate study was therefore designed to elucidate the factors associated with the type of neurological sign displayed by patients with Huntington's disease,

Received for publication 26 May 1979

recognising that many are correlated and not readily separable.

Material and methods

To obtain a representative sample, it was necessary to acquire patients with the rigid-hypokinetic or Westphal variant of Huntington's disease,¹ as well as the more common choreic form. Since rigid cases usually have an earlier onset age and a poorer prognosis than choreic cases,⁴ and since there is significant parent-offspring correlation with respect to clinical signs,⁶ the following ascertainment procedure was adopted.

Patients were included in the study if they were members of a sibship containing one or more persons whose symptoms became manifest before the age of 20 years and suitable details were available for their affected parent. The information required for entry was:

Offspring: (1) sex, (2) birth rank, (3) neurological sign (presence or absence of rigidity), (4) age at onset of symptoms.

Affected parent: (5) sex, (6) neurological sign, (7) order of symptomatology, (8) age at onset, (9) age at birth of subsequently affected offspring.

The number of Australian cases meeting these nine requirements was too small for statistical purposes so recourse was made to the material assembled from

a survey of world publications described by Brackenridge and Chamberlin.⁷

Cases for which all the information was available were entered into a linear stepwise discriminant analysis, with the generalised measure V of Rao as selection criterion, in which the significance of each of the predictive variables in explaining the amount of variation associated with the neurological sign was assessed. From variables (8) and (9), three further measures were derived. These were age of affected mother and age of affected father at the birth of a subsequently affected child and the interval factor, defined as the period in years elapsing between such a birth and the appearance of symptoms in the parent. The latter has been shown to be a significant determinant of onset age among Australian offspring.^{8,9}

Results

To determine the variables that differentiate best between the characteristics associated with the two neurological signs, the patients with Huntington's disease were grouped according to the presence or absence of rigidity for a discriminant analysis. Those variables selected as the best discriminants were entered in stepwise fashion. In this way affected parental sex, neurological sign of parent, parental onset age, birth rank and sex of patient, affected paternal age at birth of patient, and order of appearance of symptoms in the affected parent were successively added. The remaining variables made a negligible contribution.

Table 1 summarises the results obtained from a forward selection analysis for the first three discriminators. All were affected parental factors: sex, neurological sign, and onset age. The change in V is approximately distributed as χ^2_1 and, by this criterion, there was a large gap in discriminating power between the first two and the third. Thus, only sex and neurological sign warranted further examination as affected parental determinants.

TABLE 1 Discriminant analysis of 3 affected parental factors

Step	Variable entered	V	Change in V	p
1	Affected parental sex	8.71	8.71	0.003
2	Parental sign	17.03	8.33	0.004
3	Parental onset age	17.21	0.19	0.667

The joint distribution of sex and sign of affected parent and sign of 351 patients is presented in table 2. From these data the following conclusions can be drawn.

- (1) For rigid fathers, 67% of offspring were rigid, while for rigid mothers 57% were rigid; this difference is not significant ($p > 0.8$).
- (2) For non-rigid fathers, 35% of offspring were rigid, while for non-rigid mothers 13% were rigid; this difference is highly significant ($p < 0.0001$).

Alternatively, from the viewpoint of the offspring:

- (3) 67% of rigid patients had a rigid father and 35% had a non-rigid father; this difference is significant ($p < 0.009$).
- (4) 57% of rigid patients had a rigid mother and 13% had a non-rigid mother; this difference is highly significant ($p < 0.0002$).

TABLE 2 Joint distribution of neurological sign in parent and offspring with affected parental sex

Offspring rigidity	Parental rigidity			
	Present		Absent	
	Father	Mother	Father	Mother
Present	14	8	77	12
Absent	7	6	143	84
Totals	21	14	220	96

A first analysis of table 2 by the method of Mantel and Haenszel¹⁰ led to a continuity-corrected summary χ^2_1 value of 19.12, which indicates a significant association between offspring and parental sign after adjusting for the effect of parental sex. The computed relative risk of 4.98 implies that the risk of a patient manifesting rigidity is about five times as great for those with rigid parents as it is for those with non-rigid parents.

A second analysis of table 2 led to a χ^2_1 value of 15.11 which indicates a significant association between offspring sign and affected parental sex after adjusting for parental sign. The relative risk of 3.25 implies that the risk of a patient manifesting rigidity is more than three times as great for those with affected fathers as it is for those with affected mothers.

Thus, both the discriminant analysis and the Mantel-Haenszel method lead to the same major conclusion that, of the variables examined, the sex and neurological sign displayed by the affected parent are independently the two most significant factors associated with the presence of rigidity in patients with Huntington's disease.

Discussion

The neurological sign of chorea or rigidity has previously been shown to be associated with the order of appearance of neurological and psychiatric

symptoms and with the sex of the affected parent, but not with the sex of the patient.⁵ The major methodological problem in investigations of this type is to separate the variables into those which are basic and independent determinants of the factor being examined and those which are involved indirectly through correlation. Several statistical procedures have been developed to deal with this situation and, of these, two have been employed in the present context. The first is an adaptation of discriminant analysis, as discussed by Mayo *et al.*,¹¹ and the second is the Mantel-Haenszel method. The former has been used here to determine which of ten variables are basic and which are secondary through correlation. The latter has been used to confirm the significant primary association of two variables (parental sex and sign) and endorse their joint independence.

The parental sign of muscular rigidity or choreo-athetosis has not previously been shown to determine the presenting neurological sign in offspring. The familial component of this factor is apparent from the observation that 63% of rigid patients had a rigid parent and 72% of choreic patients had a choreic parent. In epidemiological terms, this is equivalent to the finding of a fivefold risk that a rigid parent will have rigid offspring compared with a choreic parent.

It is well recognised that the sex of the transmitting parent exerts a strong influence on the natural history of Huntington's disease in offspring; some aspects studied include early onset¹² and age at death.¹³ The present study suggests that effects previously associated with factors such as parental onset age¹⁴ are probably ultimately attributable to affected parental sex. If this is so, it has practical implications. Measures seeking to delay the age at onset of the disorder in a parent in the interests of an unborn child will be futile if parental sex is the prime determinant of an adverse effect. In addition, the present observation that, on average, 35% of the progeny of fathers not displaying rigidity during their illness will themselves be rigid, whereas only 13% will be so affected if their mothers do not display

rigidity, might be relevant to the treatment of offspring with suspected prodromal symptoms.

References

- ¹ Bruyn GW. The Westphal variant and juvenile type of Huntington's chorea. In: Barbeau A, Brunette JR, eds. *Progress in neuro-genetics*. vol 1. Amsterdam: Excerpta Medica, 1969:666-73.
- ² Dom R, Baro F, Brucher JM. A cytometric study of the putamen in different types of Huntington's chorea. *Adv Neurol* 1973;1:369-85.
- ³ Oepen H. Discordant features of monozygotic twin sisters with Huntington's chorea. *Adv Neurol* 1973;1:199-201.
- ⁴ Brackenridge CJ. The relation of sex of affected parent to the age at onset of Huntington's disease. *J Med Genet* 1973;10:333-6.
- ⁵ Brackenridge CJ. Relation of parental age to rigidity in Huntington's disease. *J Med Genet* 1974;11:136-40.
- ⁶ Brackenridge CJ. Familial correlations for age at onset and age at death in Huntington's disease. *J Med Genet* 1972;9:23-32.
- ⁷ Brackenridge CJ, Chamberlin M. The relation of the sex of choreic and rigid subjects to the age at onset of Huntington's disease. *Clin Genet* 1974;5:248-53.
- ⁸ Brackenridge CJ, Teltscher B. Estimation of the age at onset of Huntington's disease from factors associated with the affected parent. *J Med Genet* 1975;12:64-9.
- ⁹ Brackenridge CJ. Validation and application of an interval factor in estimating age at onset of Huntington's disease. *J Med Genet* 1978;15:23-6.
- ¹⁰ Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
- ¹¹ Mayo O, Murdoch JL, Hancock TW. On the estimation of parental age effects on mutation. *Ann Hum Genet* 1976;39:427-31.
- ¹² Merritt AD, Conneally PM, Rahman NF, Drew AL. Juvenile Huntington's chorea. In: Barbeau A, Brunette JR, eds. *Progress in neuro-genetics*. vol 1. Amsterdam: Excerpta Medica, 1969:645-50.
- ¹³ Bird ED, Caro AJ, Pilling JB. A sex related factor in the inheritance of Huntington's chorea. *Ann Hum Genet* 1974;37:255-60.
- ¹⁴ Brackenridge CJ. The relation of some features of Huntington's disease to the age at onset of symptoms in parents. *Clin Genet* 1972;3:477-82.

Requests for reprints to Dr C J Brackenridge, National Research Institute of Gerontology and Geriatric Medicine, Mount Royal Hospital, Parkville, Victoria 3052, Australia.