Genetic Heterogeneity for Dystrophia Myotonica

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The analogy of the haemoglobinopathies suggests that at any gene locus there may be numerous different mutations which will have varied clinical effects. Also, there are now a number of examples in medicine of clinically similar conditions which may be caused by mutations at more than one locus. Genetic heterogeneity is likely to be the rule rather than the exception.

It is, however, difficult to recognize that there is more than one genetic variant of a condition which, even within families, has such a varied clinical manifestation and age of onset as dystrophia myotonica. Nevertheless, in a recent study of 40 index patients and their families (Bundey, Carter, and Soothill, 1970; Renwick *et al*, 1971) there were indications from intra-familial resemblance in age of onset of the disease that there are at least 2 variants, though both are dominant conditions. The evidence is given in this paper.

Material and Methods

The index patients were a consecutive series of 8 patients from The Hospital for Sick Children attending from 1951 to 1968, and 32 patients from The National Hospital for Nervous Diseases between 1947 and 1967. These 40 index patients belong to 36 families. In the single instance of 2 sibs both being index patients at The National Hospital (family 3) it is dubious whether their attendances there were independent events. Accordingly, only the 2nd sib has been counted as an index patient in the calculations of correlations between relatives which are therefore based on 39 index patients. The patients and their first-degree relatives were visited and examined in their own homes. Many of them also attended The National Hospital for special investigation (Bundey *et al*, 1970).

We realize that the age of onset of symptoms may be difficult to determine accurately. Where a patient could date the onset of muscle weakness or myotonia, this has been accepted. Where a patient could only say that symptoms had been present 'for many years' or 'for a long time' without further clarification, his age of onset has been graded as uncertain and has not been

used in the analysis. In a number of instances, a relative was only diagnosed as being affected during a search for heterozygotes in a family study (Bundey *et al*, 1970). Where clinical myotonia was detected, this has been accepted as a symptom dated from the time of examination, as all patients were aware of the myotonia although they did not complain of it. In other cases, heterozygous relatives had no symptoms, but characteristic dystrophic lenticular opacities were detected in them by slit-lamp examination. For such individuals we arbitrarily assumed symptoms would occur 5 years later.

Results

The ages of onset in the 39 index patients range from the 1st to the 60th year.

Sibs. 19 index patients had at least 1 affected sib; but in 3 of these sibs the age of onset was not known. The age of onset in 18 index patients and their 25 affected sibs is shown in Table I and the comparison of age of onset in index patient and sib is shown in Fig. 1. The correlation for age of

FIG. 1. Comparison of age of onset in index patient and sibs.

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TABLE I
AGE OF ONSET IN DYSTROPHIA MYOTONICA IN THESE FAMILIES WITH TWO OR MORE AFFECTED MEMBERS WHERE AGE OF ONSET IS KNOWN

Number of Family		Generation	Age of Onset in Affected Sibs (yr)	No. of Unaffected Sibs	Age of Onset (yr) in Affected Parent		Other Affected Relatives where Age of Onset Known	
Bundey <i>et al</i> (1970)	Renwick <i>et al</i> (1971)				Mother	Father	Relative	Age of Onset (yr)
4	2	II	< 1	0	?(d)			
7	6	II	? < 1	1	?			
—	35	III	< 1	2	35			
—	36	IV	< 1	0	?		Mother's sister's daughter	< 1
1	1	II	22 14	1			Maternal half-sib	3
6	5	II	< 1	1	22			
23	17	III	5	2	18			
9	8	III	9 9	2	25			
3	3	II	19 (54)	1	24			
		III	10 11	0		(54)		
		III	11 (19)	0		19		
2	4	II	26 21	0	?			
		III	14 12	0				
36	26	III	18	2	21	15		
10	9	II	40 55	2				
		III	41 13	2	40			
41	189	II	38 44 50 24 (72)	9				
		III	5	2	24			
		III	16	1		38		
8	7	III	33 (65)	0			Maternal cousin	57
		IV	31	1	33			
		IV	27	1		(65)	Father's sister's son	16
14	10	III	44 32	0	66		Mother's brother's son	25
15	11	II	32 27	1		?		
22	16	II	50 34	4		?		
30	20	III	22 38	2		?		
31	21	II	29 32	1	?			
		III	22	2		32		
32	22	II	48 29 22 38 39	2				
34	24	II	(74) 38	2				
40	29	II	20	1	(65)			
43	32	II	60 55	6				
		III	(36) (32)	2		55		
45	34	II	51 50	1		70		
		III	(27)		50			
38	27	III	33 36	4	?			
		III	30 ? 26		?			
		IV	< 1	0		26		

Index patients are given in italics; the age of onset estimated from lenticular opacities is given in parentheses.

onset (with 95% confidence limits, using Fisher's 'z' transformation) in index patient and affected sib is shown in Table II. The overall correlation for age of onset in index patient and sib was 0.81 with 95% confidence limits of 0.62 to 0.91.

Parents and Children. 23 index patients had a parent who was known (either from examination or documented medical history) to be affected and in 11 of these the age of onset could be assessed with reasonable accuracy. In addition, 3 index patients had 1 affected child and 2 had 2 affected children. The ages of onset are shown in Table I, the comparisons of age of onset in Fig. 2, and the correlations for age of onset in Table II. The correlation of age of onset in index patient and parent is 0.80 (with confidence limits of 0.39 to 0.95), and in index patient and child 0.84 (with confidence limits 0.25 to 0.98).

Discussion

The high correlation of age of onset in pairs of affected relatives suggests that the patients were affected by more than one type of mutant gene. Polygenic factors modifying the age of onset of a dominant condition determined by a single mutant gene would tend to give a correlation of 0.5 between both sib and sib and parent and child. An effect of variation in the homologous 'normal' gene on the other member of the chromosome pair on age of onset would (as noted by Penrose, 1947-1949) tend to give a zero correlation between parent and child and one of 0.5 between sib and sib. However the presence of 2 or more different mutant genes both causing the disease, but with widely differing ages of onset would tend to give a high correlation of up to 1.0 between both sib and sib and parent and child (Haldane, 1941). The observed correlations between index patient and sib, index patient and

TABLE II
CORRELATION COEFFICIENTS OF AGE OF ONSET OF
DYSTROPHIA MYOTONICA

	Number of Comparisons	Correlation Coefficient (with 95% confidence limits)
<i>Sib and index patient</i> All pairs	25	0.81 (0.62-0.91)
Excluding pairs where index patient developed symptoms in infancy	21	0.64 (0.28-0.84)
Excluding pairs where index patient developed symptoms under 20 years	17	0.45 (-0.04-0.76)
<i>Parent and index patient</i> All pairs	11	0.80 (0.39-0.95)
<i>Child and index patient</i> All pairs	7	0.84 (0.25-0.98)

FIG. 2. Comparison of age of onset in index patient and parent (P) and index patient and child (C).

parent, and index patient and child (0.81, 0.80, and 0.84 respectively) are all well above 0.5, though only significantly so in the case of the sib-sib comparison. It is unlikely that common family environment would raise a genotypic correlation of 0.5 to a phenotypic correlation of 0.8. The high correlations observed therefore fit best the hypothesis that 2 or more mutant genes may cause dystrophia myotonica.

Detailed observation of the resemblances between sibs suggest that an infantile onset and an adult onset form of the disease are genetically distinct. Inspection of the sib resemblances and age of onset in Fig. 1 and Table I show a compact group

of 4 instances (in 3 sibships) where both index patient and sib had an onset of the disease in infancy. In contrast, where the index patient's age of onset is over 20 years the age of onset in an affected sib was always over the age of 20 years. There is also a suggestion from the resemblance of sibs that there is a small intermediate group with onset usually after an age of 4 years, but before the age of 20 years. If the infantile group is excluded the sib-sib correlation becomes 0.64 (confidence limits 0.28 to 0.84) which is still above 0.5 but not significantly so. If the intermediate group is also removed the correlation becomes 0.45 (confidence limits -0.04 to 0.76), which is close to 0.5.

If the families were followed into the future these correlations would be somewhat modified by the appearance of the disease in some of the relatives who at present are unaffected. However, the expected occurrence of 50% affected relatives has already been reached for the sibs of the index patients with infantile onset (5 affected out of 9 sibs) and intermediate onset (4 out of 8 sibs). The 4 surviving sibs of cases of infantile onset are aged 18 to 31 years, and the 4 surviving sibs of cases of intermediate onset are aged 18 to 44 years. Among the sibs of index patients with onset after the age of 20 years, only 9 of 27 survivors are so far affected, but the development of disease in, say, a further 4 or 5 of these, would not substantially affect the correlation, since the ages of the surviving sibs in this group range from 32 to 60 years.

The comparison of ages of onset in affected parents and children also suggest the existence of at least 2 mutant genes and provide more information on the range of variation of age of onset in each form of the disease. The age of onset in the parents of index patients will be much influenced by the fact

that a patient with early onset is not likely to reproduce, especially as early onset patients are usually mentally retarded (see Fig. 1). The age of onset in affected parents therefore will give the best guide to the latest onset of each genetic variety of the disease. All 5 index patients with onset in infancy had an affected parent and in each case this was the mother. In 2 of these the age of onset could be accurately assessed, 22 and 35 years respectively. Of the other 3 mothers, 1 died at age 37 years; 1 was living abroad, aged 34 years, and was known to be mentally slow and to have had symptoms for some years; 1 was aged 55 years and too mentally retarded to be able to give an account of her illness. Four of the index patients with age of onset after the age of 20 years had an affected parent with a known age of onset, and in each the onset was after the age of 60 years.

In contrast to affected parents the children of index patients who are found to be affected will tend to be selected for early onset (see Fig. 1). These children give the best guide to the earliest onset of any particular genetic variety of the disease. There were 3 children with onset at 5, 9, and 9 years of age who were the offspring of index patients with age of onset over the age of 20 years. However, these 2 families may be examples of the condition caused by the postulated third gene giving an intermediate age of onset since the index patients (mothers) had an onset of disease at only 25 and 24 years respectively.

If these latter families were followed into the future the correlation would be somewhat modified by the appearance of the disease in some children at present unaffected. However, already 7 of 17 children of index patients are affected.

Some further information is provided by second- and third-degree relatives. One index patient with infantile onset (pedigree DM1B1, Renwick *et al*, 1971) had a maternal half-sib affected with onset at 3 years and a mother's brother affected with age of onset 14 years; another index patient with infantile onset (pedigree DM136) had a cousin (mother's sister's child) with onset in the 1st year; the mother's sister was mentally retarded so that the age of onset could not be assessed, but was probably early. A mother's mother's brother in this family was also affected with age of onset uncertain.

Summarizing the information from relatives, there is a strong indication that at least 2 mutant genes may cause dystrophonia myotonica. The first usually causes an onset in heterozygotes in infancy but the onset may be as late as the 3rd or 4th decade. The second rarely causes an onset before the age of 20 years and may be not until the 6th or 7th

decade. A possible third gene usually causes an onset between 4 years and 25 years. If the third gene exists, there would appear to be little overlap between the age of onset in the patients with the first 2 mutant genes, though 2 of the mothers of infantile cases are examples of overlap. The third variant overlaps the first form at one end of the range and the second form at the other end of the range of age of onset.

Mutation. It is perhaps surprising that there is no instance of fresh mutation among the 5 patients with infantile onset. We think that the explanation is that this form of the disease has only recently been recognized (Vanier, 1960). Most cases without an affected parent are not recognized, but diagnosed as having mental retardation with Moebius' syndrome, or just mental retardation (Thomassen, 1948; Calderon, 1966; B. Woods, personal communication, 1971).

Maternal Effects. In the whole series there were 12 patients with known onset in infancy who were born to 6 mothers and 1 father. The observation that the affected parent of an infantile-onset case is usually the mother was first made by Vanier in 1960 (4 of her examples are included here). Harper and Dyken (1972) have put forward the interesting and original hypothesis that there is a maternal intra-uterine effect resulting in early development of symptoms in offspring. However the explanation we prefer at present is that, as early-onset dystrophonia myotonica is commonly associated with mental changes, affected men are less likely to become fathers than affected women mothers. There is probably in addition a direct effect of the gene on fertility in men, in view of their occasional complaints of impotence, the clinical appearance of testicular atrophy, and the fact that the overall reduction in fertility in this disease cannot be explained by a failure to marry (Bundey *et al*, 1970). In the whole series the 13 female patients with onset under 30 had 24 children (excluding 4 index patients), of whom 3 developed symptoms in infancy. In contrast the 14 male patients with onset of symptoms under 30 had only 13 children, none index patients, of whom 1 developed symptoms in infancy.

Linkage. The largest contribution to the positive lod score in our series, indicating linkage to secretor locus, came from the infantile and intermediate onset families (Renwick *et al*, 1971). The families which in Mohr's analysis demonstrated linkage were mostly of intermediate and late onset

(Thomassen, 1948) and therefore there is no indication that the postulated different mutant genes for the infantile, intermediate, and late onset disease are not allelic. It must however be remembered that linkage can not prove allelism.

Genetic Counselling. The distinction between the first and second forms of the disease is of some practical importance in genetic counselling. For example, the 22-year-old sister of 3 boys with an infantile onset recently asked for information on genetic risks (family DM135 of Renwick *et al*, 1971). She had no symptoms or signs. If the condition is genetically unitary she could not be considered to have passed more than about one third of her lifetime risk of developing the disease. It is, however, likely that in this family the causative mutant gene is that which usually causes an early onset of the disease, so that the odds are high that the sister is not a heterozygote.

Summary

Heterogeneity for conditions due to mutant genes of large effect is likely to be the rule rather than the exception. Such heterogeneity may not be readily apparent for dominant conditions with very varied age of manifestation. However an analysis of within-family resemblances in age of onset of symptoms in a recently reported series of families with dystrophia myotonica indicates the existence of 2 or perhaps 3 different mutant genes which may cause the disease.

The overall correlation for age of onset in affected sibs and index patients, and in affected parents and children of index patients is greater than 0.5, significantly so in the case of sibs. It falls progressively closer to 0.5 for sibs if first the pairs where the index patients had an infantile onset, and then those with a childhood onset are excluded. It is suggested that one gene causes an onset usually in infancy, but occasionally after the age of 30 years. A second gene seldom causes an onset before the age of 20 years and sometimes an onset after the age of 60 years. A third mutant gene may exist causing an intermediate age of onset usually between the age of 4 years and 25 years.

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