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Genetic Study of Sample of 70 Patients with Myasthenia Gravis

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The role of genetic factors in the causation of myasthenia gravis is not clear. Oppenheim, as early as 1900, reported familial instances of myasthenia and suggested that genetic factors were involved. On the other hand, Ford in 1937 stated, 'there is never any familial or hereditary tendency in myasthenia gravis'. However, since then, there have been several reports of familial instances of myasthenia gravis (Rothbart, 1937; Osserman, 1958; Goulon *et al.*, 1960; Simpson, 1964; Greenberg, 1964), which have been the subject of several reviews (Celesia, 1965; Kurland and Alter, 1960). Storm-Mathison in 1961 (quoted by Herrmann, 1966) found two secondary cases of myasthenia gravis among the relatives of 88 patients, and Herrmann (1966) found 6 secondary cases among the relatives of 194 patients, but in neither of these surveys were figures given for the number of unaffected relatives. There does not appear to have been a report of any previous study where an attempt was made to determine the actual prevalence of myasthenia gravis among the relatives of affected individuals.

In the present study data were collected on maternal and paternal age, birth order, ABO and Rhesus blood groups, secretor status, and PTC tasting in patients with myasthenia gravis. The prevalence of the disease among the relatives of 70 patients was studied.

Subjects and Methods

Seventy patients who had been diagnosed at the Neurological Clinic of the Manchester Royal Infirmary as having myasthenia gravis were investigated. Only cases where the diagnosis was firmly established were included in the survey, and in none of these patients was there any evidence that the myasthenia was secondary to an associated malignancy. All the patients were interviewed personally and extensive family histories were taken. Information on a relative was considered 'reliable' if the relative was seen personally or if the information was provided by a physician, or the informant had seen the relative within the past 2 years. 'Reliable' information was obtained on 448 (33·6%) relatives of the 70 probands (Table I).

Maternal and paternal age effects were assessed according to the method of Penrose (1939) and the method of Haldane and Smith (1947) was used for the analysis of birth order.

ABO and Rhesus blood groups were determined in the Clinical Pathology Laboratory at Manchester Royal Infirmary by kind permission of Dr. J. E. MacIver, and the resulting data were compared with a control population obtained from the Manchester area. The values for secretor status were also assessed in the same laboratory, using standard methods, and the resulting proportion of non-secretors was compared with the proportion of non-secretors obtained from pooled data of several European populations (Race and Sanger, 1954).

The method of Harris and Kalmus (1949) was used to assess the ability to taste PTC. A class of university students was used as a control population.

Results

In the present study no familial case of myasthenia was found among any of the 448 relatives on whom 'reliable' information was available. Neither was there any consanguinity. Among the probands, 91% had developed the disease by the age of 60. Of these relatives on whom there was reliable information, 135 (32·3%) had reached the age of 60 but none had developed myasthenia gravis. The percentage distribution of the age of onset of the condition among the 70 probands is given in Fig. 1. In one family, a woman with myasthenia

TABLE I

RELATIVES IN WHOM 'RELIABLE' INFORMATION WAS AVAILABLE

Relative	Total	No. 'Reliable'	No. over 60	No. under 60
Parents	140	28	24	4
Offspring	95	89	0	89
Sibs	267	182	52	130
Step-sibs	14	10	1	9
Paternal sibs	162	29	16	13
Paternal step-sibs	6	4	4	0
Maternal sibs	195	47	38	9
Paternal cousins	189	18	0	18
Maternal cousins	265	41	0	41
Total	1333	448	135	313

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gravis had a son with congenital ptosis of the left eye, but there was no evidence that he had myasthenia. The mother first developed symptoms of myasthenia when her son was 11 years old. The son is now 20 years of age and is in good health.

With regard to maternal and paternal age effects, the mean maternal age of 43 patients was 29·6 years and that of their unaffected sibs was 31·1 years. The mean paternal age of the patients was 31·6 years and that of the unaffected sibs was 32·7 years. The differences are not significant. There would, therefore, appear to be no apparent parental age effect.

Following the method of Haldane and Smith (1947) for estimating the effect of birth order, in studies on 69 cases the difference between the mean total of the actual values of birth order (1302) and the mean total of the estimated values (1236) was not significant. There, therefore, appears to be no birth order effect.

The distribution of the A, O, and (AB+B) groups in the patients was compared with that of a normal population* from the same area (Table II). In all three categories there was no significant difference between the patients and the controls.

The distribution of the Rhesus blood groups in patients and in a control population of blood donors from the Manchester area is given in Table II. The difference between the patients and the control population is not significant.

The proportion of non-secretors among the patients with myasthenia gravis (7/21 or 33·3%) was not significantly different from the proportion found in several populations of healthy Europeans: 542/2858 or 23·8% (Race and Sanger, 1954).

Tests for PTC tasting were carried out on 50 patients and compared with the finding in 50 controls. The threshold values were corrected for age, as suggested by Harris and Kalmus (1949). 70% of the controls and 74% of the patients were tasters. The difference between the two groups was not significant.

Discussion

The distribution of the age of onset in this particular sample of patients is in agreement with the observations of Schwab and Leland (1953), that the age of onset in females tends to occur in the earlier decades and that of males in the later decades. In this study in no decade was the difference in the age of onset of male and female cases significant. The distribution of the age of onset in the present study differs from the findings in some earlier studies (Schwab and Leland, 1953; Osserman, 1958; Garland and Clark, 1956). The significantly greater proportion of patients with onset in the sixth or subsequent decades in the series of Osserman (1958) and Schwab and Leland (1953) might be due to the inclusion of cases in which the myasthenic syndrome was secondary to bronchogenic carcinoma (Lambert, Okihiro, and Rooke, 1964). The greater proportion of younger patients in two of the studies (Osserman, 1958; Schwab and Leland, 1953) may be due to several factors: (a) to bias in selection of sample due to the interest of the physician in juvenile cases, (b) to the incorporation in the study of neonatal cases of myasthenia gravis, and (c) to the inclusion of familial cases of myasthenia, which tend to have an earlier age of onset.

There have been many reports of familial cases of

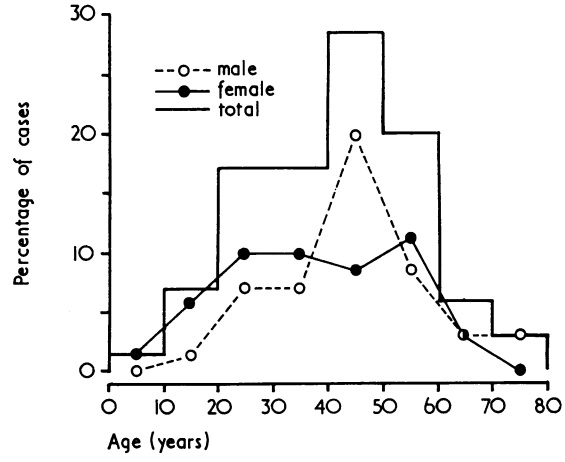

FIG. 1. Percentage distribution of age of onset among 70 probands studied.

TABLE II

DISTRIBUTION OF ABO AND RHESUS BLOOD GROUPS AMONG 39 PATIENTS WITH MYASTHENIA GRAVIS AND A CONTROL POPULATION

	Group			Total
	A	O	AB+B	
Patients	18 (46·1%)	15 (38·5%)	6 (15·4%)	39
Controls	3775 (40·3%)	4532 (48·4%)	1063 (11·3%)	9370

	Rh+	Rh−	Total
Patients	36 (92·3%)	3 (7·7%)	39
Controls	22,570 (81·4%)	5158 (18·6%)	27,728

* Figures for the ABO distribution in the Manchester area were kindly supplied by Dr. F. Stratton of the National Blood Transfusion Unit, Manchester. Figures for the Rhesus distribution in the Manchester area were kindly supplied by Dr. Ada Copec, Serological Genetics Laboratory, London E.C.4.

myasthenia gravis (see Appendix). Fig. 2 gives the distribution of the age of onset in these familial cases. Using the Wilcoxon-Mann Whitney non-parametric U test the distribution was found to be significantly different from that of our non-familial sample (Fig. 1). This suggests that the familial and non-familial forms of myasthenia

FIG. 2. Percentage distribution of age of onset among 69 familial cases of myasthenia gravis from the literature, where the age of onset has been clearly stated.

gravis might be different entities, the familial form having an earlier age of onset. No significant difference was found between the age of onset distribution of cases in which the condition appeared to be inherited as an autosomal dominant trait, and the distribution of those cases which appeared to be inherited as an autosomal recessive trait. The presentation of the reports of 'familial' myasthenia gravis in the literature was found to be inadequate for genetic analysis, which was also the conclusion of Kurland and Alter (1960).

There have been several reports of myasthenia gravis being associated with a variety of thyroid disorders, including non-toxic nodular goitre with lymphoid infiltration (Ringhertz, 1951), hyperthyroidism (Cohen and King, 1932; McEarhern and Parnell, 1948; Millikan and Haines, 1953), Hashimoto's disease (Simpson, 1964; Daly and Jackson, 1964; Becker *et al.*, 1964), and hypothyroidism (Feinberg, Underdahl, and Eaton, 1957). Patients with thyroid disorders often have a PTC threshold which differs from that found in normal persons (Kitchin *et al.*, 1959; Harris and Kalmus, 1949; Harris, Kalmus, and Trotter, 1949; Fraser, 1961). In the present study, however, no association was found between the ability to taste PTC and myasthenia gravis.

Summary

In the present study of 70 patients with myasthenia gravis no secondary cases of this disease were found among 448 relatives on whom there was reliable information. No maternal or paternal age effect was shown and no association was found between myasthenia gravis and the ABO and Rhesus blood groups, secretor status, or the ability to taste PTC. The age of onset distribution of this 'non familial' sample was found to be significantly different from that of familial cases taken from the literature.

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Appendix

Analysis of 69 Reported Cases of Familial Myasthenia Gravis

(Cases have been included only where Age of Onset was clearly stated)

DZ = dizygotic twin; MZ = monozygotic twin; Congenital cases scored as O; NI = No *clear* information in literature.

A: SIBS ONLY AFFECTED

Author	Sex of Proband	Age at Onset	Affected Sibs	Normal Sibs	Age at Onset
Marinesco (1908)	Female	29	1 F	NI	16
Hart (1927)	Female	14	1 F	NI	9
Rothbart (1937)	Male	0	3 M	2 M	0 2 0
Riley and Frocht (1943)	Female	11	1 F	3 F 3 M	8
Mancusi-Ungaro (1945)	Female	28	1 F	NI	18
Eaton (1947)	Male	0	1 M	NI	0
Bornstein (1953)	Male	7	1 M	NI	5
Macrae (1954)	Female	1	1 M	4 M (died at early age)	0
Osserman (1958)	Female	0	1 M	3 F	0
Osserman (1958)	Male		1 F	NI	26
Walsh and Hoyt (1959)	Male	1½	3 M	NI	0 0 1
Goulon *et al.* (1960)	Female	21	1 F	NI	15
Greenberg (1964)	Female	19	1 F	NI	40
Simpson (1964)	Female	0	1 F	None	0
Celesia (1965)	Female	21	1 M	NI	8
Herrmann (1966)	Male	1	1 F	2 M	3*
Herrmann (1966)	Male	30	1 M	1 F	36
Adler (1966)	Female	16	1 MZ F	NI	18
Osborne and Simcock (1966)	Female	23	1 MZ F	NI	25

B: AFFECTION IN PARENT AND OFFSPRING OR SOME DISTANT RELATIVE

Author	Sex	Age at Onset	Affected Sibs	Normal Sibs	Age at Onset	Parent Affected	Other Relation Affected	Age at Onset
Peters (1906)	Female	NI	1 F 2 M	1 M	NI 44 18	1 M	NI	NI
Noyes (1930)	Female	55	1 M	NI	60	1 M	NI	NI
Bowman (1948)	Male	3½	None	2 M		None	1 F (maternal cousin)	4
Levin (1949)	Female	0	1 M	None	0	None	2 (sex not given) 1st cousins	0 0
Osserman (1958)	Male	2	None	None		1 F	NI	NI
Osserman (1958)	Female	7	None	None		None	1 F (paternal cousin)	0
Osserman (1958)	Female	0	1 M	1 DZ M 1 M	0	None	1 M (maternal cousin)	11†
Foldes and McNall (1960)	Female	27	1 F	None	37	1 M	None	17
Simpson (1964)	Female	22	None	5		None	1 M (1st cousin once removed)	NI
Herrmann (1966)	Female	67	None	NI		None	1 F (half-brother's daughter)	30's
Herrmann (1966)	Female	55	None	NI		None	1 M (2nd cousin)	71
Herrmann (1966)	Female	51	None	NI		None	1 F (maternal aunt's daughter)	77
Herrmann (1966)	Male	8½	None	NI		1 M	None	26

* May have had drooping of eyelids at 3 but generalized weakness definitely established by 6.
† Parents were first cousins.