

Short report

Familial myasthenia gravis

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SUMMARY A family is reported in which myasthenia gravis and thyroid disease occur over three generations. The grandmother and granddaughter have ocular myasthenia and an aunt in the second generation had generalised myasthenia gravis with a thymoma. The pattern of histocompatibility antigens (HLA) haplotypes, anti-AChR antibodies, anti-striate muscle antibodies and thyroid disease is described. The haplotype HLA-A1, B8 was found in affected members of the first and third generation but the family study showed that this was not the same haplotype because the HLA-A1, B8 haplotype in the third generation was contributed by an unaffected person marrying into the family in the second generation.

Familial myasthenia gravis is rare and was first reported in two sisters by Oppenheim in 1900.¹ Herrmann² found six secondary cases in the relatives of 194 cases. Jacob *et al*³ could not find any secondary cases in 448 relatives of 70 patients with myasthenia gravis but they traced 32 reports of familial myasthenia gravis in the literature. Bunday⁴ also reviewed these families and added three more from her own survey of 58 index cases. These two genetic surveys have fully analysed the previous reports of familial myasthenia gravis; the disease may occur in siblings, parents and children and first cousins but does not follow any clear-cut mode of inheritance. The clinical features of familial myasthenia gravis are similar to the sporadic form of the disease and there is an association with other autoimmune diseases but not with thymoma.

The association between myasthenia gravis and certain histocompatibility (HLA) antigens has been demonstrated on many occasions.⁵⁻⁸ There is a strong association between myasthenia gravis and HLA-B8 especially when the disease starts under the age of 40 years and when there is no underlying thymoma. The presence of serum anti-acetylcholine

receptor (anti-AChR) antibodies and other autoantibodies strongly supports earlier suggestions⁹ that myasthenia gravis is an autoimmune disease. The association with thyroid disease has been noted in some familial cases^{3 6 10} and an association between female patients and HLA-B8, antithyroid antibodies and antinuclear antibody has been reported.⁸ The relationship between familial myasthenia gravis, HLA-B8, anti-AChR-antibody and thyroid disease is complex. This is illustrated by the family discussed in this paper which includes three generations and three female patients with different types of myasthenia gravis.

The Family

The index case (fig A, Case I) is the grandmother of case III and both have ocular myasthenia; the mother of case III did not have myasthenia gravis but her cousin (Case II) had generalised myasthenia gravis with a thymoma. Cases I and III and five unaffected relatives were HLA typed and tested for anti-AChR antibody and anti-skeletal muscle antibody. Case II died in 1979, full clinical details were available but HLA typing and measurement of anti-AChR antibody level were not performed. Cases I and II and two other female relatives had histories of hypothyroidism. No consanguinity was present in the family.

Case I An 85-year-old lady presented with a 6 month history of difficulty with vision and increasing tiredness. Hypothyroidism had been diagnosed 10 years previously and she had subsequently been taking 0.1 mg of thyroxine

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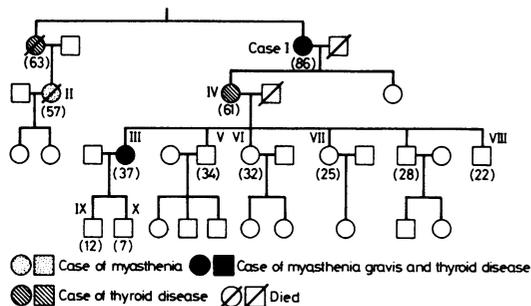


Fig A The family tree

daily. On examination she had bilateral ptosis and was unable to look upwards. No goitre was palpable, and examination of her muscle power in the limbs revealed no abnormality. Routine investigations including a chest radiograph were normal. Anti-skeletal muscle antibodies were detected but anti-AChR antibodies were negative on two occasions. Intravenous saline produced no benefit, but 10 mg of intravenous edrophonium (Tensilon) produced a dramatic response abolishing the eye signs. This improvement has been maintained on oral neostigmine. During 12 months of follow-up there has been no evidence of an underlying malignancy.

Case II The niece of the previous case developed myasthenia gravis affecting the ocular and bulbar muscles at the age of 50 years. Investigations revealed positive anti-skeletal muscle antibodies, and a positive Tensilon test consistent with myasthenia gravis. One year later she developed a thymoma which was removed but her weakness became generalised and she died at the age of 57 years.

Case III The granddaughter of case I developed diplopia and ptosis at the age of 35 years; a Tensilon test, anti-AChR, anti-parietal cell and anti-thyroid microsome antibodies were all positive. She developed hypothyroidism as a teenager. Her myasthenia has been well controlled on anti-cholinesterase drugs over the past 2 years.

It is worth noting that two other members of the family (see fig A) have also had a history of hypothyroidism.

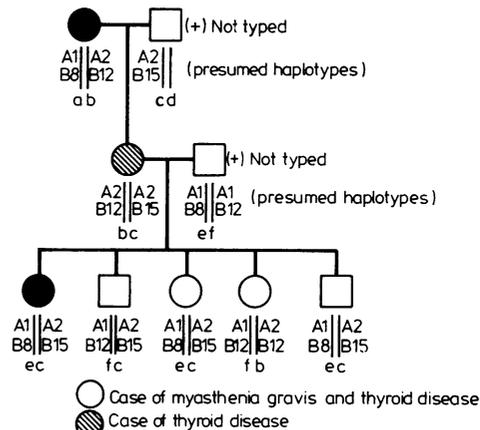


Fig B HLA haplotypes

Results

The index case, case III and five of their relatives were HLA-typed and also their titres of anti-AChR antibodies were measured. Two other relatives (that is great-grandchildren of case I) also had their anti-AChR antibodies measured. HLA haplotypes and their segregation are shown in fig B, and the anti-AChR antibody levels in the table.

Discussion

There are three differences between the family we report and the previous reports of familial myasthenia gravis. The onset in the ninth decade is unusual even in sporadic cases and has not been reported in familial myasthenia gravis. The presence of the disease in three generations is most unusual and previous reports are confined to one or two generations affecting siblings, parent-offspring or first cousins.^{3 4 11} The usual pattern of familial myasthenia gravis is that of the non-thymoma generalised type or the ocular type and there have been no

Table Anti-acetylcholine receptor antibody levels

Subject	Age (yr)	Anti-AChR antibody level (normal < 4 units)	Other antibodies detected*
Case I (Index case)	86	0	ASkA, AThA
Case II (Niece)	50	—	ASkA
Case III (Granddaughter)	37	30	AThA
Case IV (Daughter)	61	2	
Case V (Grandson)	34	0	
Case VI (Granddaughter)	32	0	
Case VII (Granddaughter)	25	0	
Case VIII (Grandson)	22	2	
Case IX (Great-grandson)	12	0	
Case X (Great-grandson)	7	1	

*ASkA—Anti-skeletal muscle antibodies.
AThA—Anti-thyroid microsome antibodies.

reports of thymomas in familial cases, as found in case II of this family.

Cases I and III possess the haplotype HLA-A1, B8 and the association of myasthenia gravis with these antigens is now well documented.⁵⁻⁸ Dick *et al*¹² found that the inheritance of HLA-B8 did not absolutely correlate with the development of myasthenia gravis and relatives with HLA-B8 did not develop the disease. Furthermore some cases of myasthenia gravis did not carry the HLA-B8 haplotype. In a report¹³ of two identical twin sisters, homozygous for HLA-B8, it was found that only one of the twins had the disease. In the present family it is of interest that the HLA-B8 haplotype found in case III was not inherited via the maternal side from the affected grandmother (case I) but from the non-affected paternal side of her family. In addition case III has a brother and a sister who carry HLA-A1, B8 and do not have myasthenia gravis.

A wide variety of autoimmune diseases and auto-antibodies have been found in patients and their relatives.^{6,10} Anti-AChR antibodies are the most important as they are directly involved in the pathogenesis of myasthenia gravis and relate to disease activity. Anti-thyroid antibodies and anti-nuclear antibodies have been associated with the younger female patients with the HLA-B8 antigen.⁸ The distribution of antibodies in the present family is shown in the table; the overall pattern is in keeping with present knowledge; for example case II had a high level of anti-skeletal muscle antibodies and a thymoma, and anti-AChR antibodies may be absent in 25% of cases of ocular myasthenia gravis⁴ (Case I). There are four members of the family with thyroid disease including case I and III and it is noteworthy that in the second generation the mother of case III appears to transmit the thyroid disease but not myasthenia gravis.

This family study shows that familial myasthenia gravis may have a more diverse age of onset and clinical pattern than previously thought. It demonstrates the relationship between myasthenia gravis, HLA-A1, B8, autoantibodies and thyroid disease but also confirms that the inheritance of HLA-A1, B8 from an affected relative is not a necessary precursor to the development of myasthenia gravis as

this family did not pass the *same* HLA haplotype through three generations.

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