Familial autoimmune myasthenia gravis: report of four families

A Evoli, A P Batocchi, G Zelano, A Uncini, M T Palmisani, P Tonali

Abstract
Four families each with two patients with autoimmune myasthenia gravis or related conditions are reported. All clinical forms of myasthenia gravis were represented and different disease types were found within the same family. Either one or two generations could be affected and no association with a single HLA haplotype was found. The frequency of familial autoimmune myasthenia gravis is very low and the genetic factors involved seem to be different from MHC genes.

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Myasthenia gravis is generally sporadic. The frequency of familial cases is not well defined. It has been reported as between 3% and 5%, but the real rate is probably lower as, before the diagnostic use of anti-acetylcholine receptor antibody (anti-AChR ab) assay, genetically determined cases could have been erroneously included. Studies have established that MHC genes play a major part in the development of some autoimmune disorders, but their relevance in susceptibility to myasthenia gravis is uncertain and, at present, under discussion.

Myasthenia gravis is often associated with other autoimmune diseases and up to 30% of patients have a positive family history of autoimmunity. This finding suggests hereditary factors predisposing to autoimmunity. The familial occurrence of myasthenia gravis could be related to the transmission of HLA alleles. For this reason, family studies could be important to clarify the contribution of these genetic factors to the aetiology of the disease.

We describe four Italian families each with two patients with myasthenia gravis or related conditions.

Methods
The diagnosis of myasthenia gravis was based on typical history and signs, positive responses to the edrophonium test, supra-maximal repetitive nerve stimulation (SRNS) (>11% decrement at the 3rd to 5th stimulus), and increased serum anti-AChR ab concentrations (>0.8 nM). In a patient with negative results on SRNS, single fibre EMG was performed.

HLA class I and II antigens were determined, with the standard lymphocyte cytoxicity test, in all patients and some relatives. Molecular analysis of DQ alleles was performed in all patients with myasthenia gravis. DQA1 alleles were identified by DNA amplification followed by hybridisation with allele specific oligonucleotide probes (ASO-PCR); DQB1 alleles were determined by a polymerase chain reaction-restriction fragment length polymorphism method. There was no parents’ consanguinity in any of the families.

Family report
FAMILY 1
Two sisters developed severe generalised myasthenia gravis at the ages of 15 and 19. They are also affected with epilepsy and one has psychosis. An edrophonium test and SRNS were positive and anti-AChR ab titre was >300 nM in both. One sister underwent thymectomy at the age of 22 with removal of a hyperplastic thymus. She improved considerably after surgery and, at present, has only mild symptoms under pyridostigmine and prednisone treatment. The other sister refused thymectomy; she is still severely affected despite high dose prednisone treatment. The HLA haplotype B8, DR3, DQ2, DQA1*0501, DQB1*0201, was present in both patients and in one healthy sister.

FAMILY 2
Severe generalised myasthenia gravis developed in the mother and son. In the mother myasthenia gravis onset occurred at the age of 40. Diagnostic tests for myasthenia gravis were fulfilled and anti-AChR ab titre was 10–5 nM. Mediastinal CT was negative, so thymectomy was not performed. The patient improved greatly with pyridostigmine and prednisone treatment.

The son developed myasthenia gravis with severe bulbar and limb involvement at the age of 35, one year after removal of an invasive thymoma. An edrophonium test, SRNS, and
Pedigrees of the four families. Squares represent males and circles represent females. Black symbols indicate patients affected by myasthenia gravis, open symbols denote unaffected subjects, the striped square represents the case of thymoma without myasthenia gravis. The ages at onset of myasthenia gravis are indicated by the numbers beside symbols; numbers in brackets represent the present ages. Serum anti-AChR antibody titres and thymoma associated with myasthenia gravis are also reported. § epilepsy; \(^*\) psychosis; \(\tau\) vitiligo; \(\%\) insulin dependent diabetes mellitus.

FAMILY 3
Two different forms of myasthenia gravis occurred in the father and son.

The father has had mild generalised myasthenia gravis since the age of 25. Diagnostic tests for myasthenia gravis were positive and anti-AChR ab titre was 2-2 nM. He was treated with pyridostigmine and underwent thymectomy with removal of a hyperplastic thymus. At present, the patient is in clinical remission under pyridostigmine treatment.

The son developed severe myasthenia gravis at the age of 15. Extraocular and bulbar muscles were mainly affected, with diplopia, nasal speech, dysphagia, and respiratory distress due to vocal cord paralysis. An edrophonium test was positive in the early stages of the disease. SRNS showed 11% decrement on the 5th stimulus, and single fibre EMG was clearly positive, although repeated assay for anti-AChR ab gave negative results. Thymectomy was performed three months after disease onset and a normal thymus was removed. Pyridostigmine and immunosuppressive treatment had little effect. Plasma exchange greatly improved myasthenia gravis symptoms and the patient’s IgG passively transferred the disease to mice. Three other brothers are in good health and anti-AChR ab assay gave negative results in all three.

FAMILY 4
One brother developed severe generalised muscle weakness at the age of 61. All diagnostic tests for myasthenia gravis were positive and anti-AChR ab titre was 3-9 nM; mediastinal CT did not show a thymic mass. The patient was treated with pyridostigmine, prednisone, and azathioprine with considerable improvement of myasthenia gravis signs. He has also had vitiligo and insulin dependent diabetes for 15 and two years respectively. A younger brother underwent thymectomy with removal of a thymoma at the age of 48. He has no symptoms of myasthenia gravis; anti-AChR ab was not titrated. In this family, vitiligo was also present in the father and in one sister.

The figure shows pedigrees of the four families with HLA haplotypes.
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Discussion
Different forms of myasthenia gravis can be identified on the basis of features such as age at onset, presence of serum anti-AChR ab, associated thymic alterations, and HLA antigens. Distinct immunogenetic mechanisms have been proposed for these different clinical subtypes. In white people, the frequency of the haplotype A1, B8, DR3, DQ2 is significantly increased in female patients with early onset disease, high titres of serum anti-AChR ab, and thymic hyperplasia; these antigens are rare in myasthenia gravis associated with thymoma; in late onset myasthenia gravis a slightly increased frequency of B7 and DR2 has been reported. More recently, it has been suggested that DQ alleles could be relevant in myasthenia gravis susceptibility. Molecular analysis of the DQ locus in patients with myasthenia gravis has shown that the alleles DQA1*0501 and DQB1*0201 are positively associated with thymic hyperplasia and negatively associated with thymoma.

In previous reports on familial autoimmune myasthenia gravis the affected members within a family had the same clinical form of myasthenia gravis. Studies on genetic markers failed to show any linkage with HLA, with the AChR β subunit, and with the T cell receptor α and β subunits.

In our series of patients all clinical types of myasthenia gravis are represented and different forms of the disease occur in the same family.

In family 1 the two patients are affected with early onset myasthenia gravis. They share the HLA haplotype, which is generally associated with this form of the disease. Nevertheless, this haplotype is also present in the healthy eldest sister.

In family 2, non-thymoma myasthenia gravis is associated with DR3 antigen and DQA1*0501/DQB1*0201 alleles in the mother. In the son, thymoma myasthenia gravis shows the unusual association with DQB1*0201, but this allele is paternally inherited.

In family 3, seropositive and seronegative myasthenia gravis are present in father and son respectively. The autoimmune pathogenesis of the seronegative disease is strongly supported by the passive transfer of the neuromuscular transmission defect by the patient’s IgG and by the therapeutic effect of plasma exchange. Both patients express the HLA DR2 antigen, which is also present in two unaffected family members and the father shows the DQA1*0501 allele usually associated with thymic hyperplasia.

In family 4, two brothers, one affected by late onset myasthenia gravis and the other by thymoma without myasthenia gravis, share the same class II HLA antigens. In this family vitiligo is present in two additional members and it seems to be paternally transmitted.

The frequency of familial autoimmune myasthenia gravis is very low: in our experience it is less than 1% (eight cases of myasthenia gravis or related conditions out of more than 800 patients). The few cases reported in the medical literature have generally occurred in siblings and an autosomal recessive inheritance has been suggested. From our data this genetic mechanism cannot be excluded even if an autosomal dominant mode seems to be operating in families 2 and 3. Moreover, familial occurrence of myasthenia gravis is not associated with a single clinical form and, as reported by other authors, is not linked to a single HLA haplotype.

The frequent association of myasthenia gravis with other autoimmune diseases within the same family suggests a more general predisposition to autoimmune. This predisposing factor seems to be different from MHC genes.

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