Short report

Familial autoimmune myasthenia gravis with different pathogenetic antibodies

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SUMMARY Two cases of familial myasthenia gravis are reported. One patient is a typical case of autoimmune myasthenia with positive ant acetylcholine receptor antibodies, while in the second patient the impairment of neuromuscular transmission is likely to be due to antibodies directed against determinants other than the acetylcholine receptors.

Acquired myasthenia gravis (MG) is usually a sporadic autoimmune disease due to antibodies directed against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction.1 2 Congenital myasthenic syndromes have a different, non autoimmune, pathogenesis.3 Familial cases are reported in both the acquired and the congenital forms of MG, but more frequently in the latter type of the diseases.4 5

We report two cases of autoimmune MG occurring in the same family; in these patients, the same pathogenetic mechanism (an autoimmune attack against the neuromuscular junction) is likely to be directed at two different targets.

Case reports

Case 1

Father, born in 1935. This patient has been suffering from mild generalised MG (2A according to Osserman) since 1955. Symptoms had always been typical; Tensilon test, repetitive supramaximal stimulations and anti AChR antibodies (assayed for the first time in 1980, as previously described6 7) were clearly positive. Thymectomy was performed within one year from onset, with removal of a hyperplastic thymus. As anticholinesterase drugs (AChE) were very effective in controlling the symptoms, immuno suppressive treatment was never required. At present, the patient is nearly asymptomatic, receiving pyridostigmine. HLA typing for DR and DQ revealed the following haplotype: DR2 DR5 DQw1.

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Case 2

Son, born in 1965. The onset of the disease was in 1980, with intermittent diplopia together with nasal speech, exertional dyspnoea and inspiratory stridor due to incomplete paralysis of vocal cords. Tensilon test was weakly but clearly positive, while 3 Hz repetitive supramaximal stimulation test showed 11% decrement on the 4th stimulus, which in our experience is the upper limit of normal controls.8 Repeated assays for anti AChR antibodies directed against sites other than the alpha-bungarotoxin binding site (measured as in case 1) or against the toxin binding site (tested according to Besinger9) gave negative results, even when increasing serum concentrations were used. Thymectomy was performed 3 months after the onset of the disease and a normal thymus was removed. As AChE had not been very effective, prednisone treatment was started in 1984 with mild improvement. The patient’s symptoms remained quite stable until 1986, when he suffered from a severe respiratory distress due to complete vocal cords paralysis. Tracheostomy was thus required, following which the patient was submitted to 11 plasma-exchange courses with marked improvement. Now he is in good condition under prednisone treatment. HLA typing for DR and DQ revealed the following haplotype: DR2 DR10 DQw2.

Clinical examination and anti AChR antibody assays were negative in the three brothers of case 2.

In vitro neuromuscular transmission

IgG fraction was purified from plasma-exchange bags by the Rivanol-ammonium sulphate method.10 Balb/c female mice were injected intraperitoneally for 3 days with 40 mg of purified test IgG from case 2 each day; on the 4th day, mice were killed, the diaphragms were removed and examined at constant temperature (25°C) during continuous perfusion with Rees solution11 bubbled with 95% O₂ 5% CO₂. Isometric contraction was examined fixing one end of the muscle by means of its ribcage attachment and the other by the central tendon to a tension transducer (Ugo Basile Isometric Transducer 7005), connected to a Tektronix equip-
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The incidence of familial cases in MG is estimated to be about 3%, their pathogenesis being either congenital or autoimmune. In our series of 423 MG patients we found six familial cases: two of them (sister and brother) were affected by a congenital myasthenic syndrome, with onset at birth and negative anti AChR antibodies; two sisters had autoimmune MG with onset in their teens and high anti AChR antibody titres. The two cases here reported, father and son, are affected by autoimmune MG. Case 1 is a typical case of autoimmune MG, both in his clinical and immunological characteristics; in contrast, his son (case 2) raises some diagnostic difficulties on account of the atypical course of the disease, the poor response to AChE, the absence of detectable anti AChR antibodies and the equivocal electromyographic data. A congenital myasthenic syndrome is unlikely on account of the late onset of the disease and the positive response to immunosuppressive drugs and plasma-exchange; the Lambert Eaton myasthenic syndrome can be ruled out by the presence of brisk tendon reflexes and the absence of the typical electromyographic findings. On the other hand, the marked improvement after plasma-exchange implies the presence of some circulating factor responsible for the disease. Using a passive transfer model coupled to an in vitro electrophysiological technique we were able to demonstrate that the pathogenic factor in this patient belongs to the IgG fraction, thus suggesting the presence of an autoimmune mechanism also in patient 2. In this respect this case is similar, both in the clinical and immunological features, to some of those reported by Mossman et al.12 These authors first demonstrated the presence of circulating antibodies directed against antigens at the neuromuscular junction other than the AChR by means of an electrophysiological technique similar to the one described here. The interest of our two cases resides in the fact that the autoimmune response is very likely to be directed against different targets: the AChR in case 1, a still unidentified component of the neuromuscular junction in case 2. Both patients express the HLA-DR2 antigen, the increased frequency of which in older-onset MG patients has already been described.13 This finding reinforces the hypothesis of a common mechanism, that is, an alteration of self tolerance, in the disease pathogenesis of our two cases. The two antigens involved can account for the different clinical courses in these patients.

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References

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