THE AUTOIMMUNE SPECTRUM OF MYASTHENIA

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Myasthenia gravis with AChR antibodies: About 85% of patients have antibodies to the AChR at the neuromuscular junction. In patients with AChR antibodies (AChR-MG) the numbers of AChRs at the NMJ are reduced to approximately 20% of normal levels with the result that the endplate potential is reduced in amplitude and fails to reach threshold in a proportion of muscle fibres resulting in muscle weakness. This failure of transmission increases during repeated effort.

AChR antibodies are high affinity, polyclonal and mainly in the IgG1 and IgG3 subclasses (which are complement-activating). Titers of AChR antibody are very variable between patients (ranging from 0 to > 1000 nM) and do not correlate well with clinical severity. However, the level of antibody *within* an individual generally changes in parallel with clinical scores after plasma exchange, thymectomy, or immunosupressive treatments. Moreover, the neuromuscular junction deficits of MG can be passively transferred from patient to mouse.

The antibodies cause AChR loss by complement dependent lysis, which causes morphological damage, by cross-linking the AChR divalently resulting in increased internalization and degradation, and by direct inhibition of the ACh binding site causing a pharmacological block of function. There are several knock-on effects of the autoimmune attack. Firstly the postsynaptic folds tend to be lost and this reduces the number of voltage-gated sodium channels, increasing the threshold for generation of the action potential and thereby enhancing the neuromuscular junction defect. However, there is also evidence for a compensatory increase in ACh release and for increased AChR synthesis. Thus the final distribution and severity of muscle weakness must reflect not only the antibody-induced AChR and secondary sodium channel loss, but also these compensatory changes.

Patients with MG can be divided into subgroups based on age at onset, HLA association, thymic involvement, and AChR antibody status. Thymoma occurs in up to 10% of MG patients, mostly presenting between the ages of 30 and 60 years. Ocular MG occurs in about 20% of patients, and only 50% have AChR antibodies.

Generalized Myasthenia Gravis without AChR antibodies

About 10% to 15% of all patients with MG and generalized symptoms do not have anti-AChR antibodies detectable by the radioimmunoprecipitation test. These patients have similar clinical presentations and response to plasma exchange as patients with AChR-antibody positive generalized MG, and their plasma or IgG preparations passively transfer defects in neuromuscular transmission to mice.

A proportion of patients without AChR antibodies have antibodies to MuSK which is a receptor tyrosine kinase restricted to the neuromuscular junction in mature muscle. Interestingly, the prevalence of MuSK antibodies among patients without AChR antibodies is highly variable between different centres around the world suggesting a possible environmental stimulus. They are mainly IgG4, and are almost never found in patients with AChR antibodies or with thymoma.

The distinctive features of MuSK-MG are the often-marked ocular, bulbar, neck or respiratory symptoms and, in contrast to AChR-MG, the patients may have normal electrophysiology in limb muscles with evidence of neuromuscular defects in facial muscles (eg. Orbicularis occuli). They respond to immunosuppression with prednisolone and azathioprine but often the response is insufficient and alternative immunosuppressive treatments such as mycophenolate or cyclosporine are required. It is not yet clear how the antibodies cause the neuromuscular junction defect.

There are still patients with typical generalized MG who do not have a serum antibody defined by a laboratory test. These patients often have less severe symptoms and are more responsive to standard treatments than the MuSK-antibody positive patients. Since their electrophysiology, thymic pathology and response to thymectomy tend to be similar to those in patients with early AChR-MG, we proposed that they have AChR antibodies undetectable by current laboratory tests. At least a proportion of these patients have AChR antibodies detectable by an immunofluorescent method using human embryonic kidney cells to express AChRs at high density (Leite, Willcox and Vincent unpublished observations). Moreover, these low affinity antibodies activate complement and are probably pathogenic.

Questions and Controversies: There is still much we don't know about myasthenia in general, and particularly about the AChR-antibody negative forms. We don't know the relative contributions of complement-dependent lysis, antibody-induced AChR degradation, or pharmacological block of function to the pathophysiology. It is not clear what determines the extent of muscle weakness in any particular muscle group and why this can fluctuate on a daily basis. There have been suggestions that MuSK antibodies may not be pathogenic, mainly because the pathophysiology of neuromuscular transmission in MuSK-MG patients is not understood. In particular, we don't understand why the bulbar muscles are more susceptible and whether this reflects differences in MuSK expression or the involvement of another antibody. There are discrepancies on the reports of response to thymectomy in MuSK-MG and wide variation in its use.