

Myasthenia Gravis and the Heart

Myasthenia gravis (MG) is well established as an autoimmune disorder with specific autoantibodies directed against the nicotinic acetylcholine receptor (AChR) in the neuromuscular junction. Involvement of the heart has been claimed and reported, but a causal connection between MG and altered cardiac function has not been found. This review summarises what is known about the possibility of heart involvement in MG.

Immunology

Whereas the AChR-antibody is the mainstay of MG, several other antibodies can be found. Some of these antibodies have been shown to react with cardiac muscle, thus being termed skeletal and heart reactive autoantibodies,¹ or striational antibodies. A proportion of this striational reactivity is due to antibodies against titin and the ryanodine receptor (RyR) found in the sarcoplasmic reticulum,² whereas other antibodies are claimed to react with myosin,³ α -actin and actinin.⁴ Non-striational antibodies have also been demonstrated in MG, directed against beta-adrenergic receptors⁵ and against AChR of the muscarinic type.⁶ Mygland demonstrated that the existence of heart muscle antibodies was related to type of MG, in finding such antibodies in MG-patients with thymoma and late-onset MG, but not in early onset MG. These heart muscle antibodies were shown to be specific for MG.⁷ Lately, the discovery of antibodies to the muscle specific tyrosine kinase (MuSK)⁸ has identified a subgroup of MG patients with rather distinct clinical characteristics. Antibodies to MuSK inhibit agrin-induced AChR-clustering, indicating a potential effect on agrin-dependent maintenance of AChRs at the neuromuscular junction. Cardiac function has not been examined specifically in MuSK-positive MG-patients.

The existence of all these antibodies – and antibodies not yet characterised – offers theoretical mechanisms for cardiac involvement in MG, by interfering with contractility, cardiac conduction, autonomous regulation or by an immunological attack on the myocardium, involving complement activation, infiltrates of inflammatory cells and with consequent necrosis.

Giant-cell myocarditis (GCM) is a condition showing a clear association to thymoma and in some cases to MG. GCM is characterised by degeneration and necrosis of heart muscle, and has been linked to IgG anti-cardiomyocyte antibodies.⁹ GCM is however extremely rare, with only a few reported cases.

However, looking beyond the rare giant-cell myocarditis, the potential immunological mechanisms are at the present insufficiently correlated to clinical cardiological findings in MG patients.

Clinical findings

ECG

Changes in cardiac function as registered by changes in the ECG have been taken as a marker for MG-related cardiac disease. Hofstad found ECG abnormalities in 14 of 87 patients (16%), regarding the findings in twelve of these patients to be directly MG-related.¹⁰ A larger study by Luomanmäki reported 97 MG-patients where 11% had abnormalities from concomitant heart disease, 9% had minor alterations (same rate as normal population) and 15% showed terminal notching of the QRS complex.¹¹ Later, Büyükkötürk reported a higher frequency of QT-prolongation, right bundle branch block, sinus tachycardia and arrhythmias than found in the normal population. Ashok found in 4 of 10 MG-patients flat to inverted T-waves, ST-depression and poor progression of R-waves in three precordial leads, all abnormalities reverting to nor-

mal following oral neostigmine.¹² On the other hand, a clinical study by Kornfeld¹³ could not demonstrate any convincing ECG-changes in MG-patients. In conclusion, no distinct features of the ECG can be assigned to MG alone, and the significance of ECG in evaluation of MG-related cardiac disease is uncertain.

Clinical cardiac function

Few studies have clinically investigated cardiac function other than ECG in MG-patients. Johannessen found a reduced peak diastolic filling rate in 25 MG-patients without any known cardiovascular disease, hypertension, diabetes mellitus or pulmonary disease.¹⁴ Ejection fraction was similar in patients and controls. Another study demonstrated a reduced global heart ejection fraction in 40% of MG patients without known cardiac disease after exercise, interpreted as a true association between MG and heart disease.¹⁵ We have recently studied cardiac function in MG-patients without known cardiovascular disease, and found a reduced cardiac tissue velocity and strain (Owe et al, in press). These findings indicate subclinical alterations in cardiac function of some MG-patients. No modality of examination has been proven to be of value in routine examination of MG patients without symptoms of heart disease, and MG-patients do not have an increased risk of heart-related deaths.¹⁶ There is a need for larger-scale clinical studies examining cardiac function in MG patients.

Post-mortem examinations and thymoma MG

The most convincing evidence for cardiac involvement in MG comes from autopsies. As early as 1901, Weigert demonstrated myocardial abnormalities in MG-patients. Later studies have confirmed the pathological findings in the hearts of MG-patients, focal inflammation and necrosis, and in the absence of atherosclerotic disease. The focal (spotty) appearance of the inflammation and necrosis bears resemblance to findings in skeletal muscles of MG-patients, and is believed to be due to lymphocytic infiltration of the myocardium. In a review from 1975, Gibson¹⁷ found myocarditic changes in 28 of 75 patients with MG, the majority being associated with thymomas. Hofstad¹⁰ reported focal myocarditis in all three examined thymoma-MG patients. Among non-thymoma MG-patients, focal myocarditis or non-specific myocardial changes were found in three of five autopsies. Thus, thymomas are usually associated with myocardial involvement, but this can also occur in non-thymoma MG-patients.

Thymoma MG-patients are in addition prone to local thymoma-infiltration and invasion of the pericardium, myocardium, large vessels and other neighbouring structures, with the possible result of altered cardiac function. The observed high frequency of myocardial pathology in thymoma MG-patients could mean that an immunological attack with resulting inflammation and myocardial necrosis represents a paraneoplastic phenomenon related to the thymoma. Furthermore, thymoma patients have a broad range of autoantibodies, providing a theoretical mechanism for altered cardiac function, whether it is due to altered contractile force or altered conduction.

Effect of acetylcholine esterase inhibitors

The effect of acetylcholine esterase inhibitors (ACh-I) on cardiac function has been highlighted in several studies. Ashok found that non-specific ECG abnormalities in MG-patients reverted towards normal following neostigmine.¹² Johannessen found an increase in the peak diastolic filling rate in MG-patients following pyridostigmine.¹⁴ We have demonstrated a normalizing of cardiac tissue velocity and



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strain following oral administration of pyridostigmine. It is unclear whether the effect of ACh-Is is a direct pharmacological effect on the myocardium, if it is an indirect effect altering the autonomous control of cardiac function or if it is due to down-modulation of receptors in MG-patients continuously treated with ACh-I, when the medication is withdrawn prior to the study. Anyhow, the effect of ACh-I on cardiac function in MG-patients, but not in controls, indicates that there is an ACh-I responsive alteration of cardiac function in some MG-patients.

Conclusions

When evaluating cardiac involvement in MG, a distinction has to be made between laboratory findings and clinical cardiac function. There is good evidence for myocardial pathology in MG patients, including a diversity of heart-reactive autoantibodies and focal inflammation with cellular infiltrates and myocardial necrosis. On the other hand, any firm clinical correlates to these findings have yet to be established. Clinical studies indicating a functional alteration in cardiac function are either too small, have conflicting results or cannot reliably distinguish any altered cardiac function caused by MG from altered function of other causes such as atherosclerotic disease. The indirect effect of MG, due to respiratory impairment and low muscle tone, can reduce venous return, altering cardiac haemodynamics. Hypoxia, hypercapnia, acidosis and associated respiratory infections in a myasthenic crisis could give rise to persisting myocardial changes. Suspected MG-related cardiac disease often occurs late in life, at a time when there is an increased risk of atherosclerotic disease. This creates a dilemma: excluding from the studies MG-patients with the slightest symptoms of cardiac disease may produce false negative findings, whereas inclusion of all MG-patients may obscure results due to presence of coexisting cardiovascular disease.

From the present evidence, one should regard thymoma MG-patients as a group at special risk for myocardial pathology. Heart symptoms in thymoma MG-patients should always be suspected as being caused by myocarditis (or pericarditis) and related to MG and autoimmunity. However, with available modalities of heart examination, there is, in our opinion, no need for MG-patients, regardless of any thymic pathology, to be examined routinely for heart disease unless cardiac symptoms arise.

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