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MYASTHENIA GRAVIS: REVIEW

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ABSTRACT

This autoimmune disease is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the involvement of extrinsic ocular muscle presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, resulting in generalized myasthenia gravis. Although the cause of the disorder is unknown, the role of circulating antibodies directed against the nicotinic acetylcholine receptor in its pathogenesis is well established. As this disorder is highly treatable, prompt recognition is crucial. During the past decade, significant progress has been made in our understanding of the disease, leading to new treatment modalities and a significant reduction in morbidity and mortality.

KEYWORDS: Ach, acetylcholinesterase, autoimmune disorder, MG.

INTRODUCTION

Myasthenia gravis is a neuromuscular disease characterized by weakness and fatigability of the voluntary muscles. Clinically, the onset of symptoms may be insidious or acute and may be manifested by weakness of the proximal limb muscles, ocular muscles, or bulbar muscles.[1]

This autoimmune disease is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the involvement of extrinsic ocular muscles (EOMs) presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, results in generalized myasthenia gravis (gMG).[2,3]

In about 10% of myasthenia gravis patients, symptoms are limited to EOMs, with the resultant condition called ocular MG (oMG) Sex and age appear to influence the occurrence of myasthenia gravis. Below 40 years of age, female: male ratio is about 3: 1; however, between 40 and 50 year as well as during puberty, it is roughly equal. Over 50 years, it occurs more commonly in males.[2,4,5]

Childhood MG is uncommon in Europe and North America, comprising 10% to 15% of MG cases. In Asian countries though, up to 50% of patients have onset below 15 years of age, mainly with purely ocular manifestations.[2,6]

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies targeting the neuromuscular junction, which in most cases are directed towards the skeletal muscle acetylcholine receptor (AChR). The pathophysiology of MG is accepted to be immune mediated. Sporadic inclusion body myositis (IBM) is considered the most common inflammatory myopathy in patients over 50 years old, but its pathophysiology remains to this day an enigma: It is still unclear whether it is a primary degenerative disease with secondary dysimmune reaction or vice versa.[3]

General recommendations

Physical exercise should be encouraged in all MG patients as it carries no risk. In addition, a sedentary lifestyle is likely to increase the risk of comorbid pathologies and cardiovascular side-effects of corticosteroid treatment. Although specific studies are sparse, recent 6 observations have reported good tolerance, improved quality of life, and better muscle strength in patients with mild disease undergoing supervised training. A multicenter randomized controlled trial (the Benefits and Tolerance of Exercise in Patients with Generalized and Stabilized Myasthenia Gravis trial) is ongoing. Several drugs have been associated with worsening of MG. Such drugs should be used with caution in MG, and only if they are clearly necessary. Association of drug use and MG exacerbation can be causal or by chance. MG patients starting a new drug should always be warned about the possibility for side-effects including MG exacerbation. This especially

applies to patients with active disease and clear signs of bulbar or respiratory weakness. However, most patients with minimal disease activity or complete remission will tolerate most of these drugs quite well, especially during short-term treatment. Vaccinations are generally recommended, including against influenza. Influenza vaccination is safe and effective in MG patients, regardless of the use immunosuppressive medication, and does not lead to immunological or clinical exacerbation. Patients taking high doses of immune-suppressant medication should not receive live-attenuated vaccines. Sleep apnea has a high frequency in MG patients and should be actively investigated and treated.[5,8,9]

Treatment

Physostigmine, neostigmine, and pyridostigmine are antiacetylcholinesterase symptomatic treatments for MG that produce transient improvements in strength, but without disease modification. These agents slow down the recycling of ACh at the neuromuscular junction allowing a longer interval for the interaction with the ACh receptors and thus overcoming neuromuscular transmission failure. Patients with very mild MG are sometimes maintained on these agents alone, but that situation is not common as an uncontrolled and prolonged immune attack at the neuromuscular junction by abnormal antibodies can lead to irreversible damage to the postsynaptic membrane and a fixed myopathy that no longer responds to ISTs. Anti-acetylcholinesterase therapies are usually adjunctive to more definitive treatment in MG. Several other symptomatic treatments in use primarily for congenital MG are ephedrine, salbutamol, and 3.4-Diaminopyridine. Congenital MG may respond to cholinergic upregulation, beta adrenergic agonists, or open-channel blockers (fluoxetine, quinidine) for slow-channel syndrome. In order to select the appropriate treatment, accurate diagnosis of the specific congenital syndrome must be made. It is advisable to be careful about the choice of treatment as some agents improve certain congenital syndromes and worsen others. Pyridostigmine is effective for many congenital MG syndromes such as fast channel syndrome, Rapsyn deficiency, and SCN4A sodium channel myasthenia, but pyridostigmine can worsen DOK-7, acetylcholinesterase deficiency and slow-channel congenital MG. 3, 4-Diaminopyridine can confer added benefit to pyridostigmine in many forms of congenital MG.[4,7,10]

Limitations of the Current Therapeutic approach

In summary, the current pharmacological treatment of MG encompasses a large array of options that differ in efficacy, time scale in which they are effective and the level of evidence and experience with that particular drug in the treatment of MG. In clinical practice, corticosteroids are still the cornerstone of treatment beside symptomatic medication due to their low cost, wide availability, relatively fast mode of action and the experience gained over decades. Corticosteroids feature prominently in published consensus statements on the treatment of MG. Consequentially, almost half of more than 500 patients participating in the Dutch-Belgian Myasthenia Registry reported using prednisone at the time of questioning. Thymectomy, although safe and effective, is at present not an option for older patients or those with longer disease duration. IVIg and plasma exchange are effective, but short-lived and relatively costly. Non-steroidal immunosuppressants such as azathioprine and cyclosporine probably have a better long term safety profile than corticosteroids. However, they have a delayed-onset effect, up to several months for azathioprine and at least two months for cyclosporine rendering them less suitable as monotherapy for severely affected patients. The indication of eculizumab, a relatively new addition to the therapeutic toolbox, is currently limited to patients with refractory MG. Usage in a larger group of MG patients might be advantageous, but is not likely to become common practice because of its prohibitive cost.[8,10,11]

CONCLUSION

Novel interventions such as complement inhibitors, FcR inhibitors, and stem cell therapy are being developed for MG and these are promising in cases when standard treatments fail or are not tolerated. Some patients who have suffered long-term disability can respond to these novel approaches. These novel pharmacologic interventions promise a new era in controlling MG, but none are ‘curative’. It is not possible yet to specifically stop the production of AChR, MuSK or LRP4 antibodies in patients with MG. Developments in this area may be the most helpful to patients suffering with MG.

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