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Review

Diagnosis and therapy of myasthenia gravis with antibodies to muscle-specific kinase

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ABSTRACT

Myasthenia gravis (MG) with antibodies to the muscle-specific receptor tyrosine kinase (MuSK-MG) is a rare disease which covers 5–8% of all MG patients. Symptoms are nearly always generalized, though more focal than in MG with anti-acetylcholine receptor antibodies, with predominant involvement of cranial, bulbar and axial muscles; early respiratory crises are frequent. Focal atrophy, mostly of facial, masseter and tongue muscles, occurs in a proportion of patients. Diagnosis is often challenging on account of atypical presentation with little or no symptom fluctuations, lack of response to acetylcholinesterase inhibitors in a high proportion of patients and negative results of electrodiagnostic studies when performed on limb muscles. Immunosuppression is the mainstay of treatment, since the response to acetylcholinesterase inhibitors is generally unsatisfactory and thymectomy does not appear to improve the course of the disease. Although corticosteroids result in marked improvement, disease flares are frequent during prednisone dosage tapering and most patients remain dependent on treatment. Since treatment with rituximab, in uncontrolled studies, induced sustained benefit in patients with refractory disease, B cell depletion is an attractive option for MuSK-MG patients unresponsive to conventional immunosuppressants.

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1. Introduction

Myasthenia gravis with antibodies to the muscle specific receptor tyrosine kinase (MuSK-MG) is a rare disease that covers 5–8% of all MG cases. Its history is a good example of fruitful interaction between clinical observation and experimental evidence; such co-operation has steadily enhanced our knowledge of disease mechanisms and has been improving its management.

The pathogenic scenario of MuSK-MG is remarkably different from that of "typical" MG associated with antibodies to the acetylcholine receptor (AChR-MG). Thymus histological alterations, such as follicular hyperplasia and thymoma, are commonly found in AChR-MG, where they are thought to play a crucial role in the disease initiation. In particular, the hyperplastic thymus contains all the cellular elements and the inflammatory microenvironment required for the generation of

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anti-AChR antibody response [1,2]; thymoma is thought to be responsible for impaired selection of auto-reactive T cells and reduced generation of T regulatory cells [3,4]. On the other hand, thymus alterations are very rare in MuSK-MG, where thymus histology is mostly normal-for-age, with sparse lymphoid infiltrates [5,6]. Antibodies to MuSK are prevalently IgG4 and, differently from anti-AChR antibodies (mostly IgG1 and IgG3), are unable to activate complement and relatively inefficient in inducing antigen modulation [7,8]; as disease animal models suggest their effector mechanism appears to involve direct inhibition of MuSK function [9].

In contrast to the relatively uniform frequency of AChR-MG [10], the positive rate of anti-MuSK antibodies in patients with anti-AChR negative MG varies remarkably in different countries, with the lowest rate in Norway [11] and the highest in Italy and Turkey [12,13]. These findings are in line with the observation that, in Europe and North America, MuSK-MG frequency seems to be inversely correlated to latitude, with the highest prevalence around 40° north of the Equator [14]. Moreover, in U.S. centers, a significantly higher rate of MuSK Abs was reported in African-Americans than in whites [15]. The disease shows a striking prevalence in women, with more than 70% female patients in all studies, and a mean age of onset younger than 40 years in most patient series [16]. Though few studies have investigated genetic susceptibility, a strong association with HLA-DQ5 was reported in two independent European surveys [17,18]. Thus, it appears that, as in other autoimmune diseases, genetic and hormonal factors play a relevant role in MuSK-MG etiology, with regional differences in prevalence suggesting environmental exposures so far unknown [19].

2. Clinical aspects

Anti-MuSK antibodies are nearly always associated with generalized MG, having been seldom reported in patients with symptoms restricted to extrinsic ocular muscles [20]. Weakness pattern tends to be more focal than in AChR-MG, with prevalent involvement of bulbar, neck and respiratory muscles [12,13,16]. The resulting phenotype, mainly consisting of dysarthria, dysphagia, facial and neck weakness, is rather typical, although not specific, for MuSK-MG. Ocular symptoms are milder than usually observed in MG patients and often evolve to symmetrical ophthalmoparesis; limb muscles are involved to a lesser extent and can be totally spared, although shoulder muscle weakness can be an early symptom in few cases. The disease course is often rapidly progressive leading, within few weeks from onset, to life-threatening symptoms frequently culminating in respiratory failure [21]. Twenty-four of 75 patients (32%) in our series suffered from myasthenic crises; such a proportion is much higher than in any other MG subtype in our population, yet in line with the crisis rates (ranging from 25% to 48%) reported by other authors in MuSK-MG [16]. Notably, 67% (16/24) of these patients experienced the first crisis within six months from the onset, and, in two cases, respiratory failure occurred as the presenting symptom. On the other hand, some patients may have mild to moderate non-fluctuating weakness or, after thymectomy and steroid treatment, may achieve stable control of their disease for years; then, they can rapidly progress to permanent bulbar symptoms, with severe dysarthria and marked facial weakness. A relatively high frequency of muscle atrophy, particularly of facial, tongue and masseter muscles, has long been recognized as a distinctive feature of MuSK-MG [22–24]. Although more common in chronic patients, atrophy can be observed at an early stage of the disease [25,26], and can resolve after aggressive treatment [27]. The focal pattern of muscle weakness in the human disease has been reproduced, to some extent, in animal models. Mice immunized with recombinant MuSK develop generalized disease, with marked kyphosis (that mimics the neck extensor muscle weakness in patients) [9], and morphologic studies revealed more severe end-plate alterations in masseter, sternomastoid and paraspinal muscles than in limb muscles [28]. In experimental MuSK-MG, both by active immunization and passive transfer, increased expression of the atrophy-related muscle-specific RING finger protein 1 (MuRF-1) was found in mouse masseter, but not in soleus or gastrocnemius [28,29], thus confirming muscle selective susceptibility to anti-MuSK antibody attack.

3. Diagnosis

MG is suspected in patients presenting with history and signs of fluctuating muscle weakness, worsening on exertion and improving at rest. The diagnosis is then confirmed by positive results on pharmacological testing, electrodiagnostic testing and serum antibody assay [30]. In MuSK-MG patients clinical presentation can be atypical and symptom fluctuation, which is a clinical hallmark of MG, can be minimal or absent. Bulbar weakness with dropped head may suggest a motor neuron disease, and, in patients with long-lasting disease, symmetrical ophthalmoparesis with a myopathic face may lead to an erroneous diagnosis of mitochondrial myopathy. Since uncharacteristic clinical findings can be associated with negative results of pharmacological testing and, to a certain extent, of electromyography (EMG), the diagnosis of MuSK-MG may be altogether overlooked or considerably delayed.

3.1. Pharmacological testing

Acetylcholinesterase inhibitors (AChE-Is) transiently improve neuromuscular transmission by increasing the availability of acetylcholine at the synaptic cleft. For diagnostic purposes, parenterally-given short-acting agents, such as edrophonium chloride (Tensilon) i.v. and neostigmine (Prostigmine) i.m., are preferred, and clinical improvement on injection, though not strictly specific [31], strongly supports the suspect of MG. Edrophonium/neostigmine testing has high diagnostic sensitivity with a 90% rate of positive responses [31], inasmuch as, until recently, unresponsiveness was generally thought to make MG diagnosis highly unlikely. In MuSK-MG, clinical improvement upon AChE-I injection is much less common (50% to 70% of positive response) than in AChR-MG [22,32]. Nicotinic side effects, such as muscle cramps and widespread fasciculations, are frequent and worsening of weakness can even be observed [16,22,32]. The basis of cholinergic hypersensitivity in these patients has recently been elucidated by passive transfer studies showing that patients' IgG, when injected into mice, interfered with MuSK-ColQ binding leading to significant reduction of AChE density at the neuromuscular junctions [33,34]. As increased weakness on AChE-I injection can lead to a cholinergic crisis, edrophonium or neostigmine test should be performed cautiously when MuSK-MG is suspected on clinical grounds, and should altogether be avoided in patients with severe bulbar weakness or impending respiratory crisis.

3.2. Electrodiagnostic testing

In MG, the underlying defect of neuromuscular transmission is detected as >10% decrement of compound muscle action potential (CMAP) on low-rate repetitive nerve stimulation (RNS) or increased jitter on single-fiber electromyography (SF-EMG). A decremental response on RNS can be obtained in most patients with generalized MG, when both distal and proximal limb muscles are tested. SF-EMG is even more sensitive, being abnormal in more than 90% of patients, including those with mild or ocular disease [35].

As the diagnostic yield of EMG depends on testing weak muscles, in MuSK-MG, in spite of symptom severity, weakness predominance in cranial and bulbar muscles accounts for the relatively low sensitivity of EMG when performed on limb muscles. A decremental response on RNS of various limb muscles was found in 12% to 57% of MuSK-MG [16] versus 80% of AChR-MG patients [22]. In a similar fashion, increased