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Diagnostic and clinical classification of autoimmune myasthenia gravis

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ABSTRACT

Myasthenia gravis is characterized by muscle weakness and abnormal fatigability. It is an autoimmune disease caused by the presence of antibodies against components of the muscle membrane localized at the neuromuscular junction. In most cases, the autoantibodies are against the acetylcholine receptor (AChR). Recently, other targets have been described such as the MuSK protein (muscle-specific kinase) or the LRP4 (lipoprotein related protein 4). Myasthenia gravis can be classified according to the profile of the autoantibodies, the location of the affected muscles (ocular versus generalized), the age of onset of symptoms and thymic abnormalities.

The disease generally begins with ocular symptoms (ptosis and/or diplopia) and extends to other muscles in 80% of cases. Other features that characterize MG include the following: variability, effort induced worsening, successive periods of exacerbation during the course of the disease, severity dependent on respiratory and swallowing impairment (if rapid worsening occurs, a myasthenic crisis is suspected), and an association with thymoma in 20% of patients and with other autoimmune diseases such as hyperthyroidism and Hashimoto's disease. The diagnosis is based on the clinical features, the benefit of the cholinesterase inhibitors, the detection of specific autoantibodies (anti-AChR, anti-MuSK or anti-LRP4), and significant decrement evidenced by electrophysiological tests.

In this review, we briefly describe the history and epidemiology of the disease and the diagnostic and clinical classification. The neonatal form of myasthenia is explained, and finally we discuss the main difficulties of diagnosis.

1. Introduction

Autoimmune myasthenia gravis (MG) is a neuromuscular disorder characterized by a defective transmission of nerve impulses to muscles. This defect is caused by an autoimmune attack against components of the neuromuscular junction (NMJ) on the postsynaptic membrane of the striated skeletal muscles. In most patients, the autoimmune response is mediated by antibodies against the acetylcholine receptor (AChR). In approximately 5% of MG patients, the autoreactive antibodies are directed against a protein called muscle specific kinase (MuSK) [1], which plays a central role in the clustering of AChRs and other postsynaptic components at the NMJ. Recently, the agrin receptor LRP4 (low-density lipoprotein receptor-related protein 4), a molecule that forms a complex with MuSK, has been identified as a novel autoantigenic target in a small proportion of MG patients without anti-AChR or -MuSK antibodies [2,3]. Fig. 1 shows a scheme of the NMJ and the targets of autoimmune attack in MG. Several entities can be defined with distinct physiopathological mechanisms.

The evolution of MG is unpredictable, but it is generally characterized by the occurrence of relapses, sometimes subsequent to remissions and a worsening trend in the first years. For 85% of MG patients, the maximum severity is reached within less than 3 years [4]. The severity of MG varies markedly from one patient to another and in the same patient from one moment to another. Involvement of the respiratory muscles and severe swallowing disorders characterize the severe forms (20–30% of patients) and can be managed in intensive care units that permit a significant reduction in mortality. In contrast, myasthenia remains mild in 25% of patients. Between these extremes, the disease is intermediate; it is debilitating because of marked fatigue, impaired swallowing, a hypernasal voice and diplopia. Myasthenia gravis may be associated with

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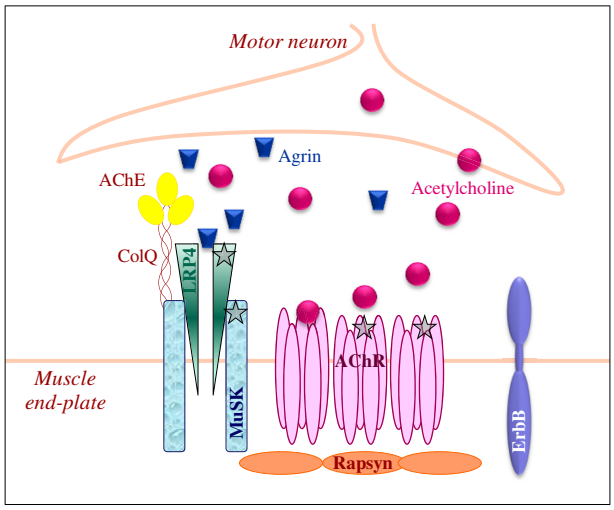

Fig. 1. Simplified scheme of the neuromuscular junction. AChE = acetylcholine esterase; AChR = acetylcholine receptor; ColQ = collagen-tail subunit of AChE; ErbB = receptors for neuregulins; LRP4 = lipoprotein related protein 4; MuSK = muscle-specific kinase. The gray stars represent the known targets in MG, the main one being the AChR.

other autoimmune diseases. The role of the thymus in the pathogenesis is highlighted by the benefit of thymectomy and the presence of frequent histologic abnormalities such as thymoma and follicular hyperplasia [5]. Fifteen to twenty percent of patients, usually those older than 40, have a thymoma caused by a proliferation of epithelial cells [6]. In 50% of patients younger than 45 years, typically female with the anti-AChR antibody, the thymus is the site of follicular hyperplasia characterized by the presence of germinal centers [7]. The role of thymic B cells in the production of anti-AChR antibodies has been clearly demonstrated [8,9].

2. History of the disease

Myasthenic bulbar symptoms were reported for the first time in 1672 when the physician Willis described a woman who “for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word”. At the end of the 19th century, Erb and Goldflam established the first description of the following clinical symptoms attributed to MG: frequent ptosis with diplopia, dysphagia, weakness of the neck, and a course of remissions and relapses. The name “Myasthenia Gravis”, composed of myasthenia, which is Greek for muscle weakness, and gravis, which is Latin for severe, was given because of a presumably neuromuscular inhibitor in the circulation of patients [10].

The chemical substance, liberated at the nerve endings, that could initiate contraction in muscle fibers was identified as acetylcholine (ACh) in the 1930s [11]. A major step forward in treatment occurred in 1934 when Mary Walker realized that MG symptoms were similar to those of curare poisoning, which was treated with physostigmine, a cholinesterase inhibitor. She showed that physostigmine improved myasthenic symptoms [12], making anticholinesterase drugs a basic therapy in MG.

The presence of thymic tumors or enlargements of the thymus was described by Norris in 1936 in most MG patients [13]. That year, Blalock removed a thymic tumor in a 19-year-old female with severe generalized myasthenia. Significant improvement suggested that thymectomy could be a potential therapy [14]. In 1944, Blalock reported successful operations on 20 patients, of which two had thymus tumors [15]. This step was followed by a large thymectomy series in London and at the Mayo Clinic with successful therapeutic results.

The immune origin of MG was suggested in the 1960s by Simpson and was based on the presence of transient MG symptoms in some newborns of myasthenic mothers (neonatal MG) [16]. In 1959, the presence of a circulating factor able to block neuromuscular transmission was suggested by Nastuk et al., in 1959 by applying plasma samples from MG patients to the frog sciatic nerve-Sartorius muscle preparation [17].

The first evidence that the AChR is implicated in the disease was demonstrated by muscle weakness after the immunization of rabbits with the AChR purified from torpedo fish [18]. In 1973, Fambrough confirmed this finding by the observation of a reduced number of AChRs on the muscle endplates of MG patients [19].

The key role of autoantibodies in MG development was confirmed by the emergence of MG-like symptoms in animals into which purified G immunoglobulins (IgGs) from MG patients were transferred and by the degradation of the AChRs on cultured muscle cells after incubation with IgGs from MG patients [20]. The titration of the antibodies in the myasthenic patient’s sera showed that almost 85% of the patients were positive for the anti-AChR antibodies [21,22].

Since the 1970s, numerous studies have explored the events at the neuromuscular junction when the anti-AChR autoantibodies are present [23,24]. The recent discovery of two novel targets (MuSK and LRP4) has reduced the percentage of patients without known antibodies [1–3], although there are still some seronegative MG patients.

3. Epidemiology

MG occurs at any age and in either gender. In the review of Carr et al. summarizing 44 epidemiological studies on MG, the incidence rate varies between 1.7 and 21.3 per million inhabitants, depending on the localization of the study, and the prevalence is between 15

Table 1
Classification of MG patients according to the nature of the autoantibodies.

	Solubilized AChR	MuSK	LRP4	Clustered AChR
Percentage of patients	85%	~5%	~2%	~5%
Targeted populations	Early onset: F > M Late onset: F = M	Young females	Young females	Similar to solubilized AChR
Severity grade	All severity grades: ocular and generalized forms	Mainly severe form	Mainly mild form	Ocular and generalized forms
Pathogenicity	In vitro and in vivo	In vitro and in vivo	In vitro	In vitro
Isotypes	IgG1, IgG3	IgG4	IgG1	IgG1
Role of complement	Yes	No	Likely	Likely
Thymic pathology	Early onset: follicular hyperplasia Late onset: thymoma	No	?	Mild follicular hyperplasia
Correlation of ab titre with disease grade	No	Yes	?	?