Autoimmunity Reviews 12 (2013) 863–874

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Etiology of myasthenia gravis: Innate immunity signature in pathological thymus

Paola Cavalcante [a], Perrine Cufi [b], Renato Mantegazza [a], Sonia Berrih-Aknin [b], Pia Bernasconi [a,*,1], Rozen Le Panse [b,1]

[a] Department of Neurology IV, Neuromuscular Diseases and Neuroimmunology, Fondazione Istituto Neurologico 'Carlo Besta', Milan, Italy
[b] Unité mixte de recherche – CNRS UMR7215/INSERM U974/UPMC UM76/AIM – Thérapie des maladies du muscle strié, Groupe hospitalier Pitié-Salpêtrière, 105 Boulevard de l'Hôpital, Paris 75651 Cedex 13 — France

ARTICLE INFO

Article history:
Accepted 12 March 2013
Available online 25 March 2013

Keywords:
Myasthenia gravis
Etiology
Thymus
Inflammation
Toll-like receptors
Viral infection

ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction (NMJ), whose clinical hallmark is muscle weakness and early fatigability. The main target of autoimmunity in MG is the acetylcholine receptor (AChR) located in the NMJ. It is now widely accepted that the thymus is probably the prime site of autoimmunity development and maintenance in AChR-positive MG patients; however, the exact mechanisms triggering and perpetuating the intra-thymic autoimmune response to AChR are still unknown. As with many autoimmune diseases, MG has a multifactorial etiology, resulting from complex interactions between genetic and environmental factors, as fully described in this review. Among environmental factors, viral infections could play a central role in autoimmunity, mainly through the induction of dysregulated Toll-like receptor (TLR)-mediated innate immune responses, which can lead to inflammation and adaptive autoimmune response. Growing evidence of chronic inflammation, TLR activation, and persistent viral infections in the thymus of MG patients, strongly supports the hypothesis that, in the context of a genetic susceptible background, the intrathymic innate immune responses to pathogen infections might contribute to MG etiology.

Contents

Abbreviations: AChR, acetylcholine receptor; EAMG, experimental autoimmune MG; EBV, Epstein–Barr virus; ENOX1, ecto-NADH oxidase 1 gene; EOMG, early-onset MG; GC, germinal center; GWAS, genome-wide association studies; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; LRP4, lipoprotein receptor-related protein 4; LOMG, late-onset MG; MG, myasthenia gravis; MuSK, muscle specific kinase; NMJ, neuromuscular junction; PTPN22, protein tyrosine phosphatase nonreceptor-22; PV, poliovirus; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TNIP1, TNF-α-induced protein 3 (TNFAIP3)-interacting protein 1.

* Corresponding author. Tel.: +39 02 23942255; fax: +39 02 70633874.
E-mail address: pbernasconi@istituto-besta.it (P. Bernasconi).

[1] Equal contribution.

1568-9972/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.autrev.2013.03.010

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction (NMJ) in which muscle weakness and abnormal fatigability on exertion are the prominent clinical features; symptoms are due to neuromuscular transmission impairment caused by autoantibodies targeting postsynaptic membrane proteins of the striated skeletal muscles. Over 80% of patients have antibodies against acetylcholine receptor (AChR) [1] or clustered AChRs [2,3] and variable proportions (37.5–70.0%) of AChR-negative patients have antibodies to the muscle kinase receptor (MuSK) [4–10]. Recently, autoantibodies to the lipoprotein receptor-related protein 4 (LRP4) have been detected in variable proportions of AChR- and MuSK-negative (seronegative) MG patients [11–13] (Table 1).

MG patients can be distinguished in purely ocular and generalized forms and in early-onset (EOMG; under 40 years old) or late-onset (LOMG; over 40 years old) forms. At onset, extraocular muscles are often the first ones to be affected and may remain the only muscles involved (pure ocular MG); however, in many cases ocular disease progresses and involves skeletal or bulbar muscles, giving rise to the generalized form of MG [1]. Distribution of age at MG onset shows a female-dominant peak in EOMG and a male-dominant peak in LOMG [14]. In the recent years, the incidence of MG in the elderly (over 50 years old) population is increasing, likely due to aging, improved recognition and diagnosis of the disease or to unknown environmental factors [15–17].

In AChR-MG, correlation between disease severity and anti-AChR antibody titers is poor, hence the antibody prognostic value is poor [18]. MuSK-MG patients present often with more severe symptoms than AChR-MG patients. They have prominent bulbar and facial weakness associated with marked muscle atrophy and are less responsive to treatments [6]. Seronegative MG patients are instead clinically indistinguishable from AChR-MG patients [19].

Growing evidence supports the involvement of the thymus in the pathogenesis of MG. The role of this organ as a prime site of autosensitization and autoimmunity is widely accepted in AChR-MG patients. In these patients, the thymus exhibits morphological and functional abnormalities, usually characterized by a thymoma or by hyperplasia [20,21]. In MuSK-MG patients, the thymic contribution to the disease remains unclear (see Section 3 for an extensive review of the thymic MG pathogenesis).

Like other autoimmune diseases, MG is multifactorial and its manifestation results from the combination and interaction of multiple genetic and environmental risk factors. AChR-MG occurring in EOMG patients and presenting with thymic hyperplasia is the most common, and also the best characterized, subtype of MG. Although anti-AChR autoantibodies have been identified almost forty years ago [22], the exact immunological mechanisms underlying the autoimmune response are still unknown. Current treatments are quite effective but complete stable remission is observed only in a proportion of patients; these observations highlight the need of better understanding the specific factors and events initiating or perpetuating the disease [23]. A more comprehensive understanding of the genetic and environmental factors associated with MG and demonstration of the pathologically relevant gene-environment interactions are crucial for improving our knowledge in MG pathogenesis.

In this manuscript, we review early and more recent data on genetic and environmental risk factors associated with MG, giving particular emphasis on the emerging role of viral infections and innate immunity in the intrathymic pathogenesis of the disease.

2. Genetic and environmental factors related to MG etiology

MG is a multifactorial disease and appears likely to be linked to a combination of predisposing factors and triggering event(s). In thymoma-associated MG, the development of thymic epithelial tumors is a clear pathogenetic event, even if thymoma is not always associated with MG. In the other forms of autoimmune MG, the event leading to the disease is not clearly defined.

2.1. Genetic factors

Autoimmune MG does not show any Mendelian hereditary. However, as for many autoimmune diseases, a genetic risk accounts for some responsibility in the disease development, as attested by the 40% concordance rate in monozygotic twins [24].

2.1.1. The HLA genomic region

The association of human leukocyte antigen (HLA) class I and class II genes with MG is clearly established [25]. These genes comprise several hundreds of alleles on the chromosome 6p21 region, encoding membrane-bound molecules of the immunoglobulin superfamily that present antigenic epitopes to lymphoid cells. In Caucasian MG patients, a strong genetic association is observed between the HLA A1–B8–DR3 haplotype and EOMG patients [26]. The HLA-DR3 and B8 alleles are part of the most conserved HLA haplotype in European populations, the "so-called" 8.1 haplotype that associates the HLA-B8 allele with DR3, along with alleles of many other HLA loci, such as HLA-A1. This haplotype has been associated with several autoimmune conditions, including rheumatoid arthritis [27] and systemic lupus erythematosus [28], which often co-occur in MG patients [29]. The 8.1 haplotype was found to have a strong and complex genetic effect on phenotype in EOMG associated with thymic hyperplasia, including high serum titers of AChR autoantibodies [25]. However, because of strong linkage disequilibrium extending across this haplotype, the causative alleles are not known yet. Some studies pointed to a major contribution of HLA-DQ alleles to MG, as DQB1*0502 which has been associated with MG Italian population [30]. A recent study demonstrated novel associations between HLA-DQ loci and EOMG in southeast Texas patients, not previously reported in European MG patients, suggesting that region-specific environmental factors may interact with HLA genes to predispose toward MG [31]. The role of this specific HLA haplotype in MG is not clear. Nevertheless, peripheral blood mononuclear cells from HLA-B8, DR3-positive and DR3-negative individuals differ in their ability to produce interleukin (IL)-2, IL-5, IL-12 and interferon type II (IFN-II) upon stimulation [32].

Other genetic associations have been recently pointed out for different MG forms. A study has demonstrated a genetic association between the HLA DRB1*15:01 haplotype and LOMG patients [33]. In MuSK-MG, the disease has been associated with the HLA-DR14–DQ5 haplotype in a Dutch cohort [34] and with the HLA-DR14–DQ5 and HLA-DR16–DQ5 haplotypes in an Italian population [35], suggesting a major role for the DQ5 allele in this MG subtype.

In MG patients with thymoma, studies associating MG with HLA I and II alleles did not give reproducible results [36,37]. A recent