Striational Antibodies in Myasthenia Gravis

Reactivity and Possible Clinical Significance

Fredrik Romi, MD; Geir Olve Skeie, MD; Nils Erik Gilhus, MD; Johan Arild Aarli, MD

Myasthenia gravis is an autoimmune disease caused, in most cases, by antibodies attaching to the acetylcholine receptor. Some myasthenia gravis patients have antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections (striational antibodies). These antibodies react with epitopes on the muscle proteins titin and ryanodine receptor, are found mainly in sera of patients with thymoma and late-onset myasthenia gravis, and may correlate with myasthenia gravis severity. Their presence may predict an unsatisfactory outcome after thymectomy. The detection of titin and ryanodine receptor antibodies provides more specific clinical information than the immunofluorescent demonstration of striational antibodies.

Arch Neurol. 2005;62:442-446

Myasthenia gravis (MG) is caused by antibodies that react mainly with the acetylcholine receptor (AChR) on the postsynaptic site of the neuromuscular junction. In 1960, Strauss et al. used indirect immunofluorescence technique to demonstrate that sera from some patients with MG contained antibodies that gave a cross-striational staining when incubated with sections of striated muscle. These antibodies were named striational antibodies (Figure 1). In 1981, Aarli et al. demonstrated antibodies attaching to a citric acid extractable striational muscle antigen. Citric acid antigen and striational antibodies correspond to each other and are found mainly in serum samples of MG patients with thymoma.

Titin is a major muscle antigen in MG and at least partly responsible for the striational binding pattern. Some MG serum samples also contain IgG antibodies that react with another muscle antigen, the ryanodine receptor (RyR), that is found in sarcoplasmic reticulum. This study reviews current data on the striational antibodies and their significance in MG.

TITIN

Titin is a giant protein (3000 kDa) and is the third most abundant protein in the skeletal and cardiac sarcomere (Figure 2A). The molecule is about 1 µm long, extending from the Z disk to the M line. Ninety percent of the titin mass is contained in a repetitive structure comprising 244 to 297 copies of 2 different 100-residue repeats; the 112 to 165 immunoglobulin superfamily domains, and 132 fibronectin-like domains. The rest of the titin mass consists of unique sequences with specialized functions. Titin molecules are arranged in a way that allow augmentation of mechanical stability and tension in the sarcomere. The titin-based tension is calcium responsive because titin is a calcium-dependent molecular spring that adapts to the physiological state of the cell.

The main immunogenic region of titin is called myasthenia gravis titin-30 (MGT-30) and is situated near the A/I-band junction (Figure 2A). Another im...
The immunogenic region is located between the N1 and N2 lines. This consists of homologous immunoglobulin domains. These are differentially expressed; 15 modules are expressed in cardiac muscle, while there may be up to 68 such modules in skeletal muscle. Antibodies to the I-band epitope are present only in sera containing MGT-30 antibodies. When I-band epitope antibodies are present, a double-band immunofluorescence technique staining is obtained (Figure 2B). Patients who have antibodies attaching to I-band epitopes also have antibodies attaching to the main immunogenic region. The presence of antibodies attaching to the I-band epitopes may indicate titin epitope spreading.

THE RyR

The RyR is a calcium release channel located in the sarcoplasmic reticulum. The name refers to the alkaloid ryanodine that binds selectively to the RyR. There are 2 forms of RyR, skeletal (RyR1) and cardiac (RyR2). The RyR antibodies from MG patients react with both. The RyR is a protein containing 5035 amino acids with a molecular weight of 565 kDa. It is composed of 4 homologous subunits that can build a tetramer with a central channel

OTHER STRIATIONAL ANTIGENS AND ANTIBODIES

Antibodies to human myosin were described in 1969. Cultured, dissociated, thymic lymphocytes from patients with MG secrete monoclonal striational antibodies that bind to skeletal muscle myosin, α-actinin, and actin. Patients with MG and thymoma have higher titers of anti-myosin and anti-actomyosin antibodies than patients with MG but without thymoma. Antibodies against rapsyn (a 43-kDa postsynaptic protein essential for anchoring and clustering AChR) have been identified in MG but are also found in serum samples from patients with lupus and chronic procainamide associated myopathy.
STRIATIONAL ANTIBODIES IN SUBGROUPS OF MG

Myasthenia gravis can be classified into several subtypes based on the immunological profile. Nearly all patients with MG and thymoma and half of the late-onset MG subgroup (onset of MG at ≥50 years of age) demonstrate an antibody profile with a broad striational antibody response. In contrast, AChR antibody–positive patients with early-onset MG (onset of MG at <50 years of age) and AChR antibody–positive MG with purely ocular symptoms have a selective high antibody response against AChR. Striational autoantibodies are rarely found in AChR antibody–negative MG.

STRIATIONAL ANTIBODIES AND THE DIAGNOSIS OF THYMOMA

Striational autoantibodies and computed tomographic scan of the anterior mediastinum show a similar sensitivity for thymoma MG. In our studies, computed tomographic scan failed to predict a thymoma in 27% of the cases. The positive predictive value for thymoma is significantly higher for RyR antibodies. The absence of these antibodies strongly excludes thymoma (Table).

STRIATIONAL ANTIBODIES AND THE SEVERITY OF MG

The AChR antibody serum concentration does not correlate with MG severity, mainly because of individual variations in AChR epitope specificity. Myasthenia gravis tends to be more severe in patients with thymoma than in the early-onset MG subgroup. The presence of striational autoantibodies is associated with a more severe disease in all MG subgroups, and citric acid antigen, titin, and RyR antibodies occur significantly more often among patients with severe MG than among patients with less severe disease. These antibodies can therefore be used as prognostic determinants in MG patients.

STRIATIONAL ANTIBODIES AND THYMECTOMY IN MG

Patients with early-onset MG may benefit from thymectomy. The AChR antibody concentration does not predict the outcome of thymectomy. Titin and RyR antibodies are not found in early-onset MG. Patients with late-onset MG benefit far less from thymectomy. An improvement appears less likely in cases with titin and/or RyR antibodies. Myasthenia gravis severity and outcome over time seem to be equal in thymoma and non-thymoma MG, but the presence of RyR antibodies in thymoma MG and titin/RyR antibodies in nonthymoma MG indicates a less favorable prognosis. The RyR antibodies are often found in patients with an invasive or malignant thymoma.

STRIATIONAL ANTIBODIES AND HLA LINKAGE IN MG

The correlation between MG and specific HLA antigens has long been recognized. Patients with MG and titin antibodies often express the HLA-DR7 haplotype, while those with thymus hyperplasia and no titin antibodies express HLA-DR3. Extended haplotypes including tumor necrosis factor α or β polymorphisms confirm the
linkage to specific major histocompatibility complex haplotypes. This supports that patients with and without striational antibodies belong to pathogenetically different subsets of MG.

DO STRIATIONAL ANTIBODIES HAVE A ROLE IN THE PATHOGENESIS OF MG?

The complement concentration in the serum of MG patients varies with disease severity, increasing during remission and decreasing during exacerbation. This can be explained by activated complement components attacking the AChR at the end plate. However, titin and RyR antibodies also activate complement in vitro through the IgG 1-mediated pathway. Complement activation caused by striational antibodies is therefore a potential mechanism for additional immune damage. The presence of titin antibodies in patients with MG correlates with their electromyographic evidence of myopathy. This does not prove any pathogenic role for titin and RyR antibodies in MG.

The initial steps in the triggering of humoral immunity in MG presumably take place inside the thymus. Fifty percent of patients with cortical-type thymoma have MG, and the presence of muscle-like epitopes within thymomas has been demonstrated. MG-associated thymomas are enriched in AChR-like epitopes and AChR-specific T-cells. Titin and RyR epitopes have also been identified on neoplastic thymoma cells. In MG associated thymoma, there is an overexpression of thymus musclelike epitopes and costimulatory molecules indicating that the T-cell autoimmunization is promoted by the pathogenic microenvironment inside the thymoma. Titin and RyR epitopes are coexpressed along with LFA3 and B7 (BB1), which are costimulatory molecules indicating that the T-cell autoimmunization is promoted by the pathogenic microenvironment inside the thymoma. Titin and RyR epitopes are coexpressed along with LFA3 and B7 (BB1), which are costimulatory molecules indicating that the T-cell autoimmunization is promoted by the pathogenic microenvironment inside the thymoma. Titin and RyR epitopes are coexpressed along with LFA3 and B7 (BB1), which are costimulatory molecules indicating that the T-cell autoimmunization is promoted by the pathogenic microenvironment inside the thymoma.

Accepted for Publication: July 14, 2004.
Correspondence: Fredrik Romi, MD, Department of Neurology, Haukeland University Hospital, N-5021 Bergen, Norway (fredrik.romi@haukeland.no).
Author Contributions: Study concept and design: Romi, Skeie, Gilhus, Aarli. Acquisition of data: Romi, Skeie, Gilhus, Aarli. Analysis and interpretation of data: Romi, Skeie, Gilhus, Aarli. Drafting of the manuscript: Romi, Skeie, Gilhus, Aarli. Critical revision of the manuscript for important intellectual content: Romi, Skeie, Gilhus, Aarli. Statistical analysis: Romi, Skeie, Gilhus, Aarli.
Funding/Support: This study was supported by EU grant QRLT-2000-019188.

REFERENCES


---

**Call for Papers**

**ARCHIVES Express**

The ARCHIVES launched a new ARCHIVES Express section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited ARCHIVES Express review. We look forward to publishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD