REVIEW ARTICLE

MEDICAL PROGRESS

MYASTHENIA GRAVIS

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TWENTY years ago, the discovery of a deficit of acetylcholine receptors at the neuromuscular junctions of patients with myasthenia gravis[1] and the development of an animal model of the disease[2] shed new light on a disorder that was first described clinically 300 years earlier by the great physiologist Thomas Willis.[3] During the past two decades, remarkable progress has been made in our understanding of myasthenia gravis, and the new knowledge has been applied directly to the clinical diagnosis and treatment of this formerly grave disease. Myasthenia gravis is undoubtedly the most thoroughly understood of all human autoimmune diseases and has served as a model for the elucidation of mechanisms underlying other autoimmune disorders.

The muscular weakness and fatigability that are the hallmarks of myasthenia gravis are known to be due to an antibody-mediated autoimmune attack directed against acetylcholine receptors at neuromuscular junctions. Several mechanisms by which the autoantibodies deplete the number of available acetylcholine receptors have been shown to contribute to the clinical severity of the disease. The target antigen, the nicotinic acetylcholine receptor, has been purified from a variety of sources, including human muscle, and its molecular structure is now known. Genes for all the subunits of the acetylcholine receptor have been cloned, and these subunits have been produced by genetic engineering. An experimental model of myasthenia gravis, induced by immunization of animals with acetylcholine receptors, has contributed to our understanding of the disease mechanisms. Advances in the diagnosis and treatment of myasthenia gravis have been equally impressive. A firm diagnosis can be made in nearly all patients. With the use of modern immunotherapy, the prognosis of the disease has improved dramatically. Formerly fatal or disabling in most patients, myasthenia can now be treated effectively, so that nearly all patients are able to lead full, productive lives.

Despite these advances, important gaps in our knowledge remain. The factors that initiate and maintain the autoimmune response in myasthenia gravis are not yet known. The cellular immunology of the disease is now the subject of intensive study: the object is to determine precisely how T cells and B cells specific for acetylcholine receptors interact to produce pathogenic autoantibodies. The heterogeneity of the immune responses of both T cells and B cells to the acetylcholine receptor makes this a challenging problem. Ideally, given the extensive knowledge of the pathogenesis and immunology of myasthenia gravis, it should be possible to devise specific methods of immunotherapy and ultimately to cure the underlying disorder.

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CLINICAL FEATURES

Myasthenia gravis is not rare, with a prevalence of 50 to 125 cases per million population,[4] or approximately 25,000 affected persons in the United States. The incidence is age- and sex-related, with one peak in the second and third decades affecting mostly women and a peak in the sixth and seventh decades affecting mostly men. The cardinal features are weakness and fatigability of skeletal muscles, usually occurring in a characteristic distribution. The weakness tends to increase with repeated activity and improve with rest. Ptosis and diplopia occur early in the majority of patients. Weakness remains localized to the extraocular and eyelid muscles in about 15 percent of patients.[5] When the facial and bulbar muscles are affected, there may be a characteristic flattened smile, "mushy" or nasal speech, and difficulty in chewing and swallowing. Generalized weakness develops in approximately 85 percent of patients[5]; it may affect the limb muscles, often in a proximal distribution, as well as the diaphragm and the neck extensors. If weakness of respiration becomes severe enough to require mechanical ventilation, the patient is said to be in crisis.

On physical examination, the findings are limited to the motor system, without loss of reflexes or alteration of sensation or coordination. The patient's base-line strength should be documented quantitatively for later evaluation of the results of treatment. The most useful quantitative measures include timed forward-arm abduction, vital capacity, and dynamometry of selected muscles. The clinical severity of myasthenia gravis is usually graded functionally and regionally, according to an adaptation of a scale devised by Osserman[6]: grade I involves focal disease (e.g., restricted to ocular muscles); grade II, generalized disease that is either mild (IIa) or moderate (IIb); grade III, severe generalized disease; and grade IV, a crisis, with life-threatening impairment of respiration.

THE NEUROMUSCULAR JUNCTION IN MYASTHENIA GRAVIS

The basic abnormality in myasthenia gravis is a decrease in the number of acetylcholine receptors at neuromuscular junctions[1] (Fig. 1). This was first demonstrated by the use of a radioactively labeled snake toxin, α-bungarotoxin, which binds specifically, quan-

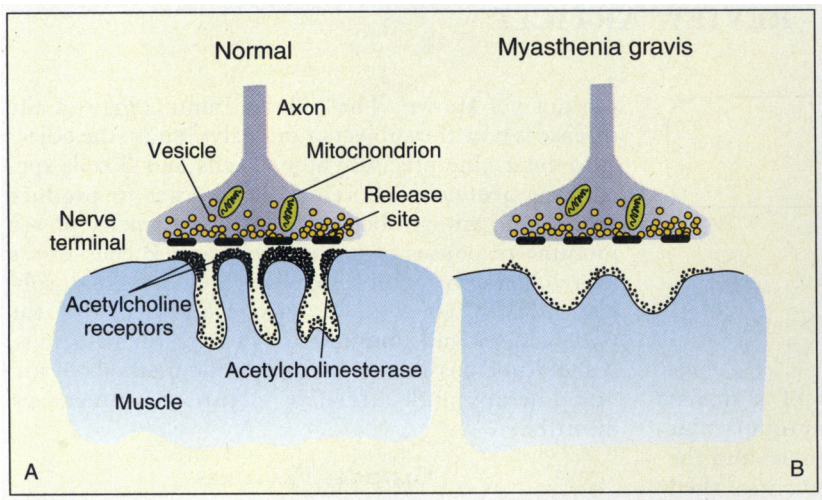

Figure 1. Normal (Panel A) and Myasthenic (Panel B) Neuromuscular Junctions.
In neuromuscular junctions, vesicles release acetylcholine at specialized release sites of the nerve terminal. Acetylcholine crosses the synaptic space to reach receptors that are concentrated at the peaks of junctional folds. Acetylcholinesterase in the clefts rapidly terminates transmission by hydrolyzing acetylcholine. The myasthenic junction has reduced numbers of acetylcholine receptors, simplified synaptic folds, a widened synaptic space, and a normal nerve terminal.

titatively, and irreversibly to acetylcholine receptors of skeletal muscles.[7] Studies of muscle-biopsy specimens showed that the neuromuscular junctions of patients with myasthenia gravis had only one third as many acetylcholine receptors on the average as those of healthy controls.[8] In general, the degree of reduction of acetylcholine receptors correlated with the severity of myasthenia gravis. However, even patients with weakness restricted to the extraocular muscles had reduced numbers of junctional acetylcholine receptors in clinically strong limb muscles. Neuromuscular junctions from patients with myasthenia gravis also show the morphologic changes of simplification of the pattern of postsynaptic membrane folding and an increased gap between the nerve terminal and the postsynaptic muscle membrane[9] (Fig. 1).

These changes at the neuromuscular junction account fully for the clinical and electrophysiologic features of myasthenia gravis. The basic principle is that muscle contraction depends on effective neuromuscular transmission, and the effectiveness of transmission depends on the number of interactions between acetylcholine molecules and acetylcholine receptors. When acetylcholine binds to the acetylcholine receptor, the receptor's cation channel opens transiently, producing a localized electrical end-plate potential. If the amplitude of this potential is sufficient, it generates an action potential that spreads along the length of the muscle fiber, triggering the release of calcium from internal stores and leading to muscle contraction. At normal neuromuscular junctions, the end-plate potentials are more than sufficient to generate muscle action potentials consistently, without failures. At myasthenic junctions, the decreased number of acetylcholine receptors results in end-plate potentials of diminished amplitude, which fail to trigger action potentials in some fibers.[10,11] When transmission fails at many junctions, the power of the whole muscle is reduced, which is clinically manifested as weakness. Neuromuscular fatigue is the most characteristic clinical feature of myasthenia gravis: when contractions are repeated, muscle power progressively declines as a result of the failure of transmission at more and more neuromuscular junctions. This results from the reduction of acetylcholine receptors at myasthenic junctions and the normal phenomenon of acetylcholine "rundown": during repeated nerve stimulation, the amount of acetylcholine released per impulse normally declines (runs down) after the first few impulses, since the nerve terminal is not able to sustain its initial rate of release.[12] At myasthenic junctions, this rundown results in the progressive failure of transmission, because of the reduced number of acetylcholine receptors.

The Acetylcholine Receptor

The nicotinic acetylcholine receptor (Fig. 2) of skeletal muscle is the target of the autoimmune response in myasthenia gravis. It is a glycoprotein with a molecular weight of approximately 250,000 that projects through the muscle membrane and is composed of five subunits, arranged like barrel staves around a central channel[13,14] (Fig. 2). Each acetylcholine-receptor molecule consists of two α subunits, one β subunit, one δ subunit, and one γ or ϵ subunit. Each of the two α subunits has an acetylcholine-binding site that is located extracellularly and centered around amino acids 192 and 193.[15] Functionally, the ion channel of the acetylcholine receptor is closed in the resting state. When the binding sites of both α subunits are occupied by acetylcholine, the channel opens transiently, allowing the rapid passage of cations.

Acetylcholine receptors normally undergo continual turnover at the neuromuscular junction.[16] Motor nerves have an important role in this process, regulating the synthesis, subunit composition, distribution, and degradation of the receptors.[17-20] There is substantial evidence that neuromuscular transmission has a key role in the neural regulation of these properties.[21] Impairment of transmission induces increased transcription of acetylcholine-receptor genes.[22] This may account for the increased transcription of acetylcholine-receptor genes that has been reported in experimental myasthenia gravis.[23] These processes of turnover and renewal of junctional acetylcholine receptors permit virtually complete recovery in patients with myasthenia gravis, once the autoimmune attack has been brought under control.

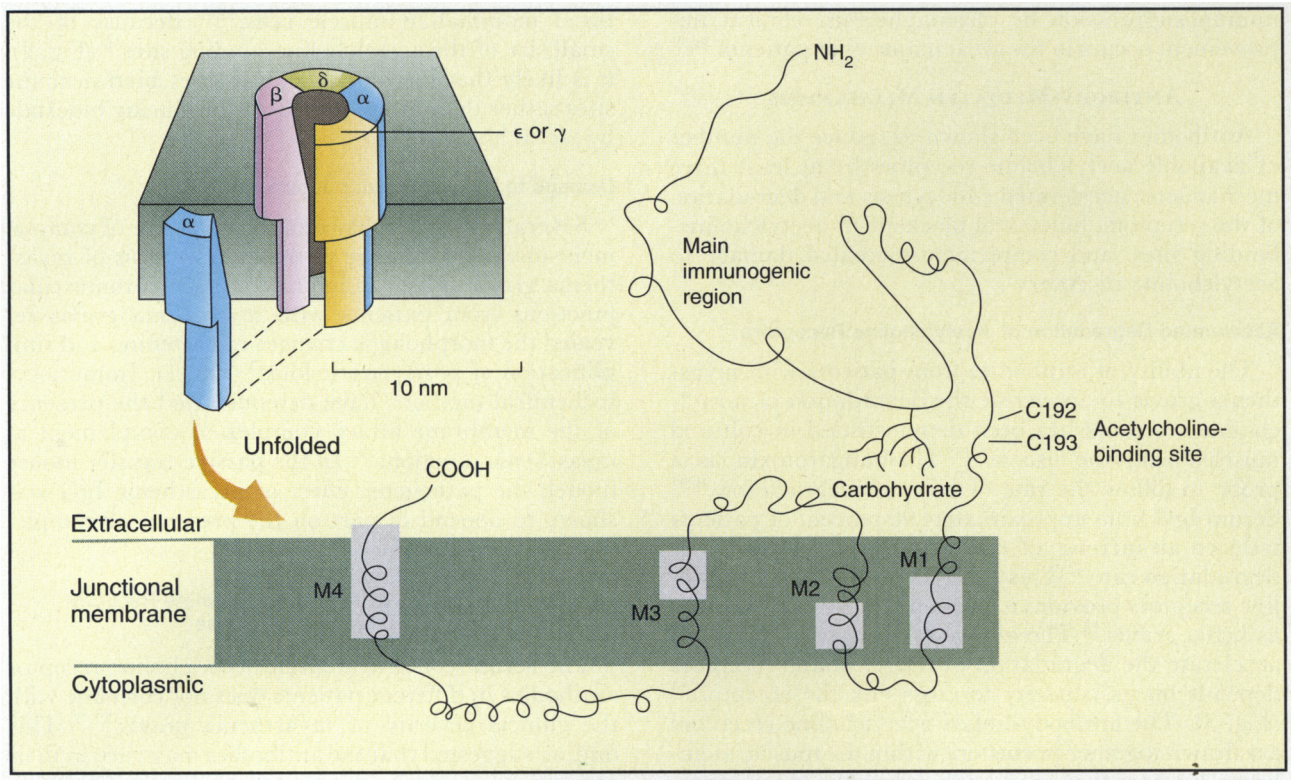

Figure 2. The Acetylcholine Receptor.

The subunits of the acetylcholine receptor — α, β, δ, and γ or ϵ — are arranged like barrel staves around the central ion pore. Each subunit winds through the junctional membrane four times (sites M1, M2, M3, and M4). In the unfolded view of the α subunit, the amino-terminal end of the α subunit is extracellular, where it is accessible to acetylcholine, which binds at the site shown (amino acids 192 and 193). In myasthenia gravis, autoantibodies may bind to various epitopes of all subunits, but a high proportion of antibodies bind to the main immunogenic region of the α subunit.

The richest natural source of acetylcholine receptors is the electric organ of the electric ray (torpedo) or eel (electrophorus), which consists of arrays of neuromuscular junction–like structures capable of producing powerful electrical discharges.[24] Human acetylcholine receptor extracted from amputated limbs is commonly used for diagnostic radioimmunoassay of acetylcholine-receptor antibodies,[25] but only relatively small amounts of pure acetylcholine receptor can be obtained from this source. One of the most important advances in receptor biology has been the sequencing and cloning of genes for all the receptor subunits of many species, including humans and electric rays.[26,27] Through the use of genetic-engineering technology it is now possible to produce fusion proteins consisting of large stretches or entire subunits of the acetylcholine receptor.[28,29] Structurally and functionally intact acetylcholine receptors have been produced by inserting subunit messenger RNA (mRNA) into cells such as frog oocytes.[30] Acetylcholine receptors generated by modern biotechnology may prove to be extremely important in future therapeutic strategies.

Immunopathogenesis of Myasthenia Gravis

It is widely accepted that the neuromuscular abnormalities in myasthenia gravis are due to antibody-mediated processes. The supporting evidence satisfies a set of five criteria[31] that define the pathogenesis of autoantibody-mediated disorders. First, antibody is present. Overall, 80 to 90 percent of patients with myasthenia gravis have serum antibodies to acetylcholine receptor that are detected by a standard assay.[32,33] Second, antibody interacts with the target antigen, acetylcholine receptor. In patients with myasthenia gravis, the presence of IgG at neuromuscular junctions, adjacent to acetylcholine receptors, has been demonstrated by the use of electron-microscopical immunochemical techniques.[34] Third, passive transfer reproduces disease features.[35] Passive-transfer experiments have provided the most direct evidence of the pathogenic role of autoantibodies. Repeated injections of IgG from patients with myasthenia gravis into mice reproduced the characteristic features of the disease. Fourth, immunization with the antigen produces a model disease.[2] Immunization of a variety of animal species from frogs to primates clearly demonstrates that an immune response directed against acetylcholine receptors is capable of reproducing the key physiologic, clinical, and diagnostic features of myasthenia gravis.[2,36,37] The experimental model of the disease has been particularly useful for testing new therapeutic strategies. Fifth, a reduction of antibody levels ameliorates the disease. When levels of acetylcholine-receptor antibody are reduced by

immunosuppression or plasmapheresis, clinical improvement occurs in the great majority of patients.[38,39]

Antibody-Mediated Mechanisms

Antibodies have been shown to reduce the number of available acetylcholine receptors by at least three mechanisms: accelerated endocytosis and degradation of the receptors, functional blockade of acetylcholine-binding sites, and complement-mediated damage to acetylcholine receptors.

Accelerated Degradation of Acetylcholine Receptors

The ability of antibodies from patients with myasthenia gravis to accelerate the degradation of acetylcholine receptors has been demonstrated in cultured muscles with the use of [^{125}I]α-bungarotoxin as a probe to follow the rate of receptor degradation.[40,41] Serum IgG from approximately 90 percent of patients induced an increase of up to two- to threefold in the degradation rate.[42] This accelerated loss of acetylcholine receptors provides a useful diagnostic test for myasthenia gravis.[43] The ability of the patients' IgG to accelerate the degradation of acetylcholine receptors depends on its capacity to cross-link the receptors[44] (Fig. 3). The antibody-linked acetylcholine receptors are drawn together in clusters within the muscle membrane,[45] where they are rapidly internalized by a process of endocytosis and then degraded. The critical step in this process is accelerated endocytosis of acetylcholine receptors. Antibody-accelerated degradation of the receptors has been demonstrated not only in cultured muscle cells but also in vivo at intact neuromuscular junctions.[46]

Blockade of Acetylcholine Receptors

Serum IgG from 50 to 88 percent of patients with myasthenia gravis has been shown to block the acetylcholine-binding sites of acetylcholine receptors in cultured mammalian muscle cells.[42,43] Because of the small size of the acetylcholine-binding sites[15] (Fig. 2), it is likely that the blocking antibodies bind near the sites rather than directly at them, producing blockade by steric hindrance.

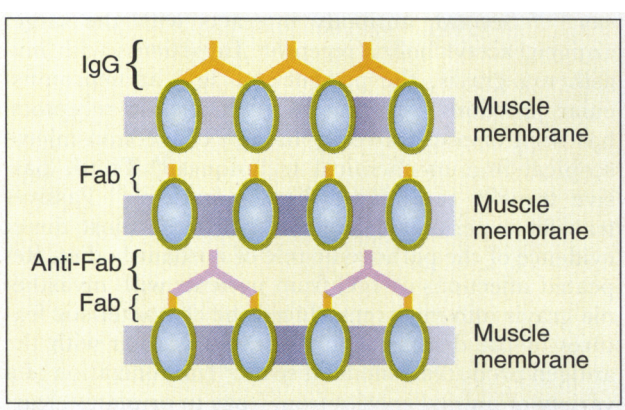

Figure 3. Cross-Linking of Acetylcholine Receptors by Antibodies.
Accelerated degradation occurs when the acetylcholine receptors (ovals) are cross-linked by intact divalent antibodies (top panel). Monovalent Fab fragments prepared by enzymatic cleavage of IgG from patients with myasthenia gravis bind to single acetylcholine receptors but do not accelerate degradation (middle panel). When a "piggyback" antibody (anti-Fab) cross-links acetylcholine receptors through the attached Fab fragments (bottom panel), degradation is accelerated.

Damage to Neuromuscular Junctions

Several lines of evidence support the role of complement-mediated damage in the pathogenesis of myasthenia gravis. Electron microscopy of neuromuscular junctions from patients with myasthenia gravis revealed the morphologic changes of flattening and simplification of postsynaptic folds[9] (Fig. 1). Immunocytochemical methods have demonstrated the presence of the membrane attack complex of complement at myasthenic junctions.[47] In the passive-transfer mouse model, the pathogenic effect of myasthenic IgG was shown to depend in part on the presence of complement in recipient mice.[35]

Functional Properties of Anti–Acetylcholine-Receptor Antibodies and the Severity of Disease

The serum concentration of acetylcholine-receptor antibodies in different patients does not correlate with the clinical severity of myasthenia gravis.[32,42] This finding suggested that the antibodies may vary in their capacity to produce myasthenic weakness. The functional activities of the antibodies in accelerating degradation or blocking acetylcholine receptors have been shown to correspond closely with the severity of myasthenic weakness.[42] Interestingly, antibodies from some patients had a more pronounced effect on degradation, whereas others produced more marked blockade of acetylcholine receptors. Their particular functional effects are probably related to the specific epitopes of acetylcholine receptor to which they bind. In addition to these functional activities, other properties of the antibodies, such as their ability to bind complement, undoubtedly contribute to their pathogenicity. Moreover, differences in neuromuscular junctions in different patients, or even in different muscles of an individual patient, can influence the degree of muscle weakness.

Properties of Acetylcholine-Receptor Antibodies

The large size and complex structure of the acetylcholine-receptor molecule suggest that autoantibodies binding to many different epitopes should exist. There is now abundant evidence that patients with myasthenia gravis have heterogeneous populations of acetylcholine-receptor antibodies and that there is only limited sharing of specificities between patients.[48,49] Acetylcholine-receptor antibodies generally recognize epitopes that are determined by their three-dimensional conformation. Most pathologically relevant antibodies bind to extracellular domains of the acetylcholine-receptor molecule[50] (Fig. 2). The majority of antibodies bind to the α subunit,[50] possibly because each molecule has two α subunits. A relatively large proportion of these antibodies bind to a restricted region of the α subunit, the "main immunogenic re-

gion"[50,51] (Fig. 2). However, even antibodies to this restricted region are heterogeneous in the fine specificities of the epitopes to which they bind.[48,50,51] Moreover, many antibodies bind to other sites on the α subunit and on each of the other subunits of the acetylcholine receptor. In addition to this heterogeneity of their binding sites, acetylcholine-receptor antibodies from patients with myasthenia gravis vary in their light-chain and subclass composition[48,52] and in their functional activities[42] (see above). The extensive heterogeneity of antibodies in the disease, and therefore of the B cells that produce them, is of paramount importance in the design of strategies for immunotherapy of myasthenia gravis.

"Antibody-Negative" Myasthenia Gravis

Paradoxically, about 10 to 20 percent of patients with acquired myasthenia gravis do not have acetylcholine-receptor antibodies detectable by radioimmunoassay.[32,33,43] Although this group includes patients with mild localized weakness, there is also a subgroup of antibody-negative patients with generalized weakness whose disease corresponds to conventional myasthenia gravis with respect to other clinical, diagnostic, and therapeutic features.[49,53-57] Actually, these patients have circulating acetylcholine-receptor antibodies that are not detected by radioimmunoassay. However, passive transfer of their immunoglobulin to mice caused the loss of junctional acetylcholine receptors and reduced miniature end-plate potentials.[49,55] Furthermore, immunoglobulin from antibody-negative patients bound to acetylcholine receptors of cultured muscle cells and accelerated the degradation of these receptors.[56] IgM from antibody-negative patients has also been reported to interfere with the function of the acetylcholine-receptor channel in a human cell line.[57] Taken together, these studies lead to the conclusion that antibody-negative myasthenia gravis is an antibody-mediated autoimmune disorder. The inability to detect acetylcholine-receptor antibodies by radioimmunoassay when they are readily demonstrated in cultured-muscle-cell assay systems suggests that the antibodies may be directed at epitopes not present in the soluble acetylcholine-receptor extract or may have too low an affinity for detection in the soluble assay system.

Role of Lymphocytes in Myasthenia Gravis

Although the production of acetylcholine-receptor antibodies is directly attributable to B cells, there is extensive evidence that T cells have a key role in the autoantibody response of myasthenia gravis in humans and animals.[58-69] Thus, T cells from patients with myasthenia gravis respond to stimulation with acetylcholine receptors[59-64] and augment the production of acetylcholine-receptor antibodies in vitro.[64] Peripheral-blood lymphocytes of patients include T cells and B cells specific for acetylcholine receptors.[65,66] T-cell lines or clones reactive to acetylcholine receptors have been isolated from peripheral blood, or more efficiently from thymuses, of patients with myasthenia gravis and have been propagated in vitro.[62-64,68,69] Although acetylcholine-receptor–specific lymphocytes are more numerous in patients with myasthenia gravis than in normal subjects, lymphocytes from normal subjects can also respond to acetylcholine receptor.[65,66,69]

In contrast to their role in the production of acetylcholine-receptor antibody, T cells probably do not act as effector cells in myasthenia gravis. Although collections of mononuclear cells are occasionally found in myasthenic muscle,[70] they are very sparse[71] and are thought to consist of monocytes or macrophages. Inflammatory cells are more prominent in experimental myasthenia gravis in animals,[72] but appear to be macrophages rather than T cells.

Much work has been done to determine the antigen-response patterns of T cells in myasthenia gravis. In general, helper T cells (CD4+) respond to antigen that has been enzymatically degraded, or processed, by antigen-presenting cells and is associated with the major histocompatibility complex (MHC) class II molecules[73] (Fig. 4). MHC class II molecules contain a groove that accommodates linear peptides approximately 15 to 20 amino acids in length.[74] The specific MHC molecule plays an important part in selecting which peptides can be bound and presented. The T-cell receptor recognizes the peptide only in association with the MHC class II molecule. Analysis of T cells from patients (and animals) with myasthenia gravis has revealed striking heterogeneity in their patterns of responsiveness. Each patient's cells respond to multiple epitopes, and there are also substantial differences in the epitopes to which different patients' cells respond.[61-63,67,75-77] Although the majority of T-cell recognition sites are on the α subunit, T cells also recognize epitopes on the other subunits. Indeed, T cells of patients with myasthenia gravis have been shown to respond to more than 30 different acetylcholine-receptor–derived peptides.[77] Efforts to analyze the repertoire of T-cell receptors that recognize acetylcholine receptors are still in progress, but there does not appear to be a consistent restricted pattern.[78,79] The evidence of T-cell heterogeneity must be taken into account when specific immunotherapeutic approaches aimed at these T cells are designed.

Origin of the Autoimmune Response in Myasthenia Gravis

One of the unsolved problems in myasthenia gravis, as in the other human autoimmune diseases, concerns the origin of the autoimmune response. The thymus has been implicated as a possible site of origin because approximately 75 percent of patients have thymic abnormalities.[80] Of these, 85 percent have hyperplasia (germinal-center formation) and 15 percent have thymomas. Thymectomy results in improvement in most patients.[81] Both T cells and B cells from the thymus glands of patients with myasthenia gravis are more responsive to the acetylcholine receptor than are T cells and B cells from peripheral blood.[68] In addi-

tion to lymphocytes, normal and myasthenic thymus glands contain muscle-like (myoid) cells[82,83] that bear surface acetylcholine receptors.[83] The myoid cells are probably the source of acetylcholine receptor and mRNA for the α subunit of the receptors that have been found in thymic extracts.[84] Because of their strategic location within the thymus, surrounded by antigen-presenting cells and helper T cells,[85] the acetylcholine-receptor–bearing myoid cells may be particularly vulnerable to immune attack. Some alteration of the myoid cells or the lymphocytes, or a breach of immune regulation, may interfere with tolerance and lead to an autoimmune response. The possibility that a viral infection of the thymus could trigger this process has been suggested, but studies have thus far failed to yield evidence of viral infection.[86]

The hypothesis that myasthenia gravis may be triggered by molecular mimicry — that is, an immune response to an infectious agent that resembles the acetylcholine receptor — has acquired some support. Antibodies obtained from 6 of 40 patients with myasthenia gravis bound to a peptide sequence of herpes simplex virus that is homologous to a sequence of the acetylcholine-receptor α subunit.[87] Cross-reactivity between bacteria and the acetylcholine receptor has also been reported.[88]

Genetic factors and abnormalities of immune regulation may increase the likelihood of myasthenia gravis. There is a moderate association of myasthenia with the HLA antigens B8 and DRw3; a stronger association with HLA-DQw2 is still controversial.[89,90] A wide variety of other autoimmune diseases have been reported to occur in some patients with myasthenia gravis and their relatives[91,92] (Table 1), supporting a defect in immune regulation as a possible cause and suggesting that the predisposition may be heritable.

Diagnosis

Patients who have been given a diagnosis of myasthenia gravis usually must undergo long-term medical or surgical treatment that entails substantial risks. It is therefore essential to establish the diagnosis unequivocally, rule out other conditions that mimic the disease, and search for associated conditions that may influence the choice of treatment. The history and physical findings are usually the most important initial clues to the diagnosis.

Table 1. Disorders Associated with Myasthenia Gravis and Recommended Laboratory Tests.

Associated disorders
Disorders of the thymus: thymoma, hyperplasia
Other autoimmune disorders: thyroiditis, Graves' disease, rheumatoid arthritis, lupus erythematosus, skin disorders, family history of autoimmune disorder
Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (aminoglycoside antibiotics, quinine, antiarrhythmic agents)
Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis
Recommended laboratory tests or procedures
Magnetic resonance imaging or computed tomography of mediastinum
Tests for lupus erythematosus: antinuclear antibody, rheumatoid factor, antithyroid antibodies
Thyroid-function tests
Tuberculin test
Chest radiography
Fasting blood glucose measurement
Pulmonary-function tests
Bone densitometry in older patients

Diagnostic Testing

Before immunotherapy is initiated, confirmatory laboratory testing is essential, and the following order is suggested: anticholinesterase test, repetitive nerve stimulation, assay for anti–acetylcholine-receptor antibody, and single-fiber electromyography (if necessary). Drugs that inhibit the enzyme acetylcholinesterase allow acetylcholine that is released from the nerve to interact repeatedly with the limited number of junctional acetylcholine receptors, resulting in enhanced strength of myasthenic muscles. Edrophonium (Tensilon) is commonly used for the anticholinesterase test, because of the rapid onset (30 seconds) and short duration (about 5 minutes) of its effect. If there is unequivocal improvement in an objectively weak muscle, the test is considered positive.[93] In repetitive nerve stimulation, electric shocks are delivered to the nerve at a rate of three per second, and action potentials are recorded from surface electrodes over the muscle. A rapid reduction in the amplitude of the evoked muscle action potential (decremental response of 15 percent) is considered a positive response.[94] The yield of positive results is increased when weak muscles or several proximal muscles are tested. A radioimmunoassay that uses detergent-solubilized human acetylcholine receptor labeled with [^{125}I]α-bungarotoxin is the standard test for anti-acetylcholine-receptor antibody.[25,32,33] Single-fiber electromyography detects delayed or failed neuromuscular transmission in pairs of muscle fibers supplied by branches of a single nerve fiber.[95]

The anticholinesterase and repetitive nerve stimulation tests are the least sensitive and specific of the tests. A positive assay for acetylcholine-receptor antibodies is specific for myasthenia gravis, but antibodies are detectable in only about 85 percent of all patients, and in an even lower proportion (approximately 50 percent) of patients with purely ocular-muscle weakness.[25,32,33] Other tests for antibodies, which measure accelerated degradation or blockade of acetylcholine receptors, are sometimes helpful in antibody-negative myasthenia gravis.[43,56] Single-fiber electromyography is sometimes helpful in difficult diagnostic situations. It is positive in 88 to 92 percent of patients, but its specificity is limited, with positive findings in other disorders of nerves, muscles, or neuromuscular junctions.[95,96]

Differential Diagnosis

Other conditions that cause weakness of the cranial and somatic musculature must be considered in the differential diagnosis of myasthenia gravis, including congenital myasthenic syndromes,[97] drug-induced myasthenia,[98-100] hyperthyroidism, Graves' disease, Lambert–Eaton myasthenic syndrome,[101,102] botulism, progressive external ophthalmoplegia,[103] and intracranial mass lesions[104] (Table 2). The con-

Table 2. Differential Diagnosis of Myasthenia Gravis.

CONDITION	SYMPTOMS AND CHARACTERISTICS	COMMENT	REFERENCE
Congenital myasthenic syndromes	Rare; early onset; not autoimmune disorders	Sophisticated electrophysiologic and immunocytochemical tests required for diagnosis	Penn et al.[97]
Drug-induced myasthenia			
Penicillamine	Triggers autoimmune myasthenia	Recovery within weeks after drug withdrawal	Bucknall et al.,[98] Kuncl et al.[99]
Curare, procainamide, quinines, aminoglycosides	Weakness in normal persons; exacerbation of myasthenia	Recovery after drug withdrawal	Howard[100]
Lambert–Eaton syndrome	Weakness; fatigue; areflexia; 60 percent of cases associated with oat-cell cancer	Incremental response on repetitive nerve stimulation; antibody to calcium channels present	O'Neill et al.,[101] Lang et al.[102]
Hyperthyroidism	Exacerbation of myasthenia; generalized weakness	Thyroid function abnormal	
Graves' disease	Diplopia; exophthalmos	Thyroid-stimulating immunoglobulin present	
Botulism	Generalized weakness; ophthalmoplegia	Incremental response on repetitive nerve stimulation; pupils are dilated	
Progressive external ophthalmoplegia	Ptosis; diplopia; generalized weakness in some cases	Mitochondrial abnormalities	Moraes et al.[103]
Intracranial mass compressing cranial nerves	Ophthalmoplegia; cranial-nerve weakness	Abnormalities on computed tomography or magnetic resonance imaging	Moorthy et al.[104]

genital myasthenic syndromes are rare, generally begin in early childhood, and require sophisticated electrophysiologic and immunocytochemical tests to identify the precise defect.[97] The Lambert–Eaton syndrome presents with weakness and sometimes autonomic and sensory symptoms.[101,102] It is not usually confused with myasthenia gravis. Thyroid-function tests should be obtained in all patients thought to have myasthenia gravis. When signs of the disease are limited to ocular or cranial muscles, computed tomographic or magnetic resonance imaging scans of the head and orbits are mandatory to rule out mass lesions compressing cranial nerves as a cause.[104]

Search for Associated Conditions

Patients with myasthenia gravis have an increased incidence of several associated disorders (Table 1). Thymic tumors occur in approximately 12 percent. Computed tomographic scanning and magnetic resonance imaging reliably reveal enlargement of the thymus gland.[105] The thymus is normally detectable until mid-adulthood, but persistence of the thymus in a patient with myasthenia gravis who is over 40 years of age, or an increase in its size in any patient on repeated scanning, raises the possibility of a thymoma. Hyperthyroidism occurs in 3 to 8 percent of patients with myasthenia gravis, and either hyperthyroidism or hypothyroidism may aggravate myasthenic weakness. Tests of thyroid function should be performed routinely. It is important to screen for other autoimmune disorders,[91,92] because they may add to the diagnostic picture of immune dysregulation and because they may complicate therapy. Disorders that may interfere with immunosuppressive therapy include unsuspected infections such as tuberculosis (a skin test should always precede immunotherapy), diabetes, peptic ulcer, occult gastrointestinal bleeding, renal disease, and hypertension.

TREATMENT

The outlook for patients with myasthenia gravis has improved dramatically in recent years. Before 1958, the mortality rate among patients with generalized myasthenia gravis was 30 percent, the condition of 31 percent deteriorated or remained unchanged, and only 29 percent had an improvement in their condition.[106] Now, with optimal care, the mortality rate is essentially zero, and the great majority of patients lead normal lives. However, most patients must take immunosuppressive medication indefinitely, despite the risks of adverse effects.

In general, four methods of treatment are currently in use[107]: enhancement of neuromuscular transmission with anticholinesterase agents, surgical thymectomy, immunosuppression, and short-term immunotherapies, including plasma exchange and intravenous immune globulin.

Anticholinesterase Agents

Anticholinesterase agents continue to be used as the first line of treatment for myasthenia gravis. Pyridostigmine (Mestinon) is the most widely used anticholinesterase in the United States. Its effect begins within 30 minutes, peaks at about 2 hours, and gradually declines thereafter. The dosage and schedule of administration must be tailored to the patient's needs. The maximal useful dosage of pyridostigmine rarely exceeds 120 mg every three hours. Higher doses may produce increased weakness. A sustained-release preparation is available but should be used only at bedtime if necessary to treat weakness occurring at night or in the early morning. Although anticholinesterase drugs benefit most patients, the improvement is usually incomplete and often wanes after weeks or months of treatment. Most patients therefore require further therapeutic measures described below.

Thymectomy

Surgical thymectomy is indicated for its therapeutic effect in myasthenia gravis or to prevent the spread of a thymoma. The goal of thymectomy as a treatment for myasthenia gravis is to induce remission, or at least improvement, permitting a reduction in immunosuppressive medication. There is now a broad consensus that patients with generalized myasthenia gravis who are between the ages of puberty and about 60 years

should have surgical thymectomy.[108] Although no adverse effects have been reported as a consequence of thymectomy in children,[109] it is preferable to delay thymectomy until puberty if possible, because of the established role of the thymus in development of the immune system. Thymectomy has been advocated for elderly patients with myasthenia gravis,[110] but there is uncertainty about the persistence of thymic tissue in such patients after the age of 60.[111] Thymectomy has also been carried out in patients with purely ocular manifestations, with good results reported.[112] Thymic tumors must be removed surgically since they may spread locally and become invasive, though they rarely metastasize. The tumor and the remaining thymus gland should be removed as completely as possible. If the thymoma cannot be removed completely, or if it is invasive, marker clips should be placed at the tumor site during surgery, and focused radiation treatment carried out postoperatively. Some patients become weaker after the removal of a thymoma, presumably as a result of the loss of a suppressive effect of the thymoma,[113] and require further immunosuppressive treatment.

Thymectomy should be performed in institutions that have extensive experience not only with the surgery but also with preoperative and postoperative management of myasthenia gravis. Under these circumstances, the mortality rate is now essentially the same as that for general anesthesia. Thymectomy is never performed as an emergency procedure. Preoperative preparation should optimize the patient's strength and especially respiratory function, but immunosuppressive agents should be avoided if possible because they increase the risk of infection. If the vital capacity is below 2 liters, plasmapheresis should be carried out before surgery to allow independent respiration in the postoperative period. The surgical technique should remove as much of the thymus as possible. A sternal-splitting approach with exploration extending into the neck optimizes the removal of all thymic tissue and related fat.[114] A cervical incision with mediastinoscopy has been advocated[115] because it is associated with a smaller scar and less postoperative pain, but the completeness of thymus removal with the use of this method has not been confirmed. The use of epidural morphine minimizes postoperative pain and thereby enhances respiratory effort.[116] The requirement for anticholinesterase medication may be decreased for a few days after thymectomy; therefore, postoperative anticholinesterase medication is given intravenously at a dose equivalent to about three fourths of the preoperative requirement. The benefits of thymectomy are usually delayed until months to years after surgery.[117] Because recent studies of the outcome of thymectomy are confounded by the use of immunosuppressive treatment, a retrospective Mayo Clinic study that compared, before the era of such treatments, computer-matched groups of patients with or without surgical thymectomy is still the most credible.[81] After thymectomy, clinical remission occurred in approximately 35 percent of patients and improvement was seen in another 50 percent — an outcome that was significantly better than the outcome in patients who were not surgically treated.

The mechanism by which thymectomy produces benefit in myasthenia gravis is still uncertain. In general, acetylcholine-receptor antibody levels fall after thymectomy,[118] although there are conflicting reports. On theoretical grounds, there are several possible mechanisms. First, removal of the thymus may eliminate a source of continued antigenic stimulation. If the thymic myoid cells are the source of autoantigen,[83,84] then their removal might allow the immune response to subside. Second, thymectomy may remove a reservoir of B cells secreting acetylcholine-receptor antibody. Although thymic lymphocytes are capable of secreting acetylcholine-receptor antibody in vitro, the amount of antibody produced in the thymus is not enough to account for the total body supply.[119] Third, thymectomy may in some way correct a disturbance of immune regulation in myasthenia gravis.

Immunosuppressive Treatment

Immunosuppressive therapy is indicated when weakness is not adequately controlled by anticholinesterase drugs and is sufficiently distressing to outweigh the risks of possible side effects of immunosuppressive drugs. Prednisone, azathioprine, and cyclosporine are the agents now used for long-term immunosuppression in myasthenia gravis, and these drugs are compared in Table 3. In general, treatment must be continued for a prolonged period, most often permanently. Because of the risks inherent in prolonged immunosuppressive treatment, conscientious medical follow-up and the patient's compliance with therapy are essential for safe and effective management.

Corticosteroids

Steroids are the most commonly used and most consistently effective immunosuppressive agents for the treatment of myasthenia gravis. They also have the largest array of potential side effects. Patients with moderate-to-severe generalized weakness are hospitalized for the initiation of steroid therapy because of the risk of transient steroid-induced exacerbation of disease, which may occur during the first weeks of treatment in up to 48 percent of patients.[120] The risk of exacerbation is minimized by increasing the dose gradually,[121] beginning with a daily dose of 15 to 20 mg of prednisone and increasing it by about 5 mg every two or three days. The rate of increase must be guided by the patient's clinical response, and the end point is either a satisfactory clinical response or a dose of 50 to 60 mg per day. Improvement usually begins in 2 to 4 weeks, with maximal benefit realized after 6 to 12 months or more. After about three months of daily high-dose treatment, the schedule is gradually modified to an alternate-day regimen to minimize side effects; occasionally, a small dose of prednisone may be needed on the "off" day to prevent fluctuations in strength. The total dose is then tapered very slowly,

but it may require months or years to determine the minimal effective dose. Few patients are able to do without prednisone entirely.

Corticosteroids exert suppressive effects at many levels of the immune system.[122,123] In myasthenia gravis, steroid treatment may reduce acetylcholine-receptor antibody levels and diminish the anti-acetylcholine-receptor reactivity of peripheral-blood lymphocytes.[124,125] In addition, corticosteroids are reported to have certain direct neuromuscular actions. Experimentally, steroids increase the synthesis of acetylcholine receptors in cultured muscle cells[126] and may enhance neuromuscular transmission,[127] but the clinical relevance of such effects in myasthenia gravis has not been established.

Azathioprine

Azathioprine (Imuran) is metabolized to the cytotoxic derivative 6-mercaptopurine. Its action is predominantly on T cells,[128] and its effectiveness in myasthenia gravis may be due to the fact that the production of acetylcholine-receptor antibody is T-cell–dependent. It is most useful in patients with myasthenia gravis for whom corticosteroids are contraindicated, in those with an insufficient response to steroids, or as an adjunct to permit a reduction in the steroid dose. It is one of the easiest immunosuppressive agents to use,[38,129] since it is well tolerated by most patients, but it has two drawbacks. First, up to 10 percent of patients have an idiosyncratic influenza-like reaction, consisting of fever, malaise, and myalgias, that precludes its use. Second, its therapeutic action in myasthenia gravis begins slowly, requiring many months to one year for an adequate therapeutic trial. Treatment is initiated with a test dose of 50 mg (one tablet) daily for one week. If this is well tolerated, the dose is gradually increased to the usual target dose of 2 to 3 mg per kilogram of body weight per day. This dose is based on total body weight, not lean body mass, even in obese patients. Concurrent treatment with allopurinol interferes with the enzymatic degradation of azathioprine; therefore, the dose of azathioprine must be reduced by as much as 75 percent and monitored closely. The measures used as indicators of an adequate dose and toxicity are outlined in Table 3, but clinical improvement in myasthenic weakness is the sine qua non of efficacy. As with treatment with other immunosuppressive agents, most patients require lifelong azathioprine therapy.[130]

Cyclosporine

Cyclosporine (Sandimmune), a potent immunosuppressive agent,[131] was first shown to be useful against myasthenia gravis in an experimental model,[132] and is now used increasingly in the treatment of patients with the disease.[133] Cyclosporine inhibits the production of interleukin-2 by helper T cells.[134] Its efficacy is similar to that of azathioprine,[135] but it works more quickly, usually within one to two months. The side effects of cyclosporine include nephrotoxicity and hypertension,[131,133] which limit its use in patients with preexisting renal disease or uncontrolled hypertension. To minimize side effects, the drug is given in two divided doses, totaling approximately 5 mg per kilogram per day. The dose should be guided by monitoring the clinical efficacy of the drug, trough plasma levels of cyclosporine, and side effects (Table 3). Once a satisfactory clinical response has been attained, the dose should gradually be tapered to the minimal required maintenance level. The high cost of cyclosporine limits its availability for some patients.

Short-Term Immunotherapies: Plasma Exchange and Intravenous Immune Globulin

Plasmapheresis removes antibodies from the circulation and produces short-term clinical improvement in patients with myasthenia gravis.[39,136,137] It is used primarily to stabilize the condition of patients in myasthenic crisis or for the short-term treatment of patients undergoing thymectomy. Typically, five exchange treatments of 3 to 4 liters each are carried out over a two-week period. The effect of plasmapheresis is rapid, with improvement occurring within days of treatment. Improvement correlates roughly with a reduction in the anti–acetylcholine-receptor antibody titers,[138] but even patients with antibody-negative myasthenia gravis may improve after plasmapheresis.[53,56,139] The beneficial effects of plasmapheresis are temporary, lasting only weeks. Repeated plasmapheresis as long-term therapy is occasionally helpful in the rare patient who does not respond to the other methods outlined above. The drawbacks of plasmapheresis include problems with venous access, the risk of infection of the indwelling

Table 3. Immunotherapy in Myasthenia Gravis.

Drug	Usual Adult Dose	Time to Onset of Effect	Time to Maximal Effect	Variables to Monitor Drug Effects
Prednisone	15–20 mg/day gradually increasing to 60 mg/day and gradually changed to every other day	2–3 wk	3–6 mo	Weight Blood pressure Blood glucose Electrolytes Ophthalmic changes Bone density 24-hr urinary calcium
Azathioprine (Imuran)	2–3 mg/kg/day (total dose, 100–250 mg/day)	3–12 mo	1–2 yr	White-cell count (<3500/mm^3)* Differential count (<1000 lymphocytes/mm^3)* Mean corpuscular volume (>100 μm^3)* Platelets Liver function
Cyclosporine (Sandimmune)	5 mg/kg/day given in 2 divided doses (total dose, 125–200 mg twice daily)	2–12 wk	3–6 mo	Blood pressure Serum creatinine Blood urea nitrogen Trough plasma cyclosporine level

*Values in parentheses are desirable levels.

catheter, hypotension, and pulmonary embolism. The benefit must be weighed against these problems and the high cost of the procedure.

The indications for the use of intravenous immune globulin are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness. It has the advantages of not requiring special equipment or large-bore vascular access. The usual dose of immune globulin is 400 mg per kilogram per day for five successive days. The improvement rate after immune globulin treatment, calculated from eight published reports, was 73 percent,[140] but this figure is likely to be biased by selective reporting of positive uncontrolled trials. In patients who respond, improvement begins within four to five days. The effect is temporary but may be sustained for weeks to months, allowing intermittent long-term therapy in patients with otherwise refractory disease. The mechanism of action of immune globulin is unknown,[141] but it has no consistent effect on the measurable amount of acetylcholine-receptor antibody. Adverse reactions occur in fewer than 10 percent of patients and include headache, fluid overload, and rarely, renal failure. Immune globulin is very expensive, and this factor as well as the possible risks should be weighed against the potential of rapid improvement.

Specific Immunotherapy: The Future of Treatment

Ideally, the goal of therapy in myasthenia gravis should be to eliminate the autoimmune response to acetylcholine receptor specifically, without otherwise interfering with the immune system. Given our detailed knowledge of myasthenia gravis, it should be possible to design rational and specific immunotherapy.

Certain features of myasthenia gravis described above are important in the design of therapeutic strategies and are therefore recapitulated here. First, the pathogenesis of myasthenia gravis depends on antibody-mediated mechanisms. Effective treatment must inhibit acetylcholine-receptor antibodies. Second, the antibody response to acetylcholine receptors is dependent on T cells. This presents an important avenue for therapy. Third, the acetylcholine receptor is a highly immunogenic antigen. Suppression of the response to the receptor may require more powerful methods than for other less potent antigens. Fourth, immune responses to acetylcholine receptor are highly heterogeneous. Therapeutic strategies must take into account the broad range of specificities of both T cells and B cells. Although there is an astonishingly large number of sites at which specific or semispecific therapeutic intervention can be applied,[142] an ideal therapeutic strategy has yet to be devised.

B-Cell–Directed Approaches

Since B cells produce the pathogenic antibodies in myasthenia gravis, it seems logical to attempt to interrupt the disease process at this crucial step. As discussed above, the B cells and the antibodies they produce are highly heterogeneous. Antibodies produced by individual B cells are capable of binding to a wide variety of acetylcholine-receptor epitopes. These antibodies act as the "address" of each B cell (Fig. 4). If acetylcholine-receptor molecules are armed with lethal "warheads," the relevant B cells will take up the lethal antigen and be killed, a strategy called "hot-antigen suicide." Experimentally, immunotoxins composed of acetylcholine receptor coupled either to the toxic A chain of ricin or to ^{125}I have been used successfully in naive (unimmunized) animals or in vitro.[143,144] In myasthenia gravis, however, precisely the same antibodies that serve as the addresses of B cells are present in the circulation. They can bind the immunotoxic molecules, forming complexes that may be precipitated in the lungs, liver, or kidneys, without ever reaching their goal, but with the risk of damaging these organs. This problem would apply to virtually any strategy designed to target acetylcholine-receptor–specific B cells.

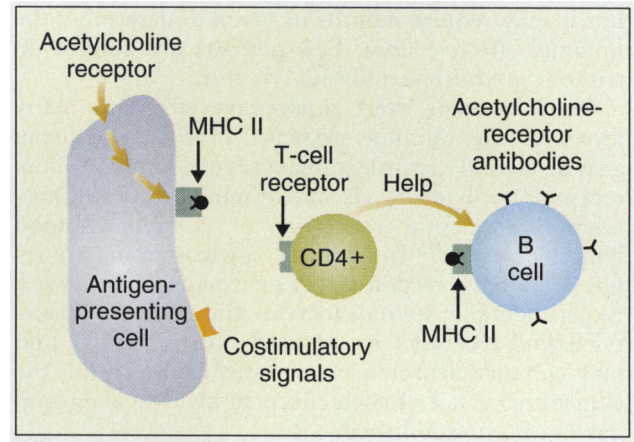

Figure 4. T-Cell–Dependent Antibody Production.
Antigen-presenting cells internalize the antigen (acetylcholine receptor), process it, and then present the processed peptides in association with major histocompatibility complex (MHC) class II molecules unique to the subject. The T-cell receptor of antigen-specific helper T cells (CD4+) binds to the specific MHC–peptide complex. The interaction of the antigen-presenting cell and the T cell requires additional costimulatory signals and is aided by adhesion molecules and cytokines, resulting in T-cell stimulation. The activated T cell helps acetylcholine-receptor–specific B cells. These B cells bind the antigen (acetylcholine receptor) to their surface antibodies, process it, and present the MHC–peptide complex, like other antigen-presenting cells. They thus interact with T cells by binding to the T-cell receptor. The T cell provides help to the B cells by means of surface molecules and cytokines (not shown), resulting in B-cell proliferation and the secretion of acetylcholine-receptor–specific antibody.

T-Cell–Directed Approaches

As noted above, T cells have a pivotal role in the autoimmune antibody response in myasthenia gravis (Fig. 4), and T cells have certain characteristics that are amenable to therapeutic approaches. T-cell receptors recognize linear epitopes (associated with MHC class II[73]) that generally differ from the conformation-

ally determined epitopes recognized by B cells.[145] This permits targeting of the relevant T cells through their receptors, while minimizing the possibility of interception by circulating antibodies. Moreover, various other surface markers on T cells can serve as semispecific "addresses" for targeting. The T cells thus targeted may be inactivated or suppressed by methods currently being tested.

An interesting but not antigen-specific therapeutic method involves the depletion of helper T cells by antibodies to the helper surface molecule (CD4).[146-148] Treatment with anti-CD4 antibodies interferes with helper T cells, producing a general immunosuppressive effect that has been used experimentally to treat myasthenia gravis in animals[149] and in a single patient to date.[150]

A semiselective strategy aimed at activated T cells is also being explored. T cells involved in an active immune response express receptors for interleukin-2, whereas resting and memory T cells do not.[151] A genetically engineered interleukin-2 toxin consisting of the receptor-binding moiety of the interleukin-2 molecule and the lethal fragment of diphtheria toxin has been developed for immunotherapy.[152] It is taken up by the activated T cells that express interleukin-2 receptors, resulting in their death. Experimentally, interleukin-2 toxin has been shown to inhibit both acetylcholine-receptor–specific T-cell proliferation and the production of acetylcholine-receptor antibody effectively in cultures.[153] A highly potent new version of interleukin-2 toxin[154] is now being tested in vivo in experimental myasthenia gravis.

The most specific therapeutic approach would involve the elimination or inactivation of all T cells capable of responding to acetylcholine-receptor epitopes. However, targeting all the relevant T cells presents a potentially overwhelming problem; as described above, T-cell responses to acetylcholine receptors are highly heterogeneous in both humans and animals with myasthenia gravis.[61-63,67,75-77,155,156] Despite its complexity, targeting T cells is the natural occupation of antigen-presenting cells, which process and present the antigen appropriately and express the correct MHC class II for a given subject (Fig. 4). A recently developed strategy uses these antigen-presenting cells as "guided missiles" to target acetylcholine-receptor–specific T cells.[157,158] If the antigen-presenting cells are allowed to process acetylcholine receptors and are then treated by fixation to eliminate their costimulatory signals (Fig. 4), they do not stimulate T cells; instead, they induce unresponsiveness (anergy) of the specific T cells with which they interact. This strategy addresses the critical issue of the heterogeneity of T-cell responses in myasthenia gravis by using a subject's immune system to induce specific T-cell anergy.

Another novel therapeutic approach that enlists the subject's immune system involves the oral administration of antigens. Although oral intake of antigens has long been known to induce tolerance,[159,160] this method has attracted renewed interest for the treatment of autoimmune diseases.[161,162] Oral administration of purified acetylcholine receptor has been found to prevent both the clinical and the immunologic features of myasthenia gravis in rat models[163,164] (and unpublished data). The effects in ongoing disease in humans have yet to be tested.

Conclusions

Much has been learned in the past 15 years about the pathogenesis, immunology, and molecular biology of myasthenia gravis. The diagnosis and practical management are well defined and usually successful. Yet despite these impressive advances, there are still important gaps in our knowledge of the origin of myasthenia gravis, the factors that contribute to chronic disease, and the way to cure the disease. The ultimate goal is specific therapy for the underlying disorder.

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 39-2011: A Woman in Her 90s with Unilateral Ptosis

Nagagopal Venna, M.D., R. Gilberto Gonzalez, M.D., Ph.D., and Lawrence R. Zukerberg, M.D.

PRESENTATION OF CASE

Dr. Xuemei Cai (Medicine): A woman in her 90s was seen in the emergency department at this hospital because of ptosis of the left eyelid.

The patient had been in her usual health until 4 days earlier when, on awakening, she was unable to open her left eye. She reported no periorbital swelling, discharge, pruritus, blurred or double vision, or weakness of her limbs. She was right-handed and had hypertension, hyperlipidemia, atherosclerosis, osteoporosis, kyphosis due to degenerative spinal disease, and complete heart block, for which a permanent pacemaker had been inserted 5 years earlier. She had had herpes zoster and a laparoscopic cholecystectomy in the past. Medications included doxazosin, furosemide, simvastatin, lisinopril, alendronate sodium, a multivitamin, calcium, and vitamin D. She was allergic to acetylsalicylic acid, penicillin, sulfa drugs, and codeine. Hydrochlorothiazide had caused hyponatremia. She was single and retired and lived independently, performing all activities of daily living, shopping with friends, and walking 50 to 60 minutes per day. She drank alcohol occasionally and did not smoke or use illicit drugs.

On examination, the vital signs were normal. There was ptosis of the left upper eyelid, and the patient was unable to elevate the left eyelid. Visual acuity was 20/40 in the left eye and 20/30 in the right eye. Extraocular movements were intact, with two to three beats of nystagmus on leftward gaze. There was 2+ bilateral pedal edema. A tremor of the hands was present at rest, which increased when the patient raised her arms. There was some past pointing on finger–nose–finger testing. The remainder of the examination was normal. The erythrocyte sedimentation rate was 18 mm per hour (reference range, 0 to 17); serum levels of glucose, calcium, phosphorus, magnesium, total protein, albumin, and globulin were normal, as were tests of renal and liver function. Other test results are shown in Table 1. Urinalysis revealed 3 to 5 white cells and 2+ squamous cells per high-power field, 0 to 2 granular casts per low-power field, and mucin. An electrocardiogram (ECG) was unchanged from 3.5 years earlier, with a paced rhythm and left atrial enlargement.

Computed tomography (CT) of the brain without the administration of contrast material and CT angiography showed extensive periventricular white-matter hypoden-

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Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On 1st Admission, This Hospital	6.5 Wk Later, Emergency Department	5 Days Later, 2nd Admission	3rd Hospital Day
Hematocrit (%)	36.0–46.0 (women)	34.6	31.7	33.2	34.3
Hemoglobin (g/dl)	12.0–16.0 (women)	12.3	10.7	11.1	11.1
White-cell count (per mm^3)	4500–11,000	6100	9600	12,800	16,600
Differential count (%)					
Neutrophils	40–70	73	85	91	95
Lymphocytes	22–44	23	12	8	3
Monocytes	4–11	3	2	1	2
Eosinophils	0–8	1	1	0	0
Sodium (mmol/liter)	135–145	138	131	139	140
Potassium (mmol/liter)	3.4–4.8	3.7	4.6	3.9	3.5
Chloride (mmol/liter)	100–108	100	93	101	99
Carbon dioxide (mmol/liter)	23.0–31.9	29.3	30.4	30.1	35.1
Methemoglobin (% of total hemoglobin)	0.4–1.5			0.6	
Arterial blood gas measurements					
Fraction of inspired oxygen				1.00	1.00
pH				7.11	6.94
Partial pressure of oxygen (mm Hg)	80–100			83	79
Partial pressure of carbon dioxide (mm Hg)	35–42			111	182
Base excess (mmol/liter)				1.2	1.5
Oxygen saturation (%)				91	

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

sities and focal occlusion of the distal right vertebral artery near the vertebrobasilar junction. There was also a rounded soft-tissue mass (1.6 cm in diameter) in the region of the left cavernous sinus with a 4-mm enhancing focus laterally that was thought to be a thrombosed aneurysm.

Dysfunction of the levator palpebrae superioris muscle, possibly caused by spontaneous disinsertion of the levator palpebrae tendon, was diagnosed. While preparing for discharge, the patient reported feeling unsteady. On reexamination, she was unable to walk without assistance and her gait was wide-based; the results were otherwise unchanged. She was observed overnight; physical therapy and occupational health consultations were obtained, and she was discharged the following day to a rehabilitation hospital for reconditioning and assistance with ambulation.

At the rehabilitation hospital, ptosis of the left eyelid and hypertension persisted. Amlodipine besylate was administered. During the first 2 weeks, the patient reported neck stiffness. On examination, the neck was flexed and a change in her voice quality was noted, which transiently improved when she raised her head. A soft cervical collar, a lidocaine patch, and heat were applied. Ten days after admission, the level of serum sodium was 130 mmol per liter. Furosemide was stopped, saline boluses and salt tablets were administered, and fluid restriction was begun. During the next 10 days, the sodium level gradually fell to a nadir of 120 mmol per liter. The level of brain natriuretic peptide was 113 pg per milliliter (reference range, 5 to 99). The systolic blood pressure rose to 159 mm Hg, and the administration of metoprolol was begun, followed by isosorbide dinitrate, with improvement. On the 14th day, CT of the head showed no change. The serum sodium level gradu-

ally rose to 130 to 131 mmol per liter, and the fluid restriction was lifted.

Approximately 6 weeks after admission to the rehabilitation hospital, dysphagia, choking, and hoarseness developed, associated with increasing fatigue and difficulty holding up her head. Repeat CT of the head revealed no changes. A modified barium-swallow study reportedly revealed aspiration of thin liquids. She was brought to the emergency department at this hospital. The blood pressure was 124/74 mm Hg, and the oxygen saturation 92 to 98% while she was breathing ambient air; other vital signs were normal. The neck was supple. There was ptosis of the left eyelid, mild intention tremor, a strong gag reflex, and 1+ deep-tendon reflexes throughout; plantar reflexes were flexor. Gait was not tested, and the remainder of the examination was normal. Results of laboratory tests are shown in Table 1. A repeat ECG was unchanged. A chest radiograph showed a dual-lead cardiac pacemaker, low lung volumes, bilateral small pleural effusions, and bibasilar atelectasis; mild enlargement of the cardiomediastinal silhouette with a tortuous and calcified thoracic aorta and diffuse osteopenia were present, unchanged from earlier studies. Gram's staining of a sputum specimen revealed polymorphonuclear leukocytes, squamous cells, and mixed gram-positive and gram-negative organisms. The administration of clopidogrel bisulfate was begun. The next morning, the patient returned to the rehabilitation hospital; a diet of pureed food and thick fluids was instituted. Further evaluation of the mass in the cavernous sinus was planned.

The next day, the patient was noted to be coughing and choking on her food and she reported difficulty breathing. The temperature was 37.8°C and the oxygen saturation 89 to 90% while she was breathing ambient air; supplemental oxygen (1 liter by nasal cannula) was administered. A chest radiograph reportedly showed an infiltrate in the lower lobe of the right lung. She was transferred to this hospital. The patient stated that she did not wish to be intubated or resuscitated in the event of respiratory failure or cardiac arrest.

On examination, she was wearing a soft cervical collar and appeared frail. The blood pressure was 147/74 mm Hg, the pulse 72 beats per minute, the temperature 36.1°C, and the respiratory rate 18 breaths per minute, with accessory muscle use. Oxygen saturation was 96% while she was breathing oxygen (4 liters) by nasal cannula and fell to 83% when she was breathing ambient air. The neck was supple, with decreased muscle tone. She was unable to extend her neck (i.e., raise her head) against gravity. Jugular venous pressure was 7 to 8 cm above the right atrium. There were heavy secretions in the oropharynx and diffuse coarse rhonchi. Reflexes were 2+ and symmetric, and the remainder of the examination was unchanged. Levels of platelets, calcium, magnesium, glucose, total protein, amylase, and lipase were normal, as were tests of liver and renal function. Other test results are shown in Table 1. An ECG was unchanged. A chest radiograph showed bilateral basilar opacities consistent with atelectasis, aspiration pneumonia, or both. There were changes that were consistent with mild interstitial edema.

Vancomycin, cefepime, metronidazole, furosemide, and methylprednisolone were administered intravenously, and albuterol and ipratropium by nebulizer. Bilevel positive airway pressure was administered intermittently, complicated by episodic hypotension (systolic pressure, 70 to 80 mm Hg); the partial pressure of carbon dioxide fell to 82 mm Hg. An ice-pack test (placing ice on the affected eyelid to determine whether ptosis is reduced) was performed, with equivocal results. Laboratory-test results on the third day are shown in Table 1. In consultation with the family, and according to the previously expressed wishes of the patient, comfort measures only were administered, and the patient died on the third day.

An autopsy was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Nagagopal Venna: This elderly woman had rapidly developing weakness starting with unilateral ptosis, followed by head drop, dysarthria, and dysphonia, and later, dysphagia and general fatigue, culminating in respiratory failure. Before this illness, she had led an active, independent life into her 10th decade. The stepwise evolution of the syndrome over an 8-week period during which different physicians observed fragments of her illness through the confounding effects of heart failure, hyponatremia, aspiration pneumonitis, and medications may have caused difficulties in the neurologic diagnosis.

In approaching the differential diagnosis, it is helpful to characterize the impairments. Unilateral ptosis indicates weakness of the levator palpebrae superioris muscle, and forward head drop denotes

weakness of cervical paraspinal muscles. Dysarthria, dysphagia, and dysphonia reflect paresis of the oropharyngeal, palatal, and vocal-cord musculature. Respiratory failure with hypercapnia is consistent with weakness of the diaphragm and intercostal ventilatory muscles. In contrast to these profound abnormalities, the patient's mental state, strength, sensation, and tendon reflexes of the limbs were not affected. Such a neurologic syndrome can result from lesions of the peripheral neuromuscular system or the brain stem. In addition, the inability to stand or walk and incoordination of the arms indicate dysfunction of the cerebellar system, whereas the tremor is suggestive of involvement of the basal ganglia.

Dr. Gonzalez, may we see the initial brain CT?

Dr. R. Gilberto Gonzalez: CT of the brain without the administration of contrast material revealed extensive periventricular white-matter hypodensities. A CT angiogram (Fig. 1A) showed narrowing of the distal right vertebral artery and a rounded soft-tissue mass (1.6 cm in diameter) in the region of the left cavernous sinus, with a 4-mm enhancing focus that is most likely a thrombosed cavernous carotid aneurysm (Fig. 1B).

Dr. Venna: This patient had clinical findings that were indicative of involvement of the brain stem, cerebellum, and peripheral nervous system. I will consider each of these separately.

BRAIN-STEM SYNDROMES

Brain-Stem Stroke

Ptosis, bulbar weakness, and loss of balance could be caused by basilar-artery thrombosis, which can evolve over days as areas of ischemia coalesce into large brain-stem infarction.[1] The patient's age and cardiac and vascular risk factors, including stenosis of the right vertebral artery, set the stage for a brain-stem stroke. Magnetic resonance imaging (MRI) is more sensitive than CT for the detection of early brain-stem infarction but was contraindicated because of a cardiac pacemaker. However, the sparing of the pupils, the intact extraocular movements, the absence of hemiparesis or quadriparesis, the lack of sensory abnormalities over the face and limbs, and the normal level of consciousness throughout the illness make this diagnosis improbable.

Central Pontine Myelinolysis

Central pontine myelinolysis results from rapid correction of hyponatremia, and thus could be considered in this patient with hyponatremia. However, her symptoms antedated the hyponatremia, and the presentation with ptosis, the severe neck weakness without limb paresis, and the subsequent respiratory failure are not consistent with this diagnosis. Serial CT scans, although not as sensitive as MRI, would have shown symmetric low attenuation reflecting demyelination in the pons.

Bickerstaff's Brain-Stem Encephalitis

Bickerstaff's brain-stem encephalitis is a rare, immune-mediated disorder resulting in acute external ophthalmoplegia, including ptosis, nystagmus, bulbar weakness, gait and limb ataxia, and in severe cases, respiratory failure.[2] Decreased alertness, coma, bilateral hyperreflexia, Babinski reflexes, quadriparesis, and sensory disturbances are frequent. The absence of these features makes this diagnosis unlikely.

DISEASES OF MOTOR NEURONS

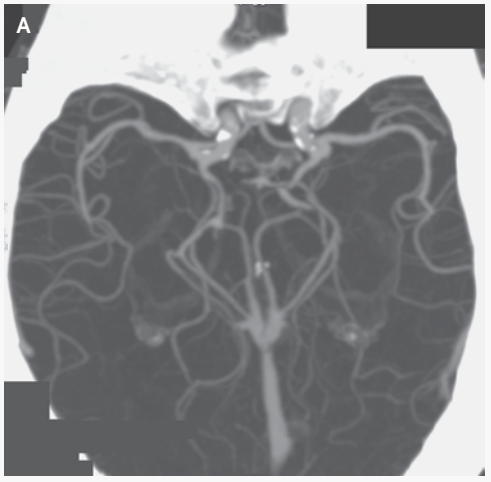
The bulbar syndrome occurs in about 20% of cases of amyotrophic lateral sclerosis (ALS), especially in older women.[3] This can spread to the cervical and thoracic spinal motor neurons, leading to neck weakness, head drop, and respiratory failure. ALS is unlikely in this case because of the abrupt onset and very rapid course. In addition, ptosis does not often occur in ALS, since ocular motor neurons are usually spared. The expected tongue atrophy and fasciculations, spastic dysarthria, and upper-motor-neuron signs in the limbs never developed.

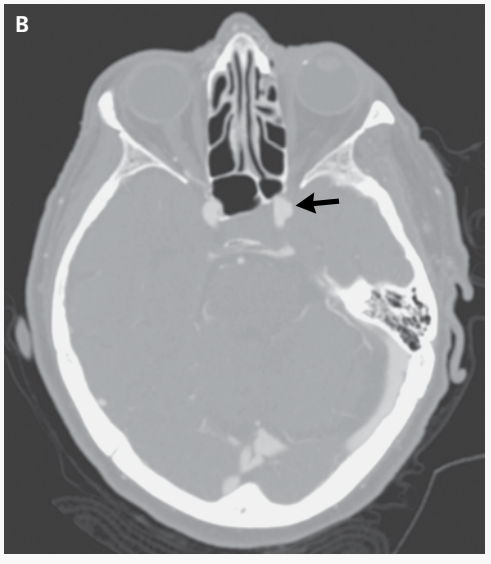
PERIPHERAL NEUROMUSCULAR DISORDERS

The acute weakness of the bulbar, neck, and respiratory muscles, without involvement of the central nervous system, points to a disorder of the nerves, muscles, or neuromuscular junction.

Cranial Neuropathies

Palsies of cranial nerves III, IX, X, and XI could account for this patient's syndrome. The usual causes of cranial-nerve palsies are metastatic meningitis (due to carcinoma or lymphoma) and granulomatous meningitis (due to sarcoidosis, tuberculosis, or a fungal infection).[4] A cranial neuropathy is unlikely in this case because of the preserved gag reflex, severe neck hypotonia, and the absence of other ocular palsies and facial sensory disturbances. The lesion in the left cavernous sinus is relevant because it could cause ptosis by compressing the oculomotor nerve and because





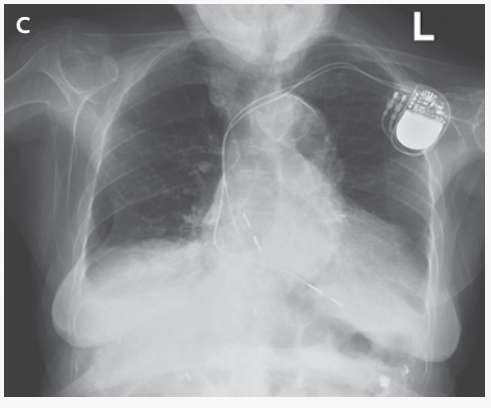


Figure 1. Imaging Studies.
A CT angiogram with restricted maximum-intensity projection reconstruction at the level of the circle of Willis (Panel A) does not reveal an intracranial aneurysm. An axial source image (from a CT angiogram of the head) at the level of the cavernous carotid arteries (Panel B) shows a lateral outpouching of the left cavernous carotid artery, most likely representing the patent component of a partially thrombosed aneurysm (arrow). A chest radiograph (Panel C) shows widening of the superior mediastinum.

it may extend to cause palsies of cranial nerve VI and the first division of cranial nerve V. However, no other signs of progressive cavernous sinus syndrome emerged. Moreover, Dr. Gonzalez has shown this lesion to be a fusiform aneurysm and not a neoplastic mass; therefore, the lesion is most likely an incidental abnormality.

Peripheral Neuropathies

A subgroup of patients with the Guillain–Barré syndrome present with ocular, bulbar, and respiratory paralysis rather than the usual paralysis ascending from the legs.[5] Gait and limb ataxia can occur before limb weakness. The absence of facial palsies, lack of weakness of upper limbs, and intact tendon reflexes throughout the course of the illness argue against this diagnosis. The Miller Fisher syndrome, a variant of the Guillain–Barré syndrome that presents with ataxia, areflexia, and ophthalmoplegia, is a consideration. However, the key features of ophthalmoplegia and generalized areflexia did not develop in this patient.[6] Even so, these peripheral-nerve disorders should be investigated by means of electrophysiological testing in this patient.

Myopathies

Acute respiratory paralysis occurs very rarely in patients with acid maltase deficiency and mitochondrial myopathies, polymyositis, and dermatomyositis and is usually preceded by insidious proximal-muscle weakness.[7] The unilateral ptosis and bulbar weakness in this patient make myopathic illness unlikely.

Disorders Affecting the Neuromuscular Junction

The Lambert–Eaton Syndrome

The Lambert–Eaton syndrome, mediated by autoantibodies to the presynaptic voltage-gated calcium channels at the neuromuscular junction, is often thought of as a cause of oculobulbar weakness. However, the cardinal findings are proximal-muscle weakness, areflexia, and autonomic disturbances such as dry eyes, erectile dysfunction, and orthostatic hypotension. This disorder does not explain

the craniocervical and respiratory-muscle weakness in this patient.

Myasthenia Gravis

Myasthenia gravis is the most common disorder occurring at the postsynaptic neuromuscular junction. Ocular-muscle weakness is a characteristic early feature and can be asymmetric and even restricted to a single muscle, as exemplified by the unilateral ptosis in this case. Fluctuation of the weakness with activity is common but not invariable.

Slight weakness of extraocular muscles may appear as nystagmus (paretic nystagmus), as the weak muscles strain to move the globe against stronger antagonists; such weak muscles may explain this patient's nystagmus. Prominent weakness of the neck muscles, leading to dropping of the head, is characteristic of myasthenia gravis.[8] Hypercapnic respiratory failure is a common and dreaded complication of myasthenia gravis.[9] Respiratory failure can happen swiftly, often precipitated by respiratory infection and the use of antibiotics, statins, beta-blockers, and high-dose glucocorticoids. All these features emerged rapidly in this patient, without sensory or reflex abnormalities in the limbs and with intact consciousness, and strongly favor a diagnosis of myasthenia gravis.

Weakness of the bulbar, neck, and respiratory muscles, with little ocular or limb involvement, as seen in this patient, occurs in 20% of patients who have myasthenia gravis with acetylcholine-receptor antibodies. Similar patterns of weakness and respiratory failure also occur in paraneoplastic myasthenia gravis associated with thymoma.[10] Less commonly, this phenotype of myasthenia gravis, sometimes accompanied by atrophy of the neck muscles, is seen in patients who test negative for acetylcholine-receptor antibody and who have antibodies to muscle-specific tyrosine kinase (MuSK), a transmembrane muscle protein at the neuromuscular junction.[11]

Myasthenia gravis is being diagnosed increasingly in patients over the age of 50 years.[12] Even so, I suspect that this patient, at more than 90 years of age, would be one of the oldest to receive a diagnosis of myasthenia. Myasthenia tends to be overlooked in elderly persons because ptosis, changes in speech and swallowing, and fatigue are usually attributed to the frailties of age, as they apparently were in this case.

Dr. Gonzalez, may we see the chest radiograph?

Dr. Gonzalez: The chest radiograph shows mild mediastinal widening (Fig. 1C). There is interstitial lung disease, and the cardiac silhouette is unremarkable.

Dr. Venna: With the suspicion for myasthenia gravis being high, even this subtle widening of the mediastinum suggests thymoma, which occurs in 10 to 15% of patients with myasthenia, and would prompt a CT scan of the chest to further define the lesion.

Diagnostic Testing for Myasthenia Gravis

When this patient was finally admitted to this hospital, myasthenia gravis was clearly a serious consideration. An ice pack was placed over the eye for 1 minute to improve neuromuscular transmission and temporarily relieve the ptosis, but her response was equivocal. Even when negative, this test does not rule out myasthenia.

Several tests are needed to confirm the diagnosis of myasthenia gravis and to overcome the problem of false negative and false positive results.[13,14] Repetitive nerve stimulation, in which a motor nerve is stimulated at 2 to 5 Hz while the response of compound motor action potential is recorded, is the key test. A progressive decrement in amplitude is the diagnostic finding. In this patient, testing the sternocleidomastoid and face muscles would be appropriate. Results of single-fiber electromyographic tests are abnormal in about 95% of cases of myasthenia gravis, even when results of repetitive stimulation are equivocal, but single-fiber electromyography is not specific. Standard nerve-conduction and needle electromyographic studies are indicated to detect demyelinating neuropathy and myopathy, which may coexist with myasthenia gravis.

Serum antibodies to nicotinic acetylcholine receptor are highly sensitive and specific for the diagnosis of myasthenia gravis. About 80% of patients without thymoma and almost all those with thymoma have such antibodies. Antibodies to the striated muscle proteins titin and ryanodine receptor are also common in thymoma-associated myasthenia gravis and may predict more severe disease and a propensity to respiratory failure.[15] If acetylcholine receptor antibodies are absent, antibodies to MuSK should be sought. Many different autoantibodies are being discovered in patients

with thymoma, resulting in a variety of paraneoplastic neurologic disorders, including neuromyotonia, limbic encephalitis, polymyositis, stiff-person syndrome, and subacute hearing loss.[16] I wonder whether the ataxia in this patient reflects paraneoplastic cerebellar degeneration.

Intravenous edrophonium — a rapid-acting, short-duration acetylcholinesterase inhibitor that increases the availability of the acetylcholine at the neuromuscular junction — is the pharmacologic test for myasthenia gravis. It is suitable for patients in whom weakness is easily visible and a response is readily ascertainable, such as the ptosis and neck weakness of this patient. In these circumstances, a positive result is seen in about 80% of cases. Because of the potential for severe bradycardia, ECG monitoring and the ready availability of atropine are necessary.

SUMMARY

In conclusion, I think this patient had myasthenia gravis complicated by myasthenic crisis as a paraneoplastic disorder due to thymoma. Paraneoplastic cerebellar degeneration may be part of the picture.

Dr. Nancy Lee Harris (Pathology): Dr. Cai, would you tell us the clinical impression that the care team had at the time?

Dr. Cai: We thought that the patient most likely had myasthenia gravis and was presenting in a myasthenic crisis. The members of the neurology service thought that anticholinesterase therapy (pyridostigmine or edrophonium) might result in increased oral secretions and the risk of aspiration, so this test was not performed. We also suspected that the mediastinal widening was due to thymoma. We obtained serum for antibody testing, as suggested by Dr. Venna, and we obtained permission for an autopsy.

CLINICAL DIAGNOSIS

Myasthenia gravis and myasthenic crisis associated with thymoma.

DR. NAGAGOPAL VENNA'S DIAGNOSES

Myasthenia gravis and myasthenic crisis.

Paraneoplastic syndrome associated with thymoma.

PATHOLOGICAL DISCUSSION

Dr. Lawrence R. Zukerberg: At autopsy, the heart was enlarged (370 g), with left ventricular hypertrophy, biatrial dilatation, and severe coronary artery disease. A pacemaker was in place. There was pulmonary edema. There was a well-circumscribed mass (4.2 cm in diameter) in the anterior mediastinum.

Microscopical examination of the mediastinal mass revealed an encapsulated cellular tumor (Fig. 2A). The tumor cells had a spindled or oval appearance with bland nuclei and dispersed chromatin (Fig. 2B). Scattered small, mature lymphocytes were admixed. The spindle cells were positive for keratin according to immunohistochemical analysis (Fig. 2C), and the lymphocytes were CD3+ T cells (Fig. 2D). These findings are diagnostic of type A thymoma (also known as medullary thymoma), according to the World Health Organization (WHO) classification system.[17] Sections of the left ventricle showed giant-cell myocarditis with infiltration by small lymphocytes and giant cells (Fig. 3A and 3B). A section of the psoas muscle (Fig. 3C) also showed myositis. Sections of the brain stem showed microglial infiltrates in the medulla and pons without involvement of the cerebral cortex or limbic structures (Fig. 3D). This distribution is consistent with a paraneoplastic process.

The results of a paraneoplastic antibody panel that was sent to the Mayo Medical Laboratory were received after the patient died. The results showed the presence of acetylcholine receptor binding muscle antibodies, acetylcholine receptor muscle-modulating antibodies, and antibodies to striational proteins. Acetylcholine receptor binding antibodies activate complement leading to loss of the receptor, whereas modulating antibodies lead to endocytosis and loss of expression of the receptor. Striational proteins, present in both heart and skeletal muscle, include the structural proteins titin and ryanodine receptor and a potassium-channel protein, Kv1.4. The patient did not have other paraneoplastic autoantibodies. The final diagnoses after completion of the autopsy are thymoma (WHO type A, noninvasive) and the associated paraneoplastic syndromes myasthenia gravis, giant-cell polymyositis involving heart and skeletal muscle, and mild brainstem encephalitis.

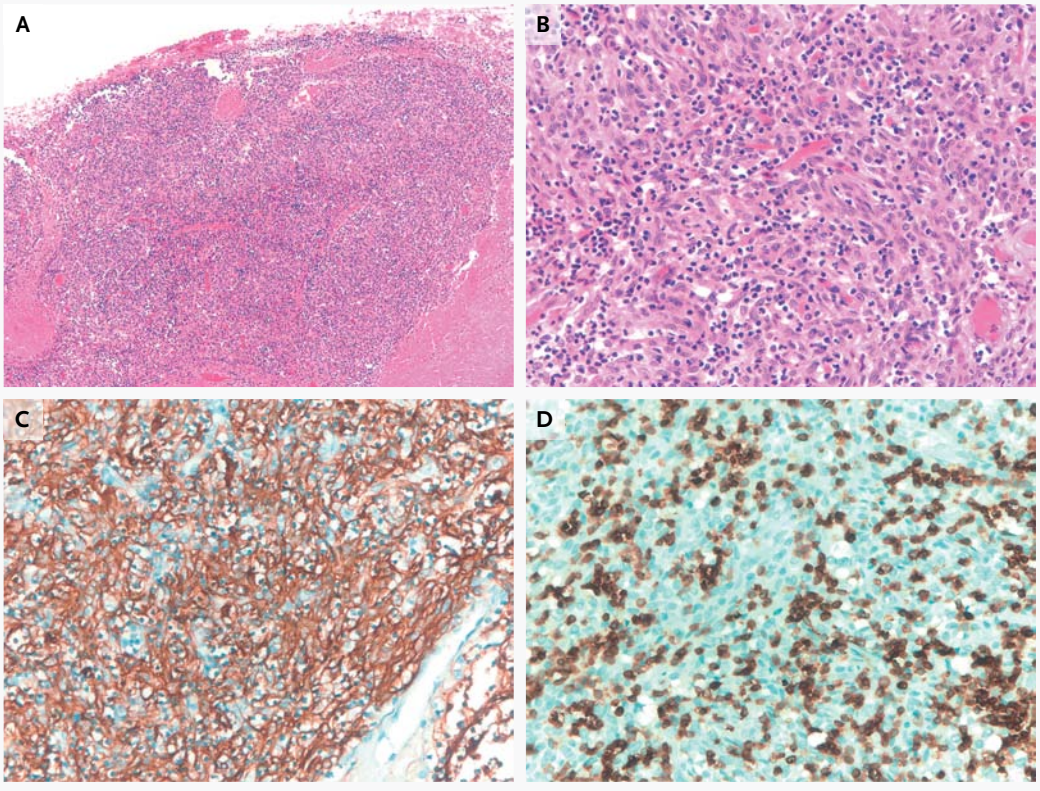


Figure 2. Mediastinal Mass.

At low magnification (Panel A, hematoxylin and eosin) the mediastinal mass contains a mixture of spindle cells and lymphocytes. At higher magnification (Panel B, hematoxylin and eosin) the spindle cells have oval, bland nuclei and the lymphocytes appear small and mature. With the use of immunohistochemical analysis, the spindle cells expressed cytokeratin (Panel C, immunoperoxidase for cytokeratin), and the lymphocytes were CD3+ T cells (Panel D, immunoperoxidase for CD3).

Paraneoplastic phenomena are seen in up to 50% of cases of thymoma; they are most common in WHO type B2 thymoma but occur in all subtypes. In addition to neuromuscular disorders, they include hematologic disorders such as red-cell aplasia and other cytopenias, hypogammaglobulinemia, and other autoimmune disorders.[18] Up to 10% of patients with myasthenia gravis and thymoma have more than one paraneoplastic syndrome, as this patient did.[16,18] A recent large study of patients with myasthenia gravis showed that the heart, skeletal muscle, or both were autoimmune targets in only 0.9% of patients; polymyositis was twice as common as myocarditis.[19] Polymyositis developed before or simultaneously with myasthenia gravis, whereas myocarditis associated with arrhythmias and heart failure developed after the onset of myasthenia gravis. All patients had anti-striational antibodies, and none had muscle-specific antibodies, findings that are similar to those in our patient.

Dr. Harris: Are there any questions for any of our discussants?

Dr. Lloyd Axelrod (Medicine): Can you relate these different diagnoses — polymyositis, brain-stem encephalitis, and myasthenia gravis — to specific clinical findings and make a pathological–clinical correlation?

Dr. Venna: Polymyositis causing respiratory and heart failure are part of the thymoma-associated neuromuscular disorder and may well have had a role in this patient's course. The ataxia and nystagmus may correlate with the mild brain-stem encephalitis found at autopsy. However, the most severe component of her illness is best explained by myasthenia gravis.

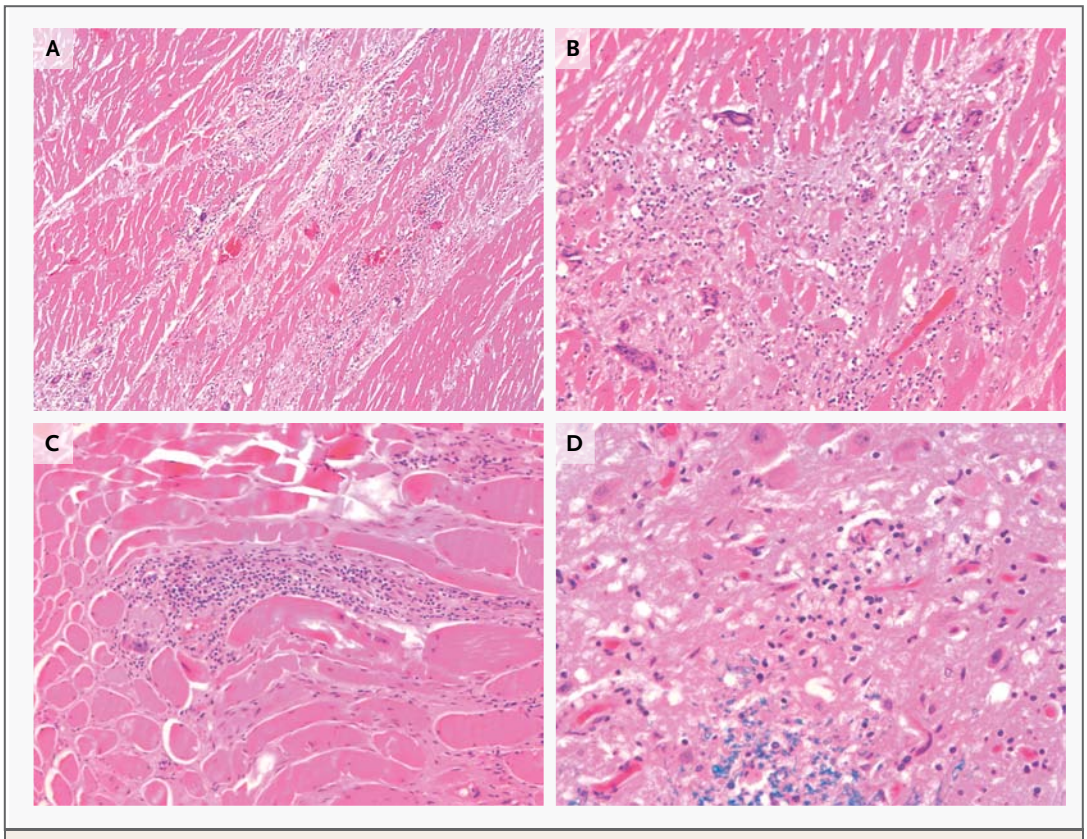


Figure 3. Paraneoplastic Phenomena (Hematoxylin and Eosin).

A section of the heart (Panel A) shows giant-cell myocarditis with infiltrating lymphocytes and multinucleated histiocytic giant cells (shown at higher magnification in Panel B). A section of psoas muscle (Panel C) also shows myositis. A section of the medulla (Panel D) shows patchy infiltrates of lymphocytes and histiocytes (microglia) that are indicative of mild brain-stem encephalitis.

Dr. Hasan Bazari (Medicine): It seems that in the initial assessment of this patient, there was premature closure around the diagnosis of dehiscence of the levator palpebrae tendon. What is the right evaluation for acute unilateral ptosis?

Dr. Venna: Dehiscence of the levator palpebrae superioris tendon can cause mechanical ptosis of the eyelid and is quite common in older patients. However, the onset of ptosis would not be so abrupt that the patient woke up with it one day. When I see a patient with new-onset ptosis, I look for a dilated pupil with decreased constriction to light and impairment of other ocular movements, since these indicate oculomotor nerve palsy and suggest a serious problem such as a cerebral aneurysm compressing the nerve. I think of myasthenia in patients with pupil-sparing, painless ptosis, and I look for other supportive signs, such as fatigability.

Dr. Harris: I think a major lesson from this case is that if an active person — no matter how old — suddenly becomes weak, causes of the weakness other than old age or deconditioning should be carefully considered.

ANATOMICAL DIAGNOSES

Thymoma — WHO type A, noninvasive — with paraneoplastic myasthenia gravis, giant-cell polymyositis and myocarditis, and brain-stem encephalitis.

This case was discussed at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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