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Myasthenia Gravis

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During the past two decades the concept of myasthenia gravis has changed radically. At one time myasthenia gravis was defined as a neuromuscular disease affecting voluntary skeletal muscles and producing weakness and fatigability. Myasthenia gravis was subsequently classified as an autoimmune disease in which antibodies directed against the acetylcholine receptor produce neuromuscular failure, weakness, and fatigability. Much of the pathophysiology of this disease has evolved in the last 20 years, and myasthenia gravis can now be considered as a prototype in terms of understanding the pathogenesis of many other autoimmune diseases.

Pathophysiology

In the 1960s there was great controversy about whether myasthenia gravis was a presynaptic disease, something that evolved from an abnormality in the packaging or manufacture of acetylcholine in the presynaptic terminal in the neuromuscular junction, or a postsynaptic disease, an abnormality in the acetylcholine receptor or in the transduction of the signal in the muscle membrane to produce muscle contraction. In the mid 1960s, Elmqvist and Lambert (1) found that the miniature end plate potential—the small depolarization of the postsynaptic membrane that came from the spontaneous release of a single quantum of acetylcholine—was reduced in amplitude to about 10% to 30% of normal. From another set of experiments, which was limited by the technology at that time, they thought that the postsynaptic membrane had a normal sensitivity and therefore suggested that myasthenia gravis was a presynaptic abnormality that resulted from small packets of acetylcholine being released (1). This was the predominant belief throughout the 1960s. However, in 1971, Engel and Santa's (2) morphometric electron microscopic studies of the postsynaptic membrane produced the following results:

1. The projections of the postsynaptic membrane where the acetylcholine receptors reside, the postsynaptic villi, were markedly altered and, in fact, destroyed.

2. The presynaptic structures, the nerve terminals, were normal. The size of the presynaptic vesicles was normal, and the presynaptic structures were not significantly altered.

3. The synaptic cleft was widened and contained debris that appeared to be the terminals of the postsynaptic membrane.

In addition to the morphologic suggestion that a postsynaptic, rather than presynaptic, abnormality was responsible for myasthenia gravis, biochemical studies in the 1970s helped to localize and quantify the acetylcholine receptors. By studying the mechanism of action of poisonous snake venom, Chang and Lee found that alpha-bungarotoxin binds specifically and irreversibly to the acetylcholine receptor (3). This enabled the production of a labeled ligand for the acetylcholine receptor that bound specifically and irreversibly, thereby allowing the identification of acetylcholine receptors in normal and in myasthenic muscle. Fambrough et al (4) documented that the acetylcholine receptors in the postsynaptic membrane of myasthenic muscles were reduced to 10% to 30% of normal.

As technology for electrophysiology improved, Albuquerque et al (5) were able to apply acetylcholine directly on to the postsynaptic membrane by using Nomarsky Optics, which documented that the decrease in sensitivity was consistent with the decrease in the number of acetylcholine receptors.

Thus, while it was firmly established by the mid 1970s that myasthenia gravis was a postsynaptic disease of acetylcholine receptors, the cause of this dysfunction was still unknown. Much of the evidence pointed toward myasthenia gravis being an autoimmune disease. This was first suggested in the late 1950s when an increased prevalence of other autoimmune diseases in myasthenic patients was noted. More evidence resulted from the development of another cholinergic ligand from poisonous snake venom. Like the alpha-bungarotoxin, alpha cobra toxin is also a very specific ligand that binds to acetylcholine receptors. However, because it is a reversible binding it was possible to attach alpha cobra toxin to a column and to purify acetylcholine receptors. Since acetylcholine receptors are found in high concentrations in the organs of the electric ray and the electric eel, it was therefore possible to use these electric organ tissues to purify large amounts of acetylcholine receptors.

Patrick and Lindstrom (6), who conducted these experiments, decided it would be interesting to study the acetylcholine receptor using a very specific antibody. Therefore, they attempted to immunize rabbits to the acetylcholine receptor, but the rabbits died consistently. From consultations with a neurologist, they

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found that myasthenia gravis was the cause of the weakness and death of these rabbits. Thus, experimental autoimmune myasthenia gravis was discovered. Investigators found that in its chronic phase experimental autoimmune myasthenia gravis is morphologically, biochemically, and electrophysiologically identical to the human form of the disease. The only difference was in the acute phase of the experimental disease in which a cellular infiltration of the end plate occurred. To our knowledge, this does not occur in human myasthenia gravis.

Following these experiments, it was thought that myasthenia gravis also might have an antibody to the acetylcholine receptor. A variety of techniques were used to detect and quantify the antibodies that bind to the acetylcholine receptor in the serum of patients with myasthenia gravis. By using specific ligands, it was possible to localize these antibodies to the end plate.

Finally, it became possible to transfer myasthenia gravis from man to mouse by using purified antibodies and injecting them chronically into mice. This experiment suggested that myasthenia gravis could be caused by a circulating agent. Indeed, about 15% of infants of myasthenic mothers are clinically weak at birth or immediately following birth. These infants have transient neonatal myasthenia gravis which clears within three to six weeks and is due to a circulating antibody.

With the discovery of antibodies against the acetylcholine receptor, it was believed that myasthenia gravis could be understood quite easily. It was initially thought that these antibodies would go into the neuromuscular junction, block the action of acetylcholine, and produce a neuromuscular blockade. However, several factors suggested that the answer was not that simple. First, there is a poor correlation between the state of the clinical disease and the titer of acetylcholine receptor antibodies in the serum of these patients. Second, if serum antibodies from a myasthenic patient are applied to a neuromuscular preparation in vitro, no blockade is produced. Investigators thus presumed that the antibody was involved in a more complicated process. It was later documented that the antibodies that bound to the acetylcholine receptor in the postsynaptic membrane activated the lytic phase series of complement so that there was complement-mediated lysis of the postsynaptic membrane with actual destruction of the tips of the membrane containing the acetylcholine receptors. A second group of experiments measuring the turnover of acetylcholine receptors in muscle culture found that acetylcholine receptor antibodies accelerated the degradation of these receptors to a level two to four times as fast as expected with normal serum. Therefore, at least two mechanisms were known to produce the loss of acetylcholine receptors in the postsynaptic membrane: the complement-mediated lysis, and the receptor modulation by the antibody.

The ultimate action of the acetylcholine receptor antibodies is still not understood. The presence of the antibody is not sufficient to explain or produce the disease. Patients who are in remission from the disease may have a very significant titer of the antibody and yet have no myasthenia gravis. One possible explanation is that acetylcholine receptors differ between one patient and another, and that difference is what mediates the variation in disease.

There are several binding characteristics of acetylcholine receptors. These receptors can be blocking or nonblocking, ie, some will block the binding of alpha-bungarotoxin and some will not. There are also two types of acetylcholine receptors: 1) those which are found in normal innervated muscles, limited to the neuromuscular junction; and 2) those which occur after denervation and spread across the muscle membrane. Studies have found that myasthenic patients have antibodies with several different binding characteristics.

The acetylcholine receptor consists of an alpha subunit that contains the acetylcholine binding site. Two of these alpha subunits, as well as three other subunits (beta, gamma, and delta), are within the acetylcholine receptor. These receptor subunits can be purified and used to produce the experimental autoimmune myasthenia gravis. The alpha subunit is the most effective subunit in producing weakness in animals; however, the native receptor is always more effective in producing the disease than any of the subunits. Within a particular myasthenic patient, most of the antibodies are directed toward an epitope referred to as the main immunogenic region which resides on the alpha subunit. While some antibodies are directed toward the other subunits, they do not appear to be important in determining the severity of the disease. Severity of disease is determined by something other than the type or titer of antibody that is found within a myasthenic patient.

Transient neonatal myasthenia gravis can help to explain the significance of the different types of antibodies. While transient weakness occurs in about 15% of infants of myasthenic mothers, about 60% of these infants have antibodies to the acetylcholine receptor. Neither the degree to which the mother is weak nor the level of her antibody titer determines whether or not transient weakness occurs. One of our cases involved a mother who had a significant titer of acetylcholine receptor antibodies but was in total clinical remission and off all medication during the last half of her pregnancy. Her infant, who had a slightly lower titer of antibody, was significantly weak and required treatment. Later, as the acetylcholine receptor was metabolized, the infant improved. This case suggests that the same antibody can have different effects on different individuals. Even though the mother was in remission, some of her antibodies circulated to the fetus, producing weakness in the infant after birth. Thus, identical antibodies can cause significant differences in the severity of weakness in two individuals. The biologically active antibody was present in the mother yet did not produce weakness. Therefore, host factors may be important in determining the clinical state in myasthenic patients. Some of these host factors may be a difference in the biochemistry of the motor end plate, ie, infants have different types of motor end plates than adults. Other possibilities include either the hormonal background in which the antibodies are acting or other blocking factors. Studies have shown that a significant percentage of myasthenic patients have anti-idiotypic antibodies circulating against the acetylcholine receptor antibody, and possibly these anti-idiotypic antibodies mediate a much more benign form of the disease in some patients with myasthenia gravis.

Incidence

In their 1971 study of over 1,200 patients with myasthenia gravis, Osserman and Genkins (7) observed that the distribution

of the incidence of myasthenia gravis is essentially a bimodal curve, with a peak incidence among young women and a second peak occurring among the elderly. In the latter group the sex distribution is essentially equal, although the incidence among elderly men tends to be somewhat higher. We have also noted the same bimodal curve, although in our series the age distribution increased by ten years, which may reflect that many of our patients began treatment at Henry Ford Hospital in the middle rather than in earlier stages of the disease. We also observed that myasthenia gravis affects two women per one man.

Symptomatology

One of the hallmarks of this disease, compared to other neuromuscular diseases, is that ocular muscles are characteristically involved. Alternating ptosis between the right and the left eye is almost pathognomonic of myasthenia gravis. Bulbar musculature is also affected. Symptoms may include hoarseness, difficulty with chewing, swallowing, and holding up the head, and respiratory crisis. Because patients are at high risk for respiratory failure, being aware of the patient's respiratory status is the key to management of this disease. At one time myasthenia gravis had a mortality rate of 20% to 30%, mostly due to respiratory failure and concurrent infection. A large number of patients may have generalized skeletal muscle weakness as well, and this may occur at the onset or later on in the course of the disease.

Classification

Myasthenia gravis has been classified in several different ways. Osserman and Genkins' (7) classification of the disease is commonly used. For adults, group 1 includes patients who have weakness localized to the eye muscles, such as ptosis and diplopia. This group represents approximately 20% of all patients with myasthenia gravis. If the disease has not progressed beyond involvement of the eye muscles within two years after onset, it is unlikely that the disease will progress further. Studies have shown that of the more than 90% of patients presenting with ocular findings, those who will progress to generalized myasthenia will do so by the end of two years. Group 2 includes patients with generalized myasthenia; mild 2A and 2B represent moderate severity with more bulbar symptoms. Group 3 includes those patients with a rapidly progressive course, usually resulting in respiratory failure within the first six months to one year after onset of the disease. Many of these patients have a thymoma. Group 4 represents a late progressive form of myasthenia gravis in which the severity of symptoms gradually increases over a period of years. Typically, the greatest degree of severity occurs within the first three years after onset.

A different type of classification, suggested recently by Compston et al (8), is based on the genetics and immunology of myasthenia gravis. Approximately 10% to 15% of myasthenic patients have a tumor of the thymus. In group 1 of this classification, no sex prevalence, HLA predominance, or characteristic HLA typing is seen. Groups 2 and 3 include patients without a thymoma. These patients appear to have a genetic predisposition toward acquiring myasthenia gravis. Those with onset before age 40 are predominately females. Patients in this age group have a 10% incidence of associated autoimmune diseases and share certain HLA antigens. Those with onset after age 40 are predominately males. The HLA types noted in this group are different from those seen in the younger age group, and these patients have a greater incidence of other associated autoimmune diseases.

In Osserman and Genkins' study (7), the more common associated autoimmune diseases included thyroid dysfunction (10% to 15%), diabetes mellitus (6%), and rheumatoid arthritis (3%). A smaller number of patients developed polymyositis, systemic lupus, vitiligo, pernicious anemia, and sarcoidosis. A variety of other autoimmune endocrine disorders have also been associated with myasthenia gravis.

Diagnosis

Myasthenia gravis is diagnosed in several steps. While associated autoimmune diseases should be considered in the initial workup, the medical history and physical examination is the first and most important step in diagnosing the disease. The second step involves repetitive nerve stimulation or single fiber electromyogram (EMG) tests to document the neuromuscular blockade. Repetitive stimulation, or the Jolly test, is carried out by stimulating the nerve at 3 cycles/sec and recording the resultant compound action potential from muscle. Myasthenia gravis would be diagnosed by seeing the typical decremental response. Single fiber EMG is a more sophisticated means of determining neuromuscular blockade and transmission failure. With proper testing of appropriate muscles, results should be positive in about 95% of patients with myasthenia gravis.

The anti-acetylcholine receptor antibody, the key figure in the autoimmune aspect of this disorder, is present in about 90% of patients with generalized myasthenia gravis and in about 50% of patients with the disease limited to the eye muscles. Antistriated muscle antibodies, discovered in the early 1960s, were the first clue to the autoimmunity in myasthenia gravis. These antibodies will stain muscle striations, such as the A band, the I band, and the Z band. Interestingly, while these antibodies are present in 30% of patients with myasthenia gravis, they apparently do not participate in the pathogenesis of the disease. Of patients with myasthenia gravis who have a thymoma, 95% will also have the antistriated muscle antibodies, although only 50% of patients with antistriated muscle antibodies will have a thymoma. Thus, the presence of antistriated muscle antibodies is a good marker for the possible presence of a thymoma. For this reason, chest x-ray and chest computed tomography are routine tests in the evaluation of the patient with myasthenia gravis. While 10% to 15% of patients will have a frank thymoma, another 70% of patients will have an enlargement of the thymus, or thymic hyperplasia.

Other diagnostic tests for myasthenia gravis include tests for collagen vascular disease, thyroid function tests, and the tensilon test. The tensilon test involves injection of a short-acting anticholinesterase which will improve neuromuscular transmission for about three to five minutes and thus aid in the diagnosis of myasthenia gravis. Although the older literature reports that the tensilon test is the key to diagnosing myasthenia gravis, this test presents two problems: 1) a large number of patients will have a false-positive tensilon test because of the severe cho-

linergic side effects of this drug, and 2) tensilon can cause respiratory failure in patients with compromised respiratory function. This can be a serious problem since some patients with compromised respiratory function may escape detection at the initial examination.

Henry Ford Hospital Experience

Approximately 147 patients with myasthenia gravis were seen at Henry Ford Hospital between 1983 and 1987, although that number has risen to over 180 patients to date. This total represents perhaps 20% of all myasthenic patients in Michigan. Clinic visits range between between 450 and 500 per year, which indicates that many patients with this disease need to be seen frequently. Whereas probably 50% of the patients are seen only once or twice a year because they are in stable condition, the others must be seen once a month or more often. We have approximately 25 hospital admissions per year, which includes one or two patients with a respiratory crisis necessitating a prolonged hospital stay.

Of the 147 patients seen between 1983 and 1987, 44 patients received thymectomies. A similar number were demonstrated to have associated autoimmune diseases. Thyroid disease was more prevalent in our group than in Osserman and Genkins' group, which is likely not a significant difference. Other frequently seen associated diseases included diabetes mellitus and vitiligo. A few patients had pernicious anemia, rheumatoid arthritis, and sarcoidosis. One patient had immune thrombocytopenic purpura, one had scleroderma, and one had polymyositis.

Treatment

Several forms of treatment are used for myasthenia gravis. The anticholinesterases, a purely symptomatic form of treatment, essentially augment the signal from nerve to muscle, stopping the breakdown of acetylcholine. Pyridostigmine bromide is the most commonly used anticholinesterase.

Thymectomy is another form of treatment. Abnormality of the thymus was one of the early clues to the autoimmunity of myasthenia gravis, and removal or irradiation of the thymus was shown to ameliorate the course of the disease. Thus, thymectomy is recommended for virtually all patients with severe or moderate myasthenia gravis. A recent study reported that thymectomy in patients without a thymoma increased the remission rate after several years to between 30% and 50% (9).

Corticosteroids have an unusual affect on myasthenic patients. When corticosteroids are given in high doses from the onset, within three days to two weeks about 30% to 50% of patients get weaker and 10% of these patients may develop respiratory crisis. However, most of these patients will improve after three to six weeks of corticosteroid therapy, and as many as 50% will go into remission. Unfortunately, corticosteroid therapy is imperfect. It is difficult to discontinue steroids in these patients after time. They become steroid-dependent, which leads to further complications.

Other immunosuppressive agents, particularly azathioprine, have been used to treat myasthenia gravis, but this has been much more popular in Europe than in the United States. While 30% to 50% of patients may go into remission with azathioprine, it may take up to one year for maximum effect to occur and patients can become dependent on the drug. Studies have shown that discontinuation of azathioprine will often result in a recurrence of the disease within six months.

We follow the principle that patients with ocular or very mild myasthenia gravis may be treated symptomatically, but an aggressive approach to the immune cause of the disease is important for patients with more severe myasthenia gravis. As mentioned previously, the key to management of myasthenia gravis is being aware of whether or not these patients have any respiratory compromise. Respiratory compromise may not be obvious when examining skeletal muscle involvement since respiratory muscles can be involved out of proportion to any other skeletal muscle involvement. However, one warning signal is when patients develop other bulbar symptoms such as difficulty with chewing or swallowing.

For patients with mild myasthenia gravis, treatment includes anticholinesterase therapy; thymectomy is also recommended only for those with generalized myasthenia gravis. Patients with the disease limited to the ocular muscles can be treated with anticholinesterases followed by small doses of steroids.

For those with moderate myasthenia gravis, thymectomy is recommended, preferably early on in the course of the disease. Anticholinesterase medications can be used as an adjunct, and steroids can be used if these patients are functionally unable to carry out their normal daily activities.

For patients with severe myasthenia gravis, the key is being aware of their respiratory compromise and protecting them against respiratory failure. These patients should be monitored in the intensive care unit. Respiratory parameters should be measured frequently in other patients who may be developing respiratory insufficiency. Plasmapheresis may produce improvement in patients with severe myasthenia gravis; however, improvement may not occur for seven days to two weeks because the neuromuscular blockade stems from a decreased number of acetylcholine receptors and the end plate must be allowed to heal. Steroids, usually begun in high doses, might also be helpful for patients with severe myasthenia gravis. Anticholinesterase may not be useful for patients in respiratory crisis since it may cause excessive bronchial secretions and make treatment more difficult for these intubated patients. Thymectomy is not recommended until after these patients are in stable condition. Azathioprine may also be considered as treatment for the long term.

Why do some patients who have had stable myasthenia gravis for a long period of time suddenly deteriorate? We have developed five categories to classify these types of patients. The first category includes patients who simply have a worsening of their myasthenia gravis. The second group includes patients who have therapeutic complications. For example, patients with excess cholinergic effects from the anticholinesterases develop a cholinergic blockade, which is manifested by other side effects such as an excess in salivation and sweating, tearing, diarrhea, and abdominal cramps. Also, patients may have a steroid myopathy or steroid-induced hypokalemia that produces excessive weakness. The third group includes patients who become worse because of changes in related diseases. For example, patients

who develop thyroid dysfunction, such as hyperthyroidism or hypothyroidism, may have a worsening of myasthenia gravis. The fourth group includes patients who become worse because of unrelated diseases. Any other intercurrent infection, particularly upper respiratory infections or pneumonia or even dental abscesses, can lead to respiratory crisis. In fact, any unrelated disease, such as cancer or stroke, can cause myasthenia gravis to worsen. The fifth group includes patients who become worse because of side effects of medication. While aminoglycoside antibiotics, which are neuromuscular blockers, do not present problems to the nonmyasthenic patient who has ten times more acetylcholine receptors than are needed, for the myasthenic patient who has only 10% to 20% of the normal number of acetylcholine receptors, a blockade of 30% or 40% of those receptors may produce a significant effect. Other medications that can produce weakness in myasthenic patients include beta blockers and membrane stabilizers.

Potential new treatments for myasthenia gravis include cyclosporine, specific plasmapheresis, and specific immunotherapy. Cyclosporine has been tried, but its effects are not sufficient to use as the sole agent for treatment of myasthenia gravis. A clinical trial will be undertaken in the near future to investigate the use of cyclosporine as a replacement for steroids. Plasmapheresis with specific filters may also be used in the future. In this procedure, the acetylcholine receptors are bound to the filters so that only the antibodies against the acetylcholine receptors will be removed, which obviates the need for plasma replacement. Specific immunotherapy to induce competing antibodies or anti-idiotypic antibodies has also been suggested. Immunization of animals with denatured acetylcholine receptors has already been shown to ameliorate the course of experimental autoimmune myasthenia gravis.

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