Immunologic Aspects of Myasthenia Gravis

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ABSTRACT

Clinical and pathologic features of myasthenia gravis suggest a possible autoimmune etiology. Myasthenia is found in association with other putative autoimmune diseases and autoantibodies including anti-muscle antibodies. There is also in vitro evidence for cell-mediated immunity to muscle in blood and thymic cells as well as a suggestion of antigenic disparity between blood and thymic cells. In addition, two experimental animal models are under investigation. It seems likely that the immune system plays a role in the pathogenesis, but what that role is and how it relates to neuromuscular block is not clear.

Introduction

Myasthenia gravis is a neuromuscular disorder characterized by variable muscle weakness often in a distinctive distribution. It is defined by a particular pharmacologic responsiveness to anticholinesterase administration and by excessive electrophysiologic fatigue on repetitive stimulation. Controversy still exists concerning the exact anatomic site and biochemical nature of the defect responsible for the clinical, pharmacologic and electrophysiologic abnormalities. From the immunologic standpoint, some fascinating clues have been found that may shed light on the pathogenesis of myasthenia gravis; it is to that area of investigation that this review is directed.

For the purposes of discussion the immunologic aspects of myasthenia gravis can be divided into clinical-pathologic aspects, autoantibodies, abnormalities of cell-mediated immunity and experimental models. It should be clear that such divisions are artificial; just as there are many important interrelationships between humoral and cell-mediated immunity in the normal immune response, the same interrelationships may be expected in states of abnormal immunologic reactivity.

Clinical-Pathologic Abnormalities

Perhaps the most compelling clinical piece of evidence for a possible autoimmune pathogenesis is the presence of abnormalities of the thymus gland in 70 to 90 percent of patients with myasthenia gravis. The thymus, a central lymphoid organ responsible for development and control of cell-mediated immunity, shows either a lympho-epitheloid thymoma or what some have termed thymic hyperplasia with prominence of Hassall's corpuscles. More recently, Goldstein has challenged the concept of thymic hyperplasia and has suggested that a more appropriate term would be "thymitis"; an inflammatory response in the thymus gland. Removal of the thymus gland surgically is generally regarded as...
having therapeutic benefit. The clinical response to ACTH, prednisone and cytotoxic agents has not always been consistent and these agents have too many effects on other systems to use responses to these drugs to support or deny the role of autoimmunity in the pathogenesis of myasthenia gravis.

Some of the clinical and epidemiologic features of myasthenia gravis are similar to those encountered in other disorders thought to be autoimmune in origin. These include female predominance, variable course, histologic evidence of immune hyperactivity, absence of a known cause, appropriate serum antibodies, association with other autoimmune diseases and animal models (vide infra). It should be pointed out that many of these criteria are indirect. Similarly, it cannot be stated that myasthenia gravis is an autoimmune disease simply because it is found in association with other probable, but not proven, autoimmune diseases such as thyroiditis or other abnormalities of the thyroid, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis. The association of myasthenia with other autoimmune diseases is accompanied by the finding of certain autoantibodies seen with these other diseases such as antinuclear antibodies, positive lupus erythematosus cell preparations, increase in rheumatoid factor, antithyroglobulin antibodies, biologic false positive tests for syphilis and positive Coombs tests.

More recently, an increased incidence of certain serologically defined histocompatibility linked antigens (HL-A) has been reported in myasthenia gravis. One group reported an increase in HL-A 3 and 8 while another found an increase in types 1 and 8. Since the "FOUR" (2nd locus) antigens, of which 8 is an example, seem to be more closely linked to the mixed leukocyte reaction defined histocompatibility antigen(s), the discrepant findings of an increase in types 1 and 3, which are both (1st locus) LA determinants, may not prove to be important. An increased incidence of certain HL-A types in other probable autoimmune diseases has also been reported, but comparisons and analogies to other diseases of as yet unknown etiologies could prove misleading. An increased representation of certain HL-A types has been reported in Hodgkin's disease. This observation is interpreted as being compatible with a genetically determined susceptibility to specific viruses resulting in certain clinical diseases such as multiple sclerosis. A further discussion of the fascinating interrelationships between viruses and autoimmunity and viruses, neoplasia and aberrant immunologic reactivity is beyond the scope of this review.

Autoantibodies

The occurrence in myasthenia gravis of certain autoantibodies, identical to those found in other diseases, has been mentioned. The most widely investigated autoimmune phenomenon in myasthenia gravis is the presence of antimuscle antibodies in the sera of 30 percent of myasthenics and 90 percent of myasthenics with thymoma. Historically, this finding was one of the first major clues pointing toward a possible autoimmune etiology of myasthenia gravis. These antibodies have been found to cross react with thymus, probably to the myo-epitheloid cells.

Problems in the interpretation of relationships between such antibodies and the pathogenesis of myasthenia gravis have arisen. Reports of localization of fluorescent immunoglobulin binding have shown different bands within muscle to be the target antigen in different patients. Moreover, with the exception of a report of antibody localized near the muscle membrane, the target antigens demonstrable by immunofluorescence are structural proteins. While such antibodies might explain certain "myopathic" features of muscle biopsies, abnormal twitch kinet-
ics and even the lack of responsiveness to drugs of some muscles, antibodies to structural proteins do not explain abnormal neuromuscular conduction,—the feature that defines the disorder. In addition, correlation between clinical severity and antimuscle antibody titer have been poor. More recently, a controversy has arisen over the presence of antibodies directed at components of nervous system nuclei and serum lymphotoxins have been reported.

Cell-Mediated Immunity

Several aspects of cell-mediated immunity have been the subject of investigation in myasthenia gravis. The first relates to the question of depression of cell-mediated immunity in patients with myasthenia. Although one group has reported depressed delayed hypersensitivity as measured by skin reactivity, others have not been able to confirm this hyporeactivity. Moreover, suppression of in vitro lymphocyte proliferative response to mitogen has not been found to be present in the peripheral blood cells of myasthenic subjects, nor have gross deviations from normal ratios of T (thymic dependent) and B (thymic independent) lymphocytes in peripheral blood been observed in the small number of patients studied so far.

A second area of interest focuses on whether or not in vitro evidence for cell-mediated hypersensitivity to muscle is present in the peripheral white blood cells of myasthenic patients. Using the technique of in vitro inhibition of peripheral blood leukocyte migration (PIF), Alpert et al have reported that muscle extracts and several purified muscle proteins are capable of inhibiting migration of buffy coat cells of myasthenics. Problems arise in the interpretation of these data. Although often equated with direct or indirect macrophage migration inhibition factor (MIF), there have been suggestions that PIF might correlate with the presence or absence of cytophilic antibody on the migrating indicator cells. Recent investigations have shown that PIF is chemically different from MIF and has a different target cell; however, both correlate with delayed hypersensitivity skin tests to standard antigens. There is now some evidence that, at least for some antigens, MIF is produced by B lymphocytes. It is of note that a strong correlation between muscle extract induced PIF and antimuscle antibodies has been reported. Using the technique of in vitro lymphocyte proliferative response, a significant response to muscle extracts has not been found in the peripheral blood cells of patients with myasthenia gravis.

Studies have also been carried out on the thymic cells of patients with myasthenia gravis. These cells have been found to be cytotoxic for fetal muscle cultures, a phenomenon reported to be present among the peripheral blood cells of patients with polymyositis. In addition, muscle extracts have also been reported to inhibit the in vitro migration of thymic cells, analogous to the PIF phenomenon exhibited by myasthenic peripheral blood cells. It has not been possible to find muscle extract induced PIF and anti-muscle antibodies has been reported. Using the technique of in vitro lymphocyte proliferative response, a significant response to muscle extracts has not been found in the peripheral blood cells of patients with myasthenia gravis.

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Experimental Models

There are two experimental animal models suggested as models of myasthenia gravis. Goldstein and co-workers have reported that sensitization of animals with
thymus or muscle results in (1) inflammatory response in the thymus, termed “thymitis”, as well as inflammation in skeletal muscle; (2) a state of abnormal electrical neuromuscular fatigue reversible by anticholinesterase agents; and (3) antimuscle antibodies. Thymectomy prevents the thymitis and neuromuscular blockade but not the development of antimuscle antibodies. Difficulties have arisen over the electrophysiologic measurements as well as the inability of other groups to reproduce the entity. Goldstein and his associates have suggested that the inflammatory response in the thymus results in the release of thymin, a substance capable of T cell induction as well as neuromuscular blockade. It was originally thought that the neuromuscular block occurred at the site of the acetylcholine receptor, but kinetic studies have now been interpreted to show a block of a different receptor which in turn may affect neuromuscular transmission at the acetylcholine receptor.

The second model results from the observation that sensitization of animals with concentrated preparation of acetylcholine receptor derived from the electric organ of the eel results in (1) clinical weakness reversible by anticholinesterase; (2) neuromuscular fatigue at low rates of stimulation (the physiologic definition of myasthenia gravis), and; (3) antibodies to receptor plaque. It remains to be seen whether this experimental disease is a result of a humoral or a cell-mediated hypersensitivity reaction to mammalian muscle receptor that presumably cross reacts with eel receptor plaque which is capable of inducing an lymphocyte proliferative response in myasthenic peripheral blood lymphocytes. A decrease in acetylcholine receptors in myasthenic muscle has also been reported. More recently, it has been shown that myasthenic immunoglobulin can inhibit the binding of α-bungarotoxin to the muscle acetylcholine receptor.

Conclusions

There is unquestionable clinical, pathologic and immunologic evidence that abnormalities of the immune system and autoimmune phenomena occur in myasthenia gravis. Much of the evidence is indirect and many reports conflict with regard to certain immunologic findings and experimental models. Therefore, a definite conclusion regarding the exact role of the immune system in the pathogenesis of myasthenia gravis is premature. Pressing research areas include (1) further basic studies on the thymus and its hormones; (2) identification of the sub-populations involved in such phenomena as MIF, PIF and lymphocyte proliferation; (3) further work on models of experimental myasthenia; (4) serial studies on myasthenic patients simultaneously measuring multiple immunologic phenomena using several techniques, and; (5) additional studies to characterize the nature and responsiveness of the cells in the myasthenic thymus.

References


41. STRAUSS, A. J. L., SIEGAL, B. C., and HUS, et al: ...


Acknowledgements

Thanks are extended to Dr. Arthur K. Asbury for his review and criticisms of the manuscript.