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Myasthenia gravis : a review of the literature

Richard Francis Brouillette
University of Nebraska Medical Center

MYASTHENIA GRAVIS - - A REVIEW OF THE LITERATURE

Richard Francis Brouillette

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INTRODUCTION AND HISTORY

The purpose of this study is to present some of the outstanding features of the clinical entity called myasthenia gravis. A review of the literature is presented with discussion concerning history, clinical features, diagnostic procedures, and current medical and surgical treatment. Special emphasis is placed upon a review of the pathogenesis of this disease with respect to the current autoimmune hypothesis.

Historically, Dr. John Maplet first described this disease in 1658. A contemporary of his, Dr. Willis, of Christ Church, Oxford, described the symptoms of myasthenia more completely in 1672. Two centuries passed before Sir Samuel Wilks, physician to Guy's Hospital, again gave a suggestive description of another myasthenic patient in 1877. Two years later a German physician, Erb, was credited with establishing features of the disease, namely, ptosis with diplopia, dysphagia, weakness of the neck, and the course of remissions and relapses. In 1893 Goldflam published an important paper on the disease and the name "Erb-Goldflam symptom" was designated in his honor. In 1899 Jolly suggested the name "myasthenia gravis", which was adopted at a meeting of the Berlin Society of Psychiatry and Neurology. In 1897 J. Collins, an American, described the condition in a patient whose first symptoms appeared during pregnancy. Mailhouse, another American, described the first child with myasthenia in

1898. In 1901 the first description of finding a thymic tumor in association with the disease was published. In 1904 T. R. Elliott offered the suggestion that there might possibly be a chemical substance liberated at nerve endings to initiate muscle response. Twenty-eight years later acetylcholine was identified by Loewi, of the University of Graz, and in 1936 Sir Henry Dale reported acetylcholine liberation at motor nerve endings, and that its action was limited by the ferment, cholinesterase.

The first breakthrough in treatment came in 1929 when Dr. Harriet Edgeworth of Tucson, Arizona, herself a myasthenic, isolated ephedrine as a beneficial agent. The most significant treatment advance came in 1934 when Dr. Mary Walker performed "The Miracle at St. Alfege's" when she injected prostigmine into a myasthenic patient. Dr. Henry Viets of Boston started the first Myasthenia Gravis Clinic in 1935 at the Massachusetts General Hospital, and here the disease has been intensively studied since that time.[1]

PATHOGENESIS

Normal, resting muscle fibers have a potential difference of approximately 90 mv. between the two sides of the surface membrane, the inner surface being negative with respect to the outer. This is the state of "polarization." Acetylcholine, the mediator of neuromuscular transmission, is released when a nerve impulse reaches the motor nerve endings. This compound becomes absorbed to receptor substances of the muscle end-plate, following which the permeability of the end-plate region for sodium and potassium ions increases temporarily, resulting in movement of sodium ions into the muscle and a less marked exit of potassium. [2, 3] The latter causes a slight reversal of the potential difference across the muscle membrane in the end-plate region or "depolarization." This depolarization is propagated along the muscle membrane as a wave of increased negativity called the muscle action potential. This in turn initiates contraction of the muscle fiber. Acetylcholine is then hydrolyzed into acetate and choline by cholinesterase enzyme concentrated in the muscle at the end-plate region. The potential difference across the membrane is then restored.

Interruption of neuromuscular transmission may occur in any step of the above sequence of events. Usually, neuromuscular block is the result of either deficient or excessive action of acetylcholine on the motor end-plates or as a result of drugs

or disease simulating these effects. [4, 5]

In myasthenia gravis there is no known abnormality of central or peripheral neural function, and the evidence for a defect in muscle contractility is not conclusive. Therefore, the manifestations of this disease are believed to be due primarily to impairment of neuromuscular transmission. The defect is believed due to some alteration in the acetylcholine mechanism. This could result from (1) an excessive concentration of cholinesterase at the neuromuscular junction, (2) failure of each nerve impulse to release a normal quantum of acetylcholine, or (3) elevation of the excitatory threshold of the motor end-plate to acetylcholine released by each nerve impulse. There is no evidence for excessive cholinesterase activity in the muscle of myasthenic patients at this time. [6]

The third possibility is incriminated in most recent literature and indicate that the defect in myasthenia gravis is due to a competitive (acetylcholine-inhibitory) block, produced by acetylcholine released in a normal manner during neuromuscular transmission, or by choline or a closely related compound following hydrolysis of the naturally released acetylcholine. [4, 7] In the majority of myasthenic patients the late block produced by the injection of intra-arterial acetylcholine or choline inhibits the depolarizing effect of acetylcholine and is reversed by the latter or by anticholinesterase compounds; i.e., it is both

acetylcholine-inhibitory and acetylcholine-reversible. However, in some myasthenic patients this late block inhibits the depolarizing effect of acetylcholine but is not reversed by this agent or by anticholinesterase compounds; i.e., it is acetylcholine-inhibitory but not acetylcholine-reversible. The latter is often referred to as acetylcholine-insensitive. [8] Such patients respond poorly or not at all to anticholinesterase medication and are clinically insensitive to the latter and to acetylcholine. Patients who do not show manifest signs of the acetylcholine-insensitive block may do so during an exacerbation of their disease. The phenomenon of acetylcholine-insensitive block may also be the explanation for the clinical observation that increasing doses of anticholinesterase medication seldom results in maximal muscle strength. It is the insensitive state that often makes management of the myasthenic patient so difficult and leads to confusion as to whether the patient is overdosed ("cholinergic crises") or underdosed (in myasthenic weakness).

Other possible causes of neuromuscular block in myasthenia gravis are reported in the literature. Some evidence has been presented that nerve endings may have an impairment of acetylcholine release. [9] Other reports suggest that anatomic abnormalities in both distal nerve endings and motor end-plates of myasthenic muscle may be impaired in this disease. [10, 11]

Reports of demonstration of a substance in the blood of myasthenic patients capable of producing neuromuscular block in experimental animals [12, 13] and of a substance in serum capable of inhibiting the synthesis of acetylcholine [14] have not been confirmed. [15, 16] Exchange transfusions between myasthenic and nonmyasthenic subjects have no effect on the strength of either. [17]

A recent development in the possible pathogenesis of myasthenia gravis is the suggestion that this disease may be due to an "auto-immune" response in which an antibody to end-plate receptor protein is produced by the reticuloendothelial system, including the thymus. [18] The antibody is then thought to combine with the end-plate protein and produce an alteration in the response of the end-plate to endogenous acetylcholine. Some support for this theory has been lent by the observation that the serum of myasthenic patients contains, in the globulin fraction, a substance which combines with normal or myasthenic muscle in the presence of complement. [19]

More recently investigations have shown lesions in the thymus of patients with myasthenia gravis that are similar to those produced experimentally by direct injection of antigen into the gland. This evidence indicates that some defect or injury to the thymus may cause the production of antibodies

which react with a protein found at the neuromuscular junction to produce the symptoms of myasthenia. White and Marshall (1962) demonstrated antinuclear factor, with the fluorescent-antibody technique, in six of sixteen patients with myasthenia gravis lending further support to the autoimmune theory. [20] Feltkamp, van der Geld, and Loghem (1963) demonstrated antibodies against skeletal muscle, thymus, and thyroid tissue in the sera of myasthenic patients. They also found the rheumatoid factor and the antinuclear factor, and felt their findings confirmative of the autoimmune hypothesis proposed for the disease. Their patients whose myasthenia was associated with a thymoma had a higher incidence of anti-muscle antibodies, and their clinical condition was also more severe. The patients with ocular myasthenia only had a lower incidence of anti-muscle antibodies. [21] Another possibility is that substances released as a result of antigen-antibody reaction competitively block acetylcholine, or interfere with its synthesis. However, the antibodies do not seem to be responsible for the neuromuscular block since antibodies were also demonstrated during remissions of the disease, and no circulating antibodies could be shown in the sera of some patients with severe myasthenia, including a patient with neonatal myasthenia.

That abnormalities of the thymus are not in themselves the primary cause of myasthenia gravis is suggested by in-

stances in which neonatal myasthenia has developed after maternal thymectomy prior to pregnancy, and by the onset of the disease after total thymectomy.

CLINICAL FEATURES

Characteristic Findings

Myasthenia gravis is a chronic disease characterized by recurrent weakness and abnormal fatigability of skeletal muscle but without obvious atrophy or other gross anatomical defect. The muscles most commonly affected are those innervated by cranial nerves, and usually those of the neck, trunk and extremities. In more severe cases, weakness and paralysis of the muscles of respiration occurs. Smooth and cardiac muscles are not involved. [22] Usually the disease becomes generalized, but in approximately one-fifth of the patients it remains limited to the extraocular muscles. The initial manifestations are most commonly referrable to this group of muscles. The initial symptom is ptosis in approximately 25% of patients, diplopia in 24%, blurring of vision in 3%, weakness of legs in 13%, generalized fatique in 6%, difficulty swallowing in 6%, slurred speech in 5%, chewing difficulties in 4%, weakness of arms, hands, neck, or face in each of 3%, and weakness of trunk or shortness of breath in 1%. [23] According to Grob, the commonest sequence is: muscles of the eyes, face, swallowing, speech, jaw, tongue, neck, shoulders, arms, hands, hips, upper legs, lower legs, trunk, and respiration. If the disease has been confined to ocular symptoms for more than two years without other

manifestations the orbicularis oculi muscles usually continue to have the localized form of the disease. [4]

Incidence

The incidence of generalized myasthenia gravis is slightly higher in females, while localized ocular myasthenia is slightly more common in males. Onset of the disease may occur at any age, but tends to be at an earlier age in females than in males, the average age of onset being 28 years in the former and 42 in the latter. [24] In children and adolescents, the disease is much more common in female patients. The incidence of onset of generalized myasthenia reaches a peak in women in the third decade, while it is fairly uniform in men from the third through the seventh decade. After 60, the onset is much more common in men.

Course of the Disease

The course of the disease is highly variable. Most patients show a gradual extension of the involved areas leading to a fairly steady state of weakness, which remains unchanged for many years, with moderate fluctuations in severity. The basic level of weakness is usually reached with the first three years after onset, most often within the first year. In patients with severe myasthenia, the average interval between onset of the disease and the first severe episode is eight months. In Grob's series of 350 patients with generalized myasthenia

gravis who had been followed for an average period of ten years, 30% died of the disease 3 months to 25 years after onset, and of these patients, 85% died within 3 years. [24, 25] Of the entire group, 13% were in complete or nearly complete remission at the end of ten years, 26% had had some improvement since their first severe episode of weakness, 21% were unchanged and 10% had become worse. [22]

Symptoms of the disease tend to fluctuate in severity from day to day in almost all patients and approximately one-fourth have a remission lasting at least 6 months, with complete or nearly complete disappearance of signs and symptoms. The average interval between onset of disease and remission was 4 years and the duration of the remissions varied up to 18 years, with an average of 4.6 years in Grob's series. [24]

In Ferguson's series of 133 patients, observed over a 28 year period, 30 who were treated medically were known to have died. Fifteen of these died of myasthenia gravis; of the others 8 died of carcinoma, the sites being gastrointestinal tract 5, breast 1, bladder 1, and bronchus 1. In the remaining 7 the causes of death were coronary occlusion 3, lung abscess 1, left ventricular failure 1, acute pancreatitis 1, and cause undetermined 1. Of 12 patients who had undergone thymectomy, 7 had died and in each case from myasthenia. [26]

Mortality Rate

The overall mortality rate is approximately 15% with the present methods of treatment. [27]

Pregnancy and Myasthenia Gravis

The effect of pregnancy on the course of the disease is quite variable and debatable. According to Grob there is no effect in most instances and in approximately one-third of the patients there is an exacerbation of the disease, usually during the 6 weeks following delivery, or less often during the pregnancy. [23] In some patients with myasthenia gravis there is mild improvement during the latter half of pregnancy. Ferguson sites Viets et. al. (1942) who concluded that pregnancy usually had a favorable effect on the mother's disease, but that relapses mainly occurred during the first trimester. Fraser and Turner (1953), also sited by Ferguson, concluded in their series of 14 pregnancies, that myasthenic patients could go through pregnancy without special difficulty, although some danger of a relapse was present in the first trimester and increased doses of neostigmine necessary occassionally. They concluded that there was no special medical indication for termination and added that in their opinion the greatest danger of relapse was in the first three weeks of the postpartum period, and about half their patients experienced a relapse. [26] Ferguson (1962) drew similar conclusions in a series of 22 patients and 34 pregnancies; 14

deteriorated during pregnancy and 12 improved. Fifteen changed in the first three months and 9 in the second three months, and he concludes by stating: "(1) Some myasthenics can go through pregnancy without any adverse change. Labeur does not seem to present a problem. (2) If a change is going to take place it is most frequent in the first three months and, to a lesser extent, in the second three months. This change is sometimes for the better and sometimes fer the worse, and (3) After only 7 of the pregnancies was there postpartum relapse in the first month, however, very careful supervision should be exercised in the postpartum period." [26]

Howard and Mulder (1964) basically agreed with these figures and state further that if repeated pregnancies occur, each pregnancy may have a different effect on the myasthenia gravis. [28]

Neonatal Myasthenia Gravis

Children born of myasthenic mothers are usually normal and never develope the progressive form of the disease according to Grobe. His review of the literature (1961) turned up 27 reported instances of neonatal myasthenia gravis lasting from several hours to seven weeks after delivery, and usually requiring anticholinesterase drugs during this period. Recovery was complete in all but one infant who died. [23] Stern, Hall, and Robinson (1964) reported the finding of 34 cases in the literature plus two of their own experience. In both cases the infants presented

with symptoms like the adult form of the disease, however, respiratory embarrassment was clinically more common. The onset of symptoms varied, in their review, from birth to within two or three days, and the illness lasted from between 10 and 90 days with an average of about three weeks. No further myasthenic symptoms have been reported in children who have recovered from the neonatal illness. They contend that the incidence of neonatal myasthenia is difficult to predict in that many cases probably aren't diagnosed and that only the severely affected infants tend to be reported. Viets and Brown (1951) found three children of 36 with the disease who were born of myasthenic mothers. Fraser and Turner (1953) found one of twenty-two. [29]

There appears to be no correlation between the clinical features of the disease in women whose infants were normal and those whose infants were affected. There is also no correlation between maternal dose of anticholinesterases and the severity of the neonatal disease.

Myasthenic mothers have had normal births before having affected children, and, although there are several records of two consecutive myasthenic infants, there is no mention of a normal baby born after a myasthenic one.

Diseases Associated with Myasthenia Gravis

Generally, figures reported in the literature suggest

that about three per cent of myasthenic patients have associated hyperthyroidism and two per cent have exophthalmos in the absence of thyroid disease. Grobe, Drachman and Bartels report similar figures in that they all three report myasthenic symptoms occurring in only a fraction of 1% of the thyrotoxic population. The two diseases often do not begin simultaneously; either one may preceed the other by many months or years and the authors reviewed also concurred in the fact that either the hyperthyroid state or hypothyroid state may cause an aggravation of myasthenic symptoms. [23, 30, 31] In the Mayo Clinic series hyperthyroidism was noted first in 54% of cases; myasthenia gravis occurred earlier in 37%. Only 9% had a simultaneous onset. [30] Ninety cases of the two diseases have been reported since the turn of the century according to Weichhardt. [32] However, it is doubtful that all such cases have been reported since muscular weakness and impairment of extraocular movement are common to both diseases. The response to neostigmine would be normal in isolated hyperthyroidism.

Engel further demonstrated that TSH given to an athyreotic had no effect on his coexistent myasthenia gravis thus concluding that TSH had no extrathyroidal effect on the disease. [33]

Greenberg reported on two sisters with myasthenia gravis and hyperthyroidism and reviewed the literature. [34] However, it would appear that there is insufficient evidence at present

to incriminate a genetic basis for either/or both diseases.

Pathologic Changes in Myasthenia Gravis

Pathologic changes are virtually limited to hyperplasia or tumor of the thymus gland, and scattered collections of lymphocytes (lymphorrhages) in some muscles. [35] A tumor of the thymus (thymoma) is present in about 15% of patients with myasthenia gravis. [23, 36] When associated with thymoma the onset of myasthenia is later in life, there is a male sex preponderance [37] and in general the disease is more severe and progressive, [23] although there is much individual variability. In some instances detection of the thymoma precedes the onset of myasthenia by many years, and in at least three instances myasthenia appeared several years following apparent total thymectomy. [23, 38, 39] In approximately half of all patients the thymus is hyperplastic; in 14% it is normal microscopically, and in 7% it is not identifiable, a normal finding in adults. [23] In about three-fourths of myasthenic patients the thymus contains numerous germinal centers, which are absent [40] or rare [41] in normal individuals. Thymic hyperplasia is more common in female patients and thymoma in males. The mortality rate of patients with the disease and a thymoma has been approximately 70%, compared to 40% for patients whose anterior mediastinum has been examined without revealing a tumor and 30% for all myasthenic patients according

to Grob (1961).[23] However, there appears to be no consistent correlation between the observed changes in the thymus and the clinical course of the disease. Patients with no detectable thymus may have severe weakness, and occasionally patients with a thymoma may have a mild form of the disease. Thymomas are almost always visible roentgenographically in the lateral view, whereas thymus glands that reportedly are enlarged without tumors are rarely seen. Grob reports that despite the large size of many tumors, only about one-fourth invade adjacent structures to produce notable signs and symptoms.[22] Mitotic figures are occasionally seen, and local implants have been reported[42] however, distant metastases are extremely rare in myasthenic patients.[23, 40] Three-fourths of nonmetastasizing thymomas observed have occurred in myasthenic patients, while the incidence of this tumor in nonmyasthenic subjects has been approximately 1 per 100,000 hospital admissions, compared to 15% in myasthenic patients, and some of the former have developed myasthenia gravis years after the tumor was noted or even following incomplete[43, 44] or complete removal of the tumor. Malignant thymic tumors with distant lymphatic or blood-borne metastases occur almost exclusively in nonmyasthenic subjects with approximately the same frequency as thymomas. These tumors, which have been classified as carcinomas[45] or seminomas,[46] are more likely to produce pain and evidence of

tracheal and superior vena caval compression. Most authors feel that a mediastinal tumor occurring in a myasthenic patient is almost certain to be a thymoma, and an extramediastinal intrathoracic tumor in such a patient is most likely to be an ectopic thymoma, or, less often, a small-cell bronchogenic carcinoma which may occasionally be associated with a "myasthenic" syndrome, [47] or some other unrelated tumor.

Although myasthenia gravis is the syndrome most frequently associated with thymic tumor, reports of other associated conditions are in the literature. Fifteen instances have been reported of the simultaneous occurrence of benign thymoma and refractory anemia, accompanied in some by thrombocytopenia or leukopenia. [23, 48, 49] Four of the latter patients had myasthenia gravis. At least two reports have appeared of agammaglobulinemia associated with thymoma, [50] and in one instance with aplastic anemia as well. [51] Approximately eleven cases have been reported of Cushing's syndrome associated with adenocarcinoma of the thymus.[51] Other disease entities associated with thymic tumors or myasthenia gravis are Grave's disease, [32] bronchogenic carcinoma, [47] polymyositis and dermatomyositis [52] and lupus erythematosus. [53] However, the evidence that has accumulated linking the latter diseases and thymus abnormalities is inconclusive at present and the possibility of coincidence are not excluded.

The Diagnosis of Myasthenia Gravis

The diagnosis of this disease can generally be made on the basis of the history, distribution, and usual fluctuating nature of the weakness that usually occurs on repeated effort of involved muscles. Confirmation of the diagnosis is made by noting the improvement in strength which characteristically follows the administration of an anticholinesterase compound, such as neostigmine (Prostigmin) or edrophonium (Tensilon) when the patient is in a "basal" state at least six hours after the last medication. Unequivocal increase in strength of more than slight degree following neostigmine or edrophonium does not occur in patients who are not considered to have myasthenia gravis, with the exception of a few patients with polymyositis, disseminated lupus erythematosus or carcinomatous neuropathy or myopathy.[54] However, the latter conditions seldom pose as diagnostic difficulties. The most widely used test substance used in making the diagnosis is neostigmine. The latter is given intramuscularly, in a dose of 1 mg. per 100 pounds of body weight. Atropine sulfate (0.5 mg. per 100 pounds) should be injected intramuscularly before or with the neostigmine to prevent the muscarinic effect of the latter drug on smooth, cardiac and secretory elements in the body. Neostigmine may also be administered intrvenously (0.5 mg following 0.5 mg. atropine).[55] Edrophonium, which has both

anticholinesterase and direct depolarizing action on muscle (2 mg. followed by 8 mg. in 30 seconds if the first injection does not produce an increase in strength) is also widely used today. Atropine is not necessary with edrophonium and for this reason, and because of its rapidity of action, edrophonium is now widely used as a diagnostic agent.

Treatment

Treatment of myasthenia gravis relies mainly on anticholinesterase compounds which are administered for the amelioration of weakness. The quaternary ammonium compounds neostigmine, pyridostigmin (Mestinon), and ambenonium (Mytelase) are among the most useful compounds used in the management of the myasthenic patient. Many longer-acting compounds are available but the danger of cumulation and overdose is much greater. Bis-neostigmine and bis-pyridostigmin are examples of this latter group. Also available are several organophesphorus anticholinesterase compounds, however the maximal strength obtained after optimal doses of any of these quaternary ammonium or organophosphorus anticholinesterases is essentially the same according to Grob.[23] Dosage is highly individualized and special precautions should be taken to familiarize the patient with signs of overdosage or underdosage, the former resulting in "cholinergic crises" and the latter in "myasthenic crises."

Dosage regulation is initiated by the administration of a dose below that necessary to produce maximal strength, usually 120 mg. of pyridostigmine, 10 mg. of ambenonium, or 15 mg. of neostigmine orally every 4 hours when awake, or 1 mg. of neostigmine intramuscularly every 3 hours. The dose is then gradually increased until no further increase in strength occurs. The interval between doses may be decreased by one hour if this proves necessary to maintain strength. Pyridostigmine and ambenonium should be adjusted at intervals of 1 to 2 days due to their longer duration and the dose of neostigmine may be adjusted at shorter intervals. The dosage should be optimal when adjusted. Optimal dosage is complicated by the great variability of the disease and the fact that different groups of the affected muscles react differently to a given dose. Onset of weakness one hour after drug administration is suggestive of overdose while onset of weakness 3 or more hours after administration is suggestive of underdose or resistance to the drug. Edrophonium may aid in establishing a dosage range in that its administration will produce a transient increase in strength if the patient is in need of more medication and if not, will produce a decrease in strength or muscarinic side effects such as lacrimation, salivation, sweating, abdominal cramps, or nausea.[56] If no change occurs it may be assumed that the

patient is near his optimal dosage range. Atropine sulfate is given intramuscularly as needed to prevent the muscarinic effects of anticholinesterase compounds. After the regulatory dose has been established, atropine may be administered (0.6 mg. orally or intramuscularly every 4 to 8 hours) if side effects are troublesome. Pro-Banthine (15 mg. every 6 hours) may also be used for the same purpose. [23]

Other Drugs Used in the Treatment of Myasthenia

Ephedrine sulfate, as an adjuvant to anticholinesterase medication, and potassium chloride (25mg. t.i.d. and 2 gm. q.i.d. respectively) are often used in the treatment of this disease. The use of guanidine is not recommended at present. Steroids have not been generally successful, but some authors still employ them. [57, 28]

Drugs to be Avoided in the Myasthenic Patient

Certain drugs must definitely be avoided in myasthenic patients. The most important of these are the competitive muscle-relaxing agents, such as curare (or d-tubocurarine) and flaxedil. While decamethonium and succinylcholine are better tolerated, it is best to avoid these drugs. Quinine, quinidine and parenteral neomycin should also be avoided, because they may increase neuromuscular block. Morphine should also be used cautiously with anticholinesterase compounds. Demerol is generally well tolerated. Local anesthet-

ics, even though they effect the neuromuscular junction, may be used with epinephrine to delay absorption. Ether and cyclopropane are also fairly well tolerated by the myasthenic patient. [23]

Exacerbations of the disease are controlled by increasing the dose of anticholinesterase medication and removing secretions and maintaining an airway with all means necessary. Potassium chloride administration, as previously stated, improves the response to acetylcholine and anticholinesterase drugs in some patients even though there is no evidence of potassium depletion. Reduction in body temperature has a similar effect in some patients. [8]

Thymectomy and Myasthenia Gravis

Results following thymectomy in the treatment of myasthenic patients have varied markedly in effectiveness of relieving or curing the disease.[58] Viets and Schwab (1960) evaluated the effect of thymectomy in 600 patients, from their own experience and that of others. While the incidence of improvement was the same after thymectomy as in the control group when the two sexes were added together, it was twice as high after thymectomy when only female patients under 40 yrs., and without thymoma, were considered. [59] Viets (1953) has recommended that the operation be performed mainly in young female patients who are not doing well on medical management.

He does not recommend thymectomy, except in rare instances, in patients over 50 or under 5 years of age, or in those who are in remission or are well adjusted on medication. [60]

Howard and Mulder (1964) give the following indications for thymectomy:

1. Thymoma demonstrated roentgenographically in any patient whose general health is good. The rationale is that a thymoma may be malignant and should be removed just as any potentially malignant tumor within the thorax.
2. Severe progressive myasthenia gravis that has been present for less than two years and has not responded well to medication in a woman less than 35 years

These authors feel that chances of obtaining a remission after thymectomy in the latter group are about twice as good as after treatment with anticholinesterase drugs only. However, they admit that remissions after this procedure are highly unpredictable, and even though females have a higher remission rate than males, they also perform thymectomies in males under the same circumstances. [28]

Irradiation of the Thymus

Irradiation to the thymus has been recommended by investigators, however the results are controversial. Its

value has not been demonstrated, but it is apparently not harmful in adults and may be tried on patients who are not doing well on medical management. There is also difference of opinion as to whether irradiation of the infant thymus may later be followed by an increased incidence of carcinoma of the thyroid. [61, 62]

SUMMARY

A review of the current literature dealing with the many aspects of myasthenia gravis is presented. Special emphasis has been placed upon the current hypothesis of an autoimmune etiology. Included also are discussions of neonatal myasthenia, incidence, myasthenia and pregnancy, diagnostic procedures, the role of the thymus gland, associated diseases, management of the myasthenic patient, and an historical review.

Many aspects of the possible autoimmune etiology are reviewed and some proposals have great merit. That the defect in neuromuscular transmission has been localized to the motor end-plate cannot be disputed. However, much is dispute is the exact mechanism for the failure of impulse transmission, and whether there is deficient acetylcholine, an unresponsive end-plate due to an elevated stimulus threshold, excessive anti-cholinesterase, or a competitive block as a result of an unknown substance, (which in itself is the result of an autoimmune mechanism) is still much in doubt. There is still no conclusive evidence, or hypothesis, that can explain all manifestations of this disease. The demonstration of multiple antibodies in myasthenia gravis, its clinical course with remissions and exacerbations, the female sex preponderance, and other features reminiscent of other autoimmune diseases might lead one to conclude that myasthenia is an autoimmune disease. However, the concept of

autoimmune disease is new, and no disease has been proven to occur by this mechanism. The most satisfactory demonstration of auto-antibodies which might be pathogenic has been in thyroiditis, but even here, similar antibodies have been found in some normal individuals. The antigen in myasthenia has not been identified. Furthermore, the identification of antigen and antibody does not in itself provide evidence of the mechanism of disease. If there is a circulating antibody, it has not been demonstrated in all cases, nor has it been proven to be the cause rather than the result of the muscular disorder.

These reservations merely indicate that much work remains to be done and it seems very likely that immunological study of myasthenia will be important in the future.

CONCLUSIONS

1. Myasthenia gravis is a chronic disease with exacerbations and remissions of muscular weakness, often involving the ocular muscles only, but frequently generalized and affecting many groups of skeletal muscles. Rest frequently restores muscle function.

2. Cardiac and visceral muscles are not affected in this ailment and there is no evidence of muscular wasting, anatomical defect in the neuromuscular junction, or central or peripheral neuronal damage.

3. Cholinergic drugs are dramatically beneficial in most instances, however cholinergic-insensitive episodes are not rare in the management of this disease.

4. Intercostal and diaphragmatic musole paralysis is the most life-threatening aspect of this disease, and a not uncommon cause of death.

5. The disease is found in any age group with a slightly higher incidence of generalized myasthenia and earlier onset in females. Onset of generalized myasthenia reaches a peak in third-decade women and is more common in males beyond 60 years of age.

6. The course of the disease is highly variable. Most often the basic level of weakness is reached within the first year after onset. Some patients experience complete remissions of their symptoms.

7. The overall mortality rate is probably just under 15% at the present time.

8. Pregnancy in the myasthenia gravis patient may cause an exacerbation of the disease (usually during the six weeks following delivery) or may even improve the patient's condition. The general feeling is that the disease is not an indication for termination of the pregnancy.

9. Neonatal myasthenia gravis is not uncommon, but likely goes undiagnosed frequently. No correlation between the severity of the mother's condition and the occurrence of neonatal myasthenia exists.

10. Approximately 3% of myasthenic patients have associated hyperthyreidism, and 2% have exophthalmos in the absence of thyroid disease. Either the hyperthyroid or hypothyroid state may cause an aggravation of the myasthenic's symptoms. Lupus erythematosus and other disease entities are frequently associated with myasthenia but the evidence for any known relationship is inconclusive.

11. Pathological changes in this disease are virtually limited to hyperplasia or tumor of the thymus gland and lymphorrhages in muscles. A thymoma is present in approximately 15%.

12. The diagnosis is most frequently attempted by using neostigmine or edrophonium and then noting the improvement in strength in the affected muscles.

13. Treatment relies mainly on the quaternary ammonium

compounds. (Anticholinesterases such as neostigmine, pyridostigmine, and ambenomium.) Ephedrine sulfate and KCl are frequently used as adjuvants to the anticholinesterase compounds.

14. Thymectomy appears to be indicated in young female patients who are not doing well on medical management, patients who have demonstrable thymomas at any age or sex, and in severely progressive forms of the disease in either sex under the age of thirty-five.

15. Irradiation to the thymus as treatment for myasthenia gravis has produced questionable results.

16. The autoimmune hypothesis currently proposed appears to be the important pathway for future investigation.

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