Myasthenia Gravis

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Myasthenia gravis (MG) is an autoimmune neuromuscular disorder manifested clinically as weakness and easy fatiguability of skeletal muscle groups, particularly of the face and extremities. The association of MG with pregnancy has been the subject of several studies, which have been collated in two review papers.[1,2] In this monograph I will bring these case reviews up to date, present new immunologic and physiologic information, and discuss current treatment modalities. Management of the myasthenic patient in pregnancy and labor is reviewed in detail, with particular emphasis on drug and anesthetic interactions with myasthenia.

Classification

The classification of myasthenic disorders was standardized in a classic article by Osserman on Genkins in 1961.[3] Neonatal myasthenia is a transient disorder of the newborn of myasthenic mothers caused by the passive transfer of antibodies from mother to infant. The adult form of the disease is classified by the severity of the disorder and whether the muscles of respiration are involved. Ophthalmic MG, mild, moderate, and late severe systemic MG, and acute fulminating MG are recognized.

Diagnosis

The clinical diagnosis of myasthenia gravis is suspected when there is a history of and demonstration of skeletal muscle weakness and rapid loss of strength with repetitive exercise and confirmed by the restoration of muscular strength with anticholinesterase drugs.

Edrophonium chloride (Tensilon, Roche Laboratories, Nutley, N.J.) is the favored short-acting anticholinesterase drug used for testing the restoration of muscle strength. Careful intravenous injection of 2 to 10 mg of edrophonium results in prompt restoration of strength to involved skeletal muscle and regression of the drooping lids of ophthalmoplegia and slurred speech of dysarthria.

New technologic sophistication enables laboratories to aid diagnosis with titers of antiacetylcholine receptor protein antibody (anti-AChR IgG) levels.[4,5] Heilbronn[6] and Roses et al.[7] caution against directly relating

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antibody levels to the severity, course, or prognosis of the disease. Immune complexes at the neuromuscular junction can now also be demonstrated in skeletal muscle biopsy material from myasthenics.[8]

Epidemiology

The prevalence of MG varies from 12 to 64 cases per million, with a world average prevalence of 40 per million.[9] MG can affect both sexes at all ages; however, most large MG series contain twice as many females as males. MG in the female follows a genetic inheritance pattern with the onset of manifestations near menarche. Among patients dying of myasthenia, there is a clear preponderance of nonwhite females.[9] Twenty percent of female patients experience the onset of their disease prior to their 20th year and follow a protracted course. The incidence of the disease peaks in the 3rd decade in females. In males, the peak incidence is in the 6th and 7th decades, and there is no racial difference in incidence.

Inheritance plays a definite but ill-defined role in MG. There is a greater than expected familial occurrence of MG, particularly in females, and most clearly in the small subset of patients with juvenile myasthenia.[10] Histocompatibility (HLA) typing and twin studies both suggest a genetic component to MG, particularly in females.[10,11]

Engle et al.[8] hypothesize that MG may be the clinical manifestation of three separate genetically coded diseases—an infantile autosomal recessive form; a hereditary X-linked form manifest in females at puberty and exhibiting a nonwhite racial predilection; and an acquired form in older men that exhibits no racial difference in incidence. Much more evidence must be accumulated before these postulates can be adequately tested.

Immunopathology

The skeletal muscle of patients with MG displays the physiologic hallmark of diminished amplitude of miniature end-plate potential. Storage and release of transmitter quanta by nerve impulses remain normal, and nerve terminals are structurally preserved.[8] The postsynaptic portion of the neuromuscular junction, however, shows degenerative expansion of terminal junctional folds and simplification of the postsynaptic membranes.[12] Acetylcholine receptors are reduced by over 70% in myasthenic postsynaptic membranes.[13]

Antibodies to human AChR are detectable in up to 90% of myasthenic patients.[4,6] Both acquired human MG and MG induced in experimental animals by immunization with AChR can be passively transferred to normal animals by the injection of immunoglobulin G (IgG) from affected donors.[4] IgG and the third component of complement (C_3) have been demonstrated on segments of the postsynaptic membrane and on degenerated fragments of junctional folds in the synaptic space.[8] The abundance of immune complexes is inversely proportional to end-plate potential amplitude. These studies confirm that a deficiency of nicotinic postsynaptic AChR protein at the motor end-plate caused by antibody-dependent complement-mediated lysis of the postsynaptic membrane is the basic pathologic lesion of MG.

Myasthenia gravis has been associated with a number of other disorders, many of which are believed to be autoimmune diseases.[3,14] (see Table 1). Hokkanen[14] found rheumatoid arthritis in 5-6% of female MG patients. Approximately 30% of myasthenics were found to have antithyroid antibodies; 20-40%, antinuclear antibodies; and 5-6%, rheumatoid factor.[14] Osserman and Genkins[3] describe Hashimoto's thyroiditis complicating MG in 13% of cases, systemic lupus erythematosus in 0.5%, and polymyositis and sarcoidosis in 1%.

Cohen et al.[15] in 1976 first proposed an association between preeclampsia and MG. Duff[16] described three such cases and speculated that an altered immune status might be an etiologic factor in preeclampsia. It is not possible to obtain the exact incidence of

TABLE 1. Diseases Associated With MG

Rheumatoid arthritis
Systemic lupus erythematosus
Hashimoto's thyroiditis
Autoimmune hemolytic anemia
Polymyositis
Sarcoidosis
Scleroderma
Ulcerative colitis
Pemphigus
Dermatitis herpetiformis
Epilepsy
Coeliac disease
Immune complex nephritis
Pernicious anemia
Penicillamine therapy
Thymoma
? Preeclampsia

preeclampsia in myasthenic pregnancies from the literature, nor can we address this issue in our own series of cases. The existence of concomitant preeclampsia is not recorded in any of the 10 Charity Hospital of New Orleans (CHNO) myasthenic pregnancies recently reported; however, pregnancy lasted beyond the 24th week in only 1 primigravida.[2]

The Effect of Pregnancy on Myasthenia Gravis

Our literature review series now numbers 314 pregnancies occurring in 217 myasthenic mothers (see Table 2 and 3). Ninety-nine pregnancies (31.5%) caused no change in the status of myasthenia through gestation and the postpartum period. The remainder had varied combinations of exacerbation and remission related to gestation. Ninety-one patients (29%) experienced at least a partial remission at some time during pregnancy. Four patients had remissions during pregnancy but exacerbation in the postpartum period.

TABLE 2. Maternal Outcome in 314 Pregnancies in 217 Myasthenic Mothers

Exacerbation during pregnancy*	128	40.8%
Remission during pregnancy†	91	29.0%
No change during pregnancy	99	31.5%
Postpartum exacerbations	96	30.6%
Maternal deaths‡	9	3.4%

*Four patients had further postpartum exacerbation.
†Four patients also had postpartum exacerbation.
‡One additional mother died 19 months after delivery of complications beginning in the puerperium.

TABLE 3. Fetal Outcome in 314 Pregnancies in 217 Myasthenic Mothers

Abortions		38	(12.2%)
Spontaneous	14		
Induced	24		
Live births		268	(85.4%)
Perinatal deaths		22	(8.2%)
Stillbirths	8 (2.9%)		
Neonatal deaths	14 (5.3%)		
Neonatal myasthenia*		47	(17.6%)

*Four additional cases were diagnosed "possible" or "probable" neonatal myasthenia. Total cases: 51 (19.1%).

There were exacerbations at some time during 128 (40.8%) of the pregnancies in women with MG and in 96 instances (30.6%) in the puerperium. No prospective study with appropriate controls has been performed to determine whether pregnancy poses a true risk of MG exacerbation and what the magnitude of this risk might be. There is a clear increase in the chances that the usually stable MG condition will change during pregnancy or the puerperium.

Postpartum exacerbations in the review series were particularly sudden and devastating, and respiratory failure was a frequent feature. Ten myasthenic mothers died. One of these died 19 months after delivery, of problems that began in the puerperium. Maternal mortality was therefore 3.4 per 100 live births to myasthenic mothers (9 of 268).

Maternal deaths in myasthenic mothers are usually related to crises in the disease or its treatment. One patient died in apparent overdose cholinergic crisis. Four died in nonreactive, anticholinesterase drug-resistant crisis, one after receiving Mg SO_4.[15] Three died of exacerbation of MG, and there was one maternal death from postpartum hemorrhage.

Hay[17] addressed the consideration of therapeutic abortion in patients who experienced myasthenic exacerbations in the first trimester. His conclusion was that there was no medical indication for termination of

pregnancy because no consistent benefit could be predicted, and, indeed, exacerbation could result from either anesthesia or surgery. Kosovsky et al.[18] reported a series of abortions in myasthenics. Seven patients who experienced spontaneous abortion seemed to improve. When therapeutic abortion was performed on six other patients, often the more seriously ill, no change in the severity of myasthenic symptoms occurred.

There are many conditions associated with pregnancy that may influence the course of myasthenia. The nausea accompanying early gestation often leads to inability to retain anticholinesterase medication on a regular dosage schedule. The patient may miss her dose of medication and become too weak to swallow or even ask for her medication if bulbar muscles are particularly affected. Sneddon's study[19] of the emotional, social, and medical problems of myasthenics called attention to this phenomenon and the importance of teaching bulbar MG patients to be ready to communicate their needs in writing. They must, of course, be near a helper who can administer parenteral medication if necessary. The patient with severe myasthenia must be supplied with parenteral medication and taught its use and the signs and dangers of overdose.

Anxiety and normal physiologic stress associated with pregnancy and obstetric complications may be partially responsible for pregnancy-related exacerbations of MG. Myasthenic mothers should get extra rest in the latter part of pregnancy, when exacerbations are most likely to occur. Myasthenic control must be carefully supervised and rest periods enforced in the months following delivery, when care of the infant increases activity and disrupts normal rest and sleep patterns.

Relative hypoventilation of basal lung segments and restricted diaphragmatic excursion due to uterine enlargement are particular risks for myasthenics whose respiratory muscles are weakened by their disease.

Abramsky[20] recently reported the interesting ability of amniotic fluid to bind anti-AChR antibodies from MG patients. He suggested that there might be in vivo binding of maternal antibodies, which could explain the development of MG in the fetus only after birth and the delay between delivery and the onset of neonatal MG. Brenner et al.[21] identified α-fetoprotein as the probable inhibiting substance in amniotic fluid. Varying α-fetoprotein levels in the serum of MG mothers may explain some of the variability of disease manifestations in pregnancy as well as the discrepancy between antibody titers and levels of muscular weakness.

Infections play a key role in the development of severe exacerbations in myasthenic mothers.[1,17,22-24] Respiratory tract infections require particularly prompt treatment. Patients should receive prenatal screening and treatment for asymptomatic bacteriuria and prompt treatment of overt urinary tract infections. The search for infections has assumed particular importance now that steroid therapy is being increasingly utilized in young women with myasthenia. Steroids may enhance susceptibility to infection and certainly make early detection of infection more difficult.

The physical stresses of labor and delivery enhance myasthenic weakness. The patient in labor must be carefully observed, particularly for respiratory compromise. Because of prolonged gastric emptying time and erratic absorption of oral medication, myasthenic drugs should be administered by the parenteral route to the myasthenic mother in labor. The patient's exertion level must be minimized, and prompt respiratory support must be available.

The Effect of Myasthenia Gravis on Pregnancy

Tables 2 and 3 show that the myasthenic woman who chooses to become pregnant places both herself and her child at increased risk. A high incidence of premature labor was first described when 6 of 10 myasthenic pregnancies at Charity Hospital of New Orleans terminated prior to the 37th week of gestation or with a fetus less than 2500 g.[25]

The true incidence of premature labor in myasthenics is difficult to discern because case reports often do not include the gestational age or infant weight. Table 4 presents a summation of 12 reports in which 19 premature deliveries (41.3%) are recorded in 46 myasthenic pregnancies.[2,15,16,22-29]

There were 268 live births (85.6%) in our review series. There were 14 spontaneous abortions and 24 induced abortions, for a total abortion rate of 12.2%. Twenty-two perinatal deaths are recorded, indicating a perinatal mortality of 82 per 1000 live births. Eight were stillbirths; 14 were neonatal deaths.

Fifty-one of 268 newborns (19.1%) were affected by passive transfer of maternal anti-AChR antibodies. Neonatal MG is discussed in a later section of this monograph.

It is uncertain whether fetal assessment tests of alterations in fetal movements or reactions to fetal movements are reliable for the myasthenic mother. A prospective study is needed to clarify this point. Fetal monitoring for signs of hypoxia is, however, important during any myasthenic exacerbation that reduces maternal respiratory capacity.

The uterine contractions of labor occur normally in the myasthenic mother. Several authors have reported the impression of shortened duration and relatively pain-free labor in individual myasthenic cases.[1,22] A review of 8 primiparous and 18 multiparous patients in labor in whom the duration of labor was recorded reveals an average labor of 12 1/3 hours in primiparas (range 5-19 hours) and 6 1/2 hours for multiparas (range 1 1/2-10 hours) (see Table 5).[1,17,22-25,30,31]

Uterine smooth muscle is not involved in the myasthenic process, because its complex contractile control mechanism does not involve the acetylcholine mechanism at neuromuscular junctions. Some of the voluntary muscles involved in the expulsive efforts of the second stage of labor may be affected by MG. Preparations to assist the patient at this stage with outlet forceps or vacuum extraction will overcome this problem and prevent overtiring of weakened muscles.

Scott[32] reported an inverse relationship between the duration of myasthenic symptoms and maternal risk of death. He stated that the greatest risk existed in the 1st year of disease and that maternal risk of death was minimal after 7 years. He proposed that pregnancy be postponed in newly discovered myasthenics, to be undertaken later when risk was diminished. We agree that pregnancy should not be considered when MG is unstable or first being brought under control. We were not, however, able to confirm Scott's observations regarding early risk of death. Table 6 reviews the interval between onset of disease and death in seven fatal maternal MG cases available for review. The mean interval was 5.2 years; only the patient with this author's 1964 index case died prior to the 2nd year of diagnosed disease. Three of the seven deaths occurred after 7 years or more of MG. Rolbin's group[24] recently reported a case of severe myasthenic crisis requiring intensive respiratory support and very nearly causing the death of a mother who had had MG for 18 years.

TABLE 4. Incidence of Premature Delivery in Myasthenic Pregnancies

	No. of Cases	Premature (Less Than 37 Weeks or 2500 g)
Plauché, 1964[1]	4	1
McNall, 1965[23]	5	3
Chambers, 1967[22]	6	4
Hay, 1969[17]	5	3
Perry, 1975[31]	2	1
Cohen, 1976[15]	1	0
Burkett, 1976[27]	2	0
Rolbin, 1978[24]	3	1
Hanson, 1978[29]	1	0
Duff, 1979[16]	4	1
Plauché, 1979[2]	10	6
Donaldson, 1981[28]	5	0
Total	46	19 (41.3%)

TABLE 5. Duration of Labor in Pregnancies Complicated by Myasthenia Gravis

	No. of Cases	Mean Duration of Labor	Range
Primiparas	8	12.3 hours	5-19 hours
Multiparas	18	6.5 hours	1½-10 hours

TABLE 6. Interval Between MG Diagnosis and Maternal Death

	No. of Maternal Deaths	Interval
Plauché, 1964[1]	1	1.5 years
McNall and Jafarnia, 1965[23]	2	7 and 9 years
Chambers, 1967[22]	1	8 years
Miller, 1968[30]	1	6 years
Hay, 1969[17]	2	2 and 3 years
Total	7	
Mean interval onset to death		5.2 years
Range		1.5–9 years

Anti-AChR IgG in the myasthenic mother may pass to the newborn in breast milk. These antibodies can enhance neonatal myasthenia. Maternal anticholinesterase drugs in breast milk may cause muscarinic symptoms in the newborn.[3] A myasthenic mother in remission, with low antibody titers and on no drugs hazardous to the fetus can breast-feed her infant safely. High antibody titers, large cholinergic drug doses, or exacerbation of maternal MG symptoms in the postpartum period preclude breast-feeding.

Our literature review of 126 MG deliveries prior to 1963 revealed a cesarean section rate of only 5.6%.[1] Among 44 pregnancies reported since this review wherein the mode of delivery was recorded, there were 7 forceps deliveries (15.9%) and 6 cases of cesarean section (13.6%). Cesarean section has not been performed in the CHNO series of 18 myasthenic pregnancies. The stress of surgery combined with the hazards of anesthetic and relaxant agents and postoperative difficulties with restricted respiration and control of bronchial secretions make cesarean section particularly hazardous for the myasthenic mother. Three of the six patients reviewed who underwent cesarean section had severe postoperative exacerbations, including one patient who died on the 16th postoperative day of a nonreactive crisis and one who failed to reestablish spontaneous respirations after undergoing general anesthesia.[26] Cesarean section should be performed only for clear obstetric indications.

Analgesia and Anesthesia for Pregnant Myasthenics

The myasthenic patient has been found to be particularly sensitive to sedative, narcotic, and tranquilizing medications, although all of these may be safely administered to these patients in doses carefully metered to the needs and responses of the patient.[23] The problems that must be avoided at all costs are depression of respiration and inspissation of bronchial secretions.

Rolbin et al.[24] have written an important current review of anesthetic considerations in the myasthenic obstetric patient. Preanesthetic evaluation is emphasized, including an electrocardiogram, which may reveal the focal myocardial necrosis present in occasional MG patients. Pulmonary function studies are noted to be of great value in indicating preexisting respiratory dysfunction and aiding in the management of respiratory insufficiency if it develops. Thyroid function tests are recommended for the MG patient with suspected thyroid dysfunction. This group reemphasizes the use of the parenteral route for the administration of anticholinesterase medication during labor.

Regional anesthesia is preferred for vaginal delivery by a majority of authorities.[23,24,31,33] Rolbin et al.[24] recommend epidural anesthesia to decrease requirements for systemic medication, prevent fatigue, and provide good anesthesia for outlet forceps to shorten the second stage of labor. There is no evidence of increased sensitivity of the neuromuscular junction to local anesthetics in myasthenics.[34] This information negates the earlier preference for low spinal anesthesia over epidural because of its lower blood levels of anesthetic agent.[33] Rolbin et al.[24] report a patient who received 400 mg lidocaine as an epidural anesthetic agent with no untoward effect.

Ester-type local anesthetic agents such as chloroprocaine and tetracaine have acquired their reputation for safety in pregnancy in part because of their rapid hydrolysis by plasma cholinesterase. Plasma cholinesterase enzyme activity may be decreased in MG

patients.[33] Amide-type local anesthetics are metabolized in normal fashion by myasthenics and are a safer choice when large quantities of the drug are to be administered, as with epidural anesthesia.[24]

General endotracheal anesthesia may be best for cesarean section, particularly in MG patients with bulbar or respiratory muscle involvement.[24] Airway and secretion management are facilitated by this choice, and high motor block is avoided in patients who already have some respiratory impairment. Awake endotracheal intubation or rapid thiopental induction with immediate intubation is favored. Myasthenics are very sensitive to nondepolarizing muscle relaxants. The use of curare or succinylcholine in anesthetic management of myasthenics by Rolbin's group is quite controversial, because there may be an exaggerated and prolonged response, particularly in the muscle groups involved in the myasthenic disorder.[33] Burkett and Rodrique[27] reported a tragic result of the use of curare with general anesthesia in a pregnant patient with previously undiagnosed MG.

Rolbin's group also suggests that halothane may be cautiously used when uterine relaxation is required for delivery; however, one must recognize that this and similar agents potentiate neuromuscular blockade. Other authors have stated that ether, chloroform, trichlorethylene, and fluothane are contraindicated in MG patients.[3,17]

Therapeutic Modalities in MG

Anticholinesterase Drugs

The treatment most widely used for myasthenia, indeed employed during the course of almost every case, is the administration of quaternary ammonium compounds, which inhibit cholinesterase activity.[3] Neostigmine (Prostigmin, Roche Laboratories) is the classic anticholinesterase drug and is usually started in doses of 15 mg every 2-3 hours and adjusted to the dose at which the patient's muscle strength is optimal, with a minimum of cholinergic side effects. Patients should be advised early in their treatment course that more drug will not continue to result in increased strength and that these drugs often cannot restore optimal strength in severe myasthenia. Excessive cholinergic medication results in unpleasant muscarinic side effects such as abdominal cramps, flatulence, diarrhea, nausea and vomiting, and excessive secretion of saliva and tears. Advanced effects include muscle weakness and respiratory failure, which may mimic myasthenic crisis and may be fatal.[15,22,26]

One of the major disadvantages of neostigmine is its very short duration of action (2-3 hours). Many patients can eventually be controlled more smoothly with longer acting cholinergic drugs such as pyridostigmine (Mestinon, Roche Laboratories) (4-6 hours). Equivalent doses of commonly used anticholinesterase drugs are shown in Table 7.

Pregnant myasthenics often require periodic adjustment of anticholinesterase drug dosage. When one is increasing drug dosage, it is often best first to reduce the interval at which medication is taken. If this adjustment does not suffice, the quantity of medication may be slowly increased by increments of 15-30 mg per dose (Mestinon) or 5-10 mg per dose (Neostigmine).[23] All CHNO pregnant myasthenic patients have been maintained successfully on a regimen that relies heavily on the use of anticholinesterase drugs.

Corticosteroids

Corticosteroids effect improvement in a high percentage of cases in all reports of their use in myasthenics.[35] There is wide-

TABLE 7. Equivalent Doses of Anticholinergic Drugs

0.5 mg intravenous neostigmine (Prostigmin)
equals
1.5 mg subcutaneous neostigmine
equals
15 mg oral neostigmine
equals
60 mg oral pyridostigmine (Mestinon)
equals
5 mg oral ambenonium (Mytelase)

spread enthusiasm among neurologists for the use of steroids, particularly in women in the reproductive age group. Johns[35] reported a representative protocol for steroid management of MG. New myasthenics are placed on high daily doses of steroids (e.g., prednisone 60-80 mg daily) until sustained improvement is noted, usually in about 2 weeks. Anticholinesterase drugs are employed to maintain respiratory and swallowing strength as needed. After sustained improvement has occurred, steroids are changed to alternate-day dosage and gradually reduced, permitting no worsening of symptoms. When maximal improvement has stabilized over several months, transsternal thymectomy is often recommended. If there is no improvement on steroids in 4 weeks, this group resorts to plasmapheresis with concomitant prednisone or azathioprine therapy. This regimen has resulted in remission or marked improvement in 77% of cases. Few myasthenics who responded to steroids were able to sustain remission if steroids were withdrawn.

Rowland[36] critically reviewed 15 reports of steroid therapy in myasthenics and indicated persisting uncertainties because of the lack of controlled studies in severe cases and lack of uniform criteria defining improvement.

The use of steroids during pregnancy is discussed in detail elsewhere in this symposium. If steroids are exonerated of long-term adverse fetal effects, one of the safest times for the myasthenic to undertake pregnancy would be during a steroid-induced remission. Sanders[37] has stated that obstetric delivery as well as surgical procedures are much easier to manage in the myasthenic who has achieved a state of marked improvement or remission on corticosteroids.

Recognition of the increasing evidence of steroid safety in pregnancy and the need to continue steroids in order to sustain MG remission has altered our recommendations regarding steroid therapy in pregnancy. We now believe that patients who become pregnant while on steroids should be maintained on the lowest dose of these drugs that controls the disease and prevents exacerbations.

Antimetabolites

Despite the almost universal praise for steroid therapy, interest continues in other treatment modalities, particularly antimetabolites and plasmapheresis. An evaluation of the efficacy and use of antimetabolite drugs in myasthenics is not addressed in this article because these drugs have not been used in pregnant myasthenics.

Plasmapheresis

Dau[38] concluded that plasmapheresis combined with immunosuppressive therapy is a powerful first therapeutic modality in severe myasthenia. Other investigators confirmed the efficacy of plasmapheresis when combined with steroid therapy in myasthenic crises; however, not all investigators echo this enthusiasm for plasmapheresis. Rowland[36] reported his results in 94 myasthenics managed with plasmapheresis. He was unable to predict which patients would improve and noted transient worsening in occasional cases. He felt that the very expensive technique of plasmapheresis should be reserved for seriously disabled patients after other therapies fail.

There are no published reports of plasmapheresis in the management of pregnant myasthenics This modality is, however, widely employed in the current management of myasthenic crisis and has been proposed when high maternal antibody titers presage the development of neonatal MG in the infant.[39]

Thymectomy

The excision of the thymus has been recommended for many years in myasthenia. Its use has remained controversial because only about half of patients improve, and improvement is often not noted until years after surgery.[40] McQuillen[41] has sounded a call for a randomized prospective study, because he feels that an equivalent incidence of remission can be achieved with medical therapy. Perlo[40] concluded that thymectomy

may be preferred to long-term steroids in young patients with MG but that, in non-thymoma cases, its use should be limited to patients under age 35 who achieve only limited improvement 6–12 months after the onset of their illness. Thymectomy is not a recommended modality for treatment during pregnancy.

Myasthenic Crisis

A crisis in a patient with MG is defined as an exacerbation of myasthenic symptoms that requires mechanical ventilation.[36] It is often precipitated by the stress of surgery, infectious diseases, obstetric delivery, or drug changes.

The differentiation of "myasthenic crisis" from "cholinergic overdose crisis" occupied much discussion in the early literature.[3,17] Edrophonium test doses have been proposed to differentiate these two entities. Rowland[36] feels that crises are temporary myasthenic exacerbations, and his goal is to support the patient until the exacerbation subsides. His standard practice is to discontinue anticholinesterase medication when an MG patient is placed on mechanical ventilation. Other authors prefer plasmapheresis, particularly when combined with steroid and/or antimetabolite therapy, as the most effective method for management of myasthenic crisis.[38]

True crisis with respiratory failure demands intensive support services, mechanical ventilation, and meticulous control of respiratory tract secretions. While these measures are instituted, consideration should be given to the potential value and minimal hazards of plasmapheresis and the institution or enhancement of corticosteroid dosage. The writings of Hay,[39] Osserman and Genkins,[3] and Bryan-Brown[42] contain excellent discussions of the intensive care of myasthenic crises.

Effects of Other Drugs on MG

A number of chemical compounds are known to enhance or even cause the muscle weakness of MG. Table 8 enumerates these drugs.

Magnesium sulfate is used in obstetrics for the prevention of eclamptic convulsions and for uterine tocolysis. Magnesium diminishes the depolarizing action of acetyl choline, reduces transmitter substances at the motor end-plate, and depresses muscle membrane excitability.[43] Cohen et al.[15] reported a severe myasthenic crisis precipitated in a pre-eclamptic patient by the administration of magnesium sulfate. Hay[17] and Burkett and Roderique[27] concur in the opinion that magnesium is contraindicated in pregnant myasthenic patients.

Many antibiotic agents have been found to increase myasthenic weakness.[3,24,31] Amnioglycosides such as gentamycin, kanamycin, and streptomycin have particularly noteworthy neuromuscular blocking properties. Neomycin, polymyxin, colistin, tetracycline, and lincomycin also potentiate myasthenic weakness.[30]

Other drugs such as propranolol, quinidine, and, particularly, lithium salts enhance the muscular weakness of myasthenia gravis. Beta-mimetic drugs such as ritodrine and terbutaline are potentially dangerous to myasthenics both because of their propensity to worsen the disease and because of the possibility of occult myocardiopathy.

Penicillamine has been used for the treat-

TABLE 8. Drugs That May Enhance Muscle Weakness in Myasthenics

Narcotics
Tranquilizers
Barbiturates
Inhalation anesthetics
Ether, halothane, trichloroethylene
Magnesium salts
Lithium salts
Penicillamine
Beta-adrenergic agents
Aminoglycosides
Kanamycin, gentamycin, streptomycin
Other antibiotics
Colistin, neomycin, tetracycline, lincomycin, polymyxin
Propanolol
Quinidine
Quinacrine

ment of rheumatoid arthritis, Wilson's disease, and progressive systemic sclerosis. Myasthenia gravis, complete with high anti-AChR antibody levels, has developed in several patients receiving penicillamine therapy.[44] The pathogenesis of this drug-induced MG is not clear.

Neonatal Myasthenia Gravis

Neonatal myasthenic symptoms (NMG) characterized by flat facies, weak suckling, feeble cry, and respiratory distress, all of which respond promptly to parenteral anticholinesterase drugs, are reported in 10–20% of infants born to mothers with myasthenia gravis.[11,28,39] The disorder usually begins 12–48 hours after birth and may last 10 days to 15 weeks (mean, 3 weeks).[32] Among the 268 live-born infants of myasthenic mothers in our review series, there were 47 definite (17.6%) and 4 additional "possible" cases of NMG (total 19.1%).

It is generally agreed that NMG is the result of passive transfer of maternal anti-AChR antibodies to the fetus. Nakao[45] demonstrated the presence of anti-AChR antibodies in affected neonates and a gradual fall in antibody levels as their disease regressed. The development of assays for anti-AChR antibodies has permitted examination of the relationship between maternal titers of antibody and the development of myasthenia in the newborn.[4] Donaldson et al.[28] reported the titers of 5 myasthenic mothers and their babies, in three of whom NMG developed. The mean titers of anti-AChR antibody were four times as high in mothers with NMG babies as in those in whose babies the disorder did not develop. Antibody titers in newborns closely reflect those of their mothers in most of the 11 other reported cases in which both titers are known.

Several puzzles remain regarding the effect of MG on the fetus and newborn. Babies with NMG do not uniformly have higher antibody titers than nonmyasthenic babies.[28] Antibody levels of anti-AChR do not consistently correlate with the extent of clinical disease in the adult; therefore, one might expect similar discordance in some infants. An exceptional case of NMG has been described in an infant of an MG mother in remission.[5] Antibody titers of this mother were, however, as high as those in active myasthenics.

Although myasthenic mothers usually report normal fetal movements, joint contractures (arthrogryposis) have been described in several infants of myasthenic mothers.[46] One might expect polyhydramnios from diminished fetal swallowing; yet polyhydramnios has not been a reported feature of myasthenic pregnancies.

The ability of α-fetoprotein to inhibit anti-AChR antibody could explain the rarity of myasthenia in utero, when the fetus has high α-fetoprotein levels.[20,21] The delayed onset of NMG may be related to falling protective α-fetoprotein titers in the newborn. The presence of residual anticholinesterase drug from the mother has historically been purported to be the cause of the latent period of NMG, but the very brief life span (4–6 hours) of these drugs in the adult mitigates against drug effect as the sole mechanism for the 12–48-hour latent period. A subtle interplay between the development of immunocompetence in utero, antibody attack, and protective mechanisms such as α-fetoprotein and others yet unknown may explain both the usual lack of myasthenic signs in the fetus in utero and the latent period prior to the development of clinically evident neonatal myasthenia.

Mothers whose antibody titers are particularly high (6 pmol ^{125}I-bungarotoxin-AChR complex bound per 1 ml of serum or higher) may be at particular risk of having infants affected in utero as well as in the newborn period.[39] Consideration should be given to more intensive treatment of these mothers; however, there is as yet no evidence that lowering maternal antibody titers (as with plasmapheresis) would effectively prevent the stigmata of this disorder in the infant.

The newborn of every myasthenic mother must be carefully watched for signs of weakness of skeletal muscles, particularly those

involved in breathing and swallowing. Support with anticholinesterase drugs must be supplied until such weakness subsides, usually about 3 weeks. Sudden respiratory failure is a major risk in these neonates.

As anti-AChR antibody titers become more widely available, they offer a marker for those infants initially at risk for NMG and can monitor the subsidence pattern of antibody levels. Early plasmapheresis has been suggested for the treatment of the rare severely affected newborn.[39]

Summary

Myasthenia gravis has been clearly shown to be an autoimmune disorder in which antiacetylcholine receptor antibodies participate in a compliment-dependent destruction of the postsynaptic membrane of the myoneural junction, resulting in decreased nerve impulse transmission. This phenomenon is expressed clinically as diminished skeletal muscle strength and rapid fatiguability.

The coexistence of MG and pregnancy results in an increased tendency for maternal myasthenic exacerbation and crisis, particularly early in the puerperium. MG medication requires frequent adjustment during pregnancy. There is an apparent increase in both pregnancy wastage and premature labor.

Treatment modalities for MG include anticholinesterase medications, corticosteroids, thymectomy, plasmapheresis, and immunosuppressant drugs. Current pharmacologic treatment during pregnancy, excluding crisis management, usually involves only manipulation of the dosage of anticholinesterase and steroid medications. Equally important in the treatment plan for pregnant myasthenics are enforced rest periods, a tranquil environment, and the detection and prompt treatment of intercurrent infections.

Labor usually progresses normally in myasthenics, and cesarean section need only be performed for obstetric indications. Anticholinesterase medication must be administered parenterally on the day of labor because of defective gastrointestinal absorption of oral medication. MG is dramatically worsened by a number of drugs, including magnesium sulfate, agents used in anesthesia and analgesia, and many antibiotics, particularly aminoglycosides. Conduction anesthesia is the safest mode of pain relief for delivery. Frequent assessment of maternal strength, respiratory capacity, and need for, and response to, medication are essential during labor. Operative assistance with forceps or vacuum extraction in the second stage helps overcome ineffective voluntary expulsion efforts and prevents tiring of the mother.

The management of myasthenic crisis requires intensive care in a hospital with facilities for long-term respirator support. Plasmapheresis combined with steroid and/or immunosuppressant therapy is presently the most widely used treatment modality for MG crisis.

Fetal assessment parameters may be altered in maternal MG due to reduced fetal movements in utero, which can in rare instances result in arthrogryposis in the fetus. There is increased risk of fetal hypoxia if the myasthenic mother experiences respiratory compromise. The passive transfer of maternal anti-AChR antibodies results in neonatal myasthenia in 19% of cases. The manifestations of this disorder may be delayed by passive transfer of maternal medications to the baby and by high levels of α-fetoprotein in the newborn, which have been shown to block anti-AChR antibodies.

The myasthenic mother thus undertakes pregnancy with increased risk for both herself and her offspring. There is a 40% incidence of exacerbation of myasthenia during pregnancy and 30% in the puerperium. Maternal mortality is 3.4% of live births. Perinatal mortality is 82 per 1000 births, at least five times that of uncomplicated pregnancies. Modern management minimizes these risks to the extent that pregnancy is certainly not precluded in myasthenic women. A happy outcome depends upon meticulous maternal and fetal prenatal surveillance, early detection and

management of exacerbation, careful support in labor, and the availability of intensive care facilities for the critical care of myasthenic crises.

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