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EXERCISE AND MYASTHENIA GRAVIS: A REVIEW

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ABSTRACT

Myasthenia gravis (MG) is characterized by weakness and fatigability of the voluntary muscles. Weakness in the muscles is worsened by exercise and relieved by rest. Some patients are told to refrain from any form of exercise or strenuous activity, while others are told to be as physically active as possible. There is not a general exercise prescription recommended for these patients. Symptoms of MG often lead to a sedentary lifestyle associated with the development of other diseases such as diabetes, obesity, and heart disease. Some common medications used for MG can increase the risk for these diseases. There is scant literature on the use of exercise in this population, however, the limited data does indicate that physical activity can provide benefits for these patients.

We reviewed the pathophysiology, classification, weakness patterns, etiology, medical management, and treatment of MG. We describe many studies on the responses to exercise in MG patients including resistance training, respiratory muscle training, aerobic & ischemic exercise studies, along with several case studies. Though there is still a dearth of data, it appears the effects of exercise on patients with MG mirror those of healthy persons, with possible improvements in strength, aerobic and respiratory capacity and functional activities.

Keywords: Neuromuscular disease; fatigue; muscle weakness; physical activity

INTRODUCTION

Scheer, Valero-Burgos and Costa (1) report on a case study of a myasthenia gravis (MG) patient who completed a 220 km, 5 day ultra-marathon. This was a very unusual case as strenuous exercise is generally contraindicated in these patients. The 52 year-old male increased his daily dose of pyridostigmine as symptoms of musculoskeletal weakness, generalized fatigue, unintelligible speech, problems swallowing, and difficulty breathing became evident during the event. While the medical team carefully administered to this runner during the competition, they cautioned against this sort of endeavor for most MG patients.

Myasthenia gravis (MG) is a potentially serious acquired (immune-mediated) autoimmune disorder characterized by weakness and fatigability of the voluntary muscles. It is caused by an autoimmune response of unknown pathogenesis against the nicotinic post-synaptic acetylcholine receptor

(AChR) at the neuromuscular junction of skeletal muscle. Loss of these receptors leads to a defect in the muscles' response to neural input, causing muscle weakness and premature fatigue.

It has been reported that the recognition and prevalence of MG is increasing. Newton (2) states that the primary reason for this increase is the longer life span of patients with this disease. Recent studies show that in addition to increased longevity, improved diagnosis might help explain the increase in prevalence. The annual incidence is about 1 in 300,000 and prevalence is about one per 17,000, but this varies among populations. This translates into approximately 36,000 cases in the United States. The incidence is similar to that of systemic lupus erythematosus (SLE) and Duchenne's muscular dystrophy (DMD). MG occurs in all races at an approximate female to male ratio of 3:2 (2). Due to a number of advances in medical technology and medications for the management of MG, mortality of MG patients has been steadily decreasing.

The initial description of this disease is usually attributed to Erb who reported on three cases in 1879 and Goldflam, who did a more comprehensive review in 1893 (3). However, descriptions of symptoms appeared well before these reports; in 1672 Thomas Willis published a description of two cases which were most likely myasthenia gravis. (4) Treatment lagged behind discovery, with the first major breakthrough in June of 1934, in the form of a letter to The Lancet from Dr. Mary Walker. Acting on the assumption that myasthenia may be a curare-like poisoning of the myoneural junction, she injected a patient with physostigmine, a cholinesterase inhibitor, which resulted in remarkable improvement in muscle power (5).

Fatigue is the most prominent and troublesome symptom reported by patients with MG (6). The weakness of skeletal muscle is worsened by exercise and relieved by rest. Fatigability tends to be the only constant in this disease, all other factors are variable. The impact of fatigue and weakness on patients' lives is immense, leading to physical debilitation and psychological distress. It has been reported that even though fatigue dominates the lives of these patients, they are often left to self-manage their symptoms(7). Information given to patients from their physicians varies, while some patients are advised to refrain from any form of exercise or strenuous activity, others are told to be as physically active as possible (7). The National Myasthenia Gravis Foundation publishes literature that suggests ways to conserve energy. These techniques, while practical, are very conservative and may cause patients to avoid any physical activity.

Alterations in activity and rest patterns can have significant roles in the cause, prevention, and alleviation of fatigue (8). Unnecessary sedentariness, prolonged bed rest, and immobilization contribute to weakness and fatigue. Deconditioned skeletal muscle, has reduced oxidative capacity and strength (9, 10) and requires increased oxygen and physical effort for comparable work than conditioned muscle.

Low cardiovascular fitness and a sedentary lifestyle increase morbidity and mortality from common chronic diseases such as cardiovascular disease, diabetes, cancer, and stroke (11). Aerobic exercise may reduce fatigue via a number of mechanisms that result in increased efficiency of energy use. In a review of rehabilitation of multiple sclerosis (MS) patients, the authors suggest that there are multiple complications that result from inactivity, including muscle wasting, decreased range of motion, respiratory infections, and negative nitrogen and calcium balance. (12). Reduced fatigue

and many health benefits have been observed in a variety of patients who perform even minimal levels of exercise. This includes patients with chronic obstructive pulmonary disease, cancer (13), systemic lupus erythematosus (14), and MS (15) To date, little research has been published on the risks and benefits of exercise in patients with MG.

Clinical Features and Symptoms of MG

Weakness in patients with MG fluctuates during the day, being less severe in the morning and more pronounced as the day progresses (16). Skarbanek (17) suggested that circadian variation in body temperature, where maximal temperature occurs in the evening, may explain the increased weakness in the evening. A preliminary study examining body cooling effects in myasthenia showed some improvement in functional capacity when core temperature was lowered (18).

The pattern of muscle involvement varies between individuals. The weakness can remain localized for many years (commonly in the eye muscles-termed ocular myasthenia) or spread to affect other muscles (generalized MG) (19). In a study of 440 patients with MG, Simpson (20), found that the most affected muscle groups were, in decreasing order, extraocular (surrounding the eyes), neck extensors, shoulder girdle and hip flexors, bulbar (muscles of breathing, facial expression, and swallowing), proximal upper extremity, proximal lower extremity, and distal upper and lower extremity. Trunk, abdominal, and respiratory muscles are among the last affected. This can lead to dypsnea, especially upon exertion, and difficulty generating a cough, which increases the risk of respiratory infections and respiratory complications after surgery (21).

The onset of symptoms may be acute or sub-acute, remissions and relapses and remissions can occur, and the rate of progression of the disease varies. Maximum weakness occurs during the first year for two-thirds of patients (51). Factors that may worsen symptoms include increases in body temperature, hypothyroidism, hyperthyroidism, pregnancy, emotional stress, and drugs that affect neuromuscular transmission (22). There is some evidence that lower body temperature and local cooling may ameliorate symptoms in some patients (18, 22, 23).

Pathophysiology of MG

MG is considered a prototype for antibody-mediated autoimmune diseases. When auto-antibodies from human plasma were injected in rodents they were found to bind at the neuromuscular junction (NMJ) (24) and cause symptoms of MG (25). Also, immunizing animals with the acetylcholine receptor (AChR) reproduces the disease (26) and plasma exchange to remove the antibodies, decreases the severity of MG (27).

Not all MG patients express auto-antibodies for the NMJ. In about 10-20% of cases, muscle weakness is associated with muscle-specific kinase (MuSK) antibodies (28), antibodies of unknown origin, seronegative MG (SNMG), Lambert-Eaton myasthenic syndrome (LEMS), some congenital myasthenic syndromes (CMS), or damage by toxins against the NMJ (29). These forms of autoimmune MG are much rarer than MG associated with the AChR. Some patients, particularly those with thymus gland tumors, have antibodies to other proteins such as ryanodine receptor (RyR), titin, myosin, tropomyosin, actin, and voltage-gated potassium receptors (30, 31). Pathological changes such as follicular hyperplasia of the thymus are common in these patients, and this tissue contains abnormally elevated amounts of mature T

cells that are AChR-reactive. In contrast, most MG patients have B cells that produce AChR antibodies generally in hyperplastic thymuses with germinal centers (19, 32).

Abnormal findings of the neuromuscular junction associated with MG

Abnormalities observed in the neuromuscular junction of MG patients include a reduced number of AChRs causing a reduced length of the post-synaptic membrane, shortening of the synaptic folds due to destruction of the terminal expansions, and widening of the synaptic clefts due to the shortening of the junctional folds. These changes are caused by the autoimmune attack on the post-synaptic membrane except in the case of Lambert-Eaton syndrome (LEMS) where the abnormality is pre-synaptic.

Classification: Subsets of MG

MG is classified according to whether or not patients have anti-AChR antibody, age of onset, the severity, etiology, and weakness patterns.

AChR antibody-positive MG

This is the most common form of the disease and makes up approximately 80-85% of all patients with generalized MG (29) and 50-60% of patients with ocular MG (32). Antibodies compromise neuromuscular transmission by three different mechanisms: (1) antibodies activate complement which causes destruction of the postsynaptic surface, (2) antibodies promote endocytosis and accelerate the degradation of AChR, and (3) antibodies bind to the AChR, changing its function (32).

AChR antibody-negative MG

Approximately 10-20% of patients with generalized MG are seronegative for AChR with about 30% of those having autoantibodies against MuSK (33). However, a high proportion of seronegative ocular MG patients are negative for both types of autoantibodies. MuSK-positive patients tend to have more severe disease than AChR-positive MG patients. They often have a lower response to immunosuppressive treatments and some patients have muscle atrophy (28, 33).

Lambert-Eaton-myasthenic syndrome (LEMS)

Voltage-gated calcium channel antibodies are found in 90% of LEMS patients, while in half of these cases there is an associated small cell lung cancer. LEMS is characterized by weakness in the proximal muscles of the legs and extends to other muscles such as the arms, ocular and bulbar muscles– generally showing a pattern that spreads in the opposite direction compared to MG. LEMS patients also present with autonomic symptoms such as dry mouth and eyes, erectile dysfunction, and hypotension. Those with small cell lung cancer tend to have a more aggressive immune response.

Thymoma in MG

A thymoma is a tumor originating from the epithelial cells of the thymus. In about 15% of cases, MG is associated with a thymoma (30, 34) , and in nearly 85% of those with thymic abnormalities, germinal hyperplasia is found. Myoid (muscle cell-like) cells are found in the thymus that express surface AChRs and are surrounded by antibody-presenting cells. Fifty percent of patients with thymoma develop MG.

Age of Onset

Myasthenia gravis occurs in all ethnic groups and both genders. It is most commonly regarded as a disease of young adult women (under 40) and older men (over 60), but it can occur at any age. Recent studies have shown a bi-modal curve for both sexes for age at onset. The prevalence of MG among middle-aged and older patients is increasing (35), perhaps because patients with early-onset MG are living longer, but also because there is an increase in the onset and/or diagnosis of the disease after age 50 (36).

MG can also occur in utero. Transient neonatal MG has also been observed and is caused by a passive transfer of maternal anti-AChR antibodies through the placenta. It also has been reported with MuSK and LEMS antibodies (37). About 15% of infants with the antibodies manifest symptoms, including weak cry, respiratory distress, hypotonia, swallowing and sucking difficulties, and facial paresis in the first few hours of life. A 21% incidence of transient neonatal myasthenia gravis (TNMG) in infants born to mothers with MG has been reported (38). In this report, 67% of infants developed TNMG within the first few hours after birth and within the first 24 hours of life in 78% of neonates. Symptoms usually resolve within a few weeks to months, but occasionally temporary treatment with anticholinesterase agents is needed (36).

Weakness Patterns

There is no explanation to date for the variability in the weakness patterns patients present. Approximately half of patients with acquired autoimmune MG have ptosis, diplopia or both at presentation. More than half of the patients with ocular MG will develop generalized MG within the first three years, while in a smaller percentage (~20%) of patients the disease will remain only ocular (29, 32).

Facial and bulbar muscle weakness is present in approximately 10% of patients at the onset of MG, and usually these patients have extraocular weakness as well. More widespread generalized weakness involves the limbs, the shoulders and pelvic girdle, and axial muscles and predominates in the proximal muscle groups (39). Differential diagnosis presents difficulties in MG patients with limb-girdle weakness, especially among young patients, and can be confused with other diagnoses including limb-girdle muscular dystrophy or other myopathies.

Weakness of distal extremity muscles is unusual, seen in less than 5% of patients (29), although it is more common in those diagnosed under age 40.

Classification of severity traditionally divides adult MG patients into four groups based on the Osserman scale which separates them into ocular, generalized, severe generalized MG, or myasthenic crisis with respiratory failure. The classification was modified in 2000 by the American MG Foundation into five, more descriptive categories to standardize the disease more precisely for research studies.

Etiology of MG

There are four classes of MG cited when the disease is categorized based on the origins of the disease:

1- Acquired autoimmune

2- Transient neonatal- passive transfer of maternal antibodies to the AChR

3- Drug-induced: D-penicillamine causes clinical presentation virtually identical to acquired autoimmune MG, including the possibility of inducing anti-AChR antibodies. This disease

remits after discontinuation of the drug. Other drugs that cause MG-like weakness include some antibiotics, quinine procainamide, high-dose prednisone, aminoglycides, curare, other calcium channel blockers, and possibly some statins.

4- Congenital myasthenic syndromes, including slow-channel and fast-channel syndrome and AChR deficiency.

Medical Management

Acute Exacerbations

Respiratory crisis due to hypoventilation in MG patients can be life-threatening. Plasma exchange (PE) and intravenous immunoglobulins (IVIg) are used to rapidly improve acute exacerbations of the disease such as respiratory crises or severe skeletal muscle weakness. These treatments are also used before thymectomy or other surgery in MG patients, during less severe exacerbations, or in conjunction with the start of immunosuppressive therapy such as steroids. The beneficial effect is rapid, but only lasts a few weeks to about a month. PE and IVIg are sometimes used at repeated intervals for patients with frequent relapses. These two techniques have similar clinical effect (27) though PE may have a somewhat faster effect. For acute situations high-dose corticosteroids can be given on top of PE or IVIg, although care is taken as severe exacerbation of muscle weakness may occur when steroids are initiated (40). Because of this, patients are often hospitalized when starting steroid therapy until clinical improvement begins, usually within 2-4 weeks(41).

Symptomatic treatment: Acetylcholine esterase (AChE) inhibitors

Pyridostigmine is most common drug treatment, along with faster-acting neostigmine as a first-line symptomatic treatment for MG. These drugs improve neuromuscular transmission by prolonging ACh availability at the neuromuscular junction (NMJ). AChE inhibitors have a short half-life, around 3-4 hours, but due to individual responses, optimal dosage is adjusted dependent on side effects and symptomatic responses. Side effects are due to autonomic cholinergic stimulation of muscarinic AChR and include increased sweating, bronchial secretions, and gastrointestinal disorders and occur in up to one-third of patients with autoimmune MG (42). Some patients with anti-MuSK-antibodies do not tolerate AChE inhibitors which can induce cramps and muscle twitching (41).

Immunosuppressants: Corticosteroids

The oral steroids prednisone and prednisolone have been used in conjunction with AChE inhibitors for MG for decades of clinical practice. Retrospective data show clinical improvement in 70-80% of MG patients (43), but clinically significant side effects occur in high numbers. These include short-term effects, such as high blood pressure and high blood glucose, and long-term side-effects such as osteoporosis and glaucoma. The minimum effective dose, taken preferably on an alternate day schedule, helps to minimize side effects.

Azathioprine is used extensively as an immunosuppressant for MG. The onset of a clinical response is slow (from 3-6 months), and maximal responses can take up to two years. Because of this, most patients start the drug together with corticosteroids. Side effects of azathioprine include liver and bone

marrow toxicity and it is listed as a drug not to be used in pregnancy.

Mycophenolate mofetil is a newer immunosupressant that looked promising in MG treatment. However, two recent randomized controlled studies did not show positive effects, (44, 45) although the short study length (9 months) may have influenced the results.

Cyclosporine A inhibits T cells and is used as an immunosuppressant after organ transplantation. A placebo-controlled randomized double-blind study with 20 patients showed promise in treating generalized MG (46). Cyclosporine A has significant side-effects, and therefore is a second or third choice for patients with moderate to severe MG who do not respond to steroids or azathioprine.

Tacrolimus (FK506) is a member of the same class of immunosuppressants as cyclosporine. This drug acts on ryanodine receptor-mediated calcium release from sarcoplasmic reticulum in muscle cells. Patients with ryanodine receptor autoantibodies have a good response to this treatment (47).

Although *methotrexate* has not been formally studied for MG, it has been used for other autoimmune disorders. *Rituximab* causes B-cell depletion in patients with B-cell lymphoma. These drugs are sometimes used in patients who do not respond to other treatment modalities (40, 41).

Thymectomy

All MG patients with thymoma should have a thymectomy to remove any potentially infiltrating tumor (48). Patients with hyperplastic thymus have less consistent results, but improvement (~65%) or remission (9%) can occur (49), especially in those with ACh antibodies and younger than 60. Although no blinded, controlled studies have been done, clinical experience suggests that thymectomy is an option for reducing the use of other ongoing medical therapies such as immunosuppressants (50).

Both the traditional trans-sternal thymectomy and the video-assisted thoroscopy, developed recently, appear to have equal outcomes for MG (40, 41). In both cases, however, postoperative improvement can take months or years, making it difficult to conclude whether thymectomy or immunosuppressive drugs led to the improvement. Mild cases or purely ocular MG do not appear to benefit from the surgery, and the benefits of thymectomy for AChR-negative and MuSK-positive patients is controversial (51).

Research on Exercise Responses in MG

As identified earlier, many patients are advised to refrain from any form of exercise or strenuous activity, while others are told to be as physically active as possible (7). Perhaps this is because of the broad range of severity of patients with MG, those with mild forms can exercise at higher levels than those with more severe cases. However, exercise can (and probably should) be prescribed to MG patients to combat muscle weakness and to maintain strength for activities of daily living. The paradox for health care providers and patients is clear. The importance of exercise prescription in this population is the same as for the normal population, to maintain muscle function and cardiovascular fitness. Lack of exercise leads to reduction in muscle mass and an increase in body fat, exacerbating the muscle weakness associated with neuromuscular diseases including MG (52). The over-riding complexity in prescribing exercise to the MG population is the pre-existing condition of fatigue.

There are few studies examining exercise and MG. Typically, these studies have used very short (1 min) bouts of exercise to examine factors other than exercise responses in patients with MG (53-56). Work by Kissel & Franklin discusses the lack of research in this area (57). They suggest that the low prevalence of MG, the variability of signs and symptoms, and the subsets of MG make it difficult to recruit a homogenous patient population, and thus an overarching exercise intervention. There is considerable research on the effects of exercise training in patients with various similar neuromuscular diseases such as multiple sclerosis (58, 59) Multiple sclerosis shares many of the symptoms of MG, such as weakness and fatigability during exercise, relief with rest, and heat sensitivity that worsen symptoms (60-62).

Resistance exercise studies

The limited research on strength training with MG patients generally shows promising results. Lohi et al. conducted a strength training program with eleven patients (10 female, 1 male) with mild or moderate MG (63). Three of the patients had mainly ocular or bulbar symptoms, and the others had symptoms in the upper and/or lower extremities. Maximal muscle force and endurance were measured in three muscle groups prior to and following the training period. The day-to-day variation in maximal voluntary contraction (MVC) and fatigue was also followed. Training lasted 10 weeks and consisted of 27 to 30 sessions of dynamic strength training of either the right arm and left leg or left arm and right leg. The contralateral extremity served as a within-subject control. A 22.9% increase in maximal voluntary force in knee extension in the trained side was found, compared to 4% in the untrained side. Only small changes were found in elbow flexion and extension. However, most subjects were unable to complete the training program for elbow extension or elbow flexion. Perhaps this was due to the use of a training program developed in patients with neuromuscular disease, but with no MG patients. None of the subjects complained of discomfort or increased MG symptoms during training. The researchers concluded that resistance training can be done safely and effectively performed by patients with mild to moderate MG. Their MVC results for the various muscle groups had a good test-re-test reliability (10-15% coefficient of variation-CV), but the fatigue test was not very reliable (23-43% CV).

Davidson et al. completed a single case study of a 78 year old man with MG (64). He was taking Prednisone and Mestinon and was placed on a six week program of callisthenic type strengthening exercises, and a walking program. For the first two weeks he exercised in the clinic, followed by four weeks of a home program. Testing included manual muscle testing, Berg balance testing, 10 meter walk speed, 6 minute walk test, and 10 point single item fatigue scale. The subject showed modest improvements in strength and gait speed, but his self-rated general fatigue decreased considerably, and he was able to walk to play golf, one of his goals.

Another single case study involved a 17 y/o Division I-AA Collegiate football player who was diagnosed as having antibody negative MG (65). He was placed on medical treatment of high-dose prednisone with potassium and calcium supplementation. He was allowed to continue conditioning work-outs but with no player-on-player contact. He ended up continuing with the team for the rest of the season, and was tapered down on the prednisone. He quit taking the prednisone against medical advice, and had only mild decreases in intense exercise tolerance.

Stout and colleagues reported a case study of a young MG patient who completed a 15-week program of resistance exercise with creatine supplementation (66). Maximal isokinetic leg flexion and extension were measured prior to and at week 15 of a training program consisting of three upper body and two lower body exercises performed three days per week. Upper body strength was not measured. The patient also took 5 g. of creatine per day in addition to his normal medications for MG. Peak strength for leg extension increased by 37.0% and leg flexion increased by 12.4%. Body weight increased 6.8% and fat-free mass (via underwater weighing) went up 4.3%. The researchers concluded that resistance exercise along with creatine supplementation may help promote strength and increase fat free mass in patients with MG. There was no control for comparison, so it is difficult to conclude the creatine played any role in the findings.

Symonette and colleagues tested 20 MG patients, comparing them to 21 healthy controls (67). The experimental protocol consisted of three phases of force measurement: baseline, fatigue, and recovery, for maximal voluntary isometric contraction (MVIC) of the shoulder abductors. They also conducted clinical examination and administered fatigue questionnaires to assess disease severity and muscle strength differences between groups. Fatigue was normalized by using a target line on the computer screen representing the subjects' highest peak torque during the baseline MVIC measurements and comparing changes in peak torque (nm) to the baseline force. They reported greater fatigue scores with their MG patients and lower strength scores. However, normalized shoulder fatigue recovery values did not differ between groups.

Exercises for Lung Function

Multiple researchers have found success in increasing lung function in MG patients following respiratory muscle training. Inspiratory muscle training (IMT) and rebreathing training are common techniques. Respiratory muscle endurance training (RMET) has also been found to be effective.

Weiner et al. (21) found that specific inspiratory training alone, or combined with expiratory training significantly improved respiratory muscle strength and endurance in MG patients. Rassler and colleagues looked at endurance training (RMET) in two separate studies (68, 69), and found that respiratory endurance and total ventilatory volume can be significantly improved in these patients.

Fregonizi et al. (70) assessed the effectiveness of interval-based IMT and rebreathing in MG patients and controls. Significant differences between groups were found in maximal inspiratory and expiratory pressure, maximal respiratory rate, and upper chest wall expansion and reduction. These results corroborate the findings of Wiener (21) and indicate that in-home training is beneficial to lung function and breathing ability of MG patients.

Elsais, Johansen, and Kerty (71) assessed lung function and exercise capacity in ten well-regulated MG patients comparing them to ten controls. Resting lung function tests and a ramped, symptom limited bicycle exercise test until exhaustion were performed. Results showed that FEV1/FVC ratio was lower in MG patients than controls. No differences were found in the exercise test results, including VO_{2max}, VO_2 at anaerobic threshold, workload, V_{Emax}, or endurance time. However, the authors identify that MG patients have a slight airway obstruction, with an obstruction pattern predominantly seen in those taking actelycholine esterase inhibitors (AChEi). The patients who were not treated

with AChEi do not have the same airway obstruction but have less exercise capacity than matched controls.

Aerobic and non-aerobic exercise studies

Early studies found on this topic used the condition of exercise in patients with MG to answer other questions. The focus was not on the effect of exercise on MG but rather on other variables such as the effect of lactate infusions, sympathetic nervous system function, and the study of enzyme levels such as creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and others to test whether there is a myopathic component in MG. For example, Ionasecu & Luca studied the relationship between block of the motor end-plate and carbohydrate metabolism in 17 patients with MG and 15 controls using ischemic exercise of the forearm (53). Sphygmomanometer cuffs were placed at the wrist and lower third of the arm and pumped to 200 mmHg. Flexion-extension of one or two fingers was performed for 45 seconds. Venous blood was drawn before and after exercise and was analyzed for lactate, pyruvate, citrate, and alpha-keto-glutarate. They showed a statistically significant decrease in lactate during ischemic exercise, and mistakenly concluded that there is a carbohydrate metabolism disorder associated with MG.

Others also examined lactate, pyruvate and serum enzyme levels in patients with MG after aerobic and ischemic exercise (54). Their stated purpose was to determine if there was a myopathic component in MG possibly leading to leakage of serum enzymes from defective muscle membrane. Two groups of subjects, 15 patients with MG and 5 controls with no known muscle disease, exercised under aerobic and ischemic conditions by repeatedly squeezing a sphygmomanometer bulb until exhaustion. The authors found elevated lactate at rest in the patients compared to controls, but no difference in the change between rest and aerobic exercise between the groups. Interestingly, CPK often elevated in primary myopathies, showed no significant differences in between groups.

The effect of lactate infusions was studied in order to investigate the possible role of lactate in producing weakness in patients with MG and those with non-myasthenic neuromuscular disorders (72). The researchers proposed that lactate produced by the working muscle has inhibiting properties that could produce clinically significant weakness in patients with MG, but not in patients with other neuromuscular diseases. Seven patients with MG and eight control patients received intravenous infusions of 5% dextrose for 30 min followed by 5 ml per kg of 1 molar sodium lactate for 20 min. Blood was drawn for the determination of lactate, calcium, pyruvate, bicarbonate, potassium, magnesium and chloride, pre- and post-infusion. Vital capacity and grip strength were also measured and clinical observations of neck, limb, voice, and eye strength were made at 10 min intervals during the infusion and for 20 min post-infusion.

During the dextrose infusion there was no worsening of vital capacity, grip strength or clinical condition in either group. During the lactate infusion, weakness and decreased vital capacity and grip strength were noted in six of the seven MG patients, while the patients in the control group had no significant changes. Changes in blood chemistry were similar between groups. The authors concluded that although the mechanism by which lactate-induced weakness occurs in MG patients is unknown, they speculate that lower serum calcium may decrease release of ACh in MG patients with a lower than normal safety margin for neuromuscular transmission. Therefore, they

hypothesized that serum calcium reduction could aggravate myasthenic weakness (72).

Catecholamine responses to 500 J of mechanical work of the forearm were studied in 10 patients with MG and 10 controls (56). The study hypothesis relates to a possible sympathetic defect in MG because of the use of ephedrine, which promotes norepinephrine (NE) release, as a therapy for myasthenia. Before and 1 min after the exercise, blood pressure and heart rate were measured and urine was collected for catecholamine assay. It was found that controls reacted to exercise with a rise in NE excretion, while MG patients increased epinephrine (E) excretion with no change or even decreased NE after exercise. No significant changes in heart rate or blood pressure were shown for either group. The researchers concluded that these data show a deficiency of sympathetic nervous system function in MG that may be involved in the muscle fatigability of these patients.

More recently, autonomic function was assessed in patients with MG (73). Though autonomic dysfunction is not associated with MG, the authors had observed wide fluctuations in heart rate (HR) and blood pressure (BP) in MG patients, especially during myasthenic crisis. A battery of tests were performed by 64 MG patients and 241 normal controls, including orthostatic tests, Valsalva maneuver, R-R interval variability, sympathetic skin responses (SSR), and HR & BP responses during isometric hand grip tests. Results showed significant increases in HR & BP in orthostatic tests in patients compared to controls. MG patients also showed a significantly steeper rise in HR & BP during isometric hand grip exercise. No significant differences between groups were found for R-R interval variation, SSR, or Valsalva maneuver. The authors state that their findings suggest a subtle sympathetic dysfunction, though a limitation was that all patients were taking pyridostigmine, a drug that can enhance both sympathetic and parasympathetic responses.

Exercise with MG and co-morbid conditions

Lucia et al. provide a case report on an adult female with MG and McArdle's disease (human muscle glycogen phosphorylase deficiency, marked by exercise intolerance and fatigue similar to MG) (74). The patient was unable to maintain a normal standing position and her severe weakness made her unable to live independently. She performed a graded exercise test and then a 12 minutes constant-load test at 50% of her maximal capacity. She was then prescribed low to moderate aerobic exercise training, building from 10 to 60 minutes of exercise at 60% percent of her maximal heart rate five days per week. The patient's exercise of choice was walking. At the end of the three month training period she was able to complete 60 min of exercise with no rest periods and no major side effects. Her VO_{2peak} results doubled (8.5 ml/kg/min to 17 ml/kg/min), Even as a case study, the authors pointed out the value of exercise prescription and intervention in patients with chronic neuromuscular disorders to improve functional capacity and well-being.

SUMMARY

In summary, there is a dearth of information in the literature regarding exercise prescription in persons with MG. This could be a combination of factors; the disease is not that common, and there is a wide range of severity, from persons who can barely walk, all the way to the football player and ultra-marathon runner described above. It appears that the overall effects of exercise on persons with MG mirror those of healthy persons, with possible improvements in

strength, aerobic capacity, and functional activity. Exercise programs should be addressed on a case by case basis, with special considerations for over exercising.

DISCLAIMER

The authors declare no conflict of interest.

GLOSSARY OF ABBREVIATIONS

AChR: acetylcholine receptor
AChE: acetylcholine esterase
BP: blood pressure
CMS: congential myasthenic syndrome
CPK: creatine phosphokinase
DMD: Duchenne's muscular dystrophy
E: epinephrine
FEV1/FVC ratio: forced expiratory volume in 1 second / forced vital capacity
HR: heart rate
IMT: inspiratory muscle training
IVIg: intravenous immunoglobulins
LDH: lactate dehydrogenase
LEMS: Lambert-Eaton myasthenic syndrome
MS: multiple sclerosis
MG: myasthenia gravis
MuSK: muscle-specific kinase
MVIC: maximal voluntary isometric contraction
MVC: maximal voluntary contraction
NE: norepenephrine
nm: nanometers
NMJ: neuromuscular junction
PE: plasma exchange
RMET: respiratory muscle endurance traing
RyR: ryanodine receptor
SLE: systemic lupus erythematosus
SSR: sympathetic skin responses
SNMG: seronegative MG
TNMG: transient neonatal MG
VO_{2peak}: the highest value of maximal oxygen consumption on any given test

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