Physical training and exercise in myasthenia gravis

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Declarations

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Abstract

Myasthenia gravis is characterized by muscle weakness and fatigue. As sustained muscle use increases the weakness, the value of physical training programs has previously been questioned. This is a review to clarify the safety and usefulness of systematic training in myasthenia gravis, based on a systematic search in available databases using the relevant key words. Ten intervention studies including 159 patients with generalized disease have been published regarding the effect of systematic physical training, three of them on respiratory muscles. Muscle strength improved, and in the majority of the studies also daily function and quality of life. The feeling of fatigue not directly related to actual muscle weakness was less influenced by physical training. Continuous training was necessary to maintain the improved function. Physical training and exercise are safe in myasthenia gravis. This can improve both muscle strength and daily function. Type and intensity of systematic training should be adapted in the individual patient. A minimum of 150 minutes of exercise per week is recommended for myasthenia gravis patients with mild and moderate disease.

Keywords Myasthenia gravis; Physical training; Exercise; Fatigue; Autoimmunity

Introduction

Myasthenia gravis (MG) is an autoimmune disease with antibodies that bind to the postsynaptic membrane on skeletal muscle cells. These antibodies impair the function of acetylcholine receptors (AChR), increase their degradation and induce morphological changes in the membrane [1]. The antibodies are directed against the extracellular part of the AChR itself, or against membrane proteins that functionally interact with AChR; muscle-specific tyrosine kinase (MuSK) or lipoprotein-related peptide 4 (LRP4).

Muscle weakness represents the key symptom in MG [2]. The weakness is induced by the disease-specific autoantibodies [3]. Typically, the weakness worsens with repetitive and prolonged use of the muscles. Rest improves the muscle strength. MG patients typically feel strong in the morning, weak at the end of the day. This variation with activity-induced muscle weakness should be considered when testing MG patients formally and is especially important when evaluating therapeutic interventions [4]. Isometric muscle strength is stable both during the day and from day to day in most MG patients and can therefore be tested with high reproducibility [5].

Although the pathogenic IgG antibodies appear in all muscles, the degree of weakness varies considerably between individual muscles. Eye muscle weakness with diplopia and ptosis appears in nearly all patients. Weakness in facial muscles with chewing, swallowing and speech difficulties is also common. Muscles in neck and shoulders are often weak, whereas leg muscles tend to retain their strength. Respiratory muscles are crucial for survival, general function and well-being. Their strength can be reduced in MG, and 10-20 % of MG patients experience a crisis with need of respiratory support during their life-time [6]. MG muscle weakness is symmetrical, the one important exception being the eye muscles.

MG patients are subgrouped according to muscle autoantibody pattern, localization of muscle weakness, thymus pathology and age at debut [7]. This subgrouping reflects differences in pathogenesis and therapeutic response. Thymectomy, symptomatic drug therapy and immunosuppressive drug therapy should all be individualized and determined after consideration of MG subgroup. It would be expected that also response to physical training and exercise differs according to MG pathogenesis and subgroup.

MG treatment tends to focus on optimal immunosuppressive treatment, mostly pharmacological treatment. New and expensive drugs are expected to change the present treatment recommendations and perhaps lead to more individualized treatment regimens [1]. Drugs specifically targeting the AChR, MuSK or LRP4 immune reaction represent a future aim. However, in daily practice supportive measures may be equally important. Prisms and glasses for diplopia [8], surgery for permanent ptosis [9], weight reduction if overweight [2], optimal treatment of comorbidities [10] and adaption of working and daily life facilities [11] are examples of such supportive therapy. Health-related quality of life is surprisingly low in many MG patients, also in those with only mild and moderate symptoms, impaired mobility and depression being core determinants [12].

Patients with MG often describe a feeling of fatigue [13]. This fatigue is generalized and not localized to individual muscles or movements, and it is not related to degree of muscle weakness as tested in formal strength tests. Such an experienced lack of energy and feeling of tiredness is sometimes called central fatigue, indicating that there might be etiological factors in addition to the antibodies binding to the neuromuscular junction. This fatigue does not usually respond to immunosuppressive treatment. It tends to discourage patients from exercising.

Physical training programs are increasingly recommended for patients with all types of both physical and psychiatric disease [14]. Numerous studies have shown an increased function and well-being, and some also a better prognosis regarding disease severity and survival. In neuromuscular disease with muscle weakness as the core symptom, regular training and exercise seem to have a positive effect on symptoms and total outcome [15, 16]. Exercise and strength training with aerobic exercises is recommended for both muscular dystrophies and congenital myopathies, although better studies with more robust methodology are needed [17, 18]. In MG, the value of training programs has been questioned, mostly from theoretical considerations [16]. The muscles become weaker after repeated use, this also proven as a neurophysiological decrement after repetitive nerve stimulation. Rest improves muscle strength in MG. Furthermore, MG is an inflammatory disease. Physical exercise was previously believed to be potentially harmful during active inflammation.

In this study, we have examined the evidence for positive and negative effects of physical training and exercise in MG. The prospective and controlled studies are especially important. Few studies, selection bias, unblinded outcomes, low numbers of included patients and short-term follow-up represent limitations of these studies. The evidence is, however, overwhelmingly in favour of individually adapted physical training as an important treatment element in patients with mild and moderate MG.

Results

We searched the databases Web of Science and Cochrane up till October 8th 2020 with the key words myasthenia gravis and physical training, which gave 14 hits. Myasthenia gravis and exercise gave 139 hits. Relevant guidelines, consensus papers and reviews have been scrutinized. We identified 10 prospective intervention studies where physical training and

exercise were tested in patients with generalized MG, both for tolerance and safety and for improvement of muscle strength, daily function and overall quality of life.

Lohi et al examined 11 MG patients with mild to moderate disease before and after an intensive muscle strength training program for 10 weeks [19]. They trained one arm and one leg, the other side serving as a control. The training program was well tolerated in all patients and there were no dropouts. A 23% increase of maximal muscle force for knee extension was found, compared to 4% in the untrained side. All patients reported better strength and resistance to fatigue.

Rahbek et al included 15 patients with mild to moderate MG for a 8 week training program [20]. There were three dropouts, two unrelated to the training interventions, one because of a worsening of bulbar symptoms. Eight patients had progressive resistance training, and 7 had aerobic training. The former group improved in muscle strength (10%) and functional capacity, whereas the latter group did not improve in aerobic power. In both groups, some patients reported temporary worsening of fatigue. Functional measures improved in both groups, and more in the group with muscle strength training.

Westerberg et al examined two MG populations, both with mild to moderate disease [21, 22]. Thirteen and 15 patients, respectively, were included for a 12-week intensive exercise program combining strength resistance and aerobic training. Six patients dropped out, two because of lack of time, three because of unrelated health problems, and one because of a spontaneous vertebral compression fracture. Muscle strength improved in some but not in all tested muscles, and ultrasound muscle thickness increased. Physical performance-based measures also improved. The patients obtained increased aerobic capacity, and also improved confidence regarding their ability to perform physical activity. None of the patients had any signs of MG activation.

Wong et al included 7 patients with mild to moderate MG in a 12-week program with balance training and muscle endurance exercises [23]. They completed 1-2 sessions per week, and the intensity was individually tailored. No adverse effects were reported. The median change in a scale of muscle strength and fatigability (QMG) was 29%. Several functional tests improved by more than 15%, and this improvement was maintained at the same level one and four weeks post intervention.

Ambrogi and Mineo examined the effect of a comprehensive rehabilitation program given to MG patients during the 3 months before and 4 months after thymectomy [24]. The intervention group was compared to a propensity-matched MG group who had undergone thymectomy previously without any training or rehabilitation program. The two groups consisted of 46 and 34 patients, respectively. The program included muscle resistance training, moderate aerobic exercises, and pulmonary rehabilitation. There were two dropouts in the intervention group. The group with active rehabilitation showed significant improvement; a reduced operative risk, a decreased early postoperative morbidity, a reduction in the need of intensive care admission from 35% to 12%, and a median hospital stay reduction from 5 to 3 days. The patients had a faster recovery at 3 months, both for muscle strength, functional measurements, fatigue score and quality of life.

Farrugia et al recruited 10 MG patients with stable disease and fatigue to a combination of physical and psychological therapy [25]. During a 10-week program there was a small improvement in fatigue, both on physical and psychosocial subscales. Three months after the end of the study, all fatigue scores declined to baseline. However, 5 of the 10 patients had made some lifestyle changes.

There are three studies that have examined the effect of respiratory muscle training in MG [26-28]. They included 14, 10 and 18 MG patients with moderate or mild disease,

respectively. Two of these studies included MG controls with no training [26, 28]. The training lasted for 4-8 weeks. One of the studies included a maintenance phase with continued training for 12 months [28]. The programs consisted of interval-based muscle endurance training combined with breathing retraining. There were some dropouts due to not coping with the training intensity and comorbidity. All three studies reported that the training was feasible and beneficial. Breathing pattern and neuromuscular coordination improved. MG score improved in one [28], but not in another study [27]. Two of the studies reported improved respiratory muscle strength and respiratory endurance [26, 27]. Patients generally felt better after the training program regarding both physical fitness and their respiration.

Discussion

Seven relatively small studies have included a total of 117 patients with generalized MG into formal general muscle training programs lasting for 8-12 weeks. The aims were to improve muscle strength, fatigue and quality of life. Muscle strength did improve, and muscle volume seemed to increase. Systematic training before thymectomy with thoracotomy lead to impressive results regarding postoperative recovery both immediately and after 3 months [24]. However, the fatigue did not seem to improve in the same way as muscle strength in these studies. This was disappointing, and may support that fatigue and muscle weakness represent unrelated or only partly related manifestations of MG. Ruiter et al found that fatigue was common also in MG patients with purely ocular symptoms [13]. The fatigue in that study was more severe in depressed MG patients, and also in females, both pointing to non-muscle pathogenic factors. Physical exercise programs alone should therefore perhaps not be expected to improve MG fatigue.

The patients with training before thymectomy seemed to have the best results [24]. They had short MG symptom duration, most of them were younger than 40 years, and all had AChR

antibodies. This may be markers for benefit of training. Furthermore, the patients in that study may have had the highest motivation for daily training as they were to undergo surgery in the near future.

Three studies including a total of 42 MG patients found that the breathing pattern improved with formal training, and also that respiratory muscle strength tended to increase. Respiratory muscles are crucial in MG, and also for health-related quality of life [29]. In addition, they can be seen as a model for other muscles in MG, illustrating how skeletal muscles in MG can improve in strength and pattern of use with systematic and adapted training. Respiratory physiotherapy should be available as a part of the total management for selected patients as dysfunctional breathing patterns may develop in MG [30]. A focus on exercise reconditioning can improve respiratory function.

All studies reported drop-outs. This occurred even if the MG patients included were selected based on motivation and feasibility. This illustrates that training programs are demanding for the patients. They had to meet regularly at the training facilities, and they were tired after each session. Several of the achieved positive effects were temporary, indicating that continuous training is necessary. The study period was relatively short in all studies. Prolonged training might have improved the results. A multicenter study with training over 3 months and a total of 6 months follow-up has been planned [31], and with the recruitment completed, but the results have yet to be published.

The listed intervention studies applied various training protocols. Training intensity varied from moderate to high. The training was performed regularly through the week, but with variation in frequency. The evaluations of resistance training, aerobic exercise and broader rehabilitation programs were all based on small numbers of patients, and this impairs comparison of the studies. A recent, detailed evaluation concluded that it is not known if any

specific training protocols are of particular benefit in MG [32]. The authors recommended that clinically stable MG patients should exercise with moderate intensity for at least 150 minutes per week. This is in line with the minimum recommended for elderly healthy adults [33]. Single patients with generalized MG and AChR antibodies that have successfully completed both several marathons and ultramarathons have been reported [34, 35], further supporting the safety of exercise in MG.

Comorbidity is frequent in MG, both as autoimmune overlap, osteoporosis due to corticosteroid treatment, and unrelated disorders [10, 36]. The majority of MG patients are elderly [2, 37]. Nearly all chronic diseases benefit of training, and also in high age [14]. Comorbidities and steroid use should strengthen rather than reduce the recommendation of at least 150 minutes of exercise per week.

Better studies regarding MG and exercise programs are needed. Studies should be prospective, randomized and with proper controls (ordinary physical activity and follow-up). Challenges for such studies include documentation that the participants have exercised strictly according to the program, heterogeneity among included patients, and also optimal selection of outcome measures. Patient-reported measures are important to include, and telemedicine may be helpful in the follow-up both of the actual exercise program and for the patient assessment. Funding of exercise studies may be more demanding than for pharmaceutical interventions. Long-term exercise is necessary to obtain an effect, but long-term usually means high drop-out rates as some patients lose their motivation or ability for daily training. Patients with severe, generalized MG or with a pending MG crisis should not be included in ordinary exercise studies.

Conclusions

Physical training and exercise are safe in patients with mild and moderate MG. Such programs are well tolerated in the majority of these patients, but they need to be motivated to continue long-term training. Patients are sometimes concerned that exercise will exacerbate their MG, and physiotherapists may be nervous to treat patients with MG. The neurologist therefore needs to explain, convince and follow-up such treatment.

Physical training programs increase muscle strength and daily functioning in MG. They can improve strength both in affected and clinically unaffected muscles. Physical training programs have a special value in the weeks before and after thymectomy. They should be dynamic and with a substantial load. Both muscle strength training and aerobic training are usually well tolerated. However, in very old patients, patients with relevant comorbidities, and patients with severe, generalized MG, such exercise programs are not always feasible. Alternative and less demanding physical activities and exercise regimes should be optimal for this group.

Specific recommendations for type and intensity of training cannot be given, and should be adapted in the individual patient. Respiratory muscle function improves with endurance training. Fatigue in MG does not necessarily improve with physical training and exercise, and it can be a limitation for training load. Studies of physical training and exercise have not been reported for MuSK-MG and LRP4-MG. We may extrapolate that data from AChR-MG have relevance also for these subgroups.

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