Kwiatkowska Klaudia, Lamtych Martyna, Kubiak Karolina, Badiuk Nataliia. Physiotherapy in myasthenia gravis. Journal of Education, Health and Sport. 2018;8(12):1027-1038. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3242665
http://ojs.ukw.edu.pl/index.php/johs/article/view/7008

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.12.2018. Revised: 22.12.2018. Accepted: 24.12.2018.

Physiotherapy in myasthenia gravis

Klaudia Kwiatkowska[1], Martyna Lamtych[1], Karolina Kubiak[1], Nataliia Badiuk[2]

[1]Student Scientific Circle at Chair of Hygiene, Epidemiology and Ergonomics, Faculty of Health Sciences, Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz, Poland
[2]State Enterprise Ukrainian Research Institute for Medicine of Transport, Ministry of Health of Ukraine, Odesa, Ukraine

Abstract

Myasthenia gravis (MG) is a rare neuromuscular disease with an autoimmune background. It is characterized by the presence of antibodies directed against the acetylcholine receptor. Diagnosing MG poses a lot of difficulties because it is characterized by high variability of symptoms. The most important symptoms of this disease are weakness and excessive muscular fatigue. Diagnosis of the MG requires carrying out a diagnostic tests with a broad spectrum. One of the elements of the comprehensive treatment of patients with MG is the implementation of appropriate physiotherapeutic procedures. Together with other forms of therapy, it alleviates the symptoms of the disease and improves the quality of life of people with myasthenia.

The aim of this work is to present diagnostic methods and physiotherapeutic possibilities in one of the neuromuscular diseases - myasthenia gravis. The bibliographic databases were searched: PubMed, Polish Medical Bibliography and Medline. Articles in Polish and English were used.

Key words: myasthenia gravis, neuromuscular disease, physiotherapy

Introduction

The development of a neuroscience and a molecular research in recent years has allowed us to learn the mechanisms and causes of many diseases, including neuromuscular diseases. These are disorders in which the nervous system and muscles function. We include myasthenia gravis (MG). Miastenia is a non-hereditary, autoimmune disease of the neuromuscular junction with high variability of symptoms [1, 2].

It is characterized by the weakening of muscle strength, especially characteristic of this disease is the drooping of the eyelid due to muscle weakening of the eyelid. Drooping eyelids is the first symptom of disease for 65-70% of patients. Miastenia is a disorder known since year 1672. For the first time symptoms of this disease were described by Thomas Willis [1, 2].

Since then, the level of knowledge on myasthenia gravity has increased, and a significant part of the main clinical features have already been described at the end of the 19th century. The development of medicine caused the discovery in the 20th century of antibodies against acetylcholine receptors (AChR). These antibodies are present in the 90% of patients [1, 2].

Modern methods of immunology and molecular biology have been dynamically developing in recent years. Their goal is to find more effective treatments than those we currently have. The progress of medicine and newly acquired knowledge have allowed to reduce mortality due to myasthenia over ten times. Currently, the incidence of this disorder is 15 cases per 100,000 people. This means that about 6,000 people are affected in Poland. Statistically, women are more often ill. Miastenia is therefore classified as a rare disease [1, 2, 3].

Myasthenia gravis - clinical picture, course of the disease, epidemiology

Myasthenia gravis (MG) is an acquired autoimmune disease characterized by the presence of autoantibodies against neuromuscular junction proteins - the acetylcholine receptor (AchR) and the receptor specific tyrosine kinase kinase. During myasthenia, the affected cells of the body that serve to destroy dangerous microorganisms, viruses, and other foreign elements begin to work against the person himself. They kill the receptors responsible for acetylcholine sensitivity.

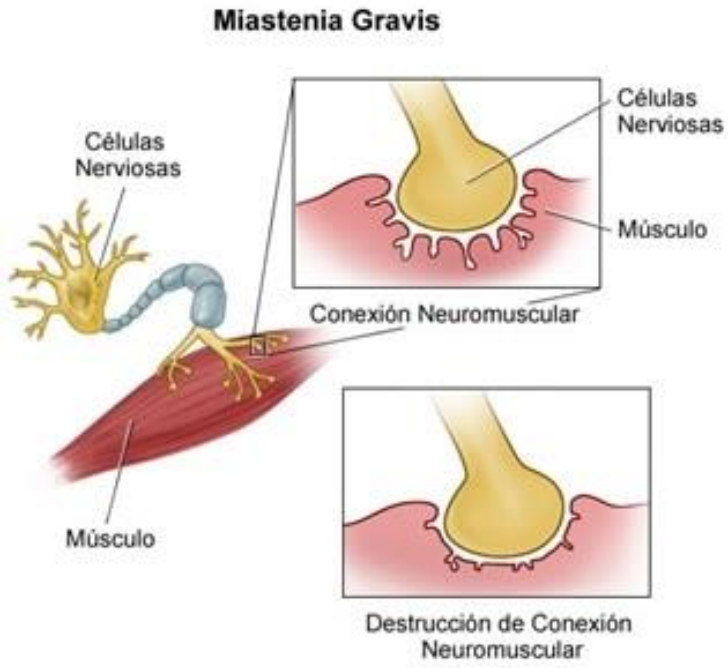

Fig. 1. Mechanism of myasthenia [4]

Antibodies bind to receptors, causing their damage. The immunologic etiology of the disease is indicated by the higher incidence of autoimmune disorders in patients with myasthenia gravis, as well as their first-degree relatives and the relationship between the disease and some of the human leukocyte antigens (HLA) - B7, B8 and DR2 [1, 5].

This disease can be found worldwide, in every latitude. Occurs with a frequency of 15 people per 100,000 population. It is estimated that about 6000 patients suffer from MG in Poland. People of all ages are ill and the first symptoms can occur as early as the age of two. However, the disease most often appears in two peaks, namely mainly women aged 20 to 30 years, and the majority of men aged 50 to 60 years [3].

The first symptoms of the disease most often affects the eye muscles - there is a disorder of their movements, double vision and ptosis. The cause of these symptoms is the weakening of the eyelid levator muscle. These symptoms are characteristic of the ocular form of myasthenia gravis, which is one of MG's forms according to Osserman's clinical division (Table 1).

Table 1. Clinical division of myasthenia gravis according to Osserman [1, 5, 7].

The form of disease	Symptoms
Ocular	Occupation of eyeball muscles, eyelid drooping, image splitting
Gentle generalized	Occupation of muscular, bulging and limb muscles
Severe generalized	The occupation of all muscles to a large extent
Severe violent	Seizure of all muscles to a greater extent than in the form of severe generalized, with the occurrence of respiratory disorders, or the occurrence of violent first symptoms

In patients with MG, there is also a tendency of bulbar muscles that change speech, it becomes quiet with a nasal noise. Weakness of the bulbar muscles is characteristic of a mild generalized form. There are difficulties in chewing and swallowing both solid and liquid food, there may also be a fall of the mandible, and facial expression is disturbed. A characteristic feature of both mild and severe generalized form of MG is apokamnosis, i.e. muscle weakness during exercise. Usually muscle weakness occurs and lasts longer at the end of the day [1, 5, 7].

Myasthenia gravis is a disease with a high variability of symptoms. In addition to the severity of muscle weakness due to fatigue during a specific effort, the variability of the occurrence of symptoms in long periods of time is also observed. Deterioration may be caused by hormonal disorders, infections, stress, both physical and mental, some medicines, and sometimes there is no specific cause. About 20% of patients in the first year of the disease develop spontaneous relapses and remissions. High variability of symptoms makes it impossible to plan therapy for more than a few months, and any significant deterioration is an indication for neurological consultation and treatment modification. There is a possibility of a myasthenic crisis - a rapid and severe exacerbation of the symptoms of myasthenia gravis with symptoms of respiratory failure [5, 6, 7].

In addition to clinical division, we also distinguish children's characters. Children's infancy up to 4 years of age is more common in boys, only in older children there is a prevalence of cases among girls [1, 7].

In childhood myasthenia disease often begins with isolated ophthalmic symptoms. Early-onset birth usually appears in women between 18 and 30 years of age. MG with late onset, more often appears in men from 5 to 8 decade of life. The first symptoms occur in

people in good condition, usually they are quite rapidly increasing ocular and bulbar symptoms [1, 7].

The clinical picture and course are not different from those typical of myasthenia gravis. This form of myasthenia affects 20% of all patients. MG appearing with the thymoma appears equally often in women and men, usually in the age range from 30-74. It is not a paraneoplastic syndrome. The clinical picture and electrophysiological examination do not differ from typical myasthenia gravis. Also, the severity of the symptoms of the disease and the response to conservative treatment are not different from that in a typical myasthenia gravis [1, 7].

Diagnostics

Diagnosing myasthenia gravis, especially in the early stages of the disease, is very difficult for clinicians. According to the literature [4], up to 20% of patients in the first year of the disease were made bad diagnoses. Unambiguous diagnosis of the MG requires different tests: neurological, immunological, pharmacological, mediastinal imaging [8, 9, 10].

Myasthenia gravis is a disease with various clinical symptoms, therefore during diagnosis it should be differentiated with: MS, faster fatigue (eg chronic fatigue syndrome), Lambert-Eaton myasthenic syndrome, bulbar SLA, progressive ophthalmoplegia (eg in the phthopharyngeal dystrophy), neurasthenia [9, 11, 12].

Neurological examination

The diagnosis process begins with gathering an in-depth interview with the patient. During the neurological examination may be found reduced muscle strength, however, in the majority of patients in the initial stage of the disease this is not observed [8].

Electrophysiological examination

Performing neuroelectrophysiological tests is an important element in the diagnosis of nervous system diseases. Thanks to the analysis of bioelectrical phenomena, the functioning of structures of this system can be assessed. Electrophysiological examination allows the diagnosis of neuromuscular conduction disorders or their exclusion, however, it does not decide on the diagnosis of myasthenia gravis - neuromuscular transmission disorders may also occur in other conditions. SFEMG (Single fiber electromyography) and RNS (Repetitive Nerve Stimulation) are used for diagnosis of MG [12, 13].

Single fiber electromyography (SFEMG) is the most sensitive technique used to assess abnormalities in neuromuscular transmission. Electrode with a diameter of 25μm and an electromyograph enable registration of extracellular functional potentials of muscle fiber during weak contraction. A pair of potentials are studied, which come from various muscle

fibers innervated by one motoneuron. The emergence of a second potential in a variable time is indicative of disturbances in neuromuscular conduction, and the time difference is called "jitter" - it is prolonged in myasthenia [12].

Repetitive Nerve Stimulation (RNS), by means of which a selected nerve is stimulated by an over-maximal pulse of different frequency (2-5 Hz or 10 Hz and more), followed by a motor response from the muscle nerved by the nerve to be examined. The potential amplitudes should be similar, and the neuromuscular transmission disorder is found in the case of the myasthenic decrement - a decrease in the amplitude of subsequent potentials during stimulation by more than 10%. The muscle to be examined should be "clinically occupied", because myasthenia does not occupy all muscle groups - the selectivity of the neuromuscular block. A minimum of three muscles should be tested. Although this study is considered essential in the diagnosis of MG, it is characterized by negative sides. Not always a negative result indicates a lack of disease, which is especially characteristic of ocular myasthenia. In addition, the test is invasive and unpleasant for patients [8, 12, 13].

Immunological examination

In the immunological diagnosis, antibodies against the acetylcholine receptor are determined - present in 70-90% of cases of generalized myasthenia and in 50% of ocular myeloma. If the value of antibodies in the blood exceeds 0.4nmol/l, this confirms the diagnosis of the disease. However, there are no antibodies of this type in seronegative myasthenia. In some cases, antibodies against acetylcholine appear after a certain time, then antibodies directed against other muscle fiber proteins play a greater role [2, 8, 9, 14].

Other antibodies present in patients with MG are anti-MuSK antibodies or antibodies directed against other muscle proteins - titin, ryanodynia. As myasthenia belongs to autoimmune diseases, antibodies specific to this type of diseases are also present: anti-parasite, antinuclear, anti-IgM, antithyroid, anti-muscular [8, 14].

Pharmacological examination

Patients suspected of having MG are given acetylcholinesterase inhibitors - endophon or neostigmine. In some patients, the improvement of muscle function is noticeable, in which weakness was previously noted. However, this is not a study by which one can make a certain diagnosis - a similar response is also found in other diseases, eg peripheral nerve neuropathy or brain stem glioma. Noteworthy is the fact that after using Tensilon, muscle performance is not always improved, and the ocular myalgia is the final diagnosis [8, 11].

Imaging examination

In the case of MG, imaging of the mediastinum is particularly important. The test gives the possibility of finding the presence of the thymus, which disappears under physiological conditionsin adulthood, and possible changes in its structure (thymus tumors, thymomas). The main purpose of thoracic imaging is not to diagnose the disease, but to decide on a possible surgical procedure. The most commonly used imaging method is computed tomography. Only the presence of large mass in the mediastinum can be seen in the X-ray [8, 11].

Physiotherapy

Performing even simple everyday activities makes patients with myasthenia a big problem, which is why few patients are physically active. Non-diseased muscle groups can be involved in physical training, and the risk of symptoms appearing characteristic of MG is lower [15, 16].

Rehabilitation is an inseparable element of the treatment process. Its purpose is to restore lost functions or if it is impossible - to limit disability. The rehabilitation program for patients with myasthenia gravis should be individually adapter to the needs of the patient and take into account the assumptions of the Polish model of rehabilitation, proposed by prof. Dega: universality, earliness, comprehensiveness and continuity. All current symptoms and the occurrence of disease exacerbations should be taken into account. It should also be remembered that the wrong tempo, high intensity of exercises (including running, bends and long-lasting exercises) and high temperaturę and air humidity, may exacerbate the symptoms of the disease [17, 18].

Respiratory rehabilitation

Weakening of muscles including respiratory muscles may lead to respiratory failure. Therefore, it is important to introduce the improvement of breathing exercises in the program. In available publications (tab. 2), the authors suggests various forms of rehabilitation - inspiratory and expiratory muscle training, breathing membrane training or endurance training. All forms of rehabilitation used bring beneficial health effects for patients, which confirms that respiratory muscle training is an important and effective element of therapy [19, 20, 21].

Table 2. List of research on respiratory rehabilitation in myasthenia [19, 20, 21].

	Weiner et al. (1998)	Fregonezi et al. (2005)	Rassler et al. (2007)
Type of examination	Prospective study	Randomized trial with blindness	Prospective study
Classification of the disease	Group A - II and III according to Osserman Group B - IV according to Osserman	Generalized myasthenia gravis	II according to Osserman
Methods	Inspiratory and exhalation training (group A) and inspiratory muscle training (group B)	The training included breathing the membrane path and breathing through the laced lips	Endurance training
Study group	Group A - 10 people Group B - 8 people	27 patients with generalized myasthenia gravis. Assigned randomly to the test and control group	10 patients
Time	3 months (6 times a week for 30 minutes)	8-week training (3 times a week for 45 minutes)	4-6 week training (20 sessions for 30 minutes)
Effects	- improvement of the strength and efficiency of the respiratory muscles - improvement of lung function - reduction of dyspnoea symptoms	- improving the strength of the respiratory muscles - improvement of respiratory efficiency - increased mobility of the chest	- improving the strength of the respiratory muscles

Training strengthening muscle strength and endurance

The progressing muscle fatigue significantly impairs the functioning of patients. It may lead to muscular atrophy, therefore it is important to use exercises that improve muscle strength and endurance. In a prospective study, Westerberg et al. [22] used physical training in 14 people with MG according to the recommendations for healthy people, with individual intensity selected. The training included: aerobic exercises (riding a stationary bike), endurance, equivalent and stretching. After 12-week training (twice a week for 90 minutes), an improvement in muscle strength was observed, and what is important - none of the patients

stopped the study due to the deterioration of their health condition.

In another prospective study [23], 10-week aerobic and resistance training was implemented in 10 patients with myasthenia gravis. Muscle strength, physical fitness, muscle enzymes and disease-specific enzymes were performed before and after the training period. Physical exercise was good tolerated by patients. The level of muscle enzymes remained normal, while the disease-specific microRNAs decreased after the training period.

The positive effect of endurance exercise is also confirmed by Davidson et al. [24] in the case of a patient with myasthenia gravis. After 6 weeks of exercise, the muscle strength was improved and the degree of fatigue was reduced. It was observed that the patient was not always able to perform the number of repetitions of the exercise that was recommended. This confirms that a high intensity of exercise for people with myasthenia gravis is not recommended, because these patients have faster muscle fatigability. Interestingly, the goal for the patient was to return to the game of golf, which proves that the right motivation is an important factor in the process of rehabilitation.

Balance training

An important part of the rehabilitation process in myasthenia is balance training. Patients with MG lead a more sedentary lifestyle compared to healthy people. This affects, among other things, the reduction of bone density and, consequently, can lead to falls and fractures. During exercise, there are various physiological effects - increased skeletal muscle mass, increased number of mitochondria, which in effect improves the efficiency of neuromuscular transmission [25]. A study conducted by S.H Wong et al, [26] in Australia in 2015, confirms the effectiveness of training aimed at improving the balance in people with MG.

Myasthenia gravis and sport

The fatigue characteristic of myasthenia causes that athletes diagnosed with a disease have a problem with physical activity. The available publications contain descriptions of individual cases of people who, despite being diagnosed with myasthenia, did not resign from sport. Birnbaum et al. [15] describe the case of a 36-year-old woman taking part in marathons. During the initial training, the symptoms most often reported by the patient were fatigue and dysphagia. After the participation in the marathon and two half-marathons, no additional difficulties or exacerbation of already existing symptoms were observed. The authors report that one year after diagnosis, the patient was found to have both normal breathing activity and endurance of limbs. There were also 6 MWT (6 Minute Walk Test), the results of which were in the normal range. During the regular training, occasional eye symptoms and weakness of

the right hand appeared in the patient. Schereer et al. [27] in their publication present a 52-year-old athlete with diagnosed myasthenia gravis. The patient - the runner completed the ultramarathon, which lasted for 5 days, which distance was 220 km. Accompanying symptoms of the patient were, among others: problems with breathing and swallowing, the severity of which decreased during rest and after administration of pyridostigmine. Lower limb weakness and fatigue were also noted.

The described cases show that myastheniais does not have to be an absolute contraindication to active sporting, but no specific guidelines have been published on the participation in sport by people with myasthenia gravis.

Summary

Miastenia gravis is a rarely occurring neuromuscular disease, the diagnosis of which is possible due to appropriate diagnostic tests. A characteristic feature of the MG is increased muscular fatigue, which is an indication for the implementation of physiotherapy. So far, few studies have been published that evaluated the effect of exercise on the functioning of patients with MG. In addition, they are carried out among small groups of patients, therefore, the results can not be generalized to all patients with myasthenia.

A clear lack in the literature on the subject regarding the application of specific training patterns in myasthenia may result from the fact that the programs should be individualized and adapted to the course of the disease.

The research shows that the combination of rehabilitation and other forms of treatment, appropriately selected activities contribute to alleviating the symptoms of the disease, improving physical fitness, increasing muscle strength, and thus improving the quality of life. There is a need to develop detailed recommendations according to which you can plan physical exercises in this group of patients.

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