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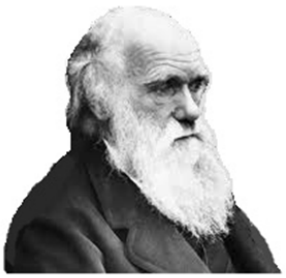

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Diagnostic and therapeutic challenges of Myasthenia Gravis: A report of 2 cases

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease that affects the neuromuscular junction and is characterized by muscle weakness. We present two clinical cases of patients with MG. The first case of the patient presents an uncharacteristic clinical picture in the form of dyspnoea with stridor. The second clinical case presents a severe form of MG, resistant to pharmacological cholinergic and immunosuppressive treatment, which resulted in a satisfactory improvement after eight plasmapheresis treatments and the conversion of pyridostigmine to the ambenonium.

***Keywords*:** myasthenia gravis, autoimmune diseases, plasmapheresis

1. INTRODUCTION

Myasthenia gravis (MG) is a relatively rare disease affecting approximately 140 people per million [1]. However, its prevalence has been increasing in recent years, especially in the elderly population.

The disease is caused by disturbances of neuromuscular transmission due to a decrease in the number of acetylcholine receptors in the postsynaptic membrane. This is due to the destruction of receptors by antibodies against acetylcholine receptors (anti-AChRs). In fewer than 5% of patients, anti-tyrosine kinase (anti-MuSK) and anti-LRP4 receptor antibodies against low-density lipoproteins are also present [1]. The principal symptom of myasthenia gravis is excessive fatigability of skeletal muscles and their weakness during exercise. Muscle

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weakness can quickly regress after rest. In about 15% of cases, MG is associated with other autoimmune diseases as: rheumatoid arthritis, lupus erythematosus, hyperthyroidism, psoriasis, polymyositis and multiple sclerosis. In such situations, the combination of symptoms of various ailments can generate a complex clinical picture, which becomes a challenge for clinicians as for correct diagnosis of the disease.

Difficulties associated with MG may refer not only to the diagnostic process but also to the selection of an effective form of therapy that would allow long-term remission of the disease. Therapeutic decisions are taken, among others based on the assessment of the patient's current condition, age of the patient, type of the disease (ocular or generalized), presence of anti-AChR and anti-MuSK antibodies, individual contraindications for a specific therapy and evaluation of the response to the previous treatment. In particular, the main focus is on the use of drug therapy, while immunomodulatory treatment is used only when the pharmacological treatment does not bring the expected results.

2. MATERIALS, METHODS AND AIM OF THE STUDY

The aim of this study is to present a diagnostic and therapeutic route in two cases of patients with myasthenia gravis. In the first case, attention was paid to the difficulties in correct diagnosing of the disease. Whereas, the second case presents a patient with severe form of MG, not responding to pharmacological treatment, who achieved good therapeutic effects after eight plasmapheresis procedures. The present article reviews scientific reports on MG.

3. CASE REPORTS

A 78-year-old male was admitted urgently to the Department of Otolaryngology in the winter of 2018 due to dyspnoea with stridor in the course of bilateral paralysis of vocal folds for diagnosis and treatment. During the neurological consultation, eyelid droop, head droop, dysarthria and gait on the extended base were all found. The history showed that the patient had been hospitalized in another hospital in the Neurology Department 4 months ago due to the diplopia of the right eye when looking straight ahead and left, the right eyelid sagging and the head falling to the right side, where the "organic vascular CNS damage, stroke of the right hemisphere of the brain " was diagnosed. During current hospitalization, head MRI was performed and there were no signs of intracranial haemorrhage (Figure 1). Next, a positive result was noted in the electromyographic test, and the antibodies against the acetylcholine receptor were measured at a concentration of 20 nmol/l. The test with pyridostigmine was also positive. These tests confirmed the diagnosis of another disease - MG.

The second clinical case is a 66-year-old male who was admitted to the Department of Neurology in winter 2018 due to an exacerbation of MG symptoms, in the form of dysphagia, dysarthria, fatigue on walking gait, dyspnoea and lower eyelid drooping occurring for 1.5 weeks. The documentation showed that in 2017, the patient was diagnosed with MG and was initially successfully treated with pyridostigmine and prednisone. During the hospitalization, human immunoglobulin i.v. treatment was used, which allowed to reduce the reported neurological symptoms. The patient was discharged home in good general condition with the addition of azathioprine to chronic treatment. After about a month, the patient again

experienced an acute exacerbation of the symptoms of MG. Due to increased dyspfagia, a nasogastric tube was inserted. Intravenous immunoglobulin with prednisone and prirodostigmine were re-used, however, no improvement of the patient's condition was achieved. In order to exclude other pathological conditions, CT of the chest and abdomen were performed, but no abnormalities were revealed.

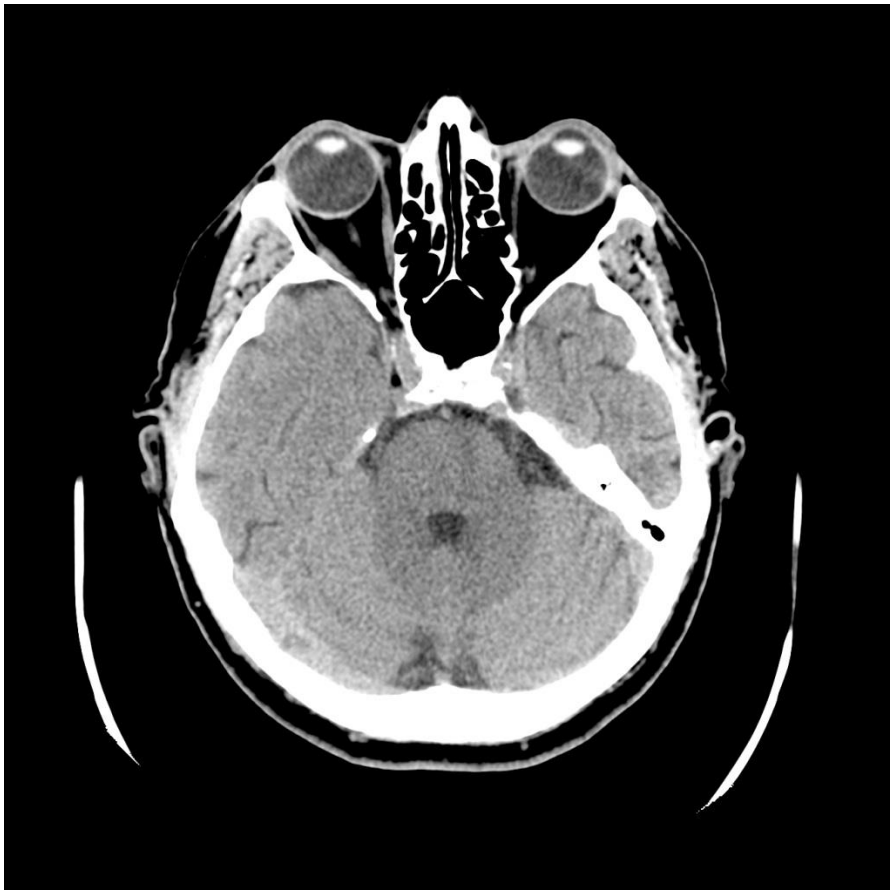

Figure 1. Head MRI T2 weighted image of the first patient case

The neoplastic markers in the laboratory were normal and the laryngological examination showed no local changes that could lead to dysarthria and dysphagia. In the absence of immunoglobulin efficacy, the immunosuppressive drug – cladribine was administered twice, which slightly improved the patient's clinical condition - less muscle weakness and better limb efficiency were found. Then the decision was made to use plasmapheresis. After the third treatment, a clinical improvement of the patient was observed. However, on the third day after the fifth course, the recurrence of the disease symptoms was noticed. In treatment, pyridostigmine was changed to ambenonium, which partially stabilized the patient, followed by another 3 cycles of plasmapheresis, thanks to which the patient's condition improved significantly. During the next days of observation, the patient did not show any recurrence of symptoms, and was discharged home in good general condition with the recommendation of taking prednisone and ambenonium.

4. DISCUSSION

The most important element that suggests MG is the patient's clinical picture characteristic of the disease. In the course of the disease, the most frequent (> 60%) are the problems with extraocular muscles. This results in diplopia, blurred vision and drooping of the eyelids. Other, equally often occupied muscles in the course of MG are the muscles of the throat, larynx and oral cavity manifesting in the form of dysphagia and dysarthria. The muscles of the upper and lower limbs are less frequently involved. However, the disease sometimes starts with the attachment of other muscle groups, which causes that its symptoms pose difficulties in making a diagnosis. In the first case presented by us, the main symptoms were dyspnoea with a stridor. In the literature can find several examples describing cases of MG with severe dyspnoea as the initial symptom of the disease [2, 3]. In such situations, it is extremely important to quickly and accurately diagnose and apply the appropriate treatment for MG to avoid the need for tracheostomy. Diagnosis of MG may pose difficulties not only because of the non-symptomatic clinical picture. The most common causes of diagnostic errors include: an atypical age of onset (pediatric MG and old aged MG) male sex and sudden onset of the disease [4]. According to data from the literature, as many as 20% of patients with the diagnosis of MG initially made an incorrect diagnosis of another disease.

In order to confirm the diagnosis of the MG, a clinical trial can be used to reveal the apocamnosis, Tensinol test (reduction of symptoms after administration of the edrophonium), electrophysiological examination (assessment of conduction disturbances between the peripheral nerve and the muscle) and the immunological laboratory tests, determining antibody titres in serum. The presence of anti-AChR antibodies in the titre from 0.4 nmol/l confirms the diagnosis of the disease, however, these antibodies occur in very different titers and there is no direct correlation between the high titre of antibodies and the severity of clinical symptoms. The antibody titer is also not an indicator of improvement after treatment. Patients with full, long-term remission may have high anti-AChR values [5]. On the other hand, the researchers showed that 15-20% of patients with full clinical manifestations of the disease do not have antibodies. This form of MG is called seronegative and it mainly occurs in patients with ocular form of the disease. It turns out that in some cases of seronegative MG other antibodies can be detected: anti-MuSK antibodies. Their presence is up to 70% in the seronegative myasthenia group [6].

In addition to diagnostic difficulties, the MG may also face therapeutic difficulties [7]. Currently, in the treatment of MG and myasthenic crisis are used: acetylcholinesterase inhibitors (pyridostigmine, ambenonium), immunosuppressive drugs (steroids, azathioprine, cyclosporin A, cyclophospham), intravenous immunoglobulin (IVIG), plasmapheresis (Therapeutic Plasma Exchange, TPE) and surgical immunosuppression (thymectomy) [8, 9, 10]. Also cladribine seems to be a safe and effective emergency therapy in MG, but more research is needed in this direction for a larger population [11].

The classic treatment of MG patients with cholinergic drugs in combination with corticosteroids brings a satisfactory improvement only in some patients. In other cases, cyclophosphamide therapy may be effective, but cyclophosphamide is a highly toxic drug. Good therapeutic effects can also be obtained with cyclosporin. The retrospective studies carried out on a large group of patients showed a good effect of the drug after a few months of use in people not responding to treatment with corticosteroids with azathioprine. Adverse drug reactions occurred only in 14% of cases [12].

The international literature emphasizes the huge increase in the frequency of immunomodulatory treatment, which includes plasmapheresis and infusions of human immunoglobulins. They are a chance for clinical improvement in patients who have failed therapy with acetylcholinesterase inhibitors and immunosuppressive therapy.

The treatment of plasmapheresis consists in the separation of the plasma along with possibly present pathogenic factors from the morphing elements of the blood [12]. The removed volume of plasma is replaced by a replacement fluid, which consists of plasma, albumin, electrolyte fluids and colloids, depending on the clinical situation. In case of MG, it is usually recommended to perform three to five plasmapheresis procedures every other day with plasma removal to 2.0-2.5 ml/kg body weight [13]. It is also possible to carry out daily plasma replacement procedures by removing smaller amounts of plasma [14]. The effective therapeutic impact of TPE is found not only in the MG, but also in more than 50 disease states, among which the following are mentioned: Guillain-Barre and thrombotic thrombocytopenic purpura syndrome [15]. The first publication regarding the use of plasmapheresis in the treatment of MG was published in 1976 [16]. The study involved three patients with severe MG who did not improve in their clinical condition despite treatment with cholinesterase inhibitors, prednisone in high doses and thymectomy.

After applying TPE, a striking clinical improvement was achieved, suggesting that there is a humoral factor associated with neuromuscular transmission in the plasma [14]. A year later, 5 cases of patients with severe disabilities caused by MG that did not improve after pharmacological treatment, were described [17]. TPE in combination with prednisone and azathioprine therapy resulted in significant improvement in all patients. These publications allowed for the recognition of plasma exchange as an effective method of elimination of antibodies and immune complexes, worthy of use in severe forms of myasthenia gravis. In 2015, the results of TPE were published in patients of one of the Indian hospitals treated in 2011-2013 due to the severity of the symptoms of MG [18]. Among 110 patients with MG who were admitted to hospital, in 35 patients there were indications to perform TPE. The average number of TPE sessions was 4.2.

All patients experienced immediate benefits from each TPE cycle. Good acceptance of the procedure was observed in 78.3% of patients. It was also noticed that the effects of plasmapheresis depend, among others, on the timing of its initiation. Delay of plasma therapy in the MG by more than 2 days from the day of admission to the hospital may lead to higher mortality and incidence of complications [19]. Among the disadvantages of plasmapheresis it is mentioned that this method seems to produce good results only in the short term [20]. Gajdos et al. in their meta-analysis regarding the use of TPE in the MG, found that it is not suitable for chronic treatment because repeated plasmapheresis often leads to insufficient peripheral venous access, which requires the placement of a double-center central catheter [21, 22]. In this situation, the risk of serious complications associated with chronic catheter, such as infection and thrombosis is increases [23]. In addition, plasmapheresis may also cause other side effects, including bleeding, hypotension, arrhythmias, muscle spasms and toxic citrate reactions used in the procedure. Despite the possible side effects of TPE, it can be safely used in patients with MG as a temporary treatment agent in severe MG. In the short-term treatment, the benefits of using TPE outweigh the risk of complications. In the analysis of 42 patients with moderate and severe MG course, who were treated with plasmapheresis in a prospective study, no complications were found in 55% of patients, while in the remaining 45% only mild complications occurred that did not require discontinuation of treatment [24].

The immunomodulatory effect in the treatment of MG in addition to TPE also shows the benefits of IVIG [25]. According to data from the literature, the mechanism of action of IVIG in myasthenia is to: inhibit the synthesis of pathogenic anti-AChR antibodies; inhibiting the binding of anti-AChR antibodies to the receptor; blocking the Fc receptor of immunocompetent cells [26]. IVIG are effective treatment of acute forms of MG at a dose of 0.4 g/kg body weight administered within 2-5 days. Most of the side effects of IVIG are mild, among them chills and headaches during and after infusion, although it should be remembered that some patients may be exposed to serious adverse events, such as anaphylactic shock or renal failure.

Numerous studies show that the efficacy and safety of TPE and IVIG use remain at a similar level [27, 28]. Both forms of treatment comparatively reduce the quantitative results of QMGS disease severity in patients with moderate and severe MG [29]. Therefore, the type of immunomodulatory treatment should be selected individually, taking into account the form of the disease, the severity of symptoms and potential side effects.

In the second case presented by us, due to the severe form of the disease and the lack of a satisfactory response to standard pharmacological treatment, the decision was made to use plasmapheresis. We did not observe side effects during the treatment. Despite the improvement of the clinical condition of the patient after the second treatment, the therapeutic effect did not last long - after the fifth procedure the patient's condition deteriorated again. However, three consecutive treatments, combined with the conversion of pyridostigmine into the ambassionum, have led to significant and long-term clinical improvement.

5. CONCLUSIONS

In conclusion one might say that MG does not always occur with typical clinical symptoms. The first case of presentation of a form of MG described by us manifesting mainly dyspnoea with a stridor caused by bilateral paralysis of vocal folds. In such situation, an accurate diagnosis enables the selection of an effective treatment that can prevent the need for tracheostomy.

In addition, in some cases of MG when clinical improvement is hard to achieve pharmacological treatment (acetylcholinesterase inhibitors, immunosuppressive drugs) is strongly recommended. In such situations, the clinical condition of the patient can be improved by the use of plasmapheresis. The second case presented by us is proof that despite the severe course of the MG with poor prognosis, a significant and long-lasting clinical improvement can be achieved thanks to the use of TPE.

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