PREOPERATIVE MANAGEMENT OF PATIENTS WITH MYASTHENIA GRAVIS: A REVIEW ARTICLE

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ABSTRACT

INTRODUCTION: Myasthenia gravis (MG) is an autoimmune neurological disorder characterized by defective transmission at the neuromuscular junction. This neuromuscular disease marked by repetitive intermittent skeletal muscle weakness and fatigue Clinical symptoms are manifested in varying degrees depending on the age of diagnosis and antibodies to acetylcholine receptors. Facial and oropharyngeal muscles are among the most affected by this disease, thus presenting a lot of difficulties when dental treatment is performed. Since the disease is known to specifically affect the masticatory, facial and oropharyngeal muscles, dental treatment proves very challenging for dentists and patients alike. In order to choose the optimal and less invasive treatment approach and avoid inherent complications, dentists must be acquainted with the clinical features of MG as well as the medications administered in MG patients.

AIM: The aim of the present study is to investigate and systematize the clinical presentations of MG in order to choose the most appropriate treatment approach and avoid complications. For this purpose, oral and maxillofacial clinicians must also be acquainted with the main groups of medications for this disease.

MATERIALS AND METHODS: This research relied on Google Scholar and PubMed publications, published in the period 2000–2022.

CONCLUSION: Myasthenia gravis is a serious and rare chronic disease. In order to avoid complications, some of which life-threatening, it is of utmost importance to know its main symptoms as well as applicable medications in dental treatment.

Keywords: *myasthenia, weakness, fatigue, neuromuscular disease*

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that is clinically marked by fluctuating or intermittent skeletal muscle weakness, unusual and abnormal fatigue following exertion that slightly improves after periods of rest (1). As the disease is known to specifically affect the masticatory, facial and oropharyngeal muscles, dental treatment proves very challenging for dentists and patients alike. Some of the most common symptoms that are of particular relevance to oral clinicians' work include fatigue of the masticatory muscles, difficulty speaking—dysarthria or nasal sounding speech, difficulty swallowing, diplopia, ocular problems, potentially acute respiratory failure due to

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Received: January 16, 2023
Accepted: March 20, 2023

breathing muscles weakness, all of which posing limitations on the duration of dental treatment. These complications are signs of the disease itself but can also be triggered by certain medications administered for the treatment of teeth and jaws. Therefore, it is crucial to know the clinical oral manifestations of MG, optimal treatment timing, effects of certain drugs as well as safe medications that would not provoke a myasthenic crisis. Treatment of patients prone to myasthenic crises must be carried out in a special environment where mechanical ventilation is available in the event of respiratory failure.

MATERIALS AND METHODS

This research relied on Google Scholar and PubMed publications, published in English in the period 2000–2022 and focused on the most recent studies of MG.

RESULTS

Etiology, Epidemiology, and Pathogenesis

The etiology of MG is not fully understood, although there is a strong link between MG and thymus involvement as well as the presence of other autoantibody-mediated disorders (2,3,4).

The disease has no predilection to gender, however, MG affects more frequently women aged 20–30 years, with a female-to-male ratio described as around 7:3. It is observed as less common in men aged over 50 years (60–70 years), with a ratio of 3:2 (5). Childhood myasthenia has also been detected but is considered very rare compared to the incidence in adults (6,7). The prevalence of MG presents with different values, ranging from 15 to 179 (8), or up to 150–200 cases per million persons (9).

Pathogenetically, MG is found to be an autoimmune reaction against the neuromuscular junction (NMJ) components of striated muscle tissue. Acetylcholine is released from the presynaptic membrane and enters the synaptic cleft by binding to receptors in the postsynaptic membrane. Muscle-specific tyrosine kinase (MuSK) located in the postsynaptic membrane plays a major role in the clustering and stabilization of acetylcholine receptors (AChRs). In patients diagnosed with MG, the structure and functions of the NMJ are significantly impaired. Antibodies to the AChRs in the postsynaptic membrane were detected in the sera of 85% of MG patients, while the remaining fractions of MG patients revealed no detectable AChRs and were marked as seronegative (10). However, they showed antibodies against MuSK (anti-MuSk) (11), apart from the more common antibodies against AChR clusters, found using cell-based assay (12). Moreover, low molecular-weight receptors related to low-density lipoprotein 4 were also detected (13). Thus, antibodies lead to a decrease in AChRs in the postsynaptic membrane, which in turn accounts for disturbances in the transmission of impulses in the neuromuscular synapse. Even in seronegative MG patients, biopsies revealed decreased numbers of AChRs in the postsynaptic membrane (14).

The thymus is clearly involved in the pathogenesis of MG and for this reason one of the treatment approaches suggests its removal. Most patients suffering from MG exhibit histological changes associated with thymoma or follicular hyperplasia leading to the development of germinal centers (1,15). But unlike patients with AChR antibody positive MG, most patients with MuSK antibody positive MG do not reveal pathological changes in the thymus (16).

Diagnosis, Clinical Features and Treatment

As far as treatment is concerned, most patients who have undergone thymectomy tend to show improvement in their general condition, and some even achieve medication-free remission (2).

The initial signs of MG more often occur in the areas innervated by the cranial nerves. Patients commonly present with ptosis (drooping of the upper eyelid), diplopia, difficulty chewing or swallowing, labored breathing, or limb weakness. In some cases, the disease is confined to muscles around the eyes, but unfortunately, in the majority of cases, it progresses to other areas as well (2). Weakness of facial and oculomotor muscles gives MG patients a particular facial expression of depression and apathy, while smiling may look more like a snarl. Another feature is lipomatous atrophy of the tongue, which appears furrowed and flaccid as the longitudinal muscles are increasing affected with MG progression (1,17,18). Weakness in the palatine and pharyngeal muscles results in dysphonia, nasal sounding speech or slurred speech. Speech impairment along with the hallmark facial expression render verbal and non-verbal communication very difficult for the patient and others. In the most severe cases, all muscles of the body

suffer, including the diaphragm, abdominal and intercostal muscles, and even the colon and bladder sphincters. Myasthenia gravis progresses over several years, with maximum weakness reported during the second year in 82% of patients (19,20).

Diagnostic evaluation of MG is made on the basis of anamnestic data on worsening of muscle weakness and fatigue, clinical symptoms in addition to clinical data—bedside assessment, edrophonium tests, serological tests (detection of AchR-Ab or MuSK-Ab) electrophysiological tests, computed tomography (CT) scan and magnetic resonance imaging (MRI) to study the thymus (19). Antibodies against both AChR and MuSkR are rarely found to coexist (21). Myasthenia gravis is generally divided into several stages, depending on the type and severity of the disease (5).

A differential diagnosis of the disease is made, depending on the affected muscle groups and symptoms. In patients with predominant ocular muscle weakness, diseases such as thyroid ophthalmopathy, oculopharyngeal muscle dystrophy, mitochondrial myopathy, bulbar amyotrophic lateral sclerosis (ALS), Miller Fisher syndrome should be excluded (5, 22). In case of weakness and rapid fatigue of the limbs, differential diagnoses include chronic inflammatory demyelinating polyneuropathy, generalized myopathy, multiple sclerosis and Lambert-Eaton myasthenic syndrome (LEMS). Lambert-Eaton myasthenic syndrome is yet another autoimmune disorder of the neuromuscular transmission affecting the calcium channels in the presynaptic membrane and is distinguished from MG by some distinctive clinical features (19).

The MG treatment is performed entirely by neurologists and aims at achieving a stable remission, improving the clinical symptoms and avoiding complications. However, some of the medications may disturb ongoing dental treatment and may have an impact on more substantial and time-consuming dental surgeries. Therefore, dentists must be acquainted with the medical management of MG.

Initial treatments for MG include acetylcholine agents or angiotensin-converting enzyme (ACE) inhibitors (pyridostigmine, neostigmine). Their application aims to slow down the reduction of acetylcholine and optimally preserve its effect as a neuromuscular mediator. Myasthenia gravis symptoms such as ptosis, dysphagia, and dysarthria respond well to ACE inhibitors. Pyridostigmine alone can be used in milder cases of MG or in combination with immunosuppressants in severe cases. In patients with rapid progression and worsening symptoms, the recommendation is for intravenous administration of immunoglobulin or plasmapheresis. In therapeutic plasma exchange, antibodies against AChR and MuSK, as well as cytokines and immune complexes, are directly removed from the blood circulation whereby rapid improvement occurs. Typically, this therapy is administered 4 to 6 times in the event of a myasthenic crisis with respiratory muscle involvement, preoperatively or in patients with refractory MG (19).

One of the most commonly applied methods of suppressing the production of antibodies against our own cells is the application of corticosteroids. Their side effects, however, including weight gain, cataracts, glaucoma, hypertension, dyslipidemia, osteoposis, etc. limit their use and duration.

Other drugs prescribed for the symptomatic treatment of MG include immunosuppressants such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, cyclophosphamide, etc. Most of them have been reported to produce side effects such as nausea, vomiting, hematological disorders, secondary infections and even malignant blood cell changes (1,19).

The thymus has been found to be directly implicated in the pathogenesis of MG. A histological examination revealed a benign formation—thymoma or follicular hyperplasia. Removal of the thymus proved to play a major role in the improvement of symptoms and achieved a relatively stable remission, primarily in patients with AChR antibodies (23). The efficacy of thymectomy is not yet clearly demonstrated in so-called seronegative patients with anti-MuSK or in those with purely ocular myasthenia (24). Moreover, thymectomy is not a treatment of choice for patients over 65 years of age (5,25).

Clinical Features of Myasthenia Gravis and Dental Treatment

Weakness in facial, masticatory and, most importantly, respiratory muscles has a direct impact on the work of dentists and oral surgeons. Accord-

ing to studies, difficulties in mastication, low bite force during eating, inability or weakness in closing the mouth are some of the hallmarks of MG (17, 23), coexisting in at least 4% of MG cases (26). They can be observed prior to the appearance of other symptoms of the disease and allow for early diagnosis and treatment (27). Restrictions in mastication and swallowing lead to different forms of malnutrition and weight loss (28, 29). Another symptom, affecting the work of a dental professional, concerns the weakness in the swallowing muscles which tend to become fatigued with prolonged speech and impede swallowing during dental procedures. In such cases, nasal regurgitation and entry of fluids into the nasal cavity are often observed. Other MG patients with weak facial muscles have difficulty closing their mouth and eyes (19). Reflexes, sensory sensitivity as well as coordination suffer (30). Myasthenia gravis patients experience difficulty swallowing and as a result may develop fear of choking. Decreased cough reflexes may increase the risk of aspiration of fluids, oral debris, and saliva. This necessitates the use of powerful aspiration during dental sessions. The use of a rubber dam is appropriate, whenever possible. A semi-upright position of the dental chair provides more comfort for the MG patient as it facilitates swallowing (1, 30). The use of dental mouth openers during a surgical procedure is not recommended as it can lead to rapid fatigue and stiffness of masticatory muscles.

Due to the specificity of the disease, it is very difficult to maintain good oral hygiene. As a consequence, there is heavy plaque and tartar build up, and patients develop gingivitis, periodontitis as well foetor ex ore. Proper plaque control demands frequent visits to the dentist's office, prescription of plaque-reducing agents and application of fluoride preparations. Onset of rapid fatigue and muscle weakness necessitate the use of electric toothbrushes.

Prosthodontic management of MG has been reported in dental literature only in few cases, mostly involving treatment with implants and none with complete denture rehabilitation (17,31,32,33). As a result of the reduced potential of masticatory and facial muscles it is very difficult to ensure retention and stability for complete removable dentures in MG patients. It has even been reported that lengthening and thickening of denture edges for better stability, may negatively impact muscle insertions, frena as well as gingivobuccal connections and lead to the MG flare or exacerbation (31). Uncomfortable dentures can put additional strain on the masticatory muscles and result in difficulty closing the mouth, tongue movement disorders, impaired speech and swallowing disorders. An option that may benefit MG patients is the so called lingual occlusal scheme, which has been found to promote denture stability and patient comfort. Lingualized occlusion reduces lateral forces, centralizes the vertical force on residual mandibular ridges and can be compensated with specific occlusal design (34).

The methods for evaluation of MG disease control and progression include assessing the period of time the patient is able to look up before ptosis of the eyelid develops and how long the patient can keep their arms outstretched (2).

Many medications used in dentistry can trigger worsening of MG, including increased muscle weakness, fatigue or breathing difficulties (28). Therefore, dentists should be aware of the clinical presentations of the disease and the choice and effects of medications for dental treatment.

Local and General Anesthetics

Nearly all dental treatments involve the administration of local anesthesia. All local anesthetics lead to a decrease in the postsynaptic membrane sensitivity to acetylcholine, which can worsen the condition of MG patients. Ester local anesthetics are primarily hydrolyzed in the blood plasma by pseudocholinesterase enzymes and always carry a risk of toxicity. Furthermore, due to rapid hydrolysis, the effect of these anesthetics is only of short duration (35). Therefore, local anesthetics of the amide group, such as lidocaine, mepivacaine, and articaine, are considered safer and more effective to utilize in patients diagnosed with MG. Nevertheless, smaller amounts of anesthetic are recommended, if possible. The addition of a vasoconstrictor in the local anesthetic preparations is known to prolong the action and reduces the dose. The amount of anesthetic in local anesthesia can be reduced through intraligamentary or intrapulpal injection techniques. Bilateral mandibular nerve block anesthesia is not recommended due to the risk of swallowing difficulty (18).

Although some patients have a good control of the disease, any emotionally charged experiences or

stress can lead to deterioration and the onset of complications. Since dental treatment qualifies as stressful enough, only routine or minor procedures ought to be performed by dentists, such as dental fillings, root canal treatment, etc. If there is a need for multiple extractions, retained wisdom teeth treatment and other major procedures, or patients with moderate MG symptoms show fear and anxiety, or there exists a high risk of paralysis of breathing muscles, dental treatment must be performed at a hospital with access to immediate mechanical ventilation (1, 18). For surgical dental treatments, nasotracheal intubation is preferred so as to ensure full access to the oral cavity and facilitate the oral surgeon and reduce operative time. However, if short-term dental treatment is required in an outpatient setting, a morning appointment must be scheduled before daily muscle weakness and fatigue build up (23).

For major procedures, it may be necessary to sedate the patient to reduce fear and emotional stress. Nitrous oxide sedation has been primarily utilized. Administration of barbiturates and benzodiazepines has been shown to cause respiratory depression and worsen the condition of MG patients (18). Other short-acting intravenous anesthetics used for sedation of MG patients include propofol, sevoflurane, desflurane, fentanyl, or remifentanil, as they allow rapid recovery at the end of the surgery. The administration of neuromuscular blocking agents (myorelaxants) during intubation is not recommended (36,37).

Anti-Inflammatory and Analgesic Agents, Antibiotics

Nonsteroidal anti-inflammatory drugs, such as aspirin and acetaminophen, can be used to alter pain sensations in MG patients as they do not impair acetylcholine metabolism and neuromuscular transmission. COX2-inhibitors are also commonly given.

Prescription of certain groups of antibiotics which are known to precipitate muscle weakness, suppress acetylcholine metabolism and disrupt the transmission of nerve impulses at the neuromuscular junction is also contraindicated. **Aminoglycoside antibiotics**—gentamycin, kanamycin, amicacin, neomycin, streptomycin—should be avoided since they block presynaptic voltage-activated calcium channels and affect the postsynaptic membrane's sensitivity to acetylcholine. They enhance muscle fatigue and weakness in MG patients (38). Tobramycin alone does not affect neuromuscular transmission (39).

Fluoroquinolones (ofloxacin, pefloxacin, ciprofloxacin, etc.,) should be avoided in MG. It is assumed that they worsen the symptoms of the disease in a two-fold manner: they affect the pre- and postsynaptic membrane and cause some toxicity, depending on the dose of administration (40,41). Cephalosporins, sulfonamides, and carbapenems, are considered relatively safe and carry fewer risks (1,17,18,23).

Macrolides (erythromycin, azithromycin) should be avoided in MG patients since they worsen symptoms. They are known to reduce neuromuscular transmission at the presynaptic level (39).

Tetracyclines must be used with caution.

Penicillin antibiotics are indicated as relatively safe for administration in myasthenia gravis, however, there are cases of worsening of symptoms (25,39,42).

Other Drugs That Are Contraindicated in Myasthenia Gravis

As most drugs for MG have particular uses and are commonly prescribed by a neurologist or a clinician, it is very important to be acquainted with their action. However, some drugs are absolutely contraindicated for use in patients diagnosed with MG, while others can be applied with caution and, if possible, in an outpatient setting to manage potential complications.

A myasthenic crisis is a complication where respiratory muscle weakness is observed and intubation is required. It can be provoked by medications, emotional stress, physical exertion, viral infections, surgical manipulations, etc. (23). When there is a risk of respiratory failure, especially during surgeries, they must be performed in an environment where artificial ventilation is available (43,44,45). Despite the huge risk of a fatal outcome, prognoses, in recent years, have significantly improved as mortality rates have dropped to 4.5% (46).

- Magnesium supplements worsen the symptoms of MG and can precipitate a myasthenic crisis (37,47).

- Heart medications (antihypertensive drugs with β-blockers and calcium antagonists, as well as antiarrhythmics—amiodarone, hydroxylchoroquine) should be avoided as much as possible (48, 49).
- Opioid analgesics (benzodiazepines, barbiturates, hypnotics), prescribed for special conditions and diseases, are contraindicated in MG as they lead to respiratory depression, worsening of symptoms and myasthenic crises (18, 23, 50).
- Antipsychotic drugs (chlorpromazine, thioridazin, haloperidol, etc.) are contraindicated (51, 52).
- Botulinum toxin, when used for cosmetic purposes, reduces acetylcholine in the presynaptic membrane and limits muscle movements. In MG patients, it can cause worsening of symptoms (53, 54).
- Interferones (IFNs), when applied for other diseases, can induce MG symptoms in patients (55).
- Estrogens may lead to exacerbations of MG in assisted reproduction procedures (56, 57).

As mentioned above, the prescription of antibacterial agents from the group of aminoglycosides, fluoroquinolones, macrolides, sulfonamides and tetracyclines must be avoided.

Effect of Myasthenia Gravis Medications on Patients' Dental Status and Treatment

Most drugs that aim to relieve the symptoms of MG are classified as immunosuppressants and chemotherapeutics and suppress the formation of antibodies to AChR and MuSK. These include corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, etc.

Acetylcholinesterase agents—ACE inhibitors, which are the primary drugs in MG, have a major drawback in dental treatment, i.e., hypersalivation (58). This leads to an increased risk of choking and aspiration of saliva or other fluids during dental sessions (18). Other side effects of acetylcholinesterase agents are bradycardia, bronchoconstriction, and increased motility of the gastrointestinal tract (30).

Corticosteroids—prolonged use can lead to the development of osteoporosis, glaucoma, and hypertension, all of which are of particular relevance to dental surgeries. Bisphosphonate therapy is required for patients with osteoporosis (19). Prolonged use of corticosteroids suppresses the immune response and may lead to adrenocortical suppression. It can also delay the process of wound healing and trigger oral infections. These drugs should not be combined with methotrexate as its excretion is reduced and thus its toxicity is increased (30).

Cyclophosphamide is rarely used, mainly in MG patients unresponsive to other immunosuppressive agents, including infusion of IVIg (59). However, its side effects are quite serious and include myelosuppression, blood malignancies, etc., which affect the hematological status and interfere with surgical work (19).

Cyclosporine can affect patients' dental status by causing dose-dependent gingival enlargement, and difficult dental plaque removal (1). Unfortunately, due to the clinical characteristics of MG, patients find it difficult to maintain good plaque control and present with gingivitis and marked periodontitis (60). Its association with medications such as antimicotic agents (fluconazole, miconazol, erythromycin, vancomycin, etc.) can increase serum levels and lead to nephrotoxicity (30).

Azathioprine leads to myelosuppression and is highly toxic to the liver. Surgical treatments involving single or multiple tooth extractions, cystectomies, etc., can lead to complications such as prolonged bleeding. In a similar way to corticosteroids, it can delay healing of surgical wounds and lead to the development of serious infections, which in turn requires prophylaxis with antibiotic treatment (30).

Prolonged use of any immunosuppressive agents provokes oral candidiasis, fungal and opportunistic infections in the oral cavity but resorting to antifungal agents has been reported to worsen MG symptoms (61,62,63,64).

CONCLUSION

Myasthenia gravis is a serious and rare chronic disease. In order to avoid complications, some of which are life-threatening, it is of utmost importance to know its main symptoms as well as applicable medications in dental treatment.

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