Abstract: Myasthenia gravis is an autoimmune neuromuscular disorder characterized by fluctuating weakness and skeletal muscle fatigue. Clinical signs and symptoms may vary considerably according to the age at presentation, patterns of autoantibodies and associated thymic abnormalities, so that therapeutic options are highly individualized. Facial and oropharyngeal muscle weakness is common at disease onset, and therefore dentists are often the first health professionals to encounter these patients. Myasthenic patients require special consideration and advice in order to ensure optimal and safe dental treatment. Oral manifestations, treatment timing and modality, the choice and effects of drugs and medications, and prevention of myasthenic crisis are all important aspects with which dentists and oral health care providers should be thoroughly acquainted.

Keywords: myasthenia gravis; dental management; autoimmune disease.

Introduction
Myasthenia gravis (MG) is an autoimmune neuromuscular disorder, clinically characterized by fluctuating weakness of skeletal muscles and abnormal fatigue on exertion. The clinical manifestations and dental implications of MG have been described (1), but the dental management of patients diagnosed as having MG still presents a challenge to oral health care providers. The present communication covers current knowledge of MG, and details the clinical aspects of the disease that are relevant to the dental care of affected patients.

Epidemiology
Although MG can occur at any age and in either gender, it is diagnosed most frequently in women in their second and third decades; men tend to be affected in their sixth and seventh decades. The incidence rate varies between 1.7 and 21.3 per million inhabitants, with a prevalence ranging between 15 and 179 per million inhabitants (2).

Pathophysiology
In most cases the disease is caused by autoimmune attack against components of the neuromuscular junction (NMJ), on the postsynaptic membrane of striated skeletal muscles (3). In most patients, the autoimmune response is mediated by antibodies against the acetylcholine receptor (AChR), which reduce the number of functional AChRs through three possible mechanisms: direct destruction of the receptors, blockade of the acetylcholine binding sites, or complement-mediated damage (4). Classically, AChR antibodies have been found in 85% of MG patients, while the rest appear to be “seronegative” (5). However, in the last decade, “seronegative” MG has become increasingly rare with the discovery of antibodies against muscle-specific kinase (anti-MuSK) (6), antibodies against clustered AChRs detected in a sensitive cell-based assay (7) and, most recently, antibodies against low-density lipoprotein receptor-related protein 4 (Lrp4) (8). The role of the thymus in the pathogenesis of MG is highlighted...
by the presence of frequent histologic abnormalities such as thymoma and follicular hyperplasia, as well as by the clinical benefits of thymectomy (9). Fifteen to twenty percent of patients, usually those older than 40, have a thymoma caused by proliferation of epithelial cells (10). In 50% of patients younger than 45 years, typically females with the AChR antibody, the thymus is the site of follicular hyperplasia characterized by the presence of germinal centers (11).

**Signs and symptoms**

In over 50% of the cases, the initial presentation of MG entails weakness of the extraocular muscles, resulting in ptosis and diplopia. However, the disease remains restricted to the extraocular muscles in only 15-20% of patients (pure ocular form). In the remaining 80-85%, widespread weakness of other muscle groups occurs (generalized form), most commonly within the first two years after onset (3,12). As the disease progresses, facial and masticatory muscle weakness may appear, leading to dysphagia, dysarthria and the appearance of an expressionless face (13). Changes to phonation with a nasal quality may occur due to soft palate muscle weakness and impaired lip movement (14). The proximal limb muscles, the diaphragm and the neck extensors are also often affected. The severity of muscular weakness tends to fluctuate during the day, being less severe in the morning, and gradually worsening as the day progresses, especially after prolonged use of the affected muscles. Myasthenic symptoms can be worsened by emotional stress, systemic illness (especially viral respiratory infections), hypothyroidism and hyperthyroidism, pregnancy, the menstrual cycle, increased body temperature, drugs and medications affecting neuromuscular transmission (15). Severe involvement of the respiratory muscles may lead to myasthenic crisis, a life-threatening respiratory collapse requiring immediate treatment with mechanical ventilation. Myasthenic crisis occurs in about 15-20% of MG patients, among which 4-8% of cases are fatal (15,16). Infections, surgical procedures, drugs and emotional stress may predispose to myasthenic crisis (16). The most widely accepted classification for the clinical severity of MG is the Myasthenia Gravis Foundation of America Clinical Classification (17).

**Clinical characteristics**

Approximately 85% of MG patients have detectable serum AChR antibodies and can be categorized according to clinical features and pathogenesis into two sub-groups: early-onset MG and late-onset MG. Early-onset MG shows a clear female predominance (sex ratio 3:1). Both bulbar and limb/trunk muscles can be quite variably affected, with no evident correlation between symptoms severity and antibody titres. Thymic hyperplasia is frequently evident, and thymectomy is often an effective therapeutic option (3,5,9). The late-onset form, on the other hand, appears to show a male predominance (18), most patients presenting with severe symptoms and bulbar involvement (3). The associated presence of thymoma is well known (10) and other autoantibodies directed against ryanodine, titin and striated muscle are frequently found (3). Among “seronegative” MG patients, those with anti-MuSK antibodies (5% of the MG population) have key clinical features, being almost exclusively young women (19), often presenting with a severe form of the disease and showing a clear correlation between symptom severity and antibody titers (3,5). Facial, bulbar and respiratory muscles are frequently involved, while ocular involvement and thymic disease are rare (3). In these patients also, myasthenic crisis and respiratory failure are common (20). Approximately 50% of “seronegative” MG patients have antibodies against clustered AChRs detected by a cell-based assay and their clinical pattern is similar to the classic form of AChR MG (7). Lastly, the majority of myasthenic patients with Lrp4 antibodies (20-50% of “seronegative” MG) are female, ranging in age from 17 to 79 years and with clinical characteristics mostly resembling MuSK MG (5).

**Diagnosis**

From a clinical viewpoint, demonstration of weakness and fatigability of skeletal muscles, with improvement following rest is by itself diagnostic of MG (21). However, detection of serum AChR antibodies is considered to be the diagnostic gold standard. These antibodies are found in 80-85% of patients with generalized MG and in 50-60% of those with ocular MG (22). The diagnosis can also be confirmed by systemic administration of acetylcholinesterase inhibitors, such as neostigmine or edrophonium (“Tensilon test”), followed by an unequivocal improvement in an objectively weak muscle (23). Among electromyography studies, repetitive nerve stimulation is a commonly used technique for investigation of neuromuscular transmission. Albeit employed for diagnostic purposes in MG, its sensitivity can be quite low, especially for patients with mild symptoms (24) and in those with anti-MuSK+ MG (25). Single-fiber electromyography has instead demonstrated excellent sensitivity (over 90% of positive results) and should always be employed in the diagnostic pathway for MG (26).
Therapeutic options

Treatment for MG primarily consists of five options, three of which are pharmacological interventions that may have an impact on dental care (Table 1). Therapy, however, is highly individualized, and a number of factors such as the rate of disease progression, degree of functional impairment, patient age and distribution of muscle weakness, all influence treatment choices (27-29). Cholinesterase inhibitors are the first therapy of choice. These drugs inhibit breakdown of acetylcholine so it can accumulate at the NMJ. The drug most commonly prescribed, pyridostigmine bromide (Mestinon), is administered orally every 4-6 h at a dosage of 30-60 mg (4). Oral corticosteroids are also widely used in the treatment of MG and achieve significant improvement in up to 80% of patients; prednisone and prednisolone are those most commonly used. The adverse effects of high steroid doses can be minimized by the use of immunosuppressive agents such as azathioprine, cyclosporine, methotrexate and cyclophosphamide. Among the newer immunosuppressive agents, tacrolimus or mycophenolate mofetil, in conjunction with steroids or even as monotherapy, can also be effective.

Recently, a significant benefit in AChR+ patients and a dramatic benefit in seronegative anti-MuSK+ disease have been reported with the use of Rituximab, a monoclonal antibody directed against the CD20 epitope on B cells (30). Short-term immunotherapy using plasmapheresis or intravenous immunoglobulin is also a valid therapeutic option for rapid and temporary treatment of acute MG exacerbation (myasthenic crisis) (4). Since its introduction over 70 years ago by Blalock et al. (31), thymectomy has gained widespread acceptance in the management of MG, and is integrated with pharmacological treatment. Benefits from this operation have been reported, especially in patients with seropositive non-thymomatous disease, associated with thymic hyperplasia (32,33). Even in the absence of any thymus abnormality, the available evidence suggests that up to 85% of myasthenic patients experience significant improvement of symptoms and that 35% achieve drug-free remission (34). Beneficial effects of thymectomy have been reported to be maximized by complete removal of the thymus gland and any ectopic thymic tissue that may be scattered throughout the mediastinal and cervical fat (35). However, the role of thymectomy in older myasthenic patients, including those with the purely ocular form of MG, or all those who are seronegative, particularly anti-MuSK+ patients, is much less clear (30).

Dental management considerations

Myasthenia gravis may represent a challenging issue for dentists, oral health care providers, and also the patients themselves. Indeed, several important features of MG may significantly impact on the dental management of affected patients.

Relevant clinical aspects

The clinical manifestations of MG frequently include facial and oropharyngeal muscle weakness, especially at the time of onset. In this regard, dentists are in a unique position, as they may be the first health professionals to encounter patients with a potential diagnosis of MG. This is particularly true for anti-MuSK+ MG, where bulbar symptoms (weakness of the muscles inner- vated by the lower brainstem) are often predominant, although they can be variably present in every form of MG (3). Therefore, being familiar with the disease and having a thorough knowledge of its pathophysiology is of paramount importance. As reported and evaluated by Weijnen et al. (36), patients with bulbar symptoms (weakness of the muscles innervated by the lower brainstem) are often predominant, although they can be variably present in every form of MG (3). Therefore, being familiar with the disease and having a thorough knowledge of its pathophysiology is of paramount importance. As reported and evaluated by Weijnen et al. (36), patients with bulbar symptoms may complain of poor masticatory performance. As a result of masseter weakness, chewing can become progressively difficult with increasing discomfort (“jaw claudication”) so that patients are forced to stop and rest during meals (34). In severe cases, they may need to support their lower jaw while eating in order to allow mastication and between meals to prevent spontaneous dropping of the jaw and opening of the mouth (37,38). Chewing difficulty, fatigable reduction in biting force, inability to close the jaw and weak jaw closure are thus typical of MG patients (34,39), occurring in at least 4% of cases (40). Therefore, dentists should be particularly aware of these clinical presentations, as they may be able to pick...
up early signs of the disease. Examining a patient who has difficulty in opening the mouth or keeping the jaw open may be aided by the use of a mouth prop, as this helps to reduce stress on the masticatory muscles (38). When using a mouth prop, ensuring efficient suction is mandatory to avoid aspiration of oral debris (38). The mouth prop can also be removed periodically to allow the patient a rest break, and overstretching should be avoided. Possible differential diagnosis between MG and temporomandibular joint dysfunction in patients with limited mouth opening should also be taken into consideration. Application of an occlusal splint in a myasthenic patient may in fact induce masticatory muscle fatigue and exasperate symptoms. Additional concerns should also be addressed in elderly patients. It is well known that severe limitations of masticatory performance, together with chewing and swallowing difficulties, may lead to malnutrition and weight loss in MG patients (37,38). However, feeding and swallowing difficulties as well as malnutrition can be common findings in the geriatric population, mostly due by poor appetite (41), stroke (42), neurological disorders (43) or dentition status (44,45). Despite its increased incidence in older adults (18), it is important not to overestimate MG. Lastly, in myasthenic patients, dentists may notice a typical, furrowed and flaccid clinical appearance of the tongue, resulting from lipomatous atrophy, triple longitudinal furrowing (myasthenic tongue) being observed only in severe cases (37,38).

Dental care for myasthenic patients
The provision of dental treatment for patients with MG requires special management considerations, as well as advice and precautions with which all oral health care specialists should be sufficiently acquainted. A complete review of the patient’s symptoms and an assessment of phonation and swallowing should be done prior to any treatment (46). Simple methods for assessing the degree of disease control and the severity of symptoms include evaluating the length of time the patient is able to look up before ptosis develops and the period of time the patient can maintain outstretched arms (46). These assessments should be conducted regularly, and any changes in symptom severity should be reported to the treating physician (46). If concern arises about a patient’s ability to breathe adequately, spirometry is a useful examination for assessment of respiratory muscle function (47). In recent years, several patient-oriented questionnaires have also been proposed for evaluation of MG patients in daily clinical practice (48-50). It is important to stress that in most instances, myasthenic patients have stable and well controlled disease with limited or mild neuromuscular involvement, so that routine dental treatments and minor procedures (root canals, fillings etc.) can be performed safely within the setting of a private dental office. A hospital-based dental clinic, with emergency intubation and respiratory support facilities, would otherwise be chosen when treating patients with severe MG symptoms, those with serious anxiety, and also when more significant oral surgery (multiple extractions, wisdom tooth extractions etc.) is planned (38). If the patient’s recent medical history is consistent with frequent exacerbations, severe bulbar and respiratory symptoms and generalized weakness, the dentist should consult the patient’s physician and a neurologist, as additional therapy may be recommended prior to treatment, especially for significant oral surgery (37,38) (Fig. 1). In all cases, multiple and short early morning appointments are preferable, in order to avoid cumulative muscle weakness, and also to take advantage of the greater muscular strength typically noted during morning hours (1). Oral anticholinesterase drugs should be preferably administered 1.5 h before dental treatment to achieve maximum effectiveness during the dental session (37,38). Emotional stress is a known risk factor for myasthenic crisis. In order to avoid it, the patient should be allowed to arrive and rest for a while prior to dental appointment, possibly in a peaceful and relaxing environment (37,38). Establishing an open and friendly relationship between the patient and the dental staff would also help to reduce emotional stress (37,38). It is also important for all necessary equipment and supplies to be set up and prepared before starting the dental session, to assure efficiency and optimization (38). Positioning on the dental chair during treatments should be carefully taken into consideration as well, especially in MG patients with bulbar symptoms. A comfortable, semi-upright position rather than a deep recline is preferred, in order to reduce the risk of closing the throat or regurgitating saliva and other fluids. Indeed, failure of the supraglottic constrictors to properly seal the laryngeal inlet, in conjunction with increased salivation often caused by anticholinesterase drugs, creates a higher risk of aspiration of saliva and oral debris (38). Isolation of the working field with a rubber dam is recommended, and good oral evacuation suction is imperative to rapidly remove all dental debris and avoid aspiration (37,38). Resting periods should be allowed during the dental session, and it is of great importance that the patient remains seated until all oral debris and fluids have been removed and muscular strength is well controlled (37).
Drugs and medications in the dental care of myasthenic patients

Many common drugs used in dentistry may lead to possible complications in MG patients by exacerbating muscle weakness or interfering with breathing (1,37). Dental procedures may require sedation to reduce anxiety and avoid emotional stress. In this setting, the use of benzodiazepines, hypnotics and barbiturates should be avoided since these drugs may lead to respiratory depression, worsening of myasthenic symptoms and myasthenic crisis (1,34,38). Nitrous oxide-oxygen sedation has instead been reported to be safe (1,37,38).

Pain control is also of prominent importance. Acetaminophen, aspirin, and non-steroidal anti-inflammatory agents do not affect neuromuscular transmission, metabolism and acetylcholine release, and can be administered safely to MG patients (1). On the other hand, morphine and other opioids may cause respiratory depression, and their use should be avoided (37).

Local anesthetics decrease the postsynaptic membrane’s sensitivity to acetylcholine and may worsen weakness in MG patients (51), so that careful attention should be paid to their usage. Ester-type local anesthetics like procaine are to be avoided. In fact, ester anesthetics are inactivated by plasma cholinesterase and, in myasthenic patients receiving anticholinesterase drugs, their

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Table 2: Drugs used in dentistry that may impact on myasthenia gravis

Fig. 1 A suggested decision-making flowchart for planning of dental treatment in myasthenic patients.
Cyclosporine can cause dose-dependent gingival overgrowth, leading to an increased risk of systemic toxicity (1,51). Amide-type anesthetics (lidocaine, mepivacaine) are instead metabolized by the liver (52) and should be considered the option of choice in view of their shorter duration and the rarity of their side effects; intravenous injection should be avoided (1,38). Combination of a vasoconstrictor such as 1:100,000 epinephrine with the anesthetic agent is advantageous for both maximizing the efficacy of anesthesia and minimizing the anesthetic dose (1,38). The dosage can also be reduced using local infiltration and the intraligamentary or intrapulpal injection technique, rather than nerve blocks (1,38). Due to swallowing problems, bilateral mandibular blocks should be avoided (38).

Certain antibiotics may cause muscle weakness due to their ability to produce partial neuromuscular blockade by inhibiting the release of acetylcholine from the presynaptic membrane (38). Aminoglycosides (gentamicin, streptomycin, amicacin, neomycin, kanamycin) must be avoided as they are known to cause clinically significant muscle weakness by blocking presynaptic voltage-activated calcium channels (53). Myasthenic crises have been documented after administration of fluoroquinolones (54), and they should not be used. The hypothesized mechanisms responsible are either blockade of the acetylcholine receptor or direct toxicity, and these effects are known to be dose-dependent (55). Sporadic worsening of myasthenic symptoms have been reported for macrolides and tetracyclines (38), while the ketolide antibiotic telithromycin (reports of fatal myasthenic crisis) is absolutely contraindicated (55-57). Penicillins, cephalosporins, sulfonamides and carbopenems have instead been widely used in MG patients and can be administered safely (34,37,38), with only occasional and uncertain side-effects reported (58,59).

**Dental implications of anti-myasthenic treatments**

Cyclosporine can cause dose-dependent gingival overgrowth, especially if dental plaque or other local irritants are present, and this may lead to gingival and periodontal disease. A number of medications, such as vancomicine, ketoconazole, and fluconazole, are also contraindicated because of their synergistic toxic effects (1,38). Anticholinesterase agents are the mainstay of treatment for MG, and hypersalivation is one of their main drawbacks (60). This is of importance since, in addition to the previously mentioned increased risk of aspiration of saliva and oral fluids during dental sessions (38), excess salivation and drooling may also result in supragingival calculus formation.

Prednisone and other immunosuppressive agents such as azathioprine are widely employed in the treatment of MG, often with good results (61). However, corticosteroids and immunosuppressants may have an unfavorable effect on the immune system’s efficiency (61). Furthermore, both thymic follicular hyperplasia and thymomas are associated with complex dysregulation of the immune system due to dysfunctional T cells and a cytokine-related pro-inflammatory environment (62,63). As a result of these intricate immune networks, MG patients (especially those with thymic abnormalities and those receiving high-dose steroids) have an increased risk of opportunistic infections such as chronic mucocutaneous candidiasis, oral infections and delayed wound healing (38). Prophylactic antibiotic therapy should always be considered for dental procedures. Lastly, as mentioned previously, plasmapheresis may be recommended prior to significant oral surgery in patients with severe myasthenic symptoms (37,38). Since the plasma exchange protocol entails the use of anticoagulants (heparin or acid-citrate-dextrose solutions), the dental procedure should be scheduled on a non-exchange day (38).

**Prevention**

Patients should be properly instructed in good preventive oral care and dental hygiene at home, underlining the importance of this aspect at every dental appointment (38). Oral musculature dysfunction, and weakness of the upper extremities and hand muscles (weakened grasp, wrist and finger extensors) are common findings that may all create challenges to oral self-care (38). Consequently, personal dental hygiene may be impaired, increasing the risk for oral infections. Patients should be encouraged to perform regular brushing using an electric toothbrush or a manual toothbrush with a modified handle to reduce muscle fatigue (38). Use of a tartar control toothpaste might be recommended to facilitate control of excess calculus deposition. Chlorhexidine or a fluoride mouth rinse to prevent decay and periodontal disease can also be used safely by MG patients.

**Myasthenic crisis**

If exacerbation of myasthenic symptoms occurs, the oral health care provider and the dental staff should be able to promptly evaluate the severity of neuromuscular involvement and eventually treat the crisis. An open airway and adequate respiratory exchange must be established in cases of respiratory collapse (38). High-speed suction should be used to rapidly remove oral fluids from the oropharynx, in order to prevent aspiration and mechanical blockage of the airway. Steps to prevent a
weakened tongue from rolling backwards and causing airway obstruction should be taken by manual retraction of the tongue using a tongue retractor. Cardiopulmonary resuscitation may be required, and it is mandatory for the dental staff to be prepared and trained in basic life support (38). Of course, collaboration with a nearby medical facility is a key point when dealing with myasthenic patients (38).

Conclusions
Myasthenia gravis is a chronic neuromuscular disease characterized by weakness and fatigability of skeletal muscles, with improvement following rest. The head, neck, and oral regions can be severely affected, making patients with MG a challenge to the dental profession. Meticulous attention to clinical signs and symptoms, medications, the timing and modality of treatments, and patient’s emotional stress is required. A complete understanding of the pathophysiology of the disease and its clinical features is vital in order to recognize and adequately treat myasthenic exacerbations. Dentists should be aware of all the clinical aspects implied in the dental management of patients suffering from MG.

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