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Myasthenia Gravis with Anti-MuSK Antibodies: Clinical Features and Histopathological Changes

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1. Introduction

Myasthenia gravis (MG) is a neuromuscular autoimmune disorder caused by binding of autoantibodies to molecules involved in neuromuscular transmission: acetylcholine receptor (AChR) and muscle specific tyrosine kinase (MuSK). It is characterized by a fluctuant weakness.

The most typical feature is a painless, variable weakness of skeletal muscles that worsens with exercise and improves with rest. It may involve different muscles and frequently the presenting symptoms are ptosis and/or diplopia due to the involvement of extraocular muscles. MG diagnosis is based on a detailed clinical history, on pharmacological test and on the measurement of antibodies against the Acetylcholine receptor (AChR-Ab). Some MG patients do not have detectable AChR-Ab and have been defined as “seronegative” (SNMG) (Vincent 2004). A high proportion of these patients have purely ocular symptoms (ocular MG). Seronegative generalized myasthenia is proving to be heterogeneous on clinical, immunological and histopathological features. A variable proportion of SNMG patients has antibodies against MuSK. These antibodies are directed against the extracellular domain of MuSK and inhibit the agrin-induced AChR clustering in muscle myotubes. Although the role of these antibodies in causing myasthenic symptoms in vivo is not still clear, MuSK antibodies appear to define a group of patients.

2. Pathophysiology

The neuromuscular junction (NMJ) is the communication between nerve and muscle where the electrical nerve impulse is translated into an electrical stimulation to initiate muscle contraction [1]. Acetylcholine (ACh) acts as the chemical messenger between the nerve fibre and the postsynaptic muscle membrane. ACh is released into the synaptic cleft on nerve depolarization and rapidly diffuses to bind to ACh receptors (AChRs). AChRs can be either nicotinic or muscarinic. The nicotinic AChR is a multimeric protein comprised in adults of two α subunits and one each of β , δ , and ϵ subunits. The nicotinic AChR is a multimeric protein made of two α subunits, which in turn are made of β , δ , and ϵ subunits. Each α

subunit has a binding site for ACh. Muscle-specific tyrosine kinase (MuSK) is an AChR-associated protein involved in clustering of AChR during synapse formation and is expressed in the mature NMJ [2].

Autoimmune disorders result from the loss of tolerance to self-antigens. In the case of myasthenia gravis (MG), an autoimmune disorder characterized by clinical fatigable weakness, the body raises an autoimmune attack on its own muscle endplate, initiated by antibody binding to AChR or, less frequently, to MuSK, resulting in abnormal neuromuscular transmission and muscle weakness.

Approximately 80% of patients have detectable serum antibodies against AChR that reduce AChR number and impair their function at the neuromuscular endplate. About 15-30% of MG patients do not have detectable AChRAb and are defined as *seronegative*. These patients may have purely ocular symptoms but a small proportion has generalized weakness. About half of seronegative MG cases has antibodies against a muscle-specific tyrosine-kinase protein (MuSK-Ab). The role of MuSK-Ab in the pathogenesis of MG is still unclear. These antibodies probably impair neuromuscular transmission, as MuSK protein plays a critical role in postsynaptic differentiation and in AChR gene expression [3]. MuSK is a transmembrane polypeptide selectively expressed in skeletal muscle. It is part of the agrin-receptor, an essential protein in building the neuromuscular synapses. Experimental data show that agrin-induced activation of MuSK by tyrosine phosphorylation results in aggregation and expression of specific muscle proteins, AChR included, and in AChR phosphorylation [4]. Anti-MuSK serum antibodies may bind the external domain and reduce the agrin-induced expression of AChR in myotubes in vitro [5]. Selcen et al. Demonstrated in a single patient on intercostal muscle biopsy, that MuSK-Ab do not cause a reduction of MuSK or AChR in neuromuscular plate [6], but its presence in the neuromuscular junction causes a 20% decrease of AChR-clusters and a decrease of agrin-induced AChR-clusters according to study in all patients [7]. MuSK-Ab also do not cause internalization of AChR, as demonstrated in AChR-Ab MG [7].

The thymus is a critical organ for T-cell education and elimination of auto-reactive T-cells, and plays a major role in MG. Thymic abnormalities are frequently present in MG, including hyperplasia in about 65% of cases and thymoma in 10%. The expression of AChR by myoid cells in the thymus plus the inflammatory environment within the MG thymus, contribute to the induction and maintenance of the anti-AChR autoimmune response [8].

3. Epidemiology

MG used to be considered a rare disease, however incidence and prevalence rates have increased over time, partly as a result of increased of diagnosis, and results of prolonged survival with the disease for new improvement protocol of patients [9]. the current incidence rates range from 9–21 per million population, with prevalence rates of 50–125 cases per million population worldwide.

The onset and incidence of MG is influenced by age and gender and MG was first thought to be a condition of the young female and old male. Epidemiological data show that women are most frequently affected than men; age at onset in MG patients with MuSK-Ab occurs predominantly before 40 years, at a younger age than MG cases with AChR-Ab [9]. Women

are frequently more affected than men [10; 11]. Recent reports indicate that MG may be under-diagnosed in the elderly [12].

4. Clinical features

Patients with MG present weakness in specific muscle groups. The main feature is a fluctuant variable weakness of skeletal muscles that worsens with exercise and improves with rest. The onset in about the 65% of patients is characterised by ocular symptoms, such as ptosis and diplopia, the remaining 25% of patients shows bulbar weakness, resulting in slurred or nasal speech, voice alterations or difficulty in chewing or swallowing. Limb weakness is a less common initial complaint [13; 14]. The degree of weakness may vary during the day, but, generally it worsens with exercises and improve with rest.

The progression of muscle weakness in MG usually occurs in a craniocaudal direction, beginning with ocular, facial, lower bulbar muscles, and progressing to torso and limb muscle involvement. Maximal weakness occurs within the first year following the onset of the disease in approximately two-thirds of the cases [15; 16]. Up to 50% of patients who presents ocular MG will progress to generalized MG within 6 months, rising up to 80% within 2 years [14].

However, in around 10–40% of cases, muscle weakness remains restricted to the ocular muscles. [13]

MG with anti-MuSK-Ab has a different phenotype from the remaining seronegative MG; in most of the cases symptoms at onset includes nasal voice, weakness of facial and limb muscles and respiratory muscles [17; 16]. Patients can show a severe predominantly facio-bulbar weakness with dyspnea and nasal speech; dysphagia sometimes is so severe that it leads to an important weight loss. In some cases, only ocular muscles can be affected [18]. A significant association between bulbar/facial muscles weakness and muscular atrophy has been described in MuSK-positive patients [7], this could justify the selective and typical bulbar involvement.

MG remains a challenging disease to diagnose due to its fluctuating character and to the similarity of symptoms to those of other disorders; the mean time to diagnosis is often over 1 year [13; 14]. Seronegative MG with anti-MuSK antibodies still remains a diagnostic challenge, because of its fluctuating character and the similarity of symptoms to with other disorders. Mean time to diagnosis is often over 1 year [13; 14]. The diagnostic value of neostigmine or edrophonium test and repetitive stimulation is low [15], while single fibre EMG has very high sensitivity.

MG with MuSK-Ab is responsive to standard therapy, but needs higher drug dosages than MG AChR-Ab positive [19], MuSK-positive patients frequently develop hypersensitivity to anticholinesterase drugs [15]. Instead, seronegative MG without MuSK-Ab seems to have a similar or less severe clinical course than seropositive ones and a similar response to pharmacological treatment [20].

5. Treatment

The treatment of MG includes both a surgical and a therapeutic approach.

Thymectomy is currently performed in patients with thymoma (usually by median sternotomy) and in generalized AChR-positive MG (cervicotomy, VATS, VATET), where it appears to increase the rate of remission. In MuSK-positive MG, thymectomy is generally thought to be of less value and the question of whether it has a role in the disease treatment is controversial. This opinion is based on clinical reports and morphological studies. These studies [17, 19], even if performed in small patient series and presenting potential confounding factors such as the effect of immunosuppressive treatment and the inclusion of patients with different disease severity and duration, have altogether failed to show a better outcome in thymectomised than in unthymectomised MuSK-positive patients, both in terms of remission rate and need for immunosuppressive therapy.

Drugs: Symptomatic drugs, such as anticholinesterase, are generally well tolerated and represent the first-line treatment in most patients, they can improve muscle strength in a minority of cases [21]. Immunosuppressive therapy is indicated for patients with symptoms not controlled with acetyl-cholinesterase inhibitors. Different drugs have been used alone or in combination: corticosteroids, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus, and rituximab [21] (Table I). In the AChR-positive disease, immunosuppressive therapy is highly effective. Short-term treatments, such as plasma-exchange (PE) and intravenous immunoglobulin (IVIG), are used to treat patients with severe, rapidly progressing disease. The response to therapy in MuSK-positive MG patients seems to be different from that in AChR-Ab positive. In MuSK-positive MG the response to anticholinesterase is generally unsatisfactory. A general impression is that MuSK MG patients fare worse than AChR-Ab-positive patients [22]. This impression is based on the remission rate. When comparing therapeutic results in MuSK-MG and AChR-MG in a meta-analysis, Evoli et al.[17] found a significant difference in remission rates: 10%–35% in MuSK-MG versus 24%–58% in AChR-MG. Because of the disease severity and the poor response to acetyl-cholinesterase inhibitors, the majority of MuSK-positive patients require immunosuppressive therapy [22].

6. Histopathological changes in muscles and thymus

Thymus pathology in MuSK-positive patients is not so far available because of the relatively minor incidence of this subgroup in the population of myasthenic patients. MG is initiated within the thymus by immunogenic presentation of locally produced nicotinic acetylcholine receptor (AChR) to potentially autoimmune T cells [23]. Because the thymus is the central organ for immunological self-tolerance, it is reasonable to suspect that thymic abnormalities cause the breakdown in tolerance that causes an immune-mediated attack on AChR in myasthenia gravis. The thymus contains myoid cells that express the AChR antigen, antigen presenting cells, and immunocompetent T-cells. Thymus tissue from patients with myasthenia gravis produces AChR antibodies when implanted into immunodeficient mice. However, in AChR-negative/MuSK-positive MG, the thymus does not appear to play such an important role in the pathogenesis as it is thought to play in non-thymoma seropositive MG [24].

Pathological studies often demonstrate thymic hyperplasia in AChR-Ab positive and in AChR-ab negative/MuSK-negative patients. In contrast, in the thymuses from MuSK-positive patients, lymphoid follicles with germinal centres are not found and the perivascular space harbors amounts of lymphoid cells are significantly less than in the

Table I. Clinical characteristics and therapy efficacy in MuSK-positive MG

Pt. Sex	Age at onset	Age at last follow up	Years of disease	MGFA score at onset	Thymectomy	Muscle biopsy	Therapy	
							ACH	STER
1 F	43	49	6	II a	Robotic Thymic atrophy	+	X	X
2 M	27	45	17	III b		+	X	X
3 F	34	39	5	IV b	Robotic Hyperplasia	+	X	X
4 F	24	30	6	II a			X	X
5 F	50	50	1	II b	Sternothomy Hyperplasia	+	X	X
6 F	22	44	21	III b		+	X	X
7 F	41	46	5	IV b	VATET Hyperplasia	+	X	X
8 F	45	53	8	II b		+	X	X
9 F	45	46	2	III b			X	X

* ACh. anticholinesterases; STER. Steroid; IM. Immunosuppressive drugs; PE. Plasma exchange

^ AS asymptomatic

AChR-Ab patients. Thymus changes in these cases resemble those in normal aging [25]. Thymectomy often results in clinical improvement in AChR-Ab positive patients, suggesting a role for the thymus in the initiation or propagation of the autoimmune attack on the myocyte. The role of thymectomy in MuSK-positive MG remains uncertain. Recent studies reported no reduction in immunosuppressive therapy or reduction in MuSK antibody titres following thymectomy, and no difference in clinical status between MuSK MG patients with or without thymectomy [17].

Diagnosis procedure in Myasthenia gravis and muscle biopsy morphology

The diagnosis of MG is based on clinical, laboratory and instrumental procedures; muscle biopsy is performed only to exclude alternative diagnosis therefore the number of muscle biopsies available is limited. Muscle biopsy of intercostal muscles is mostly used in congenital myasthenia. The biopsied muscles are usually the limb muscles (quadriceps, deltoid) thus the pathology could be different in bulbar muscles that can't be examined.

The muscle biopsies of AChR-Ab positive patients show focal and usually non-specific changes. They include atrophy of type 2 fibers, and sometimes atrophy of type 1 fibers, and rarely the presence of small angulated fibers and fiber type grouping, suggestive of denervation [26]. Ultrastructural images of endplate show the presence of reduced folds of the junction, and debris from them accumulates between the nerve and the muscle membrane. Complement and immune complexes can be demonstrated on the post-synaptic membrane, as well as the binding of autoantibodies in the serum from affected patients to neuromuscular junction has been observed. In the past no study was done to study electron microscopy or histopathology of MuSK positive biopsies. In our study [27], we analysed muscle biopsy of 13 myasthenic patients (8 women and 5 men), whose diagnosis was based on standard criteria. Seven patients were positive for AChR-Ab (serum AChR-Ab > 0.25 nmol/l) and six positive for MuSK-Ab and negative for AChR-Ab. Our findings reveal that MG associated with antibodies against MuSK and MG associated to AChR-Ab show different histopathological features. Atrophy factor in skeletal muscle biopsies is higher for both type I and type II fibers in AChR-Ab positive cases: this feature agrees with the observation that the disease affects more severely the limb than the bulbar muscles (Figure 1). Atrophy of type II fibers might be explained by a reduced muscle strength and disuse atrophy in both groups of patients. Skeletal muscle fibres of MuSK-positive cases are relatively preserved by atrophy, and this could be due either to a focal action of MuSK antibodies or to the fact that bulbar muscles are the only one partially susceptible to MuSK antibodies. In this study we observed prominent signs of mitochondrial involvement, such as COX-negative fibers or mitochondrial aggregates and myofibrillar disarray, in MuSK-positive patients, indicating that mitochondrial function could have a role in this disease (Figure 2). The presence of several COX negative fibers in patients under 40 years can be regarded as abnormal, since SOX fibres are not usually seen until after 50 years. In contrast, AChR-Ab positive showed only mild and unspecific myopathic changes, but often muscle fibre atrophy and few aggregates of normally shaped mitochondria were observed.

The ultrastructural study of biopsy from MuSK-positive patients [27] confirmed the pattern of severe myopathic changes, such as swollen mitochondria, myofibrillar loss, and sarcoplasmic reticulum lipid vesicles associated with enlarged mitochondria with electronlucent matrix and fragmented cristae [28]. Mitochondria are aggregated both in the subsarcolemmal and intermyofibrillar areas (Figure 3), adjacent to normal mitochondria.

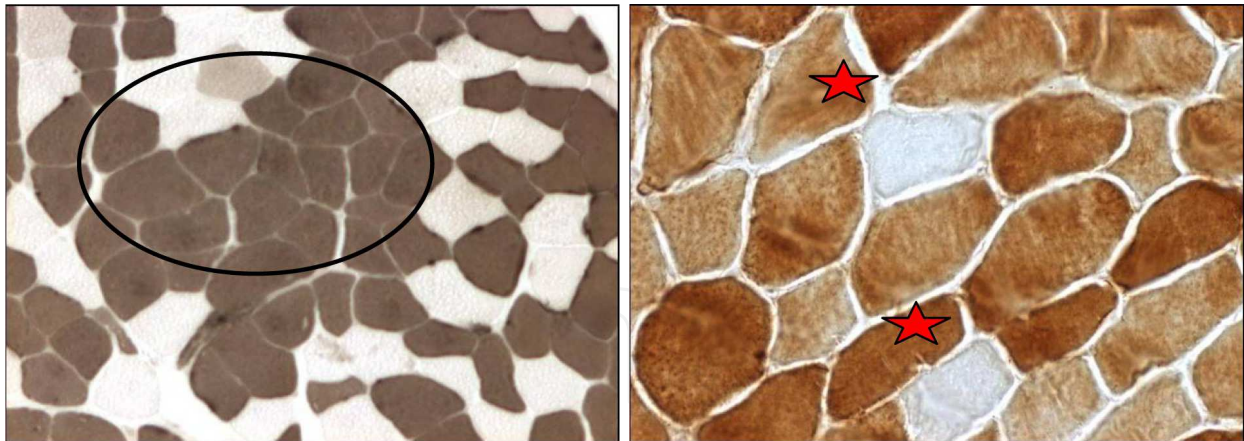


Fig. 1. Light microscopy. Acid ATP-ase stain shows type I fibre grouping in one AChR-Ab patient
 Fig. 2. COX stain shows 2 COX-negative fibers (star) in one AChR-Ab patient.

Ultrastructural studies show also that MuSK-positive cause a 20% decrease of AChR number on the surface of the postsynaptic membrane, clusters of AChR in MuSK-positive patients appear larger than in AChR-Ab positive cases, and this could be due to cluster dispersion induced by MuSK antibodies (Figure 4). These antibodies cause a decrease of AChR agrin-induced expression [2, 4]. The presence of fiber type grouping in many AChR+ patients might be explained by blockage of AChR receptor binding that causes the internalization and degradation of AChR and consequently a denervation of affected muscle [29]. Fiber type grouping in cases with anti-MuSK-Ab is less frequently observed. In a recent study of Rostedt Punga *et al.* [30] deltoid muscle of 10 MuSK+ and 40 AChR+ patients were compared. They analyzed mtDNA in the cases that presented histological mitochondrial

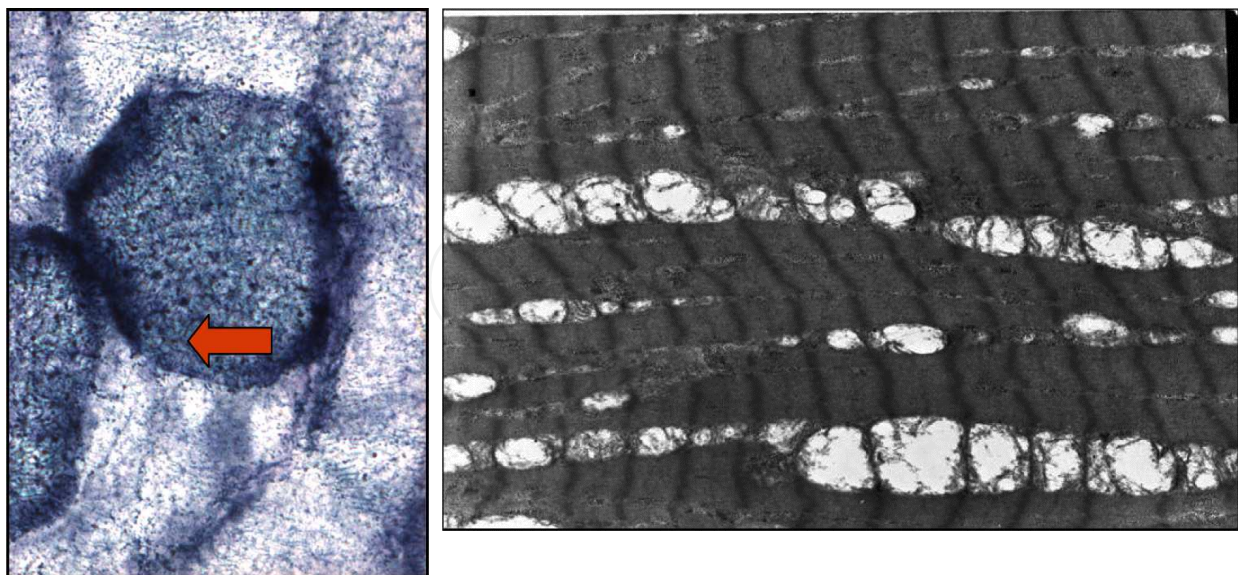


Fig. 3. NADH-TR stain. Subsarcolemmal mitochondrial rims in one MuSK-positive patient

Fig. 4. Swelling of mitochondria and cristae disruption in MuSK-positive. Dense mitochondria were disposed perpendicular to the sarcomeres

abnormalities at muscle specimens, and they found frequent deletions in mtDNA, supporting the morphological date.

In conclusion, atrophy could be due to a functional denervation in AChR-Ab positive patients while, in MuSK-positive patients, there are mild myopathic changes with prominent mitochondrial abnormalities.

Clinical aspects, electrophysiological tests, immunological presentation, thymus pathology and the therapeutic response implicate that MG MuSK-positive is a specific subgroup of seronegative MG, and has to be analysed as a peculiar muscle pathology. Treatment and diagnosis, as well as prognosis and surgical approach is different in MG with MuSK-Ab. The clinician should be alerted of this different features and have a different approach to this type of myasthenia gravis.

7. Anti-MuSK patients in clinical practice

In our Neuromuscular Centre Database we collected 279 MG patients: 171 female and 108 male. AChR-Ab were positive in 143 patients positive (51%). Among the 97 seronegative patients (35%) only 46 (16%) presented a generalized MG: MuSK-Ab were positive in 9 of them (19%).

Diagnosis was based on standard criteria [13,31], including symptoms of fluctuating muscle fatigue, supported by an electromyographic pattern (repetitive nerve stimulation). Patients were periodically examined at the Neuromuscular Diseases Centre, University of Padova. MG classification had been performed according to the Myasthenia Gravis Foundation of America. MGFA class I includes only ocular onset; class II includes mild generalized onset; class III includes moderate generalized onset; class IV includes severe generalized fatigue; class V patients need intubation. For classes II-IV, a further classification in subclass 'a' indicates prevalent limb muscle involvement, while subclass 'b' includes patients with predominant bulbar muscle involvement. Muscle strength was determined using MRC score (Medical Research Council) of every biopsied muscle at time of diagnosis. MRC score: 5 - normal force, 4 - movement against gravity and resistance, 3 - movement just against gravity, 2 - movement is possible just in absence of gravity, 1 - muscle contraction is visible but no movement is seen and 0 - no contraction is visible. Plus and minus indicates an intermediate degree of muscle strength. The clinical data collected included: age at onset, sex, therapy assessment and muscle strength conditions at the time of diagnosis.

The MuSK-positive patients were 8 females and one male with a mean age at onset of 47 ± 19.7 (Table I). At onset 2 of them presented generalized symptoms and were both in II-a MGFA score class; 7 (78%) presented bulbar symptoms: 2 were in class II-b, 3 in class III-b and 2 in class IV-b of MGFA score. Four (44%) were thymectomised: one had a thymic atrophy and 3 (75%) thymic hyperplasia.

Biopsy was done in seven patients at the time of MG diagnosis. Histopathological investigations were performed blind to the patient's clinical status. Muscle biopsies of patients were collected after informed consent; all procedures were conducted after obtaining the approval from the University Review Board.

At the last follow-up visit, after a mean duration of disease of 10 years, six patients were improved: two patients were asymptomatic, four were in class II-b. Two patients were

unchanged and only one got worse. Corticosteroids associated with anticholinesterases were sufficient only in one patient; 8 (89%) needed an additional treatment with immunosuppressive drug: four used azathioprine and had to change therapy for unsatisfactory response to the first-one: three pass to cyclosporine and one to mycophenolate mofetil. One patient used cyclosporine since MG onset. Eight patients (89%) were treated with IVIG and had a clinical improvement. PE was used in three patients, with a minor response.

Agent (trade names)	Initial dose	Maintenance dose	Onset of action
Prednisone	15–20mg q.d., Increasing by 5–10mg q2–3 days	1.5 mg/kg/day, followed by slow alternate day taper (taper by 5–10mg a month)	2–4 weeks
Azathioprine	50mg q.d. *	Increase by 50mg increments q 2–4 weeks to target of 2–3 mg/kg	2–10 months for initial response, up to 24 months for peak
Cyclosporin	100mg b.i.d. ^	Increase slowly as needed to 3–6 mg/kg on b.i.d. schedule	1–3 months
Mycophenolate	500mg b.i.d.	1000–1500mg b.i.d.	2–12 months
Cyclophosphamide	3–5 mg/kg/day, can be preceded by intravenous pulse	2–3 mg/kg a day	2–6 months
Tacrolimus/FK-506	3–5 mg/day or 0.1 mg/kg/day	Increase up to 5–7mg a day following dosage of plasmatic levels	1–3 months
Rituximab	375 mg/m ² IV every 1–2 weeks for 4 weeks	None or 375 mg/m ² every 4–10 weeks for a few months	1–3 months
Etanercept	25mg s.c. ° twice weekly	25mg s.c. twice weekly	2– months

^ b.i.d., twice daily;

* q.d., daily;

° s.c., subcutaneous

Table II. Commonly used immunosuppressant agents for myasthenia gravis

8. Case Report

A 36 years-old woman presented 2 years history of progressive dyspnea and fatigue. She complained of diffuse weakness. She had no complaint for pain or cramps but noticed an increased difficulty in climbing stairs. She had a nasal speech, but denied diplopia and ptosis. She had lost 40 kg for a progressive and severe difficulty in swallowing solid food.

Past medical history was positive only for a hiatus hernia and esophageal gastrointestinal reflux. EMG, brain MRI and mediastinal CT gave normal results. Pneumological evaluation showed a high breathways obstructive pattern.

Examination revealed normal vital signs: her gait was slow; strength testing revealed mild weakness in triceps (4+/5), deltoid and brachioradialis (4/5), gastrocnemius (5-/5) and in orbicularis oculi et oris. Extensive auto-immunity battery examination gave normal results, except for the research of anti-MuSK antibodies, that were positive. Pneumological evaluation showed a slight restrictive pattern.

Logopedic evaluation documented dysphonia and slowed deglutition. There was a depressive psychological profile. Electrodiagnostic studies with repetitive nerve stimulation were normal. Muscle biopsy revealed atrophy of muscle fibers, minicores and mitochondrial alterations. Treatment with trazodone and tocopherol was started. Despite this treatment, her condition worsened because of persistent dysphagia and rhinolalia; respiratory insufficiency became so severe that she needed a mechanical assisted ventilation during the night. IVIg and cyclosporine reversed her condition and brought a permanent improvement.

The final diagnosis was: MuSK-positive myasthenia with anorexia and ventilatory insufficiency.

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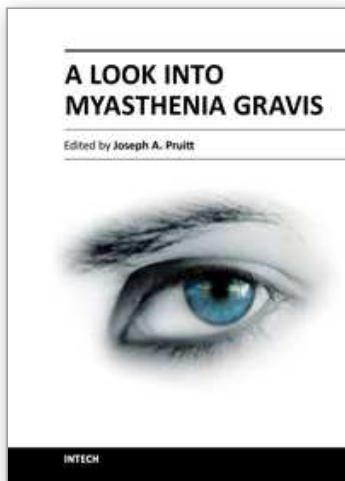
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A Look into Myasthenia Gravis

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Myasthenia gravis is presently an incurable antibody-mediated autoimmune disorder characterized by generalized voluntary skeletal muscle weakness. The cause of the weakness is a defect at the neuromuscular junction level, in which autoimmune antibodies block the receptors responsible for initiating muscular contraction. Literally translated from its Latin and Greek etymological roots, myasthenia gravis means "grave muscle weakness". Fortunately, advances in modern medicine have resulted in a reduction of the truly "grave" outcomes for those inflicted but, without a cure, the gravity surrounding the disease remains

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