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Is paravertebral muscles edema a consequence of neurogenic changes in MuSK-positive myasthenia gravis?

Sergey N. Bardakov¹, Vadim A. Tsargush¹, Pierre G. Carlier²,
Tran Minh Duc¹, Andrey Yu. Emelin¹, Alexey Yu. Polushin³,
Alexander A. Emelyantsev¹, Andrey N. Belskikh¹,
Ekaterina N. Berezhnaya⁴, Sergey V. Lapin³, Anna N. Moshnikova³,
Roman V. Deev^{4,6}

¹ S.M. Kirov Military Medical Academy, St. Petersburg, Russia; ² CEA, Frédéric Joliot Institute for Life Sciences, SHFJ, Orsay, France; ³ Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia; ⁴ I.I. Mechnikov North-Western State Medical University, Saint Petersburg, Russia; ⁵ Human Stem Cells Institute, Moscow, Russia; ⁶ Belgorod National Research University, Belgorod, Russia

Anti-MuSK myasthenia gravis (Anti-MuSK MG) is a chronic autoimmune disease caused by complement-independent dysfunction of the agrin-MuSK-Lrp4 complex, accompanied by the development of the pathological muscle fatigue and sometimes muscle atrophy. Fatty replacement of the tongue, mimic, masticatory and paravertebral muscles, revealed by muscle MRI and proton magnetic resonance spectroscopy (MRS), is considered to be a consequence of the myogenic process in anti-MuSK antibody MG in the patients with a plenty long course of the disease. However, in most experimental studies on animal models with anti-MuSK MG, complex presynaptic and postsynaptic changes are revealed, accompanied by the functional denervation of masticatory and paravertebral muscles predominantly. This study presents the MRI, nerve conduction studies (NCS), repetitive nerve stimulation (RNS) and electromyography (EMG) of neurogenic lesions of the axial muscles (m. Multifidus Th12, L3-L5; m. Erector spinae L4-L5) in two patients K. (51 years old), and P. (44 years old), both of whom were having weakness of the paravertebral muscles for 2-4 months due to anti-MuSK MG. The clinical manifestations, as well as the edematous changes in the paravertebral muscles, regressed after therapy. Thus, these clinical examples may confirm the presence of the neurogenic changes at an early stage of anti-MuSK myasthenia gravis and indicate importance of immediate initiation of therapy to avoid the development of muscle atrophy and fatty infiltration.

Key words: antibodies to MuSK, muscle MRI, neurogenic muscle edema, anti-MuSK myasthenia gravis

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Correspondence

Sergey N. Bardakov
S.M. Kirov Military Medical Academy, 6 Lebedeva str., St.
Petersburg, 194044, Russia. E-mail: epistaxix@mail.ru

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Introduction

Anti-MuSK antibody myasthenia gravis (Anti-MuSK MG) is a chronic autoimmune disease caused by complement-independent dysfunction of the agrin-MuSK-Lrp4 complex, accompanied by the development of pathological muscle fatigue and sometimes muscle atrophy. Anti-MuSK MG is a subtype of seronegative acquired myasthenia gravis, occurring in 5-8% of all cases ¹⁻³.

Four main clinical phenotypes of anti-MuSK MG were described: generalized form, oculobulbar form, lumbar-limb phenotype with involvement of the neck extensors and respiratory muscles, isolated ocular form^{4,6}.

One of the characteristic features of anti-MuSK MG is the presence of atrophy and fatty infiltration of the tongue, extraocular, mimic, masticatory and paravertebral muscles, detected by MRI and proton magnetic resonance spectroscopy (MRS)^{5,7-11}. This feature presents as a consequence of myopathic process in anti-MuSK antibody MG, which is confirmed by changes in the myopathic EMG pattern in 44-50% of cases. Those changes include a decrease in the MUAP durations, amplitudes and the presence of fibrillation potentials^{3,7,12,13}. Muscle atrophy is more common in patients with longer disease course^{7,8}. However, some cases of anti-MuSK MG were reported with a short course, characterized by the presence of neurogenic changes in the muscles¹⁴⁻¹⁶. In the studies of experimental autoimmune MG in mice, a wide range of evidence was obtained in favor of denervation changes in muscles in anti-MuSK MG¹⁷⁻¹⁹. At the same time, in humans, in most muscular morphological studies of the extremities, predominant myopathic²⁰⁻²³ and rarer presynaptic neurogenic changes were observed¹⁹. Thus, the exact nature of muscle damage in patients with anti-MuSK MG remains debated. The question is of importance since myogenic changes are less susceptible to respond to a therapeutic intervention.

In this article, we report reversible probably neurogenic changes, identified by nerve conduction studies (NCS), repetitive nerve stimulation (RNS), electromyography (EMG) and MRI, in paravertebral muscles in two patients with anti-MuSK antibody MG.

Subjects and methods

The examination and treatment of two patients: K. 51-year-old male and P. 44-year-old female with paraspinal-muscle weakness caused by anti-MuSK MG were carried out. The clinical, neurological examination and the quantitative myasthenia gravis score (QMGS) assessment were performed before and after the therapy.

All studies were conducted after the patients had signed the voluntary informed consent.

Laboratory methods included: general, biochemical blood analysis, determination of IgM, IgG and IgA levels (turbidimetric method, BTS-350, BioSystems, Spain), antibodies to antinuclear factor (ANF) by indirect immunofluorescence (iIF) test (Euroimmun, Germany), extractable nuclear antigen (ENA) by ELISA (Orgentec, Germany), anti-MuSK antibodies by ELISA (IBL, Germany), anti-AChR antibody test by ELISA (Medipan, Germany), anti-skeletal muscle antibodies (anti-SM) by iIF (Euroimmun, Germany), myositis-associated anti-

body test (MAA) (Mi2b, Ku, Pm-Sc1100, PM-Sc175, Jo-1, SRP, PL-7, PL-12 EJ, OJ, Ro-52) (Euroimmun, Germany).

Instrumental methods consisted of: nerve conduction studies (NCS), repetitive nerve stimulation (RNS) (rhythmic stimulation 3 and 50 Hz), needle electromyography (EMG), whole-body MRI using T1-weighted, T2-weighted STIR-T2 weighted sequences in three orthogonal orientations (Philips Ingenia 1.5 Tl), chest CT (Aquilon 64, Toshiba).

Treatment of patient 2. (44 y.o.) included methylprednisolone tablets (0.8 mg/kg b.w.) by an alternating scheme and five cycles of medium-volume membrane plasma exchange using PCS-2 devices (Haemonetics, USA) according to the standard technique with an exfusion volume of 25-30% of the circulating plasma volume. The replacement of the exfused plasma was carried out with crystalloid solutions. Patient 1 (51 y.o.) received only methylprednisolone tablets (1.0 mg/kg b.w.) according to an alternating scheme. In both patients, when the methylprednisolone doses were decreased, azathioprine tablets (50 mg/day) were additionally prescribed.

Description of clinical cases

Patient 1 (male, 51 years old; 186 cm tall, weighting 79 kg; BMI - 22.8) presented with a 8-month disease duration. He complained of severe muscle weakness of the back and neck, with difficulties to maintain the head and posture, inability to extend the back from a forward bend. After 2 months, the patient noted the appearance of double vision. The severity of symptoms had no significant fluctuations during the day. The neurological examination before treatment revealed moderate weakness of the neck extensors (4 points) and severe weakness of the thoracic and lumbar paravertebral muscles (3 points). When the arms were extended forward, a compensatory deviation backward of the body by 10° was observed. Weakness in the facial and proximal muscles of the upper limbs was not observed (5 points). The QMGS score was 3/39 points. The patient was MGFA class 1. The neostigmine methyl sulfate test (0.05% 2 ml) was positive.

The level of anti-AChR antibodies were 0.24 nmol/L (norm of up to 0.45); anti-MuSK antibodies were more than 23.3 IU/ml (norm of up to 0.39 IU/ml); anti-SM antibodies - less than 1:20 (up to 1:20); ANF antibodies were 1:640; anti-mitochondrial antibodies (PDC-AMA2; AMA) - 1:20 (less than 1:20); immunoblotting of antinuclear antibodies was normal. The IgM, IgG and IgA levels were normal.

On the whole-body MRI in m. multifidus at levels Th10 - L5 MR signal was heterogeneous, particularly on the left side due to areas of moderate hyperintensities on T2w images, with corresponding iso/hypointensities on

Table I. Results of RNS, assessment by QMGs and anti-MuSK level of patient 1 and patient 2 before and after treatment.

| Muscles | Patient 1 (51 y.o.) | | | | Patient 2 (44 y.o.) | | | |
|-------------------------------|---------------------|---------------|-----------------|---------------|---------------------|---------------|-----------------|---------------|
| | Before A, mV | After D, % | Before A, mV | After D, % | Before A, mV | After D, % | Before A, mV | After D, % |
| M. frontalis | 1.1 | 6.5 | 1.6 | 0.5 | 1.1 | 20.4 | 1.5 | 12.4 |
| M. orbicularis oculi | 2.4 | 23 | 2.5 | + 0.2 | 0.45 | 38.4 | 0.99 | 34.2 |
| M. nasalis | 2.8 | 8.6 | 2.7 | 2.5 | 1.81 | 25.4 | 2.62 | 3.8 |
| M. digastricus vent. anterior | 4.7 | 1.5 | 5.1 | + 0.8 | 3.61 | 18.6 | 6.78 | + 0.6 |
| M. trapezius | 5.6 | 65 | 11.9 | 13.1 | 6.85 | 17.1 | 10.1 | 1.9 |
| M. deltoideus | 20 | 19.3 | 25.7 | 5.7 | 12.8 | 16.8 | 19.1 | 2.6 |
| M. abductor digiti minimi | 14.1 | 2.4 | 14.0 | + 0.4 | 9.4 | 2.4 | 10.3 | + 0.9 |
| PAP (m. orbicularis oculi), % | 112 | | 108 | | 127 | | 123 | |
| Anti-MuSK antibodies, IU/ml | 23.3 | | 8.13 | | 25.3 | | 7.26 | |
| QMGs | 3 | | 0 | | 17 | | 1 | |

A, mV: amplitude of the first CMAP; D, %: decrement in the amplitude of CMAP between the first and fifth stimuli, expressed as a percentage, obtained with repetitive stimulation of 3 Hz; PAP: Post-activation potentiation after isometric muscle tension; 4: Pathological indicators are highlighted in bold.

T1w images. Those areas showed edematous changes. No signal anomaly was detected elsewhere, either in the paravertebral muscles or in the paravertebral soft tissues at other locations.

A L5-S1 disc protrusion was observed, up to 0.35 cm in size, without affection on the spinal roots. In the posterior group of thigh and leg muscles, mild fatty replacement was noted (Mercuri 1 grade 1 on a scale of 0 to 4).

Respiratory function indices were in the normal range.

On the repetitive nerve stimulation compound muscle action potentials (CMAP) decrement was revealed in the orbicularis oculi muscles (23%) and the proximal muscles of the upper extremities up to 65% (Tab. I). On the EMG in m. deltoideus, m. vastus lateralis, m. tibialis anterior, the MUAP amplitudes and durations were normal. In the proximal muscles increased polyphasia of MUAP was noted up to 26-33%. In m. erector spinae at the L1-L3 levels, neurogenic changes were revealed, represented by an increase in the MUAP amplitudes - 1814 μ V (343-4172 μ V), with a normal MUAP duration - 11.1 ms (8.43-16.4), an increase in polyphasic fibers up to 14%; the interference pattern corresponded to the neurogenic one. Spontaneous activity was represented by the multiple fibrillation potentials, positive sharp waves and single fasciculations.

After treatment, which included glucocorticosteroids (1.0 mg/kg b.w.in an alternate day scheme for 4 months, followed by a progressive decrease), patient 1 achieved complete clinical remission.

A control examination after 6 months of therapy showed a decrease in the anti-MuSK level to 8.13 IU/ml. At the MRI, the complete regression of edematous changes

in the paravertebral muscles was observed (Fig. 1). On the RNS, the CMAP decrement in m. trapezius persisted. In m. erector spinae at the L1-L3 levels, less pronounced neurogenic changes were observed, indicated by lower MUAP amplitudes - 1610 μ V (567-2942 μ V), with a normal MUAP duration of 10.5 ms (9.07-14.6), an increase in polyphase fibers to 32%. The interference pattern corresponded to a neurogenic one. QMGs score - 0/39 points. The patient 1 was MGFA class 0 (Tab. I).

Patient 2 (female, 44 years old, height 166 cm; weight 68 kg; BMI - 24.7) with complaints of double vision, limitation of eye movements, the drooping eyelids and rapid fatigability of the neck extensors with the development of "dropped head" syndrome in the evening. The first episode of self-regressing isolated double vision, which lasted 2 weeks was observed 8 months ago. Ophthalmoparesis was observed within 4 months. On examination before the treatment, diplopia, ophthalmoparesis, convergent strabismus, hypomimia, weakness in the neck extensors were noted. She could not raise her head in a forward tilt position (2 - 3/5 points); she had weakness in the back extensors of the thoracic and lumbar regions (4 points). Muscle strength of the upper and lower extremities was normal (5 points). QMGs score - 17/39 points. The patient 2 was stage 2a according to MGFA. The neostigmine methyl sulfate test (0.05% 1.8 ml) was positive (Fig. 1).

The level of anti-AChR antibodies was 0.21 nmoI/L (normal up to 0.45); antibodies to MuSK more than 25 IU/ml (norms up to 0.39 U/ml); anti-SM antibodies - less than 1:20 (the norm is up to 1:20). Blood cell count showed a relative lymphocytosis of up to 47.4% (norm 19.0-37.0%) with normal absolute lymphocyte number.

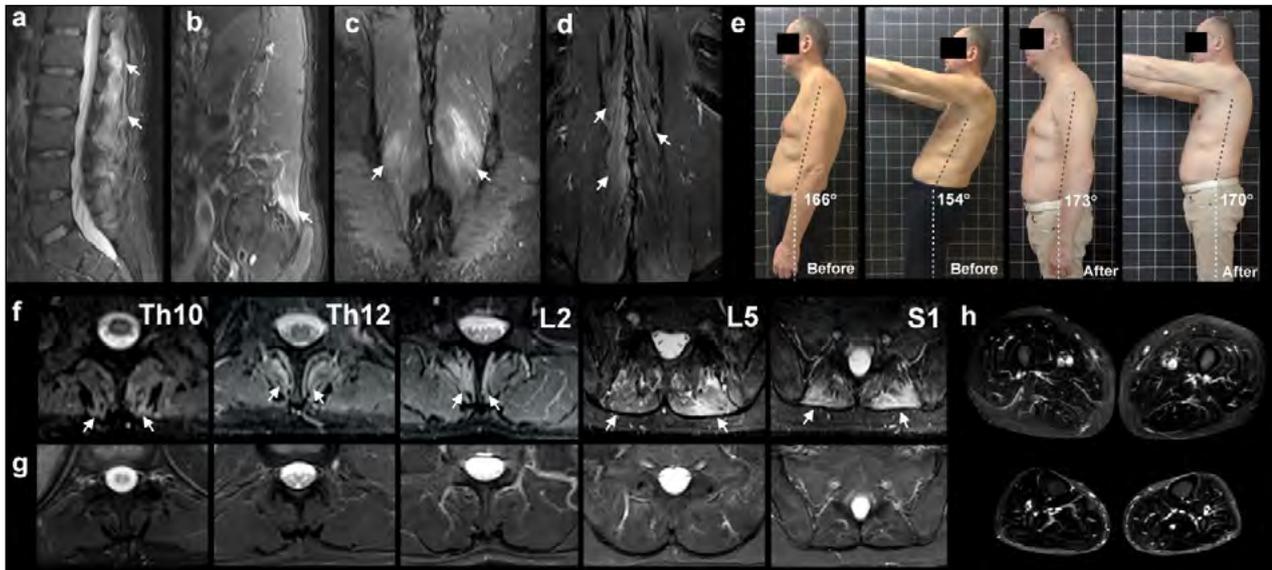


Figure 1. Patient 1, 51 (y.o.), with anti-MuSK MG had a disease duration of 5 months. There is edema of m. multifidus on STIR in the sagittal plane (A, B), in the coronal plane (C, D). Muscle weakness of the back extensors has been presented as a compensatory deviation of the trunk back when raising the arms up before and after treatment (E); edema of m. multifidus and m. erector spinae before and after therapy (F, G) on STIR in the axial plane; no pathological changes in the muscles of the thighs and lower legs on STIR in the axial plane (H), the pathological changes are marked with white arrows.

On chest CT persistence of the thymus gland was revealed (7.6x11 mm, no clear contours).

At MRI, whole-body axial STIR and T2wi in the axial plane revealed the moderate edematous changes in m. multifidus at the Th12, L3-L5 levels, m. erector spinae at the L4, L5 levels on the left (Fig. 2A). On the T1w and T2w scans in sagittal, coronal and axial projections with fat suppression, the patient had protrusions of the L3-L5 intervertebral discs measuring 0.2-0.3 cm, without signs of nerve root compression. In the STIR and T2w images of extraocular muscles, moderate symmetric edematous changes in m. rectus lateralis and m. rectus inferior were observed in the absence of structural pathological changes on T1wi. The tongue did not reveal any pathological edematous change or pronounced fatty infiltration (Fig. 2I).

Respiratory function indices corresponded to the norm.

The RNS (rhythmic stimulation 3 Hz) revealed a M-response decrement in the mimic, pharyngeal and the proximal muscles of the upper extremities by 38% (Tab. I). The EMG in m. deltoideus, m. vastus lateralis, m. tibialis anterior showed normal values of the MUAP amplitudes and durations while the MUAP polyphasia in the proximal muscles was increased up to 23-40%. In the m. erector spinae at the L2-L4 levels, neurogenic changes were revealed, represented by the increased MUAP amplitudes - 1514 μ V (292-3802 μ V), with a normal MUAP duration - 11.9 ms

(8.43-16.4), polyphase fibers - 9%; the interference patterns corresponded to the neurogenic one. Signs of spontaneous activities included multiple fibrillation potentials, single fasciculations, and positive sharp waves. The number of fasciculations prevailed on the left side where MRI identified more pronounced edematous changes.

After a 2-month treatment, which consisted of glucocorticosteroids (0.8 mg/kg b.w.) administered each other day and five medium-volume plasma exchanges, patient 1 reached a complete clinical remission. Methylprednisolone-dose was then gradually reduced and azathioprine (50 mg/day) was added.

A follow-up study 3 months after had been initiated showed the decreasing anti-MuSK antibodies to 7.26 IU/ml. A complete regression of the paravertebral muscles edematous changes was seen at the MRI, but a moderate edema still persisted in m. rectus inferior. On the RNS, the elevated CMAP decrement in m. orbicularis oculi persisted. The MUAP parameters of the paravertebral muscle were in the normal range. No spontaneous activity was detected, but the MUAP polyphasia remained up to 34%. QMGS score was 1/39 point (Fig. 1). The patient 2 was MGFA class 0.

Discussion

The first clinical case was a rare example of an-

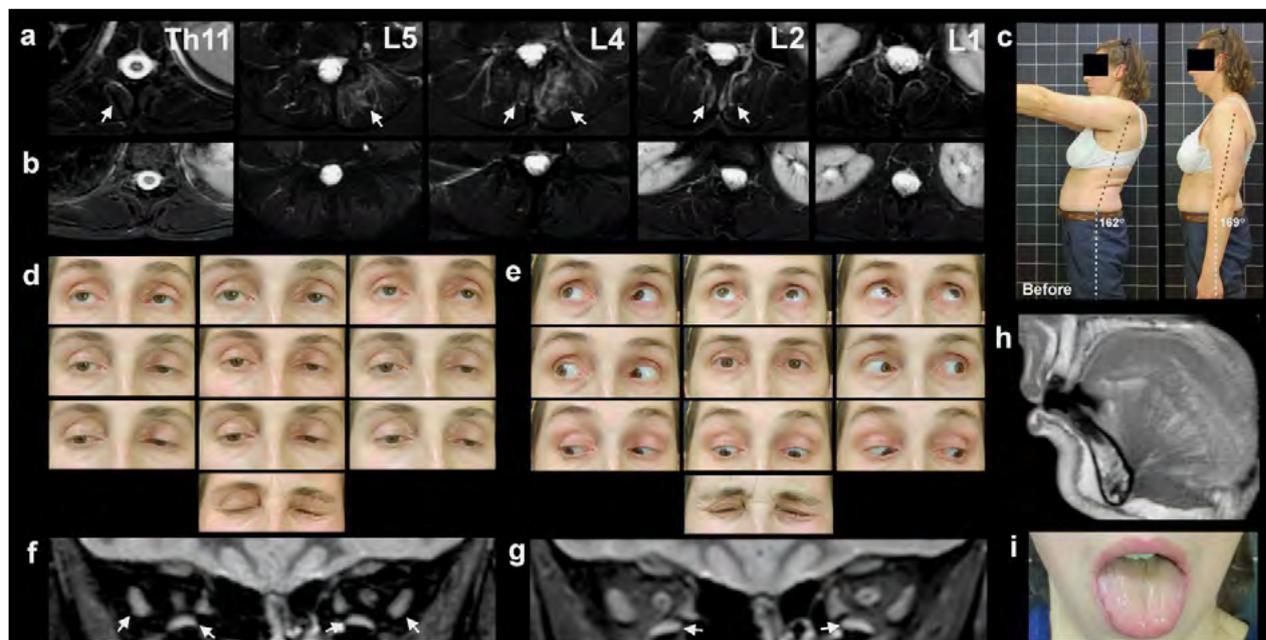


Figure 2. Patient 2 (44 y.o.) had anti-MuSK myasthenia gravis with a 7-month disease duration. Edema of m. multifidus was on STIR in the axial plane at the Th11-L1 levels before the treatment (A) and after the therapy (B). There was no significant deviation of the trunk when raising the arms up in the presence of moderate weakness in the back extensors (C). Weakness of the extraocular muscles. The motion range of the eyes before (D) and after the therapy (E); edemas of m. rectus lateralis and m. rectus inferior before the therapy (F), m. rectus inferior after the therapy (G) on STIR in the coronal plane; absence of significant fatty infiltration in the tongue muscle according to T1-WI in the sagittal plane (H); appearance of patient's tongue (I) (pathological changes are indicated by arrows).

ti-MuSK myasthenia gravis, manifested with an isolated lesion of the paravertebral muscles, predominantly of the lower thoracic and lumbosacral regions. That lesion included the pronounced difficulties in extending the trunk from bending forward and maintaining balance with arms extended forward. Previously, cases of primary involvement of the paravertebral muscles were described only in children (7 years). They were accompanied by the developing scoliosis and atrophy of these muscles at the cervical and thoracic levels^{11,24}. In both cases, the scoliotic deformity significantly decreased after treatment. The second case was characterized by a milder involvement of the axial muscles than in the first case. In particular, there was a moderate “dropped head” syndrome in the evening and mild involvement of the lower thoracic and lumbar paraspinous muscles, manifested by lumbar fatigue when standing. As it is known, the axial muscles are often involved at the cervical levels with the development of “dropped head” syndrome in patients with anti-MuSK MG^{14,25-28}, and even more often in patients over 60 years old with anti-AChR antibodies in 10% of cases^{29,30}, while in other anti-AChR patients, the lesion of the neck flexors prevails³¹.

In both cases, primary involvement of the axial musculature prompted a whole-body MRI scan to rule out my-

opathies. Unexpected edematous asymmetric changes in the paravertebral muscles were revealed. These changes were more pronounced in the first patient (the MR signal hyperintensity on STIR, T2-WI, iso/hypointensity on T1-wi) in m. multifidus at the Th10-L5 levels and m. erector spinae at the level of L5-S1 segments. Signal hyperintensity on STIR in combination with spontaneous activity on EMG characterizes muscle denervation in the acute (up to 1 month) and subacute phases (1-6 months)^{32,33}. Such changes are due to the expansion of the capillary bed and the increasing intercellular fluids³⁴, already developing 48 hours after denervation³⁵. Similar changes can be observed not only during denervation, but also during primary muscle inflammatory processes, including inflammatory myopathies³⁶. In both our cases, the presence of inflammatory myopathies was ruled out by normal level of CPK, AST, ALT, LDH, and myoglobin, as well as negative results of the myositis-associated and antimitochondrial antibodies. A STIR positivity at MRI has a sufficiently high relative sensitivity - 84% and specificity - 100% for detecting denervation (acute and subacute phases) when compared with EMG^{37,38}. In chronic phase (more than 6 months), an increase in muscle fat content and muscle atrophy are observed, which is accompanied

by the development of the MR signal intensity on T1w and a decrease in muscle mass. Similar changes are also observed in functional immobilization (for example, tendon rupture) and hereditary muscular dystrophies^{32,33}.

In most of the previously reported cases of anti-MuSK²⁴ and anti-AChR^{39,40} MG, associated with the axial muscle damage (“dropped head” syndrome, camp-tocormia), the MR signs of fatty infiltration and paravertebral muscle atrophy were described even with or without the glucocorticosteroid therapy. In patients with anti-AChR MG, a summation of similar MR-changes, the “myopathic” EMG patterns in paraspinal muscles and resistant camp-tocormia has been stated by a number of authors as an independent rare comorbid condition – “paraspinal myopathy”^{41,42}. Similar cases of the anti-AChR MG and “paraspinal myopathy” were described in patients aged 70-85 years with a long course and poor control of MG symptoms. The presence of cases of reversible camp-tocormia, “dropped head” or “Leaning Tower of Pisa” syndrome during the treatment in patients with anti-AChR and anti-MuSK MG who have myopathic EMG signs with or without atrophy, but without fatty infiltration of the paravertebral muscles, probably indicates that the damage to this muscle group is one manifestation of myasthenia gravis⁴³⁻⁴⁵. Thus, myasthenic weakness, leading to functional immobilization of the paravertebral muscles, probably determines the stage process of their affection. Initially, the development of early edematous changes is the same as for the acute and subacute phases of denervation, which corresponds to our cases. Subsequently, late changes, equivalent to chronic denervation, which corresponds to most of the previously described cases^{41,42}. This correlation indicates that the presence of the paravertebral-muscle lesion with anti-MuSK MG can lead to scoliotic deformity in childhood. At the same time in elderly patients with anti-MuSK, as well as anti-AChR MG, the paraspinal damages may cause camp-tocormia and “dropped head” syndrome.

The muscle MRI characteristics of the limbs in patients we described corresponded to the control muscles. The only exception was minimal signs of fatty infiltration in the lower extremities (grade 1 according to Mercuri), which was probably a consequence of a sedentary lifestyle⁴⁶.

Besides, in two patients, there were no edematous changes, fatty infiltration and atrophy of the tongue, mimic and masticatory muscles, probably due to short disease duration (4-6 months). These findings contradicted the typical signs of anti-MuSK MG, which were atrophy and fatty infiltration of m. orbicularis oculi, m. orbicularis oris, m. buccinators, tongue muscles⁸, mm. pterygoidei, m. masseter and m. temporalis⁹. In some cases, atrophy of the tongue muscles is reversible^{24,47}.

The severity of atrophy and fatty infiltration depends on the duration of prednisolone therapy⁸. However, in some cases, atrophies developed at an early stage even before the initiation of the treatment, which was most likely due to the independent role of anti-MuSK in this process^{9,48}. In particular, Punga, et al. (2011) showed that MuSK antibodies induced functional denervation, resulting in increased production of the skeletal-muscle-atrophy marker MuRF-1 (atrophy marker muscle-specific RING finger protein 1)⁴⁹ in a passively induced model of experimental autoimmune MG in mice^{18,50}. At the same time, a significantly greater increase in mRNA levels of MuRF-1 was observed in the masticatory muscles, while those levels decreased in the limb muscles (m. soleus). These findings explained the peculiarities of the atrophy distribution in anti-MuSK MG^{18,50}. The progression of atrophy under the anti-MuSK influence was also realized through over-expression of atrogen-1 and p21, which provoked a premature stop of the cell cycle and weakened the ability of satellite cells to replace lost muscle fibers^{18,51,52}.

Similar regularities were observed in the MR changes of the oculomotor muscles in anti-MuSK MG. Thus, in our second case, severe ophthalmoplegia lasting 4 months was characterized by moderate edematous changes (according to STIR) in m. rectus lateralis and m. rectus inferior, which corresponded to MR signs of early functional denervation. Whereas in cases of prolonged ophthalmoparesis (2-14 years) with anti-MuSK MG, the MR signs of pronounced atrophy in extraocular muscles were observed^{5,6}. In these cases, the least affected muscle was m. obliquus inferior.

Thus, muscular atrophy, especially of the mimic and bulbar muscles, has been a fairly common delayed consequence of anti-MuSK MG, reflecting the disease duration, the delayed initiation of therapy and/or the effect of prolonged exposure to high doses of glucocorticosteroids⁵³. The intricacy of mechanisms is supported by the variability of the prevalence of atrophy in anti-MuSK MG, from 5.7⁵⁴ to 23%⁷. The assessment of muscle condition by MRI at the time of diagnosis is an important to estimate the possible functional recovery under therapy^{6,9}.

The CMAP decrement with RNS of 3 Hz was revealed in both clinical cases, while the decrement curve had a steadily progressive character, in contrast to the U-shaped form in anti-AChR MG⁵⁵. In both cases, there was no hypercholinergic reaction after the first supramaximal stimuli that performed with additional potentials after the M-response⁵⁶. This result may be due to the short duration of the disease and the low doses of acetylcholinesterase inhibitor (AChEI) used (up to 180 mg/day of pyridostigmine bromide). In the first case, the decrement distribution of the examined muscles mainly reflected the focal nature of the lesion with maximum values of the

CMAP decrement up to 65% in m. trapezius. Whereas the second case was clinically similar to the generalized form of anti-AChR, characterized by a more diffuse distribution of the M-response decrement. The maximum values of the CMAP decrement corresponded to those values in the most affected muscle groups. The significant variability in the decrement distribution in anti-MuSK MG substantiated the rationality of more extended studies. At the same time, the diagnostic significance increased from 56.8²² to 85% when the neuromuscular-conduction analysis included not only distal, but also proximal muscles of the extremities, as well as facial muscles^{28,54,57}.

Needle EMG was performed to determine the neurogenic nature of the hyperintense-signal areas (on STIR) of the paravertebral muscles. Paraspinal MUAPs had increased amplitudes and normal durations with a slightly increased polyphasia up to 14%. Whereas in the limb muscles without MR lesion signs, duration and amplitude MUAPs were normal, albeit with a significantly increased polyphasia up to 40%. Spontaneous activity was only detected in the STIR hyperintense areas in the paravertebral muscles and represented by a significant number of fibrillation potentials, positive sharp waves, and single fasciculation potentials. On turn-amplitude analysis, a neurogenic pattern of the interference curve was observed in the paravertebral muscles, characterized by a high amplitude with a reduced or normal frequency of turns. In both cases after the therapy, the MUAPs almost completely returned to normal. However, in most studies of anti-MuSK patients, the myopathic nature of EMG changes was reported: a decrease in the MUAP durations and amplitudes, the presence of fibrillation potentials^{3,12,57}. Myopathic MUAPs were observed in 62-80.6% of anti-MuSK patients in facial muscles^{7,12}, although in limb muscles, they were in 33-44%^{7,13}. It should be noted that the interpretation of MUAP changes in anti-MuSK and anti-AChR is questionable, when different stages of the denervation process are not taken into account. In particular Farrugia, et al. (2007) indicated that in 50% of anti-MuSK patients with MUAP myopathic patterns in turn-amplitude analysis, the interference curve was characterized by high amplitudes and low frequency of turns¹². This result was interpreted as an insufficient strength of studied-muscle contraction, and not a sign of early functional denervation¹².

In cases with predominant lesions of the paravertebral muscles, the myopathic nature of the MUAP changes was accompanied by muscle atrophy during a long disease course¹¹. At the same time, cases with a short duration of anti-MuSK MG and axial-muscle damages were described, characterized by reduced duration of MUAPs, increased polyphasia and pronounced spontaneous activity (fibrillation potentials, fasciculations, positive sharp

waves), which was regarded as neurogenic changes and was a cause of amyotrophic lateral sclerosis (ALS) misdiagnosis^{14-16,24}. In some cases, EMG signs of fasciculations were accompanied by clinically evident fasciculations^{16,58}.

A similar nature of MUAP changes and the presence of spontaneous activity were described in studies of experimental autoimmune myasthenia gravis and in some clinical cases, in which denervation changes in the affected muscles were substantiated^{18,19,21,59-65}. The degree of nerve penetration in each muscle has been shown to correlate with their endogenous MuSK levels^{18,66}.

Summing up the available data, in anti-MuSK myasthenia gravis, most researchers have considered these muscle damages as myopathic process^{1,3,7,12,22}. Whereas our clinical examples have confirmed the presence of neurogenic changes at an early stage of anti-MuSK myasthenia gravis and indicated importance of immediate initiation of pathogenetic therapy to avoid the development of muscle atrophy and fatty infiltration.

Conflict of interest statement

The authors declare no conflict of interest.

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Author's contributions

The authors have contributed equally to the work.

Ethical consideration

Not applicable.

References

- 1 Evoli A, Alboini PE, Damato V, et al. Myasthenia gravis with antibodies to MuSK: an update. *Ann N Y Acad Sci* 2018;1412:82-89. <https://doi.org/10.1111/nyas.13518>
- 2 Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. *Muscle Nerve* 2011;44:36-40. <https://doi.org/10.1002/mus.22006>
- 3 Sanders DB, El-Salem K, Massey JM, et al. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* 2003;60:1978-1980. <https://doi.org/10.1212/01.wnl.0000065882.63904.53>
- 4 Evoli A, Alboini PE, Iorio R, et al. Pattern of ocular involvement in myasthenia gravis with MuSK antibodies. *J Neurol Neurosurg Psychiatry* 2017;88:761-763. <https://doi.org/10.1136/jnnp-2017-315782>

- 5 Chan JW, Orrison WW. Ocular myasthenia: a rare presentation with MuSK antibody and bilateral extraocular muscle atrophy. *Br J Ophthalmol* 2007;91:842-843. <https://doi.org/10.1136/bjo.2006.108498>
- 6 Ricciardi D, Todisco V, Tedeschi G, et al. Anti-MuSK ocular myasthenia with extrinsic ocular muscle atrophy: a new clinical phenotype? *Neurol Sci* 2020;41:221-223. <https://doi.org/10.1007/s10072-019-04038-4>
- 7 Nikolić AV, Bačić GG, Daković M, et al. Myopathy, muscle atrophy and tongue lipid composition in MuSK myasthenia gravis. *Acta Neurol Belg* 2015;115:361-365. <https://doi.org/10.1007/s13760-014-0364-1>
- 8 Farrugia ME, Robson MD, Clover L, et al. MRI and clinical studies of facial and bulbar muscle involvement in MuSK antibody-associated myasthenia gravis. *Brain* 2006;129:1481-1492. <https://doi.org/10.1093/brain/awl095>
- 9 Zouvelou V, Rentzos M, Toulas P, et al. MRI evidence of early muscle atrophy in MuSK positive myasthenia gravis. *J Neuroimaging* 2011;21:303-5. <https://doi.org/10.1111/j.1552-6569.2009.00456.x>
- 10 Lavrnjic D, Dakovic M, Peric S, et al. Proton magnetic resonance spectroscopy of the intrinsic tongue muscles in patients with myasthenia gravis with different autoantibodies. *J Neurol Sci* 2011;302:25-28. <https://doi.org/10.1016/j.jns.2010.12.009>
- 11 Kirzinger L, Khomenko A, Schulte-Mattler W, et al. Myopathy in childhood muscle-specific kinase myasthenia gravis. *Pediatr Neurol* 2016;65:90-92. <https://doi.org/10.1016/j.pediatrneurol.2016.08.005>
- 12 Farrugia ME, Kennett RP, Hilton-Jones D, et al. Quantitative EMG of facial muscles in myasthenia patients with MuSK antibodies. *Clin Neurophysiol* 2007;118:269-277. <https://doi.org/10.1016/j.clinph.2006.10.004>
- 13 Padua L, Tonali P, Aprile I, et al. Seronegative myasthenia gravis: comparison of neurophysiological picture in MuSK+ and MuSK- patients. *Eur J Neurol* 2006;13:273-276. <https://doi.org/10.1111/j.1468-1331.2006.01214.x>
- 14 Spengos K, Vassilopoulou S, Papadimas G, et al. Dropped head syndrome as prominent clinical feature in MuSK-positive myasthenia gravis with thymus hyperplasia. *Neuromuscul Disord* 2008;18:175-177. <https://doi.org/10.1016/j.nmd.2007.09.007>
- 15 Huijbers MG, Niks EH, Klooster R, et al. Myasthenia gravis with muscle specific kinase antibodies mimicking amyotrophic lateral sclerosis. *Neuromuscul Disord* 2016;26:350-353. <https://doi.org/10.1016/j.nmd.2016.04.004>
- 16 Furuta N, Ishizawa K, Shibata M, et al. Anti-MuSK antibody-positive myasthenia gravis mimicking amyotrophic lateral sclerosis. *Intern Med* 2015;54:2497-2501. <https://doi.org/10.2169/internalmedicine.54.4645>
- 17 Klooster R, Plomp JJ, Huijbers MG, et al. Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice. *Brain* 2012;135:1081-1101. <https://doi.org/10.1093/brain/awo25>
- 18 Punga AR, Lin S, Oliveri F, et al. Muscle-selective synaptic disassembly and reorganization in MuSK antibody positive MG mice. *Exp Neurol* 2011;230:207-217. <https://doi.org/10.1016/j.expneurol.2011.04.018>
- 19 Niks EH, Kuks JB, Wokke JH, et al. Pre- and post-synaptic neuromuscular junction abnormalities in musk myasthenia. *Muscle Nerve* 2010;42:283-288. <https://doi.org/10.1002/mus.21642>
- 20 Shiraishi H, Motomura M, Yoshimura T, et al. Acetylcholine receptors loss and postsynaptic damage in MuSK antibody-positive myasthenia gravis. *Ann Neurol* 2005;57:289-293. <https://doi.org/10.1002/ana.20341>
- 21 Selcen D, Fukuda T, Shen XM, Engel AG. Are MuSK antibodies the primary cause of myasthenic symptoms? *Neurology* 2004;62:1945-1950. <https://doi.org/10.1212/01.wnl.0000128048.23930.1d>
- 22 Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain* 2003;126:2304-2311. <https://doi.org/10.1093/brain/awg223>
- 23 Cenacchi G, Papa V, Fanin M, et al. Comparison of muscle ultrastructure in myasthenia gravis with anti-MuSK and anti-AChR antibodies. *J Neurol* 2011;258:746-752. <https://doi.org/10.1007/s00415-010-5823-x>
- 24 Sanders DB, Juel VC. MuSK-antibody positive myasthenia gravis: questions from the clinic. *J Neuroimmunol* 2008;201:85-89. <https://doi.org/10.1016/j.jneuroim.2008.05.032>
- 25 Casanovas C, Povedano M, Jaumà S, et al. Musk-antibody positive myasthenia gravis presenting with isolated neck extensor weakness. *Neuromuscul Disord* 2007;17:544-546. <https://doi.org/10.1016/j.nmd.2007.03.007>
- 26 Okano T, Fujitake J, Suzuki K, et al. A case of anti-MuSK antibody-positive myasthenia gravis with dropped head as the initial presenting symptom. *Rinsho Shinkeigaku* 2006;46:496-500.
- 27 Rodolico C, Parisi D, Portaro S, et al. Myasthenia gravis: unusual presentations and diagnostic pitfalls. *J Neuromuscul Dis* 2016;3:413-418. <https://doi.org/10.3233/jnd-160148>
- 28 Stickler DE, Massey JM, Sanders DB. MuSK-antibody positive myasthenia gravis: clinical and electrodiagnostic patterns. *Clin Neurophysiol* 2005;116:2065-2068. <https://doi.org/10.1016/j.clinph.2005.06.003>
- 29 Sih M, Soliven B, Mathenia N, et al. Head-drop: a frequent feature of late-onset myasthenia gravis. *Muscle Nerve* 2017;56:441-444. <https://doi.org/10.1002/mus.25526>
- 30 Tamai M, Hashimoto T, Isobe T, et al. Treatment of myasthenia gravis with dropped head: a report of 2 cases and review of the literature. *Neuromuscul Disord* 2015;25:429-431. <https://doi.org/10.1016/j.nmd.2015.01.014>
- 31 Morren J, Li Y. Myasthenia gravis with muscle-specific tyrosine kinase antibodies: a narrative review. *Muscle Nerve* 2018;58:344-358. <https://doi.org/10.1002/mus.26107>
- 32 Lisle DA, Johnstone SA. Usefulness of muscle denervation as an MRI sign of peripheral nerve pathology. *Australas Radiol* 2007;51:516-526. <https://doi.org/10.1111/j.1440-1673.2007.01888.x>

- ³³ Kamath S, Venkatanarasimha N, Walsh MA, et al. MRI appearance of muscle denervation. *Skeletal Radiol* 2008;37:397-404. <https://doi.org/10.1007/s00256-007-0409-0>
- ³⁴ Wessig C, Koltzenburg M, Reiners K, et al. Muscle magnetic resonance imaging of denervation and reinnervation: correlation with electrophysiology and histology. *Exp Neurol* 2004;185:254-261. <https://doi.org/10.1016/j.expneurol.2003.10.012>
- ³⁵ Fleckenstein JL, Watumull D, Conner KE, et al. Denervated human skeletal muscle: MR imaging evaluation. *Radiology* 1993;187:213-218. <https://doi.org/10.1148/radiology.187.1.8451416>
- ³⁶ May DA, Disler DG, Jones EA, et al. Abnormal signal intensity in skeletal muscle at MR imaging: patterns, pearls, and pitfalls. *Radiographics* 2000;20:S295-S315. https://doi.org/10.1148/radiographics.20.suppl_1.g00oc18s295
- ³⁷ McDonald CM, Carter GT, Fritz RC, et al. Magnetic resonance imaging of denervated muscle: comparison to electromyography. *Muscle Nerve* 2000;23:1431-1434. [https://doi.org/10.1002/1097-4598\(200009\)23:9<1431::aid-mus16>3.0.co;2-p](https://doi.org/10.1002/1097-4598(200009)23:9<1431::aid-mus16>3.0.co;2-p)
- ³⁸ Deroide N, Bousson V, Mambre L, et al. Muscle MRI STIR signal intensity and atrophy are correlated to focal lower limb neuropathy severity. *Eur Radiol* 2015;25:644-651. <https://doi.org/10.1007/s00330-014-3436-y>
- ³⁹ Rodolico C, Messina S, Toscano A, et al. Axial myopathy in myasthenia: a misleading cause of dropped head. *Muscle Nerve* 2004;29:329-330. <https://doi.org/10.1002/mus.10543>
- ⁴⁰ Zouvelou V, Rentzos M, Toulas P, et al. AchR-positive myasthenia gravis with MRI evidence of early muscle atrophy. *J Clin Neurosci* 2012;19:918-919. <https://doi.org/10.1016/j.jocn.2011.09.022>
- ⁴¹ Romano AE, Al-Qudah Z, Kaminski HJ, et al. Concurrent paraspinous myopathy and myasthenia gravis. *J Clin Neuromuscul Dis* 2017;18:218-222. <https://doi.org/10.1097/cnd.0000000000000165>
- ⁴² Devic P, Choumert A, Vukusic S, et al. Myopathic camptocormia associated with myasthenia gravis. *Clin Neurol Neurosurg* 2013;115:1488-1489. <https://doi.org/10.1016/j.clineuro.2012.11.015>
- ⁴³ Sato T, Natori T, Hata T, et al. Camptocormia as an onset symptom of myasthenia gravis. *Neurol Sci* 2017;38:515-516. <https://doi.org/10.1007/s10072-016-2752-1>
- ⁴⁴ Abboud H, Sivaraman I, Ontaneda D, et al. Camptocormia and Pisa syndrome as manifestations of acute myasthenia gravis exacerbation. *J Neurol Sci* 2015;359:8-10. <https://doi.org/10.1016/j.jns.2015.10.020>
- ⁴⁵ Kataoka H, Kiriya T, Ueno S. Myasthenia gravis can cause camptocormia. *J Neurol Neurosurg Psychiatry* 2012;83:469-470. <https://doi.org/10.1136/jnnp-2011-300311>
- ⁴⁶ Addison O, Drummond MJ, LaStayo PC, et al. Intramuscular fat and inflammation differ in older adults: the impact of frailty and inactivity. *J Nutr Health Aging* 2014;18:532-538. <https://doi.org/10.1007/s12603-014-0019-1>
- ⁴⁷ Takahashi H, Kawaguchi N, Ito S, et al. Is tongue atrophy reversible in anti-MuSK myasthenia gravis? Six-year observation. *J Neurol Neurosurg Psychiatry* 2010;81:701-702. <https://doi.org/10.1136/jnnp.2009.171793>
- ⁴⁸ Moon SY, Lee SS, Hong YH. Muscle atrophy in muscle-specific tyrosine kinase (MuSK)-related myasthenia gravis. *J Clin Neurosci* 2011;18:1274-1275. <https://doi.org/10.1016/j.jocn.2011.01.010>
- ⁴⁹ Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 2001;294:1704-1708. <https://doi.org/10.1126/science.1065874>
- ⁵⁰ Benveniste O, Jacobson L, Farrugia ME, et al. MuSK antibody positive myasthenia gravis plasma modifies MURF-1 expression in C2C12 cultures and mouse muscle in vivo. *J Neuroimmunol* 2005;170:41-48. <https://doi.org/10.1016/j.jneuroim.2005.08.016>
- ⁵¹ Boneva N, Frenkian-Cuvelier M, Bidault J, et al. Major pathogenic effects of anti-MuSK antibodies in myasthenia gravis. *J Neuroimmunol* 2006;177:119-131. <https://doi.org/10.1016/j.jneuroim.2006.05.017>
- ⁵² Sandri M, Sandri C, Gilbert A, et al. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell* 2004;117:399-412. [https://doi.org/10.1016/s0092-8674\(04\)00400-3](https://doi.org/10.1016/s0092-8674(04)00400-3)
- ⁵³ Vincent A, Leite MI. Neuromuscular junction autoimmune disease: muscle specific kinase antibodies and treatments for myasthenia gravis. *Curr Opin Neurol* 2005;18:519-525. <https://doi.org/10.1097/01.wco.0000180660.57801.3f>
- ⁵⁴ Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in MuSK-antibody positive myasthenia gravis: a U.S. experience. *Muscle Nerve* 2010;41:370-374. <https://doi.org/10.1002/mus.21533>
- ⁵⁵ Sanders DB, Cao L, Massey JM, et al. Is the decremental pattern in Lambert-Eaton syndrome different from that in myasthenia gravis? *Clin Neurophysiol* 2014;125:1274-1277. <https://doi.org/10.1016/j.clinph.2013.11.007>
- ⁵⁶ Punga AR, Flink R, Askmark H, et al. Cholinergic neuromuscular hyperactivity in patients with myasthenia gravis seropositive for MuSK antibody. *Muscle Nerve* 2006;34:111-115. <https://doi.org/10.1002/mus.20515>
- ⁵⁷ Oh SJ, Hatanaka Y, Hemmi S, et al. Repetitive nerve stimulation of facial muscles in MuSK antibody-positive myasthenia gravis. *Muscle Nerve* 2006;33:500-504. <https://doi.org/10.1002/mus.20498>
- ⁵⁸ Simon NG, Reddel SW, Kiernan MC, et al. Muscle-specific kinase antibodies: a novel cause of peripheral nerve hyperexcitability? *Muscle Nerve* 2013;48:819-823. <https://doi.org/10.1002/mus.23907>
- ⁵⁹ Chroni E, Punga AR. Neurophysiological characteristics of MuSK antibody positive myasthenia gravis mice: focal denervation and hypersensitivity to acetylcholinesterase inhibitors. *J Neurol Sci* 2012;316:150-157. <https://doi.org/10.1016/j.jns.2011.12.016>
- ⁶⁰ Cole RN, Ghazanfari N, Ngo ST, et al. Patient autoantibodies deplete postsynaptic muscle-specific kinase leading to disas-

- sembly of the ACh receptor scaffold and myasthenia gravis in mice. *J Physiol* 2010;588:3217-3229. <https://doi.org/10.1113/jphysiol.2010.190298>
- ⁶¹ Ghazanfari N, Trajanovska S, Morsch M, et al. The mouse passive-transfer model of MuSK myasthenia gravis: disrupted MuSK signaling causes synapse failure. *Ann NY Acad Sci* 2018;1412:54-61. <https://doi.org/10.1111/nyas.13513>
- ⁶² Cole RN, Reddel SW, Gervásio OL, et al. Anti-MuSK patient antibodies disrupt the mouse neuromuscular junction. *Ann Neurol* 2008;63:782-789. <https://doi.org/10.1002/ana.21371>
- ⁶³ Xu K, Jha S, Hoch W, et al. Delayed synapsing muscles are more severely affected in an experimental model of MuSK-induced myasthenia gravis. *Neuroscience* 2006;143:655-659. <https://doi.org/10.1016/j.neuroscience.2006.09.022>
- ⁶⁴ Hesser BA, Henschel O, Witzemann V. Synapse disassembly and formation of new synapses in postnatal muscle upon conditional inactivation of MuSK. *Mol Cell Neurosci* 2006;31:470-480. <https://doi.org/10.1016/j.mcn.2005.10.020>
- ⁶⁵ Liyanage Y, Hoch W, Beeson D, et al. The agrin/muscle-specific kinase pathway: new targets for autoimmune and genetic disorders at the neuromuscular junction. *Muscle Nerve* 2002;25:4-16. <https://doi.org/10.1002/mus.1218>
- ⁶⁶ Punga AR, Maj M, Lin S, et al. MuSK levels differ between adult skeletal muscles and influence postsynaptic plasticity. *Eur J Neurosci* 2011;33:890-898. <https://doi.org/10.1111/j.1460-9568.2010.07569.x>