CHAPTER 5

Myasthenia gravis with muscle specific kinase antibodies mimicking amyotrophic lateral sclerosis.

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ABSTRACT

Muscle-specific kinase (MuSK) myasthenia gravis (MG) is hallmarked by the predominant involvement of bulbar muscles and muscle atrophy. This might mimic amyotrophic lateral sclerosis (ALS) presenting with bulbar weakness. We encountered four cases of MuSK MG patients with an initial misdiagnosis of ALS.

We analysed the clinical data of the four misdiagnosed MuSK MG patients, and investigated the presence of MuSK autoantibodies in a group of 256 Dutch bulbar-onset ALS patients using a recombinant MuSK ELISA and a standard MuSK radio immunoprecipitation assay.

Clues for changing the diagnosis were slow progression, clinical improvement, development of diplopia and absence of signs of upper motor neuron involvement. No cases of MuSK MG were identified among a group of 256 bulbar ALS patients diagnosed according to the revised El Escorial criteria.

A misdiagnosis of ALS in patients with MuSK MG is rare. We recommend to carefully consider the diagnosis of MuSK MG in patients presenting with bulbar weakness without clear signs of upper motor dysfunction.

INTRODUCTION

In myasthenia gravis (MG) with muscle-specific kinase (MuSK) antibodies, bulbar muscles are severely affected throughout the course of the disease (1). Exacerbations often consist of worsening of bulbar symptoms, while ocular muscles are generally spared (2). In addition, MuSK MG patients may have manifestations of muscle fiber hyperexcitability, including fasciculations (3). MuSK MG could be confused with amyotrophic lateral sclerosis (ALS) with bulbar-onset, as previously reported in patients presenting with progressive dyarthria, dropped head or dysphagia (4;5). Obviously, confusing MuSK MG, a treatable disorder, with a fatal disease like bulbar onset ALS, should be avoided. The authors recommended testing for MuSK antibodies as part of the diagnostic work-up of patients with predominant bulbar ALS (3).

Four MuSK MG patients that were referred to one of our neuromuscular centres were initially diagnosed with ALS. This prompted us to investigate the occurrence of MuSK antibodies in a large cohort of ALS patients.

CASE REPORTS

A summary of the four cases is given in table 1.

Case 1

A 69 year old man had problems with swallowing since one year. He lost weight from 75 to 69 kg and developed a dysarthria. Complaints tended to get worse during the day, but did not fluctuate, indicating slow progression of symptoms over time. After walking for half an hour he was unable to hold his head upright. He was known with alternating strabismus since childhood and denied double vision. On physical examination he had severe nasal dysarthria, and could not lift his soft palate. He could not put his tongue in the cheeks nor perform fast alternating movements with his tongue. The left eye was in abducted position, but he did not complain about diplopia. Flexion of the neck was weak, while the limb muscles were strong. Tendon reflexes were brisk, with flexor plantar responses.

Electromyogram showed spontaneous muscle fiber activity in the trapezius and gastrocnemius muscles, and fasciculations in trapezius and deltoid muscles. In several muscles, signs of reinnervation were found. Small polyphasic motor unit action potentials were present in the paraspinal muscles at C7 level.

A diagnosis of progressive bulbar spinal atrophy was made in the referring hospital, based on a pure motor syndrome without fluctuations or diplopia or ptosis. Patient did not fulfill the revised El Escorial criteria, the dysarthria had the aspect of nasal speech, and upper motor neuron signs were lacking. Subsequent doubt, because there was no further progression, led to testing for MuSK antibodies and a muscle biopsy, showing slight variation in fibres size, that were classified as non-specific. Serum MuSK antibodies were found one and a half year after onset of the dysphagia. Treatment with cholinesterase inhibitors worsened his symptoms.

Table 1. Overview of MuSK MG patients with a previous diagnosis of ALS

Patient	Sex	Age at onset	Presenting symptom	Diagnostic delay (months)
1	Male	69	Bulbar weakness	18
2	Female	61	Extremities and bulbar weakness	22
3	Male	56	Bulbar weakness	168
4	Female	64	Dyspnea	4

Immunosuppressive treatment with plasmapheresis, prednisone and azathioprine led to a complete remission.

Case 2

A previously healthy 61 year-old woman presented with progressive weakness in arms and legs since two years. The complaints had started in the right arm, with an inability to raise her arm. In the following two years she developed a comparable weakness in the left arm. She also complained of weakness in both legs with difficulties walking stairs, dysarthria, dysphagia, and difficulty keeping her head erect. There were no fluctuations during the day and no diplopia.

Physical examination showed dysarthria with a nasal speech. Neck extensors, deltoid, triceps, and biceps were weak with wasting of the deltoid muscle bilaterally. She had hip flexor weakness and could not rise from a chair without using the arms. No fasciculations were noted. Knee tendon jerks were brisk bilaterally, with bilateral ankle clonus. Plantar responses were flexor. Laboratory investigations, including CK, thyroid, MRI of head and neck were normal.

Electromyogram showed spontaneous muscle fiber activity and polyphasic potentials in the right flexor carpi radialis muscle, the right first dorsal interosseus muscle and left biceps muscle. In the legs there were signs of denervation and re-innervation bilaterally in gastrocnemius muscle. In the quadriceps and anterior tibial muscle there were only signs of re-innervation. In the paravertebral muscles there were signs of denervation at all investigated levels. Fasciculations were seen in almost all investigated muscles. The patient refused examination of the bulbar muscles.

Bulbar ALS was considered because of weakness and atrophy in the brainstem, cervical and lumbosacral region with denervation in muscles from 3 regions. Riluzole was started. However, the patient did not fulfill the revised El Escorial criteria as signs of upper motor neuron dysfunction were lacking She needed a speech enhancer,

Diagnostic clue	Therapy	Post-intervention status
No progression after initial severe symptoms	Prednisolone, azathioprine, nocturnal ventilator support	Pharmacologic remission
Spontaneous improvement after 12 months	Prednisolone, azathioprine, mycophenylate mofetil, rituximab	Pharmacologic remission
Slow progression and diplopia 4 years after onset of nasal speech and swallowing difficulties	Plasmapheresis, pyridosti gmine, azathioprine	Improved. Stable, moderate bulbar weakness with severe atrophy
Asymmetric ptosis	Plasmapheresis, prednisolone, mycophenolate mofetil, nocturnal ventilator support	Pharmacologic remission

there were increasing swallowing difficulties and progressive axial weakness. Twenty-two months after the initial presentation however, speech and strength spontaneously improved. She was able to speak without mechanical assistance and could lift her arms above her head for the first time in 3 years. ALS was considered unlikely, and the patient was reanalyzed. At that time EMG showed a decrement of 23% on repetitive stimulation in the left m. nasalis, 23% in the right m. trapezius, but no decrement in the right m abductor digiti minimi. Single fiber EMG of the left m. frontalis was normal, with only 2 out of 20 fibers with a jitter above the normal range and no blocking. Serum MuSK antibodies were present. She was treated with prednisolone, azathioprine, mycophenolate mofetil, and rituximab and made a clinical complete remission without any treatment for the last 14 months.

Case 3

A 56-year-old man complained about difficulties moving his lips or tongue, nasal speech and regular choking. He had had a few moments of diplopia, which quickly resolved. In addition to the clinical symptoms above, physical examination showed an increased masseter, nasopalpebral, knee jerk and Achilles tendon reflexes, and absent abdominal skin reflexes. Both plantar reflexes were reported as equivocal extensor. The palmomental and snout reflexes were negative. No fasciculations were seen. Extensive additional tests were normal and included blood, urine, CSF, X-thorax, ECG, and EEG. EMG of the mm. orbicularis oculi and orbicularis oris dexter showed signs of spontaneous muscle fiber activity, while the trapezius, sternocleidomastoid, deltoid, and pectoralis major muscles were normal. A muscle biopsy of the sternocleidomastoid muscle was reported normal. A neostigmine test was negative, but fasciculations were reported to be present in both the right and left mm. pectoralis major and serratus anterior. Bulbar ALS was diagnosed based on weakness, atrophy and spontaneous muscle fiber activity on EMG in the brainstem region, in spite of the fact that signs of upper motor neuron involvement were lacking.

Thus, the patient did not fulfil the revised El Escorial criteria. In the following years the disease stabilized. Myasthenia gravis was considered, but rejected because of the atrophy. Several years later he was seen again and complained about a "thick" tongue, nasal speech, and regular choking, He needed to drink to be able to swallow the food more easily. He lost weight from 67 to 62,5 kg. He experienced difficulties in moving the tongue and complained of weak lip closure. The symptoms showed a slow progression. When asked, he admitted that there might be some minor fluctuations. He had no complaints about weakness of arm or leg muscles.

Physical examination showed pronounced atrophy of the facial musculature and tongue. Frowning, whistling or smiling was not possible. There was severe dysarthria with a nasal voice. The pharynx did not move, also not after sensory stimulation. Eye movements were completely normal. There were no pseudobulbar or increased reflexes, plantar reflexes were normal. Serum MuSK antibodies were positive. He was treated with plasmapheresis without a clear response. Immunosuppressive treatment with prednisone and azathioprine for several months induced a mild speech improvement, but no major change was seen, most likely due to the severe atrophy.

Case 4

A 64 year old female, without relevant medical history, suffered from unexplained dyspnea by the end of 2002. After a couple of weeks, she was referred to a cardiologist, who found no abnormalities. In the next four weeks, some nasal dysarthria and hoarseness developed with a diurnal variation. Furthermore slight swallowing problems were reported. There were no abnormalities at clinical examination, but a progressive pseudobulbar palsy was surmised. Electromyography showed no abnormalities, for reasons of completeness 3 Hz repetitive nerve stimulation was performed in the upper extremities without finding any decrement. Clinical symptoms worsened, especially her dyspnea, and the diagnosis of ALS was made, although there were no signs of upper motor neuron involvement, and the patient did not fulfil the revised El Escorial criteria. Another EMG-investigation again showed no neurogenic abnormalities. Eventually, she was referred to another center for chronic ventilary support and she ended up in the respiratory care unit with severe dyspnea and moderate bulbar symptoms as described. There the diagnosis myasthenia was suggested by an asymmetric ptosis. No acetylcholine receptor antibodies were found, EMG with repetitive nerve stimulation at the ICU was normal again. She was treated with plasma-exchange and high-dose steroids and recovered completely within 2 weeks. Thereafter the clinical course was fluctuating with tapering and increasing of the medication. She remained on nocturnal ventilator support for four years. Anti-MuSK-antibodies were found in 2005. She is now free of symptoms on a decreasing dose of mycophenolate mofetil since 2008.

METHODS

Sera of 256 patients diagnosed with ALS, and fulfilling the revised El Escorial Criteria for possible, probable laboratory-supported, probable or definite ALS were included. Patients were identified from 1 January 2006 to 1 September 2011 in a large, prospective population based case control study on ALS in the Netherlands (6). All ALS patients had a bulbar onset. Twenty patients with MuSK MG and oculobulbar weakness were used as positive controls. Twelve healthy controls or patients with other autoimmune diseases were included as controls. Information on the previous diagnosis in 18 other Dutch MuSK MG patients was collected from the patient files. The studies were approved by the Medical Research Ethics Committee of the University Medical Centers of Utrecht and Leiden.

Sera were tested twice for MuSK antibodies using an ELISA based on recombinant MuSK (7). These experiments were blinded and performed in duplicate. A sample was considered positive when it had reactivity to MuSK above average background reactivity plus 3 times standard deviation. Samples that fulfilled these requirements were tested in duplicate in a standard diagnostic radio-immunoprecipitation assay (RIA) for MuSK reactivity (RSR, Cardiff, UK).

RESULTS

Average MuSK reactivity in ELISA is presented in Figure 1a. Twenty-four (9%) ALS sera gave signals just above background at least once. All these samples were measured a third time and 9 tested above background at least twice in three experiments. In a MuSK RIA 24 double positive samples were negative (Fig. 1b). In conclusion, none of the 256 tested ALS sera contained MuSK antibodies. In 18 confirmed MuSK MG patients an earlier diagnosis of seronegative MG (12x), Lambert-Eaton myasthenic syndrome (1x), chronic progressive external opthalmoplegia (1x), facioscapulohumeral muscular dystrophy (1x), or acquired inflammatory myopathy (1x) was made. However, motor neuron disease was not considered in any of these patients before the diagnosis of MuSK MG.

DISCUSSION

The clinical presentation of MuSK MG can be confused with that of bulbar ALS, or progressive spinal muscular atrophy, causing a diagnostic delay or inappropriately withholding an effective treatment. The diagnostic delay in our four patients was between one and 3 years, while an earlier publication described one patient that was diagnosed four years after onset of symptoms (3). All patients presented with prominent bulbar weakness without diplopia. One patient experienced temporary diplopia at the onset of the disease. In MuSK MG, 5% of patients never have ocular muscle involvement. This is in contrast to non–MuSK MG, where ocular muscles are almost always involved at some point (2). Two patients admitted to have fluctuations at the onset of symptoms, but around the time of diagnosis, weakness appeared

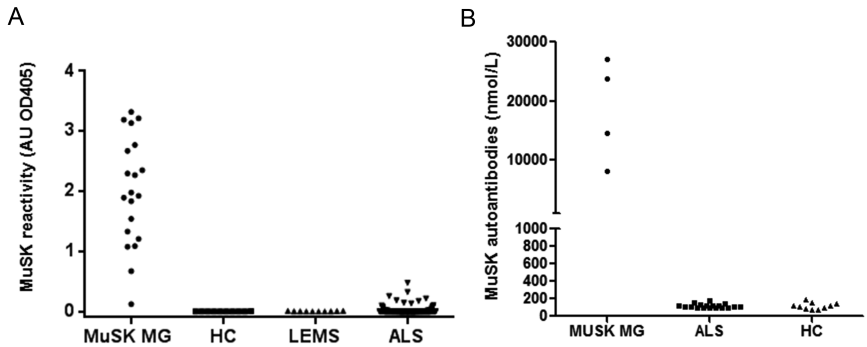

Figure 1: MuSK reactivity levels in sera from ALS patients, MuSK MG patients and controls measured by ELISA (a) and RIA (b).

rather stable. In addition, fasciculations were recorded in three patients, which often are seen as a sign of motor neuron disease. Preferential involvement of bulbar muscles in MuSK MG has been well documented and is probably due to the lower expression level of the MuSK protein in these muscles (2;8). Also, one third of patients with ALS start with bulbar weakness (9). It should be stressed that none of our four patients had clear signs of upper motor neuron dysfunction, and the dysarthria was characterized by a nasal voice, although clinical distinction between flaccid, spastic or mixed dysarthria can be quite difficult (10). Thus, none of these patients fulfilled the revised El Escorial criteria for ALS. We tested 256 sera from bulbar ALS patients diagnosed according to revised El Escorial criteria in a tertiary center and none were positive for MuSK antibodies, suggesting that a false-negative diagnosis of MuSK MG is not common among patients with bulbar ALS diagnosed if the revised El Escorial criteria are properly used. In conclusion, we would not recommend to routinely check all ALS patients for MuSK antibodies. However, prominent bulbar weakness, a prolonged disease course or minor fluctuations, and the absence of signs of upper motor neuron involvement should alert the physician.

REFERENCE LIST

1. Evoli A, Tonali PA, Padua L, Monaco ML, Scuderi F, Batocchi AP, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 2003 Oct;126(Pt 10):2304-11.
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 Jul;44(1):36-40.
3. Simon NG, Reddel SW, Kiernan MC, Layzer R. Muscle-specific kinase antibodies: a novel cause of peripheral nerve hyperexcitability? Muscle Nerve 2013 Nov;48(5):819-23.
4. Burrell JR, Vucic S, Kiernan MC. Isolated bulbar phenotype of amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2011 Jul;12(4):283-9.
5. Furuta N, Ishizawa K, Shibata M, Tsukagoshi S, Nagamine S, Makioka K, et al. Anti-MuSK Antibody-positive Myasthenia Gravis Mimicking Amyotrophic Lateral Sclerosis. Intern Med 2015;54(19):2497-501.
6. Huisman MH, de Jong SW, van Doormaal PT, Weinreich SS, Schelhaas HJ, van der Kooi AJ, et al. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry 2011 Oct;82(10):1165-70.
7. Huijbers MG, Zhang W, Klooster R, Niks EH, Friese MB, Straasheijm KR, et al. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. Proc Natl Acad Sci U S A 2013 Dec 17;110(51):20783-8.
8. Punga AR, Maj M, Lin S, Meinen S, Ruegg MA. MuSK levels differ between adult skeletal muscles and influence postsynaptic plasticity. Eur J Neurosci 2011 Mar;33(5):890-8.
9. Chio A, Calvo A, Moglia C, Mazzini L, Mora G. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry 2011 Jul;82(7):740-6.
10. Van der Graaff M, Kuiper T, Zwinderman A, Van de Warrenburg B, Poels P, Offeringa A, et al. Clinical identification of dysarthria types among neurologists, residents in neurology and speech therapists. Eur Neurol 2009;61(5):295-300.