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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 analyzed 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 radioimmunorecipitation 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 neuron dysfunction.

Keywords: Amyotrophic lateral sclerosis; Myasthenia gravis; MuSK; Neuromuscular junction; IgG4

1. 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 centers were initially diagnosed with ALS. This prompted us to investigate the occurrence of MuSK antibodies in a large cohort of ALS patients.

2. Case reports

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

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

Patient	Sex	Age at onset	Presenting symptom	Diagnostic delay (months)	Diagnostic clue	Therapy	Post-intervention status
1	Male	69	Bulbar weakness	18	No progression after initial severe symptoms	Prednisolone, azathioprine, nocturnal ventilator support	Pharmacologic remission
2	Female	61	Extremities and bulbar weakness	22	Spontaneous improvement after 12 months	Prednisolone, azathioprine, mycophenylate mofetil, rituximab	Pharmacologic remission
3	Male	56	Bulbar weakness	168	Slow progression and diplopia 4 years after onset of nasal speech and swallowing difficulties	Plasmapheresis, pyridostigmine, azathioprine	Improved. Stable, moderate bulbar weakness with severe atrophy
4	Female	64	Dyspnea	4	Asymmetric ptosis	Plasmapheresis, prednisolone, mycophenolate mofetil, nocturnal ventilator support	Pharmacologic remission

2.1. Case 1

A 69 year old man had problems with swallowing since one year. He lost weight from 75 kg 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 fiber sizes 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. Immunosuppressive treatment with plasmapheresis, prednisone and azathioprine led to a complete remission.

2.2. 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 and 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.