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Research Report

Dysautonomia as the Presenting Symptom in Anti-Muscle-Specific Kinase Antibody Myasthenia Gravis

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Abstract. In an minority of Myasthenia Gravis (MG) patients, the autoantibodies bind to muscle-specific kinase (MUSK). These MuSK antibody-mediated MG (MuSK MG) patients are not only immunologically distinct, but also have different characteristic clinical features. Dysautonomia in MG is rarely reported. We present a MuSK MG patient who suffered from life-threatening autonomic dysfunction. MuSK MG should be considered in the differential diagnosis in cases of unclarified dysautonomia, given the potential for treatment in those cases.

Keywords: Myasthenia gravis (MG), muscle-specific kinase (MuSK), anti-MuSK antibody myasthenia gravis (MuSK MG), dysautonomia, autonomic dysfunction

HIGHLIGHTS

- The patient suffered from unclarified episodes of transient loss of consciousness.
- MuSK MG patients have different characteristic features, including dysautonomia.
- Physicians should consider MuSK MG in patients with autonomic dysfunction.

INTRODUCTION

Myasthenia gravis (MG) is an auto-immune disease of the neuromuscular junction (NMJ) in which antibodies against different targets on the post-synaptic muscle membrane impair neuromuscular transmission. Antibodies to the acetylcholine receptor (AChR) are found in the majority of cases, whereas in a minority of patients the autoantibodies bind to muscle-specific kinase (MuSK) [1]. MuSK is a transmembrane tyrosine receptor kinase that is crucial for the development and maintenance of AChR clusters at the NMJ [2]. Pathogenic antibodies are mainly of the IgG4 subclass and inhibit Agrin-stimulated MuSK activation by preventing the interaction between MuSK and lipoprotein receptor-related protein 4 (Lrp4) [3]. MuSK antibody-mediated MG (MuSK MG) patients are not only immunologically distinct, but also have different characteristic clinical features. They often present with a pattern of weakness of the neck, bulbar, shoulder girdle and respiratory muscles. Dysautonomia in MG is rarely reported [4]. We present a case of MuSK MG in which autonomic dysfunction was life threatening.

CASUS

A 58-year man was admitted to our Emergency Unit with his fifth episode of transient loss of consciousness (TLOC), lasting 2-3 minutes, while

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descending a staircase. The first TLOC had occurred five weeks earlier, one day after prostatectomy surgery because of a neoplasm. This TLOC was, preceded by a sensation of shortness of breath, sweating, and light-headedness for several seconds. In the weeks following, he suffered three TLOCs after arising from a couch or a bed, or leaving the shower. After two to three minutes, he would fully regain his consciousness. Usually he tried to lay down as soon as possible when the preceding symptoms occurred in order to prevent losing consciousness. A diagnosis of idiopathic orthostatic hypotension had been made at an Emergency Unit elsewhere, and he had been sent home without further treatment. His family had witnessed TLOCs and confirmed this history. Myoclonic movements or urine incontinence had not been observed.

Physical examination showed a sinus tachycardia of 113 bpm and tachypnoea of 22 breaths per minute. In supine position, blood pressure was 171/107 mmHg with a heart rate of 110 bpm. In upright position, blood pressure decreased to 105/61 mmHg with a slight increase in heart rate up to 120 bpm after which he immediately recognized the symptoms described above. Laboratory results showed an elevated D-dimer (537 ng/l, normal value <500 ng/ml) and an arterial hypercapnia (pCO2 8.0 kPa, normal value 4.7–5.9 kPa) with an elevated bicarbonate (31 mmol/l, normal value 21–27 mmol/l). ECG was normal. CTA-thorax excluded pulmonary embolism. He was hospitalized for further analysis. To the consulting neurologist he mentioned having difficulty lifting his head from the pillow since the surgery 5 weeks prior. In addition, his whole body felt weak and he experienced instability in his legs when standing. He further complained about a lack of appetite, and difficulties swallowing food and water since about two weeks. His vision was blurred and he had double vision looking to the left or right side ever since the first TLOC.

Neurological examination showed a cachectic, mildly dyspnoeic man with a respiration frequency of 35 breaths per minute and superficial breathing. He had difficulty swallowing and spoke in a low voice, but without dysarthria. He had a slight bilateral ptosis. Ocular movements were limited in both horizontal and vertical directions without fluctuations. Eye closing was incomplete for the right side. Frowning was diminished. He could not lift his head from the pillow. His legs were atrophied and fasciculations were seen in the left arm and lower leg. Paresis was also found in the proximal arms (MRC 4/4) and legs (m. iliopsoas MRC 4/4, hamstrings MRC 4/4, m. quadriceps MRC 4/4). There was no sensory impairment, reflexes were normal, and there was no ataxia.

Later that day, the patient was not feeling well. While sitting in bed he lost consciousness (Glasgow Coma Score 3) with a blood pressure of 75/35 mmHg and a regular pulse. His breathing was insufficient with periods of apnoea, and salivation. Because of stiffening of the jaws, a mayo tube could not be inserted. At the arrival of the Rapid Response Team, he suffered a cardiac arrest. The initial heart rhythm was Pulseless Electrical Activity (PEA). Cardiopulmonary resuscitation was started and spontaneous circulation returned within five minutes. The cause of the in hospital cardiac arrest with PEA was thought to be secondary to hypoxia due to prolonged hypoperfusion, apnoea, and airway obstruction. Because of the combination of muscle weakness, speech and swallowing difficulties, and fluctuating ptosis, a myasthenic crisis was suspected. Prednisolone (1 mg/kg/day) for 10 days and intravenous immunoglobulin (0.4 mg/kg/day) for five days were started. Initially, his symptoms improved. However, in the following weeks his ophthalmoparesis alternated, and he again suffered from recurrent episodes of hypotension, apnoea, and tachycardia.

AChR antibodies were negative (0,4 nmol/l, normal value <0,5 nmol/l). An MRI of the brain showed mild frontal leukoaraiosis. Cerebral spinal fluid, including paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ri, anti-Tr, ant-Ma1/2, anti-CV2 (CRMP5), anti-amphiphysin) and anti-ganglioside antibodies (anti-GM-1, anti-GM-2, anti-GQ1B, anti-GD1A) was normal. Two EMGs, including repetitive stimulation of the ulnar nerve, done with an interval of six days revealed no abnormalities. Tracheotomy was performed because of expected long-term need of respiratory support. Three weeks after admission, MuSK antibodies were found to be positive. MuSK antibodies were assessed by a commercial MuSK ELISA (IBL International).The MuSK antibody concentration, calculated as a positive:negative ratio was 20 (reference value <1). The patient was now treated with plasma-exchange and azathioprine 50 mg t.i.d. Prednisolone was restarted at 1 mg/kg/day. Ten days later, he was decannulated and he could be dismissed from the hospital for outpatient medical rehabilitation three weeks after the initiation of this second treatment episode. After a few months, the orthostatic symptoms had resolved. Two years later, taking

azathioprine 50 mg, three times a day and 20 mg prednisolone, he had no symptoms except for less stamina physically.

DISCUSSION

The autonomic nervous system controls basic functions such as heart rate, breathing rate, sweat glands and the digestive system. Dysautonomia, the condition in which the autonomic nervous system does not work properly, may result in orthostatic intolerance, whereby an upright position triggers symptoms of light-headedness, nausea, sweating, and transient loss of conscience, due to a fall in blood pressure. Other features are an inability to alternate heart rate with exercise, digestive difficulties such as diarrhoea, constipation, and loss of appetite. Autonomic dysfunctions of glands lead to inadequate sweating. Vision may be affected by the inability of the pupils to react to light leading to a blurred vision. Often there is voiding and sexual dysfunction [5, 6]. Dysfunction of the autonomic nervous system is associated with a range of neurodegenerative disorders such as Parkinson's disease, pure autonomic failure, multi system atrophy, as well as all kinds of neuropathies [6]. Dysautonomia is not widely recognized as part of the clinical presentation of MG. One study showed different degrees of autonomic impairment in subgroups of MG [4]. The majority of patients with AChR-positive thymoma-associated MG (N = 27) in this study had some clinical signs of autonomic failure, most frequently urinary and sexual dysfunction and warmth intolerance. In the group of thymoma-negative AChR-positive MG patients (N = 25), similar clinical signs of autonomic dysfunction were present in about half of the patients. Of the 23 MuSK MG patients, 18 were found to suffer from autonomic dysfunction, in particular orthostatic related dizziness, warmth intolerance, dry mouth, and sexual dysfunction. Another case report described a patient who complained of orthostatic and warmth intolerance with a heart rate of 150–170 bpm mostly during standing, one month after being treated for MuSK-MG with prednisolon and azathioprine. ECG showed signs of paroxysmal supraventricular tachycardia along with the presence of pre-excitation syndrome. After two months of treatment with mycophenolate mofetil, heart rate alterations improved [7]. A recent study into the spectrum of autonomic dysfunction in patients with a myasthenic crisis found that 15 of the 16 patients scored on the COMPASS questionnaire for autonomic dysfunction, mostly involving the gastrointestinal (80%), orthostatic, pupillomotor (both 67%), and sudomotor domains (33%) [8]. Of these 16 patients, only nine were AChR antibody positive, but the presence of anti-MuSK antibodies was not investigated in remaining seven. The authors suggested damage to the postsynaptic AChR resulting in lower excitatatory potentials and increased latency in feedback loops as a causative factor.

In peripheral autonomic ganglia, AChRs are expressed by neurons in sympathetic, parasympathetic, and enteric ganglia, in a similar way as the muscle AChRs at the neuromuscular junction. Defective ganglionic transmission would thereby cause autonomic failure [9]. Autonomic dysfunction in MG may also be due to antibodies to components of the heart and the autonomic system such as the anti-voltage-gated K+ channel subunit Kv 1.4 as suggested in a study of 650 anti-AChR antibody positive patients [10]. However, MuSK-MG patients in general have no antibodies against the AChR or antigens outside the neuromuscular junctions such as titin or the ryanodine receptor, generally referred to as antistriated muscle antibodies [11]. Although the skeletal muscle cell is the major site for MuSK expression, MuSK is also expressed in the central nervous system, where it is concentrated at excitatory synapses. Here, its role is poorly understood [2, 12]. Although there is no clear explanation for the role of MuSK antibodies in autonomic failure, the resolution of these symptoms upon immunosuppressive treatment after a follow-up of 2 years suggests a causal relationship.

We present a MuSK MG patient who suffered from life-threatening autonomic dysfunction. Considering the close relation between the treatments and the resolving of symptoms, we assume a causal relationship between the dysautonomia and the MuSK MG. MuSK MG should be considered in the differential diagnosis in cases of unclarified dysautonomia, given the potential for treatment in those cases.

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