



A misdiagnosed myasthenia gravis with anti-muscle-specific tyrosine kinase antibodies with possible childhood onset

Pogrešno dijagnostikovana miastenija gravis sa antitelima prema tirozin kinazi specifičnoj za mišić sa mogućim početkom u detinjstvu

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Abstract

Introduction. Childhood onset myasthenia gravis associated with anti-muscle-specific tyrosine kinase antibodies is very rare and atypical in presentation. **Case report.** As a baby, the presented patient was choking and sleeping with open eyes. She had weak cry and breathing difficulties. In childhood, there were frequent falls and fluctuating swallowing difficulties. At the age of 19 she was misdiagnosed with Miller Fisher syndrome due to the presence of diplopia, ataxia and hyporeflexia with spontaneous recovery. Repetitive nerve stimulation test was normal. Four years later, after several relapses, there was significant decrement on facial muscles. Neostigmine test was negative, provoking muscle fasciculations. Serum anti-muscle-specific tyrosine kinase antibodies were positive. With cyclosporine therapy she achieved the minimal manifestations status. **Conclusion.** The presented case confirms that childhood onset myasthenia gravis associated with anti-muscle-specific tyrosine kinase antibodies is often with atypical presentation and spontaneous remissions, so it could be easily misdiagnosed.

Key words:

myasthenia gravis; child; diagnosis, differential; antibodies; protein-tyrosine kinases.

Apstrakt

Uvod. Miastenija gravis udružena sa antitelima prema tirozin kinazi specifičnoj za mišić u dečijem uzrastu veoma je retka i sa atipičnom prezentacijom. **Prikaz bolesnika.** Kao beba, prikazana bolesnica gušila se i spavala sa otvorenim očima. Slabo je plakala i imala je smetnje sa disanjem. Tokom detinjstva, imala je česte padove i fluktuirajuće smetnje sa gutanjem. U uzrastu od 19 godina pogrešno joj je postavljena dijagnoza Miller Fisher sindroma zbog pojave diplopija, ataksije i hiporefleksije sa spontanom oporavkom. Test repetitivne stimulacije bio je negativan. Četiri godine kasnije, posle nekoliko relapsa, registrovan je značajan dekrement na mišićima lica. Neostigmin test bio je negativan, provocirajući mišićne fascikulacije. Serumaska antitela prema tirozin kinazi specifičnoj za mišić bila su pozitivna. Uz terapiju ciklosporinom postignut je status sa minimalnim manifestacijama. **Zaključak.** Ovaj prikaz ukazuje na činjenicu da je miastenija gravis sa antitelima prema tirozin kinazi specifičnoj za mišić u dečijem uzrastu često atipične kliničke prezentacije i sa spontanom remisijama, tako da se može lako prevideti prilikom postavljanja dijagnoze.

Ključne reči:

miastenija gravis; deca; dijagnoza, diferencijalna; antitela; protein kinaze.

Introduction

Anti-muscle-specific tyrosine kinase antibodies (anti-MuSK Ab) have been found in around 50% of acetylcholine receptor (AChR) negative myasthenia gravis (MG) patients¹. MuSK positive MG is a clinically separate entity¹ and it usually affects young adults. It is extremely rare in pediatric population and it has been described in only several case reports and one small case series² so far.

We presented misdiagnosed patient with MuSK positive MG, who might have the childhood disease onset.

Case report

The presented female patient was born prematurely, in the 7th month. She was choking during breast feeding and was sleeping with her eyes open. She did not cry and there were difficulties in breathing. She had slower motor development

and started walking at the age of 2 years. During the whole childhood, there were fluctuating swallowing difficulties and frequent falls without loss of consciousness. At the age of 11, she had Henoch Schonlein purpura.

She was examined in our Clinic for the first time at the age of 19 years. At that time, after the flu, she presented with double vision, right eyelid drop, slight dysphagia and nasal speech with more severe presentation in the evenings.

Neurological examination revealed right eyelid ptosis, diplopia, nasal speech, mild hypotonia, diminished muscle stretch reflexes and mild ataxia of the right leg. Repetitive nerve stimulation test of the deltoid and nasal muscle was normal. At that point, the patient was diagnosed with Miller Fisher Syndrome, but additional investigations showed normal nerve conduction studies and cerebrospinal fluid findings. The spontaneous recovery appeared with the persistence of only mild right eyelid ptosis.

During the next several years the patient had several relapses of the same symptoms, always with spontaneous recovery. One of the most severe exacerbations started after respiratory infection four years after the first admission.

At that time, neurological examination revealed bilateral ptosis, facial muscle weakness, nasal speech, dysarthria, dysphagia and severe tongue weakness. Neostigmine test was negative, provoking severe muscle fasciculations. Repetitive nerve stimulation test showed decremental response on nasal muscle (47%), while it was normal on deltoid muscle. Electromyography revealed myopathic pattern in the facial muscles. Single fibre electromyography showed mildly increased jitter only in *orbicularis oculi* muscle and normal finding in *extensor digitorum communis* muscle. Brain magnetic resonance imaging showed extensive cortical atrophy of the right cerebellar hemisphere. At this point, the diagnosis of myasthenia gravis was made. Serum anti-AChR antibodies were negative (< 0.2 nmol/L), while anti-MuSK antibodies were positive (0.43 nM; normal < 0.05 nM). Chest computed tomography scan was normal. Treatment with small dose of pyridostigmine and prednisone was initiated and 6 months later she has significantly improved with the persistence of only mild facial muscle weakness. The favourable effect of this therapy was temporary, so in the later course of the disease, due to frequent relapses, cyclosporine was introduced in the dosage of 300 mg *per* day. Since then, our patient has significantly improved, achieving the minimal manifestations status. For the last five years the presented patient has been without any symptoms, and in the neurological examination only with signs of persistent mild facial muscle weakness and mild right leg ataxia due to the right cerebellar hemisphere atrophy. We also performed serum anti-low density lipoprotein receptor related protein 4 (Lrp4) antibody analysis and it was negative.

Discussion

MuSK MG is a rare form of this disease and it usually affects adults. There have been only a few cases of childhood onset MuSK MG reported so far. We presented a case of initially misdiagnosed MuSK MG with the possible childhood onset. We are aware of the fact that most of the symptoms present at birth

were most likely due to the prematurity, but fluctuating swallowing difficulties throughout the years spoke in favour of MG. When our patient was admitted to our Clinic for the first time, the clinical expression was atypical, partially due to the unknown presence of cerebellar atrophy, which led to the erroneous diagnosis of Miller Fisher syndrome. In the later course of the disease, the patient had variable symptoms, which were consistent with MuSK MG: ptosis, double vision, facial muscles weakness, dysphagia, dysphonia and tongue weakness¹. Before establishing the correct diagnosis, the patient had several episodes of exacerbations of these symptoms, but always with spontaneous recovery. There was incomplete response with hypersensitivity to anticholinesterases and variable response to corticosteroids, which is also consistent with MuSK MG¹. A significant improvement was achieved after introduction of cyclosporine. This reactivity to immunotherapy and the presence of anti-MuSK antibodies ruled out the congenital myasthenic syndrome. Also, our patient's mother did not have MG, she was negative for both anti-AChR and anti-MuSK antibodies, so our patient did not have transient neonatal MG.

During the first admission, repetitive nerve stimulation test was negative and it became positive several years later, which is consistent with the fact that almost half of MuSK MG patients have no decrement on repetitive nerve stimulation test¹. Another finding in our patient, consistent with MuSK MG was the presence of decremental response to repetitive nerve stimulation test and increased jitter on single fiber electromyography only in the facial muscles and normal findings in the extremity muscles. Facial muscles are known to be among most severely affected in MuSK MG patients and electrophysiological tests are often positive only in these muscles¹, which implicates the necessity of their electrophysiological examination. The presented patient also showed signs of myopathic lesion in the facial muscles on electromyography, which was the reason for their persistent weakness. Such myopathic pattern is also typical for MuSK MG¹.

We assume that the onset of the disease in the presented patient was in early childhood. Most of the symptoms present at birth could be explained by the prematurity, but fluctuating swallowing difficulties throughout the whole childhood and adolescence and the absence of any symptoms presently speak in favour of MG. After extensive investigations and clinical follow up we concluded that our patient had childhood onset MuSK positive MG with incomplete response to anticholinesterases and variable response to corticosteroids. A significant and long-term improvement was achieved after introduction of cyclosporine.

The presented case, together with other cases of childhood onset MuSK MG published so far, signifies that MuSK MG is not an adult onset disease and that it can affect also very young children. At that age, it is often with atypical presentation, so it could be easily misdiagnosed, as was in the presented patient. Also, another characteristic of childhood onset MuSK MG is the presence of spontaneous and some time long remissions, present also in our patient and other published cases³⁻⁵. On the other hand, such spontaneous remissions are extremely rare in adult onset MG associated with anti-MuSK antibodies.

Conclusion

MuSK MG is very rare in pediatric population and it often has certain peculiarities different from adult onset disease. Due

to often atypical clinical presentation and spontaneous remissions it can easily be misdiagnosed. So, cases like the presented one are very valuable for better understanding of the very broad spectrum of MuSK MG.

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