CASE REPORT

Congenital familial myasthenic syndromes: disease and course in an affected dizygotic twin pair

Piero Pavone,¹ Andrea Domenico Praticò,² Vito Pavone,³ Raffaele Falsaperla¹

¹Unit of Pediatrics and Pediatric Emergency, University Hospital OVE-Policlinico, Catania, Italy

²Unit of Clinical Pediatrics, University Hospital OVE-Policlinico, University of Catania, Catania, Italy

³Unit of Orthopaedics, University Hospital OVE-Policlinico, University of Catania, Catania, Italy

Correspondence to

Dr Piero Pavone,
ppavone@mbox.unict.it

SUMMARY

The present report describes clinical variability in an affected dizygotic twin pair. Twin 1 showed classical features of the congenital myasthenic syndromes (CMS), that is, ptosis, dysphonia, asthenia and hypotonia. In twin 2, these clinical signs were less pronounced, but subtle resulting in severe lumbar hyperlordosis. Molecular analysis, performed for both twins, revealed the presence of three polymorphisms in the heterozygous form in RAPSN gene. The present report highlights the clinical variability of the CMS.

BACKGROUND

Congenital myasthenic syndromes (CMS) are uncommon disorders of neuromuscular transmission, classified into three subgroups according to the affected component of the neuromuscular junction: presynaptic, postsynaptic or synaptic basal lamina-associated.¹

We herein report on dizygotic twins, heterozygous for RAPSN gene mutation, affected by postsynaptic CMS who showed clinical variability and different course.

CASE PRESENTATION

The male twins were born at 34 weeks of gestation with two chorions. Parents were healthy and non-consanguineous.

Twin 1

The child was born with talipes equino-varus, treated with Ponseti casts. Since the first months of life, the child showed bilateral ptosis more evident in the right, dysphonia and dysphagia, smooth voice and respiratory failure. Afterwards he, also, complained of hypotonia, frequent fall down and muscle pain. During the subsequent years some clinical signs such as ptosis, dysphagia and smooth voice spontaneously became less frequent while hypotonia, muscular fatigue persisted.

The child was first admitted at the Pediatric Unity Hospital Vittorio-Emanuele of Catania, Italy at 6 years of age. Myasthenic syndrome was soon suspected. Laboratory test showed no alteration in the blood cell count, erythrocyte sedimentation rate, reactive protein, ammonia and lactate. Cranial MRI, electroencephalography and abdominal ultrasonography were normal as were sensory nerve conduction and motor conduction velocity and electromyography. A decrease on the 3 and 5 Hz repetitive stimulations in abductor digiti minimi and abductor pollicis brevis muscles was observed.

Acetylcholine receptor (AChR) antibodies were negative. The tensilon test was positive and treatment with pyridostigmine therapy was started with dosage of 60 mg three times daily. Treatment was initially unsatisfactory and a few months later, the child was submitted to muscle biopsy which gave normal results. The increase of the treatment of pyridostigmine four times a day resulted in an improvement of the clinical signs.

The patient was again admitted at our unit at the age of 9.5 years. Physical examination was normal. He showed good school performances, with an IQ of 98. Recently, at the treatment with pyridostigmine was joined bromide pyridostigmine 3/4 tablet. This resulted in an improvement in his clinical condition during the night. Delay of treatment causes asthenia, muscular fatigue and sometimes ptosis after 20 min.

Twin 2

The parents reported that he had begun to complain of muscle fatigue and weakness at the age of 2.5 years, but less intense than his twin. He had frequent fall down episodes and difficulty in running. He also showed waddling gait, internal rotation of the right foot, difficulty in jumping and dyspnoea after exertion. By the age of 8 years, he had developed mild kyphosis with pelvic and scapular asymmetry with the right side higher than the left.

He came at our observation at the age of 7.5 years. Sensory nerve conduction and motor conduction velocity and electromyography were normal. No decrease in the repetitive muscular stimulation was observed. AChR antibodies were negative. Tensilon test was positive and the treatment was started with pyridostigmine 60 mg every 6 h. The scholastic performance was good.

At the present age of 11 he showed a severe lumbar hyperlordosis (figure 1). As his brother, he complains of asthenia and signs of fatigue, but about 1 h after delay in the treatment.

Molecular analysis

Parents were negative for known mutations.

In the twins analysis for the detection of the known RAPSN gene (11p11.2) mutations A25V, R91L, L361R and K373del in TE671 cells, and mutations in CHRNA1, CHRNE and the CHRNE promoter was negative. Three polymorphisms were detected: c.456t>c (p.Y152Y) in exon 2; c.1143T>C (p.P81P) in exon 7 and IVS3-11delC in intron 3.

To cite: Pavone P, Praticò AD, Pavone V, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007651

Figure 1 Severe hyperlordosis in twin 2 at the age of 11.

DISCUSSION

The dizygotic twins were affected by CMS of postsynaptic type. The diagnosis was made on personal history, on dynamic signs and symptoms and positive response to pyridostigmine, while other diagnostic results (electrophysiological and muscle biopsy) were inconclusive.

Clinical features of CMS in twin 1 were more evident than in twin 2, and disease onset was earlier (see table 1). Furthermore, twin 1 showed features absent in twin 2, such as, bilateral ptosis, dysphonia, dysphagia and episodes of respiratory insufficiency. Clinical course was progressive in twin 1 and mildly progressive in twin 2. However, even if the clinical muscular signs were more relevant in twin 1 its progresses more subtly in the twin 2 causing a severe lumbar hyperlordosis.

As happened in the twins, the results of ancillary tests (muscle biopsy or electrophysiological studies) may be misleading. In fact, muscle biopsy often reveals non-specific myopathic features,^{2 3} while neurophysiological studies may fail to demonstrate a positive response to repetitive nerve stimulation (RNS), in about 25% of the cases.^{4 5} Although single fibre electromyography-jitter may be more sensitive for the detection of a disturbance of the neuromuscular junction than RNS, the results of the examination in affected cases may be within the normal range.⁴

The majority of CMS patients present with mutations within the RAPSN coding region and are usually homozygous for N88K or heteroallelic for a second mutation;^{6–8} rapsyn binds to the long cytoplasmatic loop of the AChR subunits and is essential for the clustering and anchoring of the AChR within the postsynaptic membrane. Mutations in rapsyn cause endplate AChR deficiency and thus compromise the safety margin of neuromuscular transmission.

The molecular analysis performed in the twins disclosed the presence of three polymorphisms (c.456t>c (p.Y152Y) in exon 2; c.1143T>C (p.P81P) in exon 7 and IVS3-11delC in intron 3) in heterozygous form.

The molecular polymorphism reported in our patients seems not to correlate with the disease presented by the twins. In fact, two of the polymorphisms in exons 7 and 2 do not cause amino acid changes and thus cannot be related with the effect on the disease. The third mutation, being intronic, may have acted in the twins as transcriptional or conformational changes of the protein, but this would need further investigations, not performed in our patients.

Reported cases of CMS in twins are rare. Nishida *et al*⁹ described two siblings with congenital myopathy, myasthenic features and cataracts. In these patients the muscle weakness fluctuated, and was alleviated by edrophonium chloride.

In our patients, remarkable was the variability of the clinical signs and the different clinical course even if the response to the treatment was effective in both the children.

Table 1 Clinical features of the twins

Twin	Clinical signs at birth	Clinical signs at 1 year	Age at diagnosis Clinical signs	Complementary laboratory findings	Follow-up at 11 years		
					Treatment	Response to treatment	Onset of clinical signs after delay of treatment (min)
1	Talipes equino-varus	Bilateral ptosis Smooth voice Dysphonia and dysphagia Respiratory failure	6 years Muscle fatigue Unilateral ptosis Muscle pain Asthenia	Decrease on the 3 and 5 Hz repetitive stimulations in abductor digiti minimi and abductor pollicis brevis muscles	Pyridostigmine and pyridostigmine bromure	Good	20
2	–	–	7.5 years Muscle fatigue Hypotonia	–	Pyridostigmine	Good	60

Learning points

- ▶ Congenital myasthenia is a rare disease. Prevalence is estimated in 1–2/500 000 newborns.
- ▶ The patients were twins born from two chorions. They showed clinical variability, one of them being more affected.
- ▶ Initial clinical signs in twin 1 were smooth voice, easy fatigability and bilateral ptosis; in twin 2 the clinical signs appeared later and were less evident but had subtle course resulting in progressive lumbar hyperlordosis.
- ▶ In the twin molecular analysis revealed the presence of three polymorphisms in heterozygosis in RAPSN gene.
- ▶ Treatment with pyridostigmine was diagnostic and efficacy in both twins.

Acknowledgements We wish to thank Professor Raffaella Brugnoli, Laboratory NBS Biotech, Fondazione Istituto Neurologico Carlo Besta, Milan, for molecular analysis and Bioedit Ltd for editing the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Engel AG, Sine SM. Current understanding of congenital myasthenic syndromes. *Curr Opin Pharmacol* 2005;5:308–21.
- 2 Gurnett CA, Bodnar JA, Neil J, *et al.* Congenital myasthenic syndrome: presentation, electrodiagnosis, and muscle biopsy. *J Child Neurol* 2004;19:175–82.
- 3 Bonifati DM, Willcox N, Vincent A, *et al.* Lack of association between acetylcholine receptor epsilon polymorphisms and early-onset myasthenia gravis. *Muscle Nerve* 2004;29:436–9.
- 4 Pitt M. Neurophysiological strategies for the diagnosis of disorders of the neuromuscular junction in children. *Dev Med Child Neurol* 2008;50:328–33.
- 5 Rabie M, Jossiphov J, Nevo Y. Electromyography (EMG) accuracy compared to muscle biopsy in childhood. *J Child Neurol* 2007;22:803–8.
- 6 Müller JS, Mildner G, Müller-Felber W, *et al.* Rapsyn N88K is a frequent cause of congenital myasthenic syndromes in European patients. *Neurology* 2003;60:1805–10.
- 7 Milone M, Shen XM, Selcen D, *et al.* Myasthenic syndrome due to defects in rapsyn: clinical and molecular findings in 39 patients. *Neurology* 2009;73:228–35.
- 8 Gaudon K, Pénisson-Besnier I, Chabrol B, *et al.* Multiexon deletions account for 15% of congenital myasthenic syndromes with RAPSN mutations after negative DNA sequencing. *J Med Genet* 2010;47:795–6.
- 9 Nishida Y, Kobayashi T, Machi M, *et al.* Congenital myopathy with myasthenic features and congenital cataract in two siblings. *J Neurol* 1989;236:161.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow