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CASE REPORT

Intrafamilial variation in clinical manifestations and response to salbutamol in siblings with congenital myasthenic syndrome caused by DOK7 mutations

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Abstract

The congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders arising from genetic defects in presynaptic, synaptic, and postsynaptic proteins of the neuromuscular junction (NMJ) resulting in variable and characteristically fatigable muscle weakness affecting limb, ocular, bulbar, trunk, and respiratory muscles from early life. DOK7 mutation resulting in synaptic and postsynaptic CMS clinically presents with limb-girdle myasthenia with sparing of facial and EOM. They characteristically worsen with conventional treatment and show excellent response to salbutamol/ ephedrine. Here we present a case highlighting a varied presentation beginning in late childhood and its evolution to reveal its congenital nature and subsequent management with salbutamol.

Keywords: congenital myasthenic syndrome; ephedrine; salbutamol; neuromuscular junction; DOK7; repetitive nerve stimulation

Introduction

The congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders arising from genetic defects in presynaptic, synaptic, and postsynaptic proteins of the neuromuscular junction (NMJ)[1]. The resultant disorders of neuromuscular transmission usually lead to presentation in early life with variable and characteristically fatigable muscle weakness affecting limb, ocular, bulbar, trunk, and respiratory muscles [2]. A recently described major postsynaptic CMS arises from mutations in the cytoplasmic protein Dok-7 [3]. Dok-7 'Downstream of Kinase 7' is an adaptor protein that is a key component of the muscle-specific tyrosine kinase (MuSK) signaling pathway and is essential for the postsynaptic specialization of the NMJ [3]. The clinical phenotype is typically characterized by the definite onset of weakness in early childhood (may even be present at birth), sparing of the external ocular muscles (EOM) in most cases, and a predominant limb-girdle distribution of weakness; hence the name Limb-Girdle myasthenia [3]. A surprising feature of this form of CMS is the lack of response or worsening of weakness with anticholinesterase treatment and a variable response to 3,4-diaminopyridine (3,4-DAP) [3]. Ephedrine was first reported to be effective in the treatment of myasthenia gravis in the 1930s [4] [5]; salbutamol has been shown to have class IV evidence for this syndrome [3]. We discuss an interesting case who presented to us in late childhood with progressive weakness, with similar genetics but variable clinical presentation within the family. Good response to salbutamol was noted in this family.

Case Report

A 15-year-old boy was seen by us with history of progressive limb weakness over four years. He was able to walk only short distances and found it difficult to get up from the floor. He would fatigue easily with activities of daily living and needed support. He was previously investigated elsewhere with nerve conduction studies that revealed proximal neuronopathy/ axonopathy. Clinical suspicion of Spinal Muscular Atrophy type 3 was entertained, but the survival motor neuron (SMN) genetic testing was negative. He was subsequently lost to follow up till he presented to us. On

examination, he had significant proximal muscle weakness of both upper and lower extremities, with a waddling gait, and early wasting in the proximal muscles. He had bilateral ptosis, but no fatigability and no ophthalmoplegia.

Repeat nerve conduction studies on the boy showed normal motor and sensory conduction, with repetitive nerve stimulation demonstrating a markedly abnormal decremental response in both deltoid and right trapezius. Electromyogram (EMG) showed myopathic potentials in proximal muscles of both upper and lower limb. Anti-Acetylcholinesterase antibodies were positive (titres 1.52; >0.4 is high), and CT scan of the thorax revealed a mass in anterior mediastinum, suspected to be thymus enlargement. A working diagnosis of acquired myasthenia gravis was considered and a trial of pyridostigmine was initiated. Pyridostigmine caused an increase in his weakness. Subsequently he was put on steroids and underwent an uneventful thymectomy. A few months later, he presented in myasthenic crisis requiring ventilation, plasmapheresis, azathioprine and eventually rituximab, following which he gradually improved and was discharged home. Subsequently, he presented with a second episode of myasthenic crisis within a few months. Repeat testing for Anti-acetylcholinesterase antibodies was negative. Given a poor response to conventional treatment, Congenital Myasthenic Syndrome was considered likely. Repeat nerve conduction study (particularly looking for slow channel CMS) showed significant decrement on low frequency (2Hz) repetitive nerve stimulation(RNS) in the right Deltoid and right Trapezius (Fig 2) and no incremental response to high-frequency RNS (presynaptic defect ruled out) (Table 1).

Table 1 Repetitive nerve stimulation (RNS) at 2Hz

Right	Deltoid		Trapezius		Orbicularis oculi	
Drug	Salbutamol		Salbutamol		Salbutamol	
% decrement	Pre	Post	Pre	Post	Pre	Post
At rest	-14.4	-15.1	-11.8	-12.4	-2.9	-13.3
Immediately after exercise	-25.2	-13.3	-12.1	-11	0.29	-11.3
1 minute after exercise	-21.6	-19.6	-12.3	-9.3	-3.4	-21.7
2 minutes after exercise	-26.3	-20.1	-13.4	-12	-6.1	-22.6
3 minutes after exercise	-27.1	-24.6	-13.4	-12.6	-2.6	-18.8

Repetitive compound muscle action potential (R- CMAP) was present in the right abductor digiti minimi. Electromyography revealed myopathic potentials in the right deltoid (Fig 1). A trial of fluoxetine [6] was given, while tapering

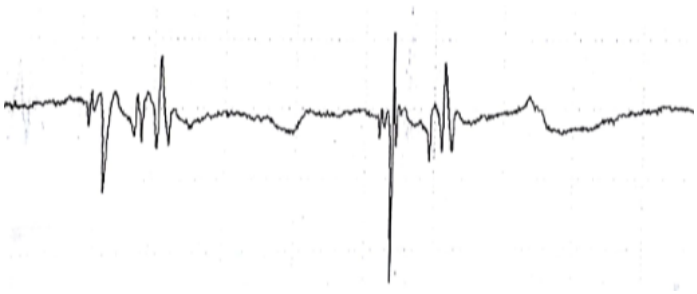

Figure 1 Electromyogram of right deltoid

him off the pyridostigmine and steroids. However fluoxetine was discontinued after no particular benefit was noted. By this time he was exceedingly weak, with deteriorating gait, worsening ptosis, inability to climb stairs and requiring Bilevel Positive Airway Pressure (BiPAP) ventilation at night. Meanwhile, the Next Generation Sequencing analysis identified a compound heterozygous mutation in DOK7 gene.

He was then commenced on oral salbutamol at 6 mg/day and his Quantitative Myasthenia Gravis score was monitored pre and post-treatment. He responded dramatically to the salbutamol with improved respiratory function, improved gait and ability to walk long distances and climb stairs unaided. The BiPAP was weaned off within a month of initiating salbutamol. He successfully completed schooling and now attends college with independent daily function. He remains on salbutamol 6 mg/day and is showing consistent improvement in his scores (Table 2).

Table 2 Quantitative Myasthenia Gravis (QMG) Scores in the index patient

Date	At diagnosis on CMS	3 months later	6 months later	1 year later
QMG Score	15	12	9	8
Clinical Notes	Azathioprine + Rituximab + Steroids BiPAP at night	Azathioprine + very low dose steroids No BiPAP	Salbutamol 6 mg/day	Salbutamol 6 mg/day

His ptosis, although better, persists. A review of childhood photographs revealed that the ptosis was present since birth. Repeat EMG/NCV (Figure 2) shows no myopathic potential and improvement in decrement response (Table 1).

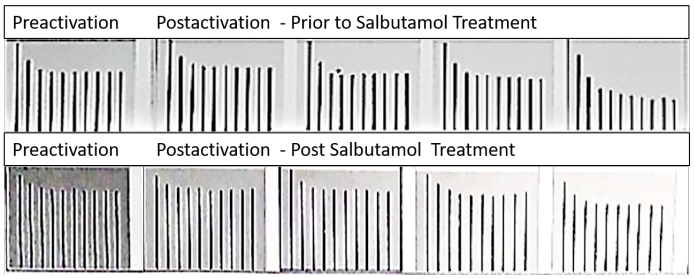

Figure 2 Repetitive Nerve Stimulation (RNS) response pre and post salbutamol treatment

He has three female siblings aged 29, 25 and 22 years of age. The eldest sister was asymptomatic. The second sister had a long standing history of being clumsy in school with limited physical abilities. She also had proximal weakness with ptosis but no ophthalmoplegia. Her weakness progressed considerably after an uncomplicated delivery of a normal baby girl, with significant difficulty in climbing stairs and easy fatigability. The second sister underwent nerve conduction study with similar results as the index case (Table 3).

The third sister refused to get examined or tested till date but gives a history of generalised weakness. The whole family was screened by targeted gene analysis for DOK7 muta-

Table 3 Repetitive Nerve Stimulation (RNS) at 2 Hz in sibling

	Right deltoid	Right orbicularis oculi
	% decrement	% decrement
At rest	-49	-6.2
Immediately after exercise	-51.8	-5
1 minute after exercise	-55.6	-7.1
2 minutes after exercise	-50.8	-6.5
3 minutes after exercise	-57.1	-10

tion, the results of which are shown in Table 4. The second sister being clinically symptomatic was also commenced on salbutamol with excellent benefit. She stopped the treatment after six months, and her weakness relapsed. Salbutamol was recommenced, again demonstrating marked clinical improvement. Thus, two or probably three siblings within a family (Figure 3) with same mutations of DOK7 exhibited varying clinical features, but similar good response to salbutamol in those treated.

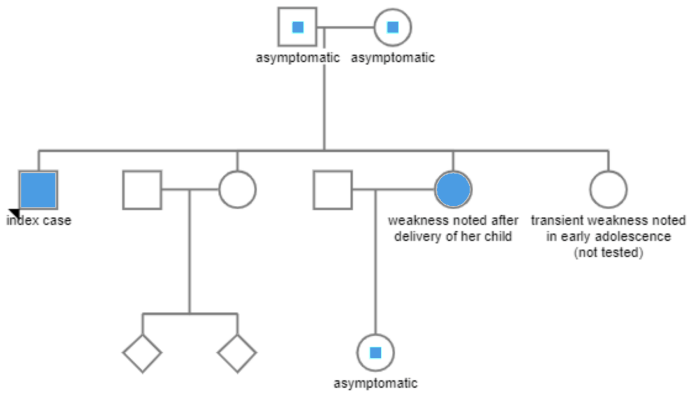

Figure 3 Family pedigree

Discussion

Clinical presentation Congenital Myasthenic Syndromes (CMS) are a group of inherited disorders resulting from dysfunction of the neuromuscular junction at the level of the presynaptic nerve terminal, the synaptic cleft and the postsynaptic apparatus. Dok-7 is an adaptor protein that is a key component of the muscle-specific tyrosine kinase (MuSK) signaling pathway and is essential for postsynaptic specialization of the NMJ [3] [7]. It is strongly expressed in skeletal muscle and heart. The pathophysiologic consequence of DOK7 mutation appears to arise from impaired activation of MuSK signaling leading to abnormally small, simplified, and unstable neuromuscular junctions affecting both presynaptic and postsynaptic structures and mild myopathic changes on muscle histology[3]. The clinical picture of CMS due to DOK7 mutation can be variable, with the age of onset between birth to third decade [8]. It is clinically characterized by a predominant limb-girdle pattern of weakness, ptosis, respiratory muscle involvement but sparing of the extra-ocular muscles and hence the term limb-girdle myasthenia. Muller et al. presented the clinical and genetic data of 14 patients in 12 CMS kinships with DOK7 gene mutation and confirmed the above clinical phenotype. Additionally, they described a characteristic 'sinuous' gait in these patients and also facial/bulbar muscle weakness in many. They described two pairs of siblings within their cohort, of which one pair had varying age of onset and severity of clinical manifestations despite an identical mutation. Selcen et al. also discussed the phenotypic variability in their report of 16 unrelated patients with DOK7 mutations [9].

Our index case presented in late childhood with symptoms of progressive limb-girdle weakness and ptosis, sparing facial/bulbar and extra-ocular muscles. His siblings were also affected at different ages and in varying severity, despite carrying the identical mutation. This highlights the intrafamilial phenotypic variation of DOK7 myasthenia syndrome even with same genotype.

Misdiagnosis Due to the phenotypic variability of CMS with DOK7 mutation, these patients often become diagnostic dilemmas and get misdiagnosed as either congenital muscular dystrophy or myopathy and thus present particular problems in management. Accurate diagnosis is often delayed despite early onset in many cases. Our index case had progressive symptoms through the years and was given various (mis)diagnoses before his genetic studies revealed the DOK7 mutation. He was initially thought to have Spinal Muscular Atrophy type 3 based on denervation on the early nerve conduction study, but the survival motor neuron (SMN) genetics disproved this. With clinical progression, ptosis became more significant and along with presence of anti-AChR antbodies, acquired myasthenia gravis was diagnosed. However, the failure of response to conventional treatment with cholinesterase inhibitors was a big clue leading to repeat nerve conduction testing that pointed towards CMS. Finally the genetic screening for CMS clinched the accurate diagnosis of DOK7 mutation.

Several case series and reports have revealed different presenting features such as congenital stridor, myopathy, and muscular dystrophy and also acquired myasthenia gravis [10] [11] [12] [13]. Thus, it is important to consider CMS as a differential diagnosis early on in the clinical story, irrespective of age of presentation, in order to facilitate appropriate and timely treatment initiation.

Treatment Options It is known that some types of CMS do not predictably respond to conventional anti-myasthenia treatment options. Generally speaking, the pharmacologic therapy is dictated by the defect underlying the CMS and drugs benefiting one type of CMS may be detrimental to other types [6]. With accurate molecular diagnosis of the type of CMS, appropriate drugs can be chosen for treatment. And objective assessments using various scales/scores for therapeutic benefit are important in monitoring response to treatment. CMS due to DOK7 mutation is proposed to occur by the following mechanisms [9]: a) Suppression of phosphorylation and aggregation of Acetylcholine receptor (AChR) on the postsynaptic membrane, b) Decrease in the

length, complexity and beta phosphorylation of the AChR clusters and c) Destruction and simplification of synaptic structures

Cholinergic agents like Pyridostigmine are of uncertain benefit in CMS due to DOK7 mutation, being effective in some, albeit with limited long term improvement, and deterioration in others even after few days of therapy [6]. The adverse response to pyridostigmine is paradoxic because the synaptic response to acetylcholine is decreased rather than increased [9]. In our index case, pyridostigmine was tried with no benefit and subsequent presentation with respiratory compromise. It remains unclear whether this was due to a lack of response to or paradoxical worsening with pyridostigmine. Beta-adrenergic agonists like ephedrine [5] [4] [14] and salbutamol [15] [16] [17] have been reported to be beneficial in DOK7 myasthenia. These agents activate the cyclic AMP-protein kinase A that feeds into the MuSK signalling pathway at the neuromuscular junction [18] [19]. Burke et al. [16] suggested that this salbutamol induced increase in kinase activity may partially compensate for the reduced MuSK signaling resulting from the impaired Dok-7 function and thus provide a compensatory mechanism to stabilize the endplate.

Given the undesirable side-effects with ephedrine and its unavailability in our country, we used salbutamol to treat the myasthenic symptoms in our index case and his sister. Salbutamol was given as daily oral dose of 6 mg/day. Clinical response to salbutamol was monitored using QMG scores at baseline and then 3, 6 and 12 months after commencing salbutamol (Table 3), and monitoring for side-effects of salbutamol was continued. Both the patients showed dramatic improvement in their symptoms with gain of considerable strength. The index case came off all the other immunosuppressant medications and remains solely on salbutamol which is well tolerated. Witting et al. [20] reported in their review that there was no evidence that age at disease onset, age at treatment start, drug dosage or mutation type influenced the treatment results. They also reported that the magnitude of treatment effect with ephedrine or salbutamol seems to increase gradually, peaking after approximately 6 to 8 months. Based on our experience with this family, we agree with their suggestions that salbutamol should be considered first choice of treatment in DOK7 myasthenia and that it is never too late to initiate treatment.

Conclusion

Congenital myasthenia syndrome due to DOK7 mutation can present at varying ages and severity within the same family carrying identical mutation. Early consideration of CMS is important to facilitate appropriate management. Salbutamol remains highly effective and well-tolerated in CMS due to DOK7 mutations.

Abbreviations

AchR Acetylcholine Receptor
BiPAP Bilevel Positive Airway Pressure
CMS Congenital Myasthenic Syndrome
EMG Electromyogram
EOM External Ocular Muscle
MuSK Muscle Specific Tyrosine Kinase
NCV Nerve Conduction Velocity
QMG Quantitative Myaesthenia Gravis
RNS Repetitive Nerve Stimulation
SMN Survival Motor Neuron

Competing interests

The authors have declared that they have no competing interests.

Authors' contributions

All the authors contributed to data collection and also critically reviewed the manuscript. The final version of the manuscript was approved by all the authors.

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Table 4 Gene variants found in index case and family members

Family Member	Gene (Exon 7; Heterozygous)	Variants	Clinical Condition
Index case	DOK7 (+)	chr4:3494833-3494834insGCCT (Het); c.1120_1121insGCCT;p.Ala378SerfsTer30 chr4:3495091_3495092insC (Het); c.1378_1379insC; p.Gln460ProfsTer59	Symptomatic
Father	DOK7 (+)	chr4:3494833-3494834insGCCT (Het); c.1120_1121insGCCT;p.Ala378SerfsTer30	Asymptomatic
Mother	DOK7 (+)	chr4:3495091-3495092insC (Het); c.1378_1379insC; p.Gln460ProfsTer59	Asymptomatic
Sibling 1	DOK7 (+)	chr4:3494833-3494834insGCCT (Het); c.1120_1121insGCCT; p.Ala378SerfsTer30	Asymptomatic
Sibling 2	DOK7 (+)	chr4:3494833-3494834insGCCT (Het); c.1120_1121insGCCT;p.Ala378SerfsTer30 chr4:3495091_3495092insC (Het); c.1378_1379insC; p.Gln460ProfsTer59	Symptomatic
Niece	DOK7 (+)	chr4:3494833-3494834insGCCT (Het); c.1120_1121insGCCT; p.Ala378SerfsTer30	Asymptomatic