Limb Girdle Weakness Responding to Salbutamol: An Indian Family with DOK7 Mutation

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Background: Congenital Myasthenic Syndromes (CMS) are heterogeneous genetic diseases. **Case characteristics**: Two siblings presented with progressive limb girdle weakness without significant fluctuations or ocular muscle weakness. Repetitive nerve stimulation showed a decremental response and there was no response to pyridostigmine therapy. **Outcome**: A trial of salbutamol produced a remarkable, consistent improvement. Mutation in exon 5 of the *DOK7* gene was found in both siblings. **Message**: Patients with congenital myasthenic syndrome with DOK 7 mutation benefit remarkably with salbutamol.

Keywords: *Congenital myasthenic syndrome, Mutational analysis, Treatment.*

Congenital Myasthenic Syndromes [1] are disorders of neuromuscular transmission presenting in early life. They pose a diagnostic challenge, as features characteristically associated with neuromuscular transmission disorders like fatigability and fluctuations may be subtle. Pathology can be pre or post-synaptic, and few show remarkable improvement on therapy. Response to salbutamol is seen in a set of CMS patients having genetic abnormalities in *DOK7*; a protein important for neuromuscular synaptogenesis [2]. We herein report two siblings with congenital myasthenic syndrome, who had *DOK7* mutations and responded satisfactorily to salbutamol.

CASE REPORT

A 10-year-old girl presented with steadily progressive proximal and distal weakness of limbs, neck and trunk muscles since 8 years. She did not have significant circadian fluctuations in muscle strength. There was no ptosis, and extra-ocular movements were normal. Mild bifacial weakness was present and tongue and pharyngeal examination showed normal results. Neck flexor and extensors were weak and she could barely lift her neck off the bed. She had significant truncal and limb weakness but no clinical fatigability could be demonstrated. Deep tendon reflexes, sensory system and coordination were also normal and her gait was lordotic.

Her 6-year-old younger brother was evaluated and the examination showed a similar phenotype, but with a milder presentation. Both the siblings showed a delay in achieving all motor milestones and continued to lag in sporting activities. Parents were not consanguineous and no other family members were known to be affected.

Thus, both the children had very early onset, gradually progressive, pure motor, generalized disease. Possibility of congenital muscular dystrophies and congenital myopathies were considered. In the index case, serum creatine kinase was 93 IU/L and sensory and motor conductions were normal. Repetitive CMAPs were absent and on slow rate repetitive nerve stimulation, both trapezius muscles showed significant decremental response (Right 23%, Left 18%). Acetyl choline receptor and anti-MuSK antibodies were negative.

With demonstration of significant decrementing response, diagnosis of Congenital myasthenic syndrome was considered. The index case was given pyridostigmine up to 180 mg per day; however, she did not improve and treatment was stopped. Left quadriceps biopsy showed fiber-size variation. There were no inflammatory cells, nuclei were peripheral in location, and there were no de or regenerating fibers. Index case was subsequently given trial of salbutamol 1 mg thrice daily after consent from the parents, and the treatment was increased over 10 days to 2 mg thrice daily with blood pressure and pulse monitoring. She showed remarkable improvement in her muscle power and functional status.Younger sibling also showed good improvement. No adverse effects were encountered. On re-examination on day 14 and after two months, further clinical improvement was noted. Whole exon sequence was performed in both patients. Genetic analysis confirmed the presence of one copy of pathogenic mutation c.601C>T (p.R201X) in the exon 5 of *DOK7* gene in both patients. One copy of variant of unknown significance c.887A>G (p.Q296R) was also identified in exon 7 of *DOK7* gene in both siblings in the subsequent sanger sequence analysis. These results confirm the most possible diagnosis of Congenital myasthenic syndrome due to *DOK7* mutations.

DISCUSSION

Our patients were found to have familial congenital myesthenic syndrome, which responded to salbutamol

and not to pyridostigmine. Among congenital myesthenic syndrome those that respond to salbutamol, *DOK7* and *COLQ* mutations are common (20 to30%), while others like *AGRN, MuSK, LAMB2* gene mutations are much rare [1,3], Repetitive CMAPs can differentiate between these two common types. In the present case, absence of repetitive CMAP on electrophysiology suggested the possibility of *DOK7* mutation. We also successfully identified one copy of nonsense pathogenic mutation in the *DOK7* gene by using whole exome sequencing analysis in both patients.

DOK7 congenital myasthenic syndrome was first discovered in 2006 [2] and is believed to account for 10 to 15% of all Congenital myasthenic syndrome cases [1,3]. It can have prenatal, neonatal or early childhood onset. Neonates can develop difficulty in breathing, feeding and occasionally stridor. Most patients are affected with limb girdle pattern of weakness with or without ptosis, facial weakness, head drop or respiratory weakness. The natural history is usually progressive and patient may eventually require a wheelchair [4,5]. Sometimes, lack of circadian variability of symptoms and subtle electrophysiological changes may lead to mis-diagnosis as congenital muscular dystrophy [6].

DOK7 (through activation of MuSK) is essential for neuromuscular synaptogenesis and maintenance [2,7]. Mutations of *DOK7* have been shown to produce mild myopathic changes [7], which explains EMG and muscle biopsy findings in our case. Interestingly the nonsense mutation (c.601C>T (p.R201X)) identified in these siblings has also been reported in German patient as pathogenic mutation [2, 8] for congenital myasthenic syndrome.

Salbutamol is currently the first line of therapy for *DOK7* Congenital myasthenic syndrome patients of all ages. Stimulation of beta 2 receptor on pre synaptic and post synaptic terminals activates c-AMP-protein kinase A which directly feeds into MuSK signaling pathway, thus partially supplementing DOK7 protein activation through MuSK [8,9]. Salbutamol (0.1-0.3 mg/kg/d in children up to 6 years and 6-18 mg/d in adults) is effective for patients of all ages and causes significant improvements even if therapy is started late in the course of disease, as was observed in the present case [10]. Patients continue to improve progressively over 6 to 8 months with this treatment [10].

Patients of congenital myasthenia with *DOK7* mutation remarkably improve with salbutamol, which is easily available, inexpensive and safe.

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REFERENCES

1. Engel AG. Current status of the congenital myasthenic syndromes. Neuromuscul Disord. 2012;22:99-111.
2. Beeson D, Higuchi O, Palace J, Cossins J, Spearman H, Maxwell S, *et al*. Dok-7 mutations underlie a neuromuscular junction synaptopathy. Science 2006;313:1975-8.
3. Abicht A, Müller JS, Lochmüller H. Congenital Myasthenic Syndromes. 2003 May 9 [Updated 2012 Jun 28]. *In*: Pagon RA, Adam MP, Ardinger HH, *et al.*, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1168/
4. Müller JS, Herczegfalvi A, Vilchez JJ, Colomer J, Bachinski LL, Mihaylova V, *et al*. Phenotypical spectrum of *DOK7* mutations in congenital myasthenic syndromes. Brain. 2007;130:1497-506.
5. Palace J, Lashley D, Newsom-Davis J, Cossins J, Maxwell S, Kennett R, *et al*. Clinical features of the *DOK7* neuromuscular Junction synaptopathy. Brain. 2007;130:1507-15.
6. Mahjneh I, Lochmüller H, Muntoni F, Abicht A. DOK7 limb-girdle myasthenic syndrome mimicking congenital muscular dystrophy. Neuromuscul Disord. 2013;23:36-42.
7. Selcen D, Milone M, Shen XM, Harper CM, Stans AA, Wieben ED, *et al*. Dok-7 myasthenia: phenotypic and molecular genetic studies in 16 patients. Ann Neurol 2008; 64:71– 87.
8. Hamuro J, Higuchi O, Okada K, Ueno M, Iemura S, Natsume T, *et al*. Mutations causing DOK7 congenital myasthenia ablate functional motifs in Dok-7. J Biol Chem. 2008;283:5518 -24.
9. Yamanashi Y, Higuchi O, Beeson D. Dok7/MuSK signaling and a congenital myasthenic syndrome. Acta Myologica. 2008;27:25-9.
10. Witting N, Vissing J. Pharmacologic treatment of downstream of tyrosine kinase 7 congenital myasthenic syndrome. JAMA Neurol. 2014;71:350-4.