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Salbutamol benefits children with congenital myasthenic syndrome due to *DOK7* mutations

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Abstract

Congenital myasthenic syndromes due to *DOK7* mutations cause fatigable limb girdle weakness. Treatment with ephedrine improves muscle strength. Salbutamol, a β_2-adrenergic receptor agonist with fewer side effects and more readily available, has been effective in adult and anecdotal childhood cases. This study reports the effects of salbutamol on motor function in childhood *DOK7* congenital myasthenic syndrome. Nine children (age range 5.9–15.1 years) were treated with oral salbutamol, 2–4 mg TDS. The effect on timed tests of motor function, pre- and up to 28 months post-treatment, was audited retrospectively. All 9 reported functional benefit within 1 month, with progressive improvement to a plateau at 12–18 months. Within the first month, all 3 non-ambulant children resumed walking with assistance. Although improvements were seen in some timed tests (timed 10 m, arm raise time, 6 min walk time) this did not fully reflect the observed functional benefits in daily living activities. No major side effects were reported. We conclude that oral salbutamol treatment significantly improves strength in children with *DOK7* congenital myasthenic syndrome and is well tolerated. Outcome measures need to be refined further, both to accurately reflect functional abilities in children and to document progress and treatment response.

Keywords: Congenital myasthenia; Salbutamol; *DOK7*

1. Introduction

Mutations in *DOK7*, encoding the skeletal muscle adaptor protein Dok-7, result in congenital myasthenic syndrome (CMS) associated with small, simplified neuromuscular junctions [1]. The resulting phenotype is variable, but typically patients present in childhood with a limb-girdle pattern of weakness and ptosis. Ophthalmoplegia is rare but progressive respiratory impairment frequently occurs. Treatment with cholinesterase inhibitors is ineffective and response to 3,4-diaminopyridine variable [2–4]. Ephedrine has been shown to be helpful, with patients reporting an improvement over a 1–24 month period [5,6]. However, ephedrine has both α and β-adrenergic effects and concern remains regarding central and cardiac adverse effects, particularly with long term use in children. Salbutamol, a selective β_2 agonist, has been used

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successfully for many years in paediatrics as a bronchodilator to treat asthma and, more recently, to improve muscle strength in SMA [7] and some congenital myopathies [8,9], with a good safety profile. In the USA, where ephedrine is no longer available, it was postulated that salbutamol may have similar benefit to ephedrine in CMS and this has recently been confirmed in an open label study of predominantly adults with *DOK7* synaptopathy, with patient reported functional improvement on albuterol, the USA equivalent of salbutamol [10]. Although ephedrine is still available in the UK, we offer salbutamol as first line treatment to children (including infants) with *DOK7* CMS, to reduce the potential for α-adrenergic side effects. In our multidisciplinary paediatric myasthenia clinics, children are assessed regularly with objective timed measures of fatigue and functional motor ability, in addition to detailed clinical review. The timed tests used are targeted to be brief, to maintain interest and motivation in younger children and are easily administered in the clinic setting. Here we present a retrospective review of the effect of salbutamol on functional ability and timed tests in nine children with *DOK7* mutations followed in our clinics for up to 28 months.

2. Patients and methods

2.1. Patients

This is a retrospective case review of clinical data and timed tests of muscle fatigability recorded at routine clinic visits. The study was approved by the Clinical Audit Team at Great Ormond Street Hospital. Nine children from eight unrelated families with genetically confirmed *DOK7* mutations were included. Molecular analysis of the *DOK7* gene was performed by the Oxford NCG service as previously described [1]. All mutations have been previously reported.

Patient 8 had received pyridostigmine from the age of 17 months with some improvement initially but she remained non-ambulant. The pyridostigmine was stopped 3 months after salbutamol was started, with no decline in functional ability. Patient 2 had received ephedrine from the age of 8.3 years but due to parental choice it was changed to salbutamol after 7 months. None of the other children had received pharmaceutical treatment for their congenital myasthenia before commencing salbutamol.

Prior to starting oral salbutamol, each child had detailed clinical review, cardiac examination, baseline BP and 12 lead ECG. Three had transthoracic echocardiograms. Children aged 5–8 years were prescribed salbutamol liquid, 1 mg TDS for 1 week, increasing to 2 mg TDS thereafter. Older children were offered slow release salbutamol tablets, 4 mg once daily, increasing after 1 week to 4 mg twice daily. The 15 year old boy, unable to swallow tablets, took salbutamol liquid 4 mg TDS. Each child was longitudinally assessed clinically, using the medical research council (MRC) scale of muscle strength, BP, heart rate and spirometry to assess vital capacity.

2.2. Timed assessments

The following timed tests of motor function and muscle fatigability were performed where possible: timed rise from sitting on the floor, timed 10 m walk, maximum time maintaining 90° forward flexion of the right arm at the shoulder (up to 120 s), number of repeated sit to stand from a chair (in 1 min) and grip myometry (Newtons) using a Citec hand held dynanmometer (C.I.T. Technics, Netherlands). During the study period we also introduced a 6 min walk time assessment, performed according to standard protocols, in those clinics where the facility was available and the children were able to walk that distance. Accordingly, full results including baseline pre-treatment were only achieved for patient 4.

Children were evaluated at baseline pre-treatment, at 1–3 months, 6–8 months and approximately 6 monthly post-treatment thereafter. ECG was repeated at 1–3 months, then yearly.

3. Results

Nine children (6 females and 3 males) from eight unrelated families were included in the study. Patients 4 and 5 are sisters. Clinical demographics are shown in Table 1. Their age at starting salbutamol ranged from 5.9 years to 15.1 years. Six had symptoms from birth but genetically confirmed diagnoses were delayed in all. All had limb girdle weakness and three were non-ambulant at baseline (patients 6, 7 and 8). The non-ambulant children had knee and hip flexion contractures and patient 7 had undergone spinal surgery for scoliosis. In addition to limb girdle weakness, facial weakness (8/9) and ptosis (6/9) were common, but ophthalmoplegia (2/9) was rare and consisted of limited upgaze only. This is consistent with the phenotype described by others [2,3].

3.1. Effect of salbutamol on functional ability

All families reported functional improvement within one month of starting salbutamol. Onset of improvement was noted as early as 2 weeks, with a gradual increase to a plateau at 6–18 months. Ambulant children reported improved endurance for distances, ability to run and climb stairs (previously not possible in some) and fewer falls. One no longer had fluctuation in motor abilities. The three non-ambulant children resumed walking: within 2 weeks of starting salbutamol patient 5 could rise from the floor, walk with a crutch and go upstairs – he now walks 30 m unaided. Patient 6 was able to stand and walk assisted after 1 month of treatment, took 30 steps unaided at 7 months and now can walk at least 10 m unaided. Patient 8 at 1 month of treatment was able to take 23 steps with hands held and use the bathroom unaided. At 5 months she climbed stairs with a rail and continues to improve. Walking was achieved in all 3 despite ongoing knee flexion contractures. Improvement in functional ability was often