Ephedrine treatment in congenital myasthenic syndrome due to mutations in *DOK7*

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ABSTRACT

Background: Mutations in the postsynaptic adaptor protein Dok-7 underlie congenital myasthenic syndrome (CMS) with a characteristic limb girdle pattern of muscle weakness. Patients usually do not respond to or worsen with the standard CMS treatments: cholinesterase inhibitors and 3,4-diaminopyridine. However, anecdotal reports suggest they may improve with ephedrine.

Methods: This was an open prospective follow-up study to determine muscle strength in response to ephedrine in Dok-7 CMS. Patients were first evaluated as inpatients for suitability for a trial of treatment with ephedrine. The response was assessed at 2 and 6 to 8 months follow-up clinic visits using a quantitative myasthenia gravis (severity) score (QMG) and mobility measures.

Results: Ten out of 12 of the cohort with *DOK7* mutations tolerated ephedrine. We noted a progressive response to treatment over the 6 to 8 months assessment period with a significant improvement at the final QMG score ($p = 0.009$). Mobility scores also improved ($p = 0.0006$). Improvements in the subcomponents of the QMG score that measured proximal muscle function (those muscle groups most severely affected) were most marked, and in some cases were dramatic. All patients reported enhanced activities of daily living at 6–8 months.

Conclusion: Ephedrine appears to be an effective treatment for Dok-7 CMS. It is well-tolerated by most patients and improvement in strength can be profound. Determining the long-term response and the most effective dosing regimen will require further research.

Classification of evidence: This study provides Class IV evidence that ephedrine given at doses between 15 and 90 mg/day improves muscle strength in patients with documented mutations in DOK7. *Neurology*® 2010;74:1517–1523

GLOSSARY

3,4-DAP = 3,4-diaminopyridine; **CMS** = congenital myasthenic syndrome; **EOM** = external ocular muscles; **FVC** = forced vital capacity; **MuSK** = muscle-specific tyrosine kinase; **NMJ** = neuromuscular junction; **QMG** = quantitative myasthenia gravis (severity) score.

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.[3-7] 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.[8,9] The pathophysiologic consequence of Dok-7 CMS appears to arise from impaired activation of MuSK signaling leading to abnormally small, simplified, and unstable neuromuscular junctions affecting both presynaptic and postsynaptic structures[3,6,10] and mild myopathic

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Study funding: Supported by the Medical Research Council UK, the Muscular Dystrophy Campaign, and the Myasthenia Gravis Association.
Disclosure: Author disclosures are provided at the end of the article.

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changes on muscle histology.[5,6] The clinical phenotype is typically characterized by definite onset of weakness in early childhood, although in retrospect symptoms consistent with a CMS may have been present at birth, sparing of the external ocular muscles (EOM) in most cases and a predominant limb-girdle distribution of weakness.[3-5] 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),[4,5] the conventional CMS treatments.

Ephedrine was first reported to be effective in the treatment of myasthenia gravis in the 1930s[11,12] but was subsequently superseded by anticholinesterases and corticosteroids. The mechanism by which it may affect neuromuscular transmission at pharmacologic doses is unclear.[13-15] Anecdotally, patients with CMS have reported benefit from ephedrine, often tried because of a failed response to other therapies,[16] but this has not been consistent or demonstrable by objective measures. Three of the 15 patients with Dok-7 CMS whose clinical details we previously reported[5] were already prescribed ephedrine prior to the identification of their genetic mutation and had reported benefit. Because CMS due to *DOK7* mutations is a rare disorder, numbers are not sufficient for randomized trial designs. We have now prospectively followed up 10 patients with Dok-7 CMS who started ephedrine treatment over the past 2 years but have excluded the 3 previously reported because we did not have baseline strength measurements on them.

METHODS This was an open prospective study of a cohort of patients with CMS with mutations in *DOK7* to examine if treatment using ephedrine resulted in improvement in their muscle strength as measured by the quantitative myasthenia gravis score (QMG)[17] and mobility scores.

Standard protocol approvals, registrations, and patient consents. Written informed consent for publication of data was obtained from all patients participating in this study. Ethical approval for analysis of DNA and tissue samples was obtained from the Oxford Research Ethics Committee B, ref. 04.OXB.017 and Oxfordshire Research Ethics Committee C Review Board, ref.09/H0606/74.

Procedure. All patients were shown to have mutant Dok-7, although in one pair of siblings, for whom a muscle biopsy sample was not available, we were only able to identify the common 1124_1127dupTGCC mutation[3] on one allele (table).

Patients with Dok-7 CMS who had inadequately controlled symptoms, had not previously tried, and were not already taking ephedrine, were offered a trial of treatment. Ephedrine was

Table Response of DoK-7 CMS patients after 6 to 8 months of treatment with ephedrine

Patient	Kinship	Identified mutations	Age at onset, y	Age ephedrine started, y	Ephedrine dose	Other treatment	QMG baseline/39	QMG end/39
1	1	c.1124_1127dupTGCC IVS1+14del15	Birth	11	30 mg twice a day		16	4
2	1	c.1124_1127dupTGCC IVS1+14del15	3	8	15 mg twice a day		20	5
3	2	c.1124_1127dupTGCC c.1124_1127dupTGCC	21	21	15 mg 3 times a day		2	1
4	2	c.1124_1127dupTGCC c.1124_1127dupTGCC	13	19	15 mg once a day		13	10
5	3	c.1124_1127dupTGCC	Birth	38	30 mg 3 times a day		25	22
6	3	c.1124_1127dupTGCC	Birth	46	15 mg 3 times a day		19	18
7	4	c.473G>A c.1124_1127dupTGCC	3	29	30 mg 3 times a day	3,4-DAP	10	10
8	5	c.414C>T c.1339_1342dupCTGG	3	42	15 mg 3 times a day	3,4-DAP	18	7
9	6	c.496G>A c.1124_1127dupTGCC	Birth	5	7.5 mg 3 times a day		12	10
10	7	c.1378C>T c.1339_1342dupCTGG	Birth	11	15 mg 3 times a day		23	21

Abbreviations: 3,4-DAP = 3,4-diaminopyridine; QMG = quantitative myasthenia gravis (severity) score.

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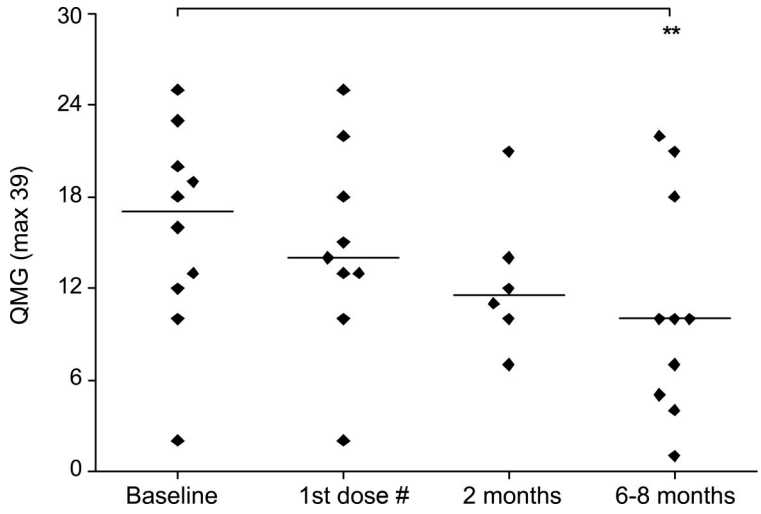
started on an inpatient basis with dosage dependent on body weight and tolerability, but ranged between 0.5 and 1 mg/kg/day (although 1 patient reduced his dose to below this level). Blood pressure, heart rate, and ECG were performed at the same time and were also monitored by the general practitioner in between. Patient 6 was unable to attend as an inpatient and so ephedrine was started under the supervision of the general practitioner, with the same monitoring. Some patients were already taking 3,4-DAP, and in these cases ephedrine was added rather than substituted.

Strength measures included the QMG (severity) score[17] and a mobility score taking the form of either a timed walk over a fixed distance or a timed stair climb, dependent upon the patient's ability. These were recorded pre and 1 hour post treatment and then again in the outpatient setting at 2 and 6–8 months following initiation of treatment. In those patients also taking 3,4-DAP, baseline measurements were performed following 3,4-DAP and all subsequent measurements after taking both medications together, in order to provide an accurate comparison for combined treatment. The dose of 3,4-DAP used did not vary throughout the follow up-period.

The QMG score is made up of 13 components, each scored from 0 (normal) to 3 (severe weakness). Components for ptosis, diplopia, swallowing, speech, and facial muscles are based on clinical interpretation and/or assignment to a descriptive category. Components for arm raise time, leg raise time, grip strength, head lift time, and forced vital capacity (FVC) are based on objective, continuous values assigned to a range (e.g., for arm raise time 0 = >240 s, 1 = 91–240 s, 2 = 11–90 s, 3 = <11 s). These continuous values are amenable to subanalysis and are thus more sensitive at detecting change.

The QMG scale has not been fully validated in children. Specifically, the scoring ranges for vital capacity and grip strength, which are age dependent, cannot be applied, so these components were omitted from the QMG score in such patients and the total corrected to allow for the different denominator. In addition, the number of squats performed was measured in 2 children (siblings). Lifestyle improvements were recorded.

Figure 1 **Quantitative myasthenia gravis (severity) (QMG) scores of patients treated with ephedrine**



QMG is a severity score with a maximum of 39. Children underwent a limited scale with a maximum of 30 and the total corrected to/39. **p = 0.009 Wilcoxon signed rank test. #One patient started ephedrine treatment when not directly under our supervision.

In order to reduce the problems of multiple comparisons, our primary outcome was set as the QMG difference between baseline and 6- to 8-month follow-up using paired samples (Wilcoxon matched pairs test). This ensures a robust assessment of treatment response because the QMG score is the least sensitive to change.

RESULTS Twelve Dok-7 patients not on ephedrine sought better control of their weakness and were admitted for a trial of treatment. Two patients were unable to tolerate the test: 1 child had lack of sleep and became distressed and 1 adult experienced an elevation of blood pressure (165/88 increased to 194/118). Ten patients ranging from 5 to 46 years of age, from 7 kinships, tolerated ephedrine at initiation and throughout the follow-up period (see table). To illustrate the response to therapy, we briefly describe 3 cases (patients 1, 4, and 7).

Case 1. An 11-year-old girl with onset at birth was only able to walk short distances within the home using a k-walker and required a wheelchair for any distance. Examination revealed severe proximal pattern of muscle weakness. She tolerated a relatively high dose of ephedrine (30 mg twice daily), although the nocte dose of a three times a day regimen caused insomnia. At 2 months, her parents reported she was "like a new child" and she could jump for the first time. Whereas she could only manage to perform 5 squats previously she could now do more than 50. Her timed stair climb had halved and her proximal weakness was markedly improved. The improvement was progressive and at 8 months the time for keeping her left arm outstretched had increased from 28 seconds to greater than 240 seconds, for keeping her left leg raised the time increase was from 9 seconds to 83 seconds, and FVC increased from 1.1 to 1.5 (L).

Case 2. A 19-year-old man, with late onset at 13 years, was walking with the aid of 2 crutches. He had previously been prescribed pyridostigmine, which had made him weaker and rendered him wheelchair bound temporarily. Although he was prescribed ephedrine 15 mg 3 times a day, he only took it once per day. At 6 months he was walking without crutches, doing sit-ups, and his timed walk had reduced from 55 to 22 seconds. Additionally, he was able to manage a short jog in the evenings.

Case 3. A 29-year-old woman with onset at age 3 years had been taking 3,4-DAP since 2006. She had moderate limb and facial weakness; during her teenage years, she used a wheelchair for long distances and was managing to walk slowly with a lordotic gait at baseline. She started ephedrine 15 mg 3 times a day and by 2 months reported a marked improvement in her walking such that she could wear high-

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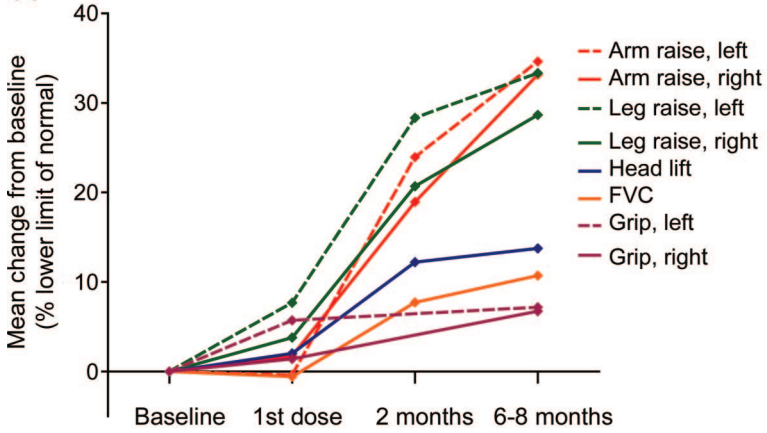
Figure 2 Change in performance for subcomponents of the quantitative myasthenia gravis (severity) (QMG) scores

A



B

Component	Lower limit of normal	Baseline	6-8 months	
Left arm raise (s)	240	51.1	134.2	+163%
Right arm raise (s)	240	43.1	122.7	+185%
Left leg raise (s)	100	32.9	72.9	+122%
Right leg raise (s)	100	37.7	72.1	+91%
Head lift (s)	120	53.4	69.9	+31%
FVC (L)	2.5 (F) 3.5 (M)	1.9	2.2	+14%
Left grip (Kg)	31 (F) 45 (M)	21.8	24.2	+11%
Right grip (Kg)	31 (F) 45 (M)	21.6	24.3	+13%

(A) Change in percentage of the lower limit of normal (minimum required to achieve 0 in the QMG scale). (B) Mean values at baseline and at 6- to 8-month follow-up. Values for patients 1, 2 (arm, leg, and head raise), 3 (head raise), 4 (arm, leg, head raise and grip), and 8 (leg raise) were capped at 100% of the lower limit of normal at the time of measuring.

heeled shoes for the first time. At 6 months, her partner reported that she was managing prolonged shopping trips which he found a challenge. In addition, there was a marked improvement in her facial expression and her posture when walking.

Clinical scores. In all measured outcomes and from the patients' own observations, there was little immediate improvement within 1 hour of the first dose of ephedrine, but progressive improvements were documented at 2 and at 6–8 months.

Quantitative myasthenia gravis (severity) score. QMG scores calculated at baseline, following the first dose, and then at follow-up 2 months and 6–8 months following initiation, are given in figure 1. The median QMG severity scores (measured out of a total of 39) significantly improved from baseline to the 6- to 8-month follow-up (the primary outcome measure) from 17/39 to 10/39, $p = 0.009$ (Wilcoxon signed rank test).

QMG components. To further assess in which muscle groups improvements occurred, the component scores of the QMG were examined. Scores for diplopia, swallowing, and counting subscores were normal at baseline and thus had no scope for improvement. Scores for facial muscles, FVC, and hand grip were mildly abnormal at baseline and showed only a small change. Improvements over the follow-up period occurred in scores for ptosis, head lift, arm raise time, and leg raise time, i.e., where weakness is usually most profound in the Dok-7 CMS phenotype.

Changes in the QMG subcomponents with continuous values were also most marked in measures of proximal limb function, most notably arm and leg raise times (figure 2). Within these most improved measures, there was individual variability in response as demonstrated in figure 3, A and B. One mildly affected patient performed at the maximum throughout.

Mobility scores. The mobility assessment was either a timed walk or timed stair climb according to the patient's ability. The assessment could not be performed in all patients at all time points but clearly improved, when measured, over the 6- to 8-month follow-up (figure 4). Taking the 6- to 8-month score vs baseline, $p = 0.0006$ (2-tailed paired t test).

DISCUSSION This study provides Class IV evidence that ephedrine given at doses between 15 and 90 mg/day improves muscle strength as measured by the QMG severity score and mobility score in Dok-7 CMS. Symptoms of Dok-7 CMS may deteriorate in early childhood but are then usually stable or slowly progressive.[4-6] These cases demonstrate that ephedrine produces a delayed and progressive improvement in muscle strength over months which leads to a relevant improvement in daily activities in Dok-7 CMS. This is in contrast to the negative effect with anticholinesterases and variable response of 3,4-DAP in this type of CMS. In addition, the latter treatments work immediately when effective in other myasthenic syndromes, whereas only a minor immediate improvement was seen with ephedrine. It is likely that any immediate effect seen in some patients is at least partly due to the recognized stimulant action of ephedrine.[18] The improvement seen over the subsequent 6 to 8 months is interesting, and it is not yet clear if the improvement may continue beyond this period and may depend on the dose and the degree of weakness.

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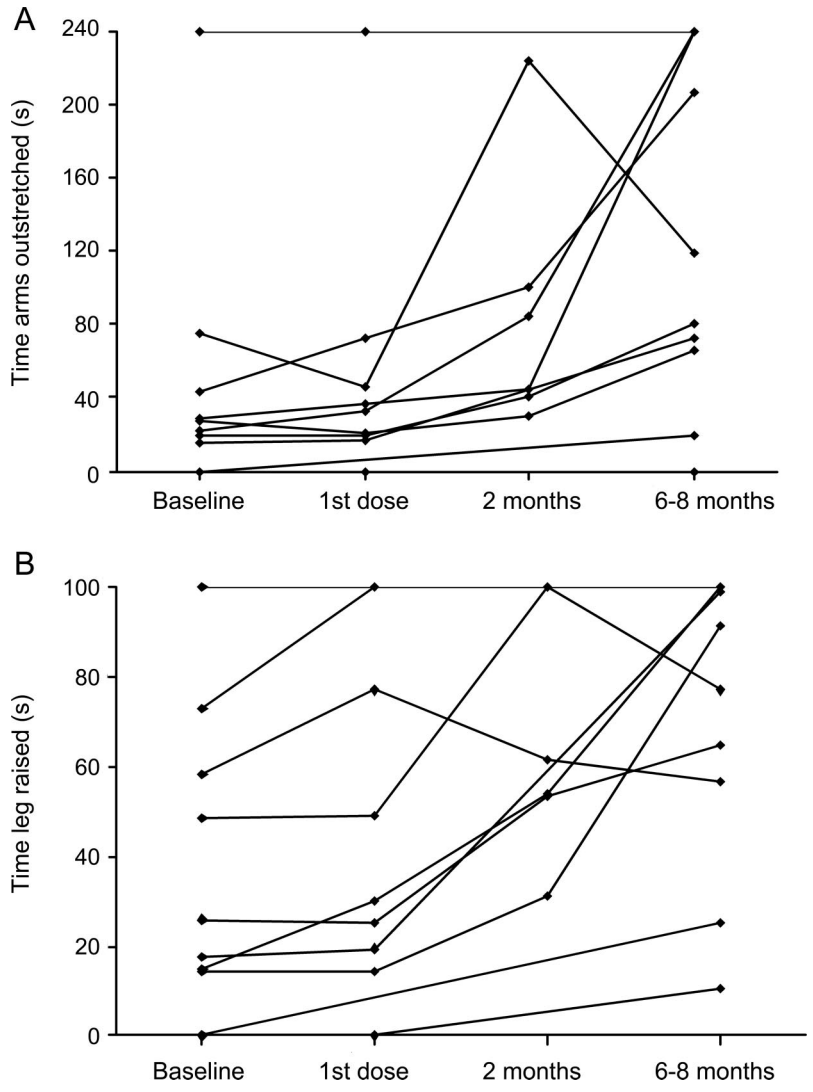
Figure 3 Individual variability in response to treatment



Time (seconds) of individual patients for (A) left arm raised 90 degrees and (B) right legs raised 45 degrees. Data points are mean of right side and left side scores. Values for patients 1, 2, and 4 (arm and leg) and 8 (leg only) were capped at 240 s (arm) and 100 s (legs).

The more marked improvement in the measures of proximal strength such as arm outstretched and leg raise times may relate to the fact that Dok-7 patients have predominant proximal limb weakness. There was a large across-patient variability in the improvement although longer follow-up of the very weak patients could show further benefit. We were impressed in some instances that the patient perception of the positive treatment response in the way their daily activities improved was more profound than the objective measurement scores revealed. This may be partly due to the stimulant effect of ephedrine although patients usually reported the improvement over months rather than immediately. Additionally, the outcome measures may not always directly correlate to daily tasks being undertaken by the patients.

The precise pathogenic mechanism for *DOK7* mutations has not yet been established. They affect the integrity and stability of the neuromuscular junction,[3,6,10] but they also lead to mild myopathic changes in many patients that can include change in oxidative enzyme activity and muscle fiber necrosis.[6,19] If this latter feature was a result of damage secondary to overstimulation of the remaining AChRs, this might explain the poor response to myasthenic treatments that increase neuromuscular transmission. The positive effect of ephedrine has also been reported in *COLQ* CMS, where reduced anticholinesterase activity leads to a hyperpolarization state,[16,20,21] and also in a recent report of a mutation in *AGRN*.[22]

The pathway for the beneficial effect of ephedrine is not known. In vitro studies suggest possible effects on quantal release of ACh or on AChR kinetics[14,15] but not at levels used for treating patients. It is more likely that the beneficial effects are generated by its action as a β2-adrenergic receptor agonist. β2-Agonists are well-known for their muscle anabolic actions,[18] and thus the effect of ephedrine in our patients may be to counteract the secondary myopathy. The phosphorylation and autophosphorylation of MuSK is thought to drive a downstream kinase signaling pathway that orchestrates and maintains the integrity of the neuromuscular junction.[23-25] Thus, a second possibility is that a downstream effect, from the stimulation of the β2-adrenergic receptors and subsequent activation of cAMP-protein kinase A, feeds into the MuSK signaling pathway at the neuromuscular junction.[26,27] This could partially compensate for the loss of MuSK signaling due to mutant Dok-7. Indeed, ephedrine, through the β2-adrenergic receptors, may act both to enhance muscle strength and to partially stabilize neuromuscular junction synaptic structure.

The optimal ephedrine treatment regimen remains to be established and may prove difficult to study systematically in this rare disorder. One patient (patient 4) reduced his fairly low 3 times a day starting dose to once daily and still improved, suggesting that it may be possible to use lower doses than presently prescribed. However, another patient noted that reducing her dose from 30 mg 3 times a day to 15 mg 3 times a day resulted in a worsening of strength. Longer-term follow-up of more patients with adjustment of the dosage and delayed and objective outcome measures will hopefully inform us further. Follow-up studies using muscle MRI and possibly repeat muscle biopsies might help elucidate mechanisms of action of ephedrine in the treatment of Dok-7 myopathy. Very recently, another report of ephedrine therapy in 8 patients with Dok-7 CMS

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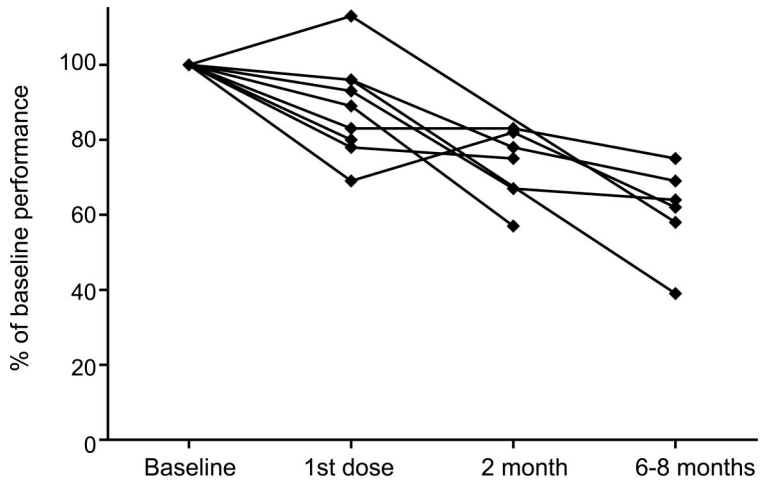
Figure 4 **Mobility assessment**



Individual points show the percentage reduction in time required for patients to carry out the test. Performances are normalized to the baseline record prior to treatment.

similarly describes improved clinical symptoms.[28] Ephedrine is well-tolerated by most patients and can lead to a profound improvement in activities of daily living as perceived by patients and their carers. We now recommend ephedrine treatment in Dok-7 CMS. In some countries ephedrine is not easily available. In these countries or in cases where ephedrine is not tolerated, treatment with salbutamol (Albuterol) has been recommended.[6] Salbutamol is well-tolerated in young children with other neuromuscular disorders and a slow release preparation is available, given twice daily. Further studies of the optimal ephedrine dosage regimen and comparison of its effectiveness with salbutamol will help further refine management of Dok-7 CMS.

ACKNOWLEDGMENT

The authors thank the patients who participated in this study.

DISCLOSURE

Dr. Lashley has received funding for travel from Merck Serono. Dr. Palace serves on scientific advisory boards for Merck Serono, Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., Novartis, and Sanofi-Aventis; has received funding for travel from Merck Serono; and receives research support from the Multiple Sclerosis Society and the Department of Health Risk Sharing Scheme (Clinical Coordinator). Dr. Jayawant and Dr. Robb report no disclosures. Dr. Beeson receives research support from the Medical Research Council UK and the Muscular Dystrophy Campaign.

Received October 23, 2009. Accepted in final form February 4, 2010.

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