



Ephedrine therapy in eight patients with congenital myasthenic syndrome due to *DOK7* mutations

U. Schara^{a,*}, N. Barisic^b, M. Deschauer^c, C. Lindberg^d, V. Straub^e, N. Strigl-Pill^f, M. Wendt^c, A. Abicht^f, J.S. Müller^e, H. Lochmüller^e

^a Dept. of Pediatric Neurology, University of Essen, Germany

^b Dept. of Pediatrics, Clinical Medical Center, University of Zagreb, Croatia

^c Dept. of Neurology, Martin-Luther-University, Halle-Wittenberg, Germany

^d Neuromuscular Centre, Sahlgrenska University Hospital, Gothenburg, Sweden

^e Institute of Human Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

^f Friedrich-Baur-Institute, Dept. of Neurology, Ludwig-Maximilians-University, Munich, Germany

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ABSTRACT

In congenital myasthenic syndrome with *DOK7* mutations ephedrine was reported to be beneficial in single patients. We carried out a small, open and prospective cohort study in eight European patients manifesting from birth to 12 years. Five patients showed limb-girdle and facial weakness, three a floppy infant syndrome with bulbar symptoms and/or respiratory distress. Ephedrine was started with 25 mg/day and slowly increased to 75–100 mg/day. Within weeks after starting therapy an improvement was observed in all patients and clinical follow-up disclosed positive effects more pronounced on proximal muscle weakness and strength using MRC scale. Effects on facial weakness were less pronounced. Vital capacity measurements and repetitive stimulation tests did not improve in the same way as clinical symptoms did. These investigations are appropriate to confirm the diagnosis in case of pathological results, but they might not be appropriate means to monitor patients under ephedrine therapy.

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1. Introduction

Congenital myasthenic syndromes (CMSs) are a genetically and clinically heterogeneous group of disorders in which the safety margin of neuromuscular transmission is compromised by several mechanisms as described previously [1–7]. To date, mutations in 11 different genes are known to cause a CMS [1–8]. In 2006, the skeletal muscle receptor tyrosine kinase (MuSK)-interacting cytoplasmic protein termed Dok (“downstream-of-kinase”)-7 has been identified and mutations in the encoding gene *DOK7* were found as a further cause of postsynaptic CMS [9]. The Dok-family cytoplasmic proteins play a role in signalling downstream of receptor and non-receptor phosphotyrosine kinases. Dok-7 is essential for aneural activation of MuSK and the subsequent clustering of acetylcholine receptors (AChR); it is also important for agrin-dependent activation of MuSK and AChR clustering. Overall, these data provide evidence for a crucial role of Dok-7 in maintaining synaptic size and structure [10–13]. Mutations of the *DOK7* gene are among the most common underlying genetic defects of CMS and result in

a variable phenotype. Age of onset may vary between birth and the third decade. Most of the patients suffer from a characteristic limb-girdle pattern of weakness, a waddling or sinuous gait and ptosis without ophthalmoparesis; additionally respiratory problems are frequent. In a smaller group of children a phenotype with congenital onset like a floppy infant syndrome with bulbar symptoms and/or respiratory distress was described [2,3,12,14–17]. In CMS with *DOK7* mutations long-term therapy with esterase inhibitors is ineffective [18,19], but ephedrine was reported to be beneficial in single patients [2,3,14–19].

Here, we present a small, open and prospective cohort study on the therapeutic effects of ephedrine in eight patients with *DOK7* mutations. We describe an improvement of clinical symptoms as well as side effects over a period of 12–24 months.

2. Patients and methods

Eight patients from seven unrelated families (patients 6 and 7 were brothers, Table 1) with genetically proven *DOK7* mutations, six males and two females, were included. Positive results and side effects, repetitive stimulation tests and vital capacity were monitored during follow-up after 3, 6 and 9 months, then every 3–6 months. Total follow-up time under ephedrine therapy was

* Corresponding author. Address: Dept. of Pediatric Neurology, University of Essen, Hufelandstr. 55, D-45122 Essen, Germany. Tel.: +49 201 723 2356; fax: +49 201 723 5389.

E-mail address: ulrike.schara@uk-essen.de (U. Schara).

Table 1
Therapeutic effects of ephedrine therapy in eight patients with *DOK7* mutations.

Patient/Gender/Origin Mutations in <i>DOK7</i> (cDNA)	Age at onset/ Age at diagnosis/ inclusion (years) Ephedrine, daily dose	Symptoms before/ after 12 or 24 months of ephedrine therapy	Muscle strength (MRC) prox/ dist gait	Ptosis/ ophthalmoparesis/ facial weakness/ bulbar symptoms	Respiratory difficulties/vital capacity/non- invasive ventilation	Repetitive nerve stimulation distal or proximal/ decrement
1/Male/Germany 601C>T 1124_1127dupTGCC	Birth/18 100 mg	Before	MRC 3/MRC 4 sinuous gait	+/-/+	+28% of n.v./+	+14% proximal
		After 24 months	MRC 4/MRC 4+ sinuous gait	(+)/(+)/(+)-	(+)/23% of n.v./+	+13% proximal
2/Male/Germany 1124_1127dupTGCC 1124_1127dupTGCC	12/48 75 mg, additional 4× 10 mg pyridostigmine	Before	MRC 3/MRC 4 waddling gait	+/-/+/-	+60% of n.v./+	+33% proximal
		After 24 months	MRC 4/MRC 4-5 waddling gait	-/-/-/-	+57% of n.v./+, improvement	+27% proximal
3/Female/Germany 555delC 1296_1311del16	2/42 45 mg, additional 2× 60 mg pyridostigmine	Before	MRC 3-4/MRC 4 waddling gait	+/-/+	+66% of n.v./-	+50% proximal
		After 24 months	MRC 4-5/MRC 5 waddling gait	(+)-/(+)+	+64% of n.v./-	n.d.
4/Male/Germany 1124_1127dupTGCC 1124_1127dupTGCC	6/13 50 mg	Before	MRC 4/MRC 5+ waddling gait in childhood, sinuous gait later	+/-/-/-	-83% of n.v./-	+normal
		After 24 months	MRC 5/MRC 5 normal gait	-/-/-/-	-84% of n.v./-	n.d.
5/Female/Croatia 1124_1127dupTGCC 15-nt deletion in intron 1 (54 + 14_28delGGGGGGGGGGGGCGC)	Intrauterine, birth/11 37.5 mg, additional 4× 30 mg pyridostigmine	Before	MRC 3-4/MRC 4 waddling gait	+/+/+	+48-53% of n.v./-	+34% proximal
		After 24 months	MRC 4-5/MRC 4-5 normal gait	(+)-/(+)(+)	-56% of n.v./-	+12% proximal
6/Male/Sweden 1263insC 1124_1127dupTGCC	10/49 40 mg	Before	MRC 3-4/MRC 4 waddling gait	+/-/(+)-	+40% of n.v./+	n.d.
		After 12 months	MRC 4-5/MRC 4-5 waddling gait	(+)-/-/-	+40% of n.v./+	n.d.
7/Male/Sweden 1263insC 1124_1127dupTGCC	1/58 40 mg	Before	n.d./waddling gait	+/-/-/-	-86% of n.v./-	n.d.
		After 12 months	MRC 4+/MRC 4-5 waddling gait	(+)-/-/-	-86% of n.v./-	n.d.
8/Male/UK 1124_1127dupTGCC 1339_1342dupCTGG	At birth/10 45 mg	Before	MRC 3-4/MRC 4+ sinuous gait	+/-/+	-72% of n.v./-	n.d.
		After 12 months	MRC 4-4+/ MRC 5 normal gait	(+)-/-/-	-71% of n.v./-	n.d.

dist, distal; mg, milligram; MRC, Medical Research Council Scale; n.d., not done; n.v., normal value; prox, proximal; +, symptom can be observed; (+), symptom can be mildly observed; -, symptom cannot be observed.

between 12 and 24 months. In patient 5 (Table 1) we were able to collect data up to 36 months. Written informed consent was obtained from patients and/or parents. The study complies with the ethical guidelines of the institutions involved.

All patients were followed by one of the authors. Detailed neurological examination was performed in regular time intervals during follow-up. Additional investigations were performed according to standard procedures. Muscle strength was measured with the medical research council (MRC) scale [20,21] by the same investigator in every centre.

Electrophysiological studies including repetitive stimulation tests with 3 Hz were done in six of them. Muscle action potentials from abductor pollicis brevis and abductor digiti minimi muscle caused by stimulation of medianus and ulnaris nerve, respectively,

as well as muscle action potentials from trapezius muscle caused by stimulation of accessorius nerve were performed. High frequency 10 Hz stimulation was not investigated in any patient; in patient 8 (Table 1) a single fibre EMG was done from the nasalis muscle by stimulation of the facialis nerve disclosing pathological results after 6 months of ephedrine therapy. Reinvestigation after 12 months of therapy was not performed. Creatine kinase (CK) levels, AChR and MuSK antibodies were not detected in any of the patients.

A cardiology assessment including electrocardiogram (ECG) and echocardiogram was performed in all patients. Respiratory function was assessed spirometrically and vital capacity (VC) was also performed in every patient. In three patients a polysomnography (PSG) including an overnight oxygen saturation oximetry was done

to disclose nocturnal hypoventilation. Further data concerning clinical course under ephedrine therapy were assessed in a semi-standardized questionnaire.

Additional cardiological work-up and vital capacity measurements were done every 3–6 months after starting ephedrine therapy together with clinical re-evaluation.

Conventional muscle biopsies were performed in single patients and displayed only unspecific changes. No endplate biopsies were available for analysis. CK levels were normal in all patients.

Molecular genetic analyses were done in all eight patients, their parents and siblings, if available. Genomic DNA was isolated from venous blood samples using blood DNA extraction kit according to the manufacturer's recommendations (Promega, Mannheim, Germany). The *DOK7* gene was analysed as described previously [15]. Seven different mutations of the *DOK7* gene have been identified in our Caucasian patient cohort (4 German patients, 1–4; 1 Croatian patient, 5; 2 Swedish patients, 6 and 7; and 1 English patient, 8, Table 1). Genetic data to patients 1–3 were published, previously [10,15]. Mutations identified in patients 4–8 were previously reported, too [10]. The clinical features of these patients were compatible with CMS caused by *DOK7* mutations. After disclosing a *DOK7* mutation as the underlying defect ephedrine was started in all patients with a daily dose of 25 mg/day and slightly increased to a maximal daily dose of 100 mg (varying from 37.5 to 100 mg in individual patients). Ephedrine efficacy was tested in all patients approximately two hours after intake at all follow-up investigations. All patients were asked to comment on the influence of therapy on their quality of life in a semi-standardized questionnaire.

3. Results

Eight patients, two females and six males, were included in the study (Table 1). All were born after an uneventful pregnancy; manifestation varied from birth to 12 years, age at inclusion/diagnosis from 10 to 58 years. The time interval between first symptoms and starting ephedrine therapy was between seven and 40 years. The diagnosis was confirmed by genetic analysis; six different mutations in *DOK7* were identified.

Five patients showed a limb-girdle pattern of weakness more pronounced in the pelvic girdle in four patients (3, 4, 6, 7) and in the shoulder girdle in one woman (patient 2). Muscle weakness distal compared to proximal was milder in all five patients; MRC scale in distal muscles varied from 4 to 5. Muscle atrophy and contractures were not present in any of these five patients. Facial weakness was mild, combined with ptosis but without ophthalmoparesis (patients 2–4, 6, 7).

Three patients (1, 5, 8) manifested at birth with a floppy infant syndrome and either bulbar symptoms (patient 5) or respiratory distress (patient 1). Motor development in these three patients was slightly delayed; they became able to walk in the second or third year of life. Before start of therapy they also showed muscle weakness but, in comparison to the other five patients, more generalized and combined with muscle hypotonia in all three, as well as muscle atrophy, generalized in patients 1 and 5, in the shoulder girdle only in patient 8. Facial involvement was mild in all; patient 5 additionally suffered from bulbar weakness (Table 1). In patient 1 contractures were seen in the elbows and hips, in patient 5 in the elbows. Diurnal fluctuation was not reported by any of the eight patients but all reported on a fluctuation over several days or weeks.

Because of symptoms suggestive for CMS six patients (1–6) had received esterase inhibitor therapy (5 mg/kg BW/day) earlier, but without positive effects; in patients 1–3 worsening of symptoms under esterase inhibitor therapy was observed. At the beginning

of the study, patients 3 and 5 still received pyridostigmine at a moderate dose (120 mg/day) not resulting in clear clinical benefit.

Patients 1–5 were observed over 24 months; in patient 5 we collected data up to 36 months which did not differ from those after 24 months of ephedrine therapy (therefore not mentioned in Table 1). Patients 6–8 were followed over a period of 12 months. Within 1–4 weeks after starting ephedrine therapy positive effects were observed; patients started with 25 mg/day and slightly increased their medication according to the optimal daily dose for each individual patient (varying from 37.5 to 100 mg/day). This was defined either by the dose of optimized improvement of clinical symptoms or the highest possible dose without side effects; identifying the best therapeutic window took between 3 and 6 months. All patients described an improvement in muscle strength and exercise tolerance more pronounced in the proximal muscles without a clear difference between shoulder and pelvic girdle. Positive effects were also observed in the distal muscles, but to a lesser extent, because of a better muscle strength before ephedrine therapy (Table 1).

Muscle hypotonia in patients with neonatal manifestation (1, 5, 8) improved whereas contractures in the elbows and hips as well as generalized muscle atrophy did not change significantly. Only patient 4 showed a complete normalization of muscle strength and exercise tolerance, but all the others also showed a clear improvement with MRC grades ranging from 4+ to 4–5 in proximal muscles and from 4 to 5 in distal muscles (Table 1). These findings did not correlate with age at onset, age at diagnosis and start of treatment; even in patients with long delay between onset of symptoms and start of treatment positive effects were observed. All patients and their families reported on an improved quality of life, i.e. becoming more independent at several occasions such as daily activities at home, going to school or to work, and participating in social life. Patient 2 was able to reduce the duration of nocturnal ventilation; in patients 1 and 6 nocturnal ventilation did not change (Table 1).

Vital capacity measurements were performed before treatment in all patients and were reduced in six of them ranging from 28% to 72% of the normal age dependent value (patients 1–3, 5, 6, 8). Three patients (1, 2, 6) in our cohort needed ventilatory support over several hours at day and/or night time. The same measurements were performed under ephedrine therapy in all patients and showed pathological results in five of them (patient 1–5 varying from 27% to 79% of the age dependent normal value), no major changes were observed as compared to measurements before ephedrine therapy (Table 1).

Repetitive stimulation tests were performed in 5/8 patients at baseline (patients 1–5); a pathological decrement was found by stimulation of proximal nerves in patients 1–3 and 5, whereas pathological decrements were recorded neither by distal nor by proximal stimulation tests in patient 4. No electrophysiological examination before ephedrine therapy was performed in patients 6–8 and in patients 6 and 7 repetitive stimulation tests were not performed at any follow-up visit. Repetitive nerve stimulation tests under medication with ephedrine were done in patients 1–5 after 12 months and in patients 1, 2 and 5 after 24 months. Pathological results after 24 months were recorded by proximal stimulation tests in patients 1–3 and 5; there was no significant change observed compared to neurophysiological results prior to ephedrine therapy (Table 1).

Cardiological work-up including ECG and echocardiogram was normal in all eight patients before and under ephedrine therapy, and did not reveal any abnormalities.

Different side effects were observed at the beginning of and during ephedrine therapy (in patients 1–5, 8) like tachycardia (patients 1 and 5), epistaxis (patient 2), disrupted sleep and muscle cramps (patient 3), sweating (patient 4) and cold extremities and

nervous feeling (patient 8). Side effects improved after the first 4 weeks in patients 1, 2, 4, 5 and 8 without reducing the dosage and in patient 3 after reduction of the daily ephedrine dose to 37.5 mg/day. All patients reported side effects as tolerable during further clinical course compared to the positive effects of ephedrine therapy. In patient 2 clinical symptoms were not sufficiently improved and 3, 4-diaminopyridine was added in a daily dose of 4 × 10 mg providing additional benefit like an increase of muscle strength, exercise tolerance and a slight increase of the walking distance from 100 to 150 m. At the 24-months follow-up under ephedrine therapy patient one described “a dry mouth” at a daily dose of 100 mg, but this was tolerable. He described a reduced positive effect under the same daily dose of 100 mg after 22 months of therapy when he observed a slight decrease of muscle strength and exercise tolerance. He needed more time for his daily living activities at home, he used his wheelchair more than before and reported on a reduced exercise tolerance. Trying to increase the daily dose to 125 mg failed because of tachycardia and an unacceptably dry mouth.

4. Discussion

Here, we report on therapeutic effects of ephedrine therapy in eight patients with CMS due to *DOK7* mutations. To our knowledge, this is the first report on a prospective cohort study over 24 months.

Dok-7 is thought to play a crucial role in maintaining synaptic size and structure by either agrin-dependent or aneural activation of MuSK and the subsequent clustering of AChR [1,9–13]. The mechanisms of ephedrine effects in CMS caused by *DOK7* mutations are not fully understood. Ephedrine may increase the quantal release of acetylcholine (ACh) and affects AChR kinetics in a dose dependent manner, but this is reported *in vitro* using doses not applicable in patients [22–24]. Ephedrine shows positive effects in CMS patients with *COLQ* mutations and possibly in patients with a slow-channel CMS. Therefore, other mechanisms may be assumed, possibly through sympathomimetic activity.

Ephedrine therapy was well tolerated in our patients. Similar results were reported in patients with CMS due to *COLQ* mutations [18,19,22]. Ephedrine was started with 25 mg/day and then increased in 25 mg steps every 5–7 days until an optimized improvement or side effects were observed. In case of side effects a dose reduction was necessary in 12.5–25 mg steps in order to find the maximal individual dose without side effects. Side effects were observed within the first 4 weeks after beginning in all but one patient (patient 3) and did not necessitate the withdrawal of the medication.

In our cohort both positive and negative therapeutic effects of ephedrine were observed in all eight patients and this did not correlate with age of onset, symptoms at onset or the time interval between manifestation and start of therapy. An improvement was seen within 1–4 weeks predominantly in proximal muscle weakness using the MRC score [20,21]. Given that proximal muscle weakness is one of the most frequent and disabling symptoms in *DOK7*-associated CMS, even a small improvement of proximal muscle strength and endurance may have major significance for daily life activities. Effects on facial weakness are mild but also demonstrable (Table 1); the influence on contractures and muscle atrophy is not significant although this did not diminish the positive effect of ephedrine on the clinical course. Further objective measures like myasthenia scores, dynamometric measurements and different time function tests (rising from the floor or running 10 m) were performed in single patients. Results depended on compliance and performance of the single time function test and were not comparable. Consequently, we were not able to draw

any conclusion by comparing these data. However, an improvement of muscle strength and weakness can be clearly demonstrated by the data of clinical follow-up and the MRC scale which were equally performed in every centre.

An optimization of the individual dose may take 3–6 months; positive effects were stable over 12 months in three (6–8) and 24 months in five patients (1–5). Patient one in our cohort reported on a habituation of positive effects after 24 months of ephedrine therapy. The effect was restored by increasing the daily dose from 75 to 100 mg. Habituation has not been reported in *DOK7* patients so far, but further observation is necessary as this may be a limiting factor for a long-term therapeutic option. This dosing regimen may need to be adapted according to local circumstances and requirements, but has generally worked well for the patients and centres involved in this study. Improvement of symptoms and side effects in CMS associated with *DOK7* mutations using ephedrine has been indicated in a number of case studies, but not reported in detail on a larger series of patients [1–3,5–7,15–19]. Our data may suggest the following to the therapeutic strategy in *DOK7*-related CMS: after confirmed diagnosis it is necessary to start ephedrine therapy as soon as possible; independent of age at onset, age at diagnosis and duration of symptoms positive therapeutic effects can be expected. However, results of repetitive stimulation tests and vital capacity measurements may not correlate with clinical improvement. Vital capacity is the key investigation in patients with neuromuscular disorders disclosing weakness of the respiratory muscles. In cases with respiratory problems due to scoliosis maximal inspiratory and expiratory pressure can be a helpful item in addition to vital capacity measurements. But it depends on the patients compliance and several measurements during individual long-term follow-up are necessary [25,26]. In our cohort scoliosis was not the limiting factor for respiratory problems; therefore, we decided to measure the vital capacity.

To date, the most important parameter for follow-up is the clinical investigation including MRC score. In contrast, repetitive stimulation tests and vital capacity measurements were shown to be useful to monitor esterase inhibitor therapy where an improvement was demonstrated [2,7,17–19].

This small study emphasizes the potential of ephedrine therapy in patients with CMS due to *DOK7* mutations. Further studies are necessary to document the long-term follow-up of a larger cohort and to determine better measurements revealing objective data correlating with the clinical improvement.

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References

- [1] Beeson D, Webster R, Cossins J, Lashley D, Spearman H, Maxwell S, et al. Congenital myasthenic syndromes and the formation of the neuromuscular junction. *Ann NY Acad Sci* 2008;1132:99–103.
- [2] Engel AG. Congenital myasthenic syndromes. In: Engel AG, editor. *Handbook of clinical neurology. Neuromuscular junction disorders*, vol. 91. Elsevier; 2008. p. 285–331.

- [3] Engel AG, Shen XM, Selcen D, Sine SM. Further observation in congenital myasthenic syndromes. *Ann NY Acad Sci* 2008;1132:104–13.
- [4] Kinali M, Beeson D, Pitt MC, Jungbluth H, Simonds AK, Aloysius A, et al. Congenital myasthenic syndromes in childhood: diagnostic and management challenges. *J Neuroimmunol* 2008;201–202:6–12.
- [5] Müller JS, Mihaylova V, Abicht A, Lochmüller H. Congenital myasthenic syndromes: spotlight on genetic defects of neuromuscular transmission. *Expert Rev* 2007;9:1–20.
- [6] Nogajski JH, Kiernan MC, Ouvrier RA, Andrews PI. Congenital myasthenic syndromes. *J Clin Neurosci* 2009;16:1–11.
- [7] Palace J, Beeson D. The congenital myasthenic syndromes. *J Neuroimmunol* 2008;15:201–2.
- [8] Maselli RA, Ng JJ, Anderson JA, Cagney O, Arredondo J, Williams C, et al. Mutations in *LAMB2* causing a severe form of synaptic congenital myasthenic syndrome. *J Med Genet* 2009;46:203–8.
- [9] Okada K, Inoue A, Okada M, Murata Y, Shigeru K, Jigami T, et al. The muscle protein DOK-7 is essential for neuromuscular synaptogenesis. *Science* 2006;312:1802–5.
- [10] Beeson D, Higuchi O, Palace J, et al. Dok-7 mutations underlie a neuromuscular junction synaptopathy. *Science* 2006;3:1975–8.
- [11] 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.
- [12] Vogt J, Morgan V, Marton T, Maxwell S, Harrison B, Beeson D, et al. Germline mutation in *DOK7* associated with foetal akinesia deformation sequence. *J Med Genet* 2009;46:338–40.
- [13] Yamanashi Y, Higuchi O, Beeson D. Dok-7/MuSK signalling and a congenital myasthenic syndrome. *Acta Myol* 2008;XXVII:25–9.
- [14] Andersen J, Ng JJ, Bowe C, McDonald C, Richman DP, Wollmann RL, et al. Variable phenotypes associated with mutations in *DOK7*. *Muscle Nerve* 2008;37:448–56.
- [15] 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.
- [16] 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.
- [17] Selcen D, Milone M, Shen XM, Harper C, Stans AA, Wieben ED, et al. Dok-7 myasthenia: phenotypic and molecular genetic studies in 16 patients. *Ann Neurol* 2008;64:71–87.
- [18] Engel AG. The therapy of congenital myasthenic syndromes. *Neurotherapeutics* 2007;4:252–7.
- [19] Schara U, Lochmüller H. Therapeutic strategies in congenital myasthenic syndromes. *Neurotherapeutics* 2008;5:542–7.
- [20] Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trials in Duchenne dystrophy. I. The design of a protocol. *Muscle Nerve* 1981;4:186–97.
- [21] Medical Research Council. Aids to the investigation of peripheral nerve injuries. War memorandum. Revised 2nd ed. London: HMSO; 1943.
- [22] Bestue-Cardiel M, Sáenz de Cabezón-Alvarez A, Capablo-Liesa JL, et al. Congenital endplate acetylcholinesterase deficiency responsive to ephedrine. *Neurology* 2005;65:144–6.
- [23] Milone M, Engel AG. Block of endplate acetylcholine receptor channel by the sympathomimetic agents ephedrine, pseudoephedrine and albuterol. *Brain Res* 1996;18:346–52.
- [24] Sieb J, Engel AG. Ephedrine: effects on neuromuscular transmission. *Brain Res* 1993;623:167–71.
- [25] Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders – congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II), 4–6 April 2003, Naarden, The Netherlands. *Neuromuscul Disord* 2004;14:56–69.
- [26] Mellies U, Dohna-Schwake C. Neuromuscular disorders. In: Hammer J, Eber E, editors. *Pediatric pulmonary function testing. Progress in respiratory research*, vol. 33. Basel: Karger; 2005. p. 1–14.