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Muscle slowness in a family with nemaline myopathy

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Abstract

All patients of a large family with nemaline myopathy complained of slowness in movement. We confirmed this clinical complaint physiologically by showing lower contractile speed in quadriceps muscle. Electrically evoked contractions of the quadriceps muscle elicited a lower rate of relaxation and a tendency for slower torque generation. Here, we demonstrate for the first time slow muscle characteristics as a physiological correlate for the clinical complaint of slowness.

Keywords: Nemaline myopathy; Muscle slowness; Relaxation

1. Introduction

Nemaline myopathies are diseases of the skeletal muscle sarcomere. Until now five genes are associated with these diseases, which all encode for thin filament proteins [1–5]. Recently, we described a five-generation family with an autosomal dominant nemaline myopathy with a different genetic locus on chromosome 15q [6] and a remarkable phenotype [7]. In addition to proximal muscle weakness patients complained of slowness in movement, which is a hitherto not reported feature in neuromuscular diseases.

Slowness in movement is usually associated with disorders of the pyramidal or extrapyramidal systems and, in specific neuromuscular diseases, with myotonia. The presented patients showed no signs or symptoms of pyramidal and extrapyramidal disorders or myotonia on neurological and EMG examinations.

As all genetically characterised nemaline myopathies [1–5] are diseases of the thin filament, and although the gene in the present family is not yet identified, the slowness might be due to a defect in the interaction of the thin and thick filament. Therefore, we measured characteristics of muscle speed, i.e. rates of torque rise and relaxation, in electrically evoked isometric contractions of the quadriceps muscle in patients and controls.

2. Patients and methods

2.1. Patients

Ten patients and three non-diseased members from a five-generation family with autosomal dominant nemaline myopathy [7] linked to chromosome 15q, agreed to participate in the present study. Five non-familial age and sex matched control subjects were also included (Table 1). Four patients and one non-diseased family member gave permission to take a needle muscle biopsy from the quadriceps (vastus lateralis) muscle.

All patients complained of mild to moderate muscle weakness in the proximal limbs as exemplified by difficulties with climbing stairs, jumping, running and lifting heavy objects. Muscle weakness started in early childhood (motor milestones in de first years of life were normal). Only elderly patients experienced disease

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Table 1
Physiological data of 10 nemaline patients (from one family) compared to eight healthy controls showing significantly lower maximal voluntary torque (MVT), lower maximal rate of relaxation (MRR), expressed as percentage of peak torque (T_{max}), higher time to peak twitch torque (TPT) and higher torque ratio 10/150 Hz (Tr10/150)

	Nemaline myopathy patients (mean±SD)	Healthy controls (mean±SD)	*P*
Number (total/females)	10/6	8/5	
Age (years)	44.8 (±23)	45.7 (±34)	0.89
MVT (Nm)	125 (±32)	194 (±57)	0.005
MTR (% $T_{max/s}$)	1.4 (±0.5)	1.8 (±0.3)	0.057
MRR (% $T_{max/s}$)	1.03 (±0.14)	1.27 (±0.15)	0.003
TPT (ms)	109 (±12)	88 (±9.0)	0.0007
10/150 Hz	0.51 (±0.15)	0.26 (±0.11)	0.001

In addition, there was a tendency for a lower maximal rate of torque rise (MTR).

progression, especially after the fifth decade, but none of them had become wheelchair-bound. Activities of daily life were not or only slightly impaired. Physical examination showed muscle weakness in the neck flexors and proximal limb muscles (MRC grade 4).

Most remarkable was the complaint of slowness in movement in all patients. There were no prompt motor responses to sudden unexpected events. If the patients stumbled they were unable to correct themselves from falling over and were sometimes even too late to stretch out their arms to break the fall. Running was impossible, although they could walk for hours. This slowness was constant and was not influenced by temperature, diets or other variables. The complaint of slowness could not be detected on regular neurological examination or on routine EMG examination.

All subjects provided written informed consent after they had received a careful explanation about testing procedures and involved risks. The local Medical Ethical Committee approved the study.

2.2. Methods

2.2.1. In vivo contractile measurements

Characteristics of the quadriceps muscle were measured according to methods described previously [8]. In short: subjects were seated on a computer controlled lower-limb dynamometer at 60° knee-flexion angle (0° corresponding with full knee extension). The subject's shin was connected to the lever arm of the dynamometer and torque was measured at the motor axis. Subjects were asked to perform a maximal voluntary contraction of the left knee extensors to study the presence and degree of muscle weakness.

To investigate muscle slowness, we measured the rates of torque development and relaxation in electrically evoked (via surface electrodes) quadriceps contractions. From these data, we measured four parameters for slowness:

– Maximal rate of relaxation (MRR), as an indication for relaxation speed, was calculated from the torque response of stimulation with 150 Hz (700 ms; Fig. 1(A)) [9].
– Maximal rate of torque rise (MTR) is an indication for contraction speed, and was calculated from the torque response of a brief supramaximal stimulation at 300 Hz (70 ms; Fig. 1(A)) [9] at which frequency

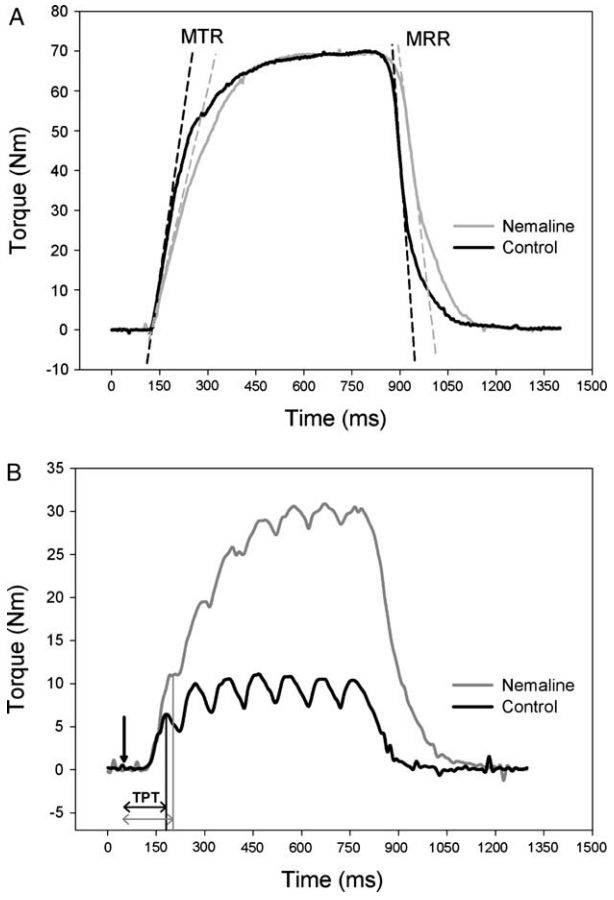

Fig. 1. Example of typical torque responses of the quadriceps muscle resulting from 150 Hz (A) and 10 Hz (B) stimulation in a nemaline patient and a healthy family control (with similar strength). (A) Indicated are the maximal slopes for torque rise (MTR) and decrement during relaxation (MRR). Note that MTR and MRR are presented only for illustrative purposes in a contraction with 150 Hz stimulation. (B) Indicated is the time to peak twitch torque (TPT). The vertical arrow indicates the start of the electrical stimulus. This figure shows also that due to slower contractile properties the individual twitches of the nemaline patient show more fusion and hence, a higher torque generation at low stimulation frequencies (10 Hz).