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Quantitative myotonia assessment: an experimental protocol

Abstract Severe clinical myotonia can be physically disabling and socially imparing but as yet there is no standardized treatment regimen. The aim of our study is to present a protocol to measure myotonia using quantitative muscle assessment measures. The proposed protocol addresses two main issues. Muscle strength is assessed in 8 muscles on the right and on the left using a myometer (QMA, quantitative muscle assessment) and by testing strength manually using the 5-point MRC scale (5 = normal) in 15 muscles on the right and on the left. Grip myotonia is assessed by: (a) measuring 1/2 and 3/4 relaxation times (RT) after maximum voluntary contraction (MVC) using QMA apparatus; (b) functional tests (time to open a fist 10 times, time to open and squeeze the eyes 10 times, time to climb 10 steps starting from a seated position, time to protrude the tongue 10 times, time to step onto a chair 10 times; (c) subjective measures of the severity of myotonia using an arbitrary 4-point scale (0 = absent, 4 = severe); and (d) electromyography (EMG) relaxation times after MVC. Although QMA seems to be a reliable tool to measure myotonia, there are still a number of unsolved issues. Further studies are needed to ensure the ability of QMA to quantify myotonia and to guarantee the reliability of the results for clinical research purposes.

Key words Myotonia • Myometry • Quantitative muscle assessment • Muscle strength • Clinical trials • Therapy

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Introduction

Myotonia is a phenomenon of delayed muscle relaxation associated with repetitive electrical depolarization following a single induced muscle contraction. Commonly, myotonia is found in the myotonic dystrophies [1] and in the non-dystrophic myotonias like hyperkalemic periodic paralysis, paramyotonia congenita and myotonia congenita (Table 1).

Treatment of myotonia has been directed at electrical stabilization of the muscle membrane mainly using antagonists of voltage-dependent sodium channels, responsible for the repetitive electrical activity which characterizes the myotonic phenomenon. Myotonia has been previously assessed by measuring the relaxation time necessary to completely open the fist after maximum voluntary contraction (MCV) [2], by self-evaluation arbitrary scales [3], by functional tests [3, 4], and by myotonic afterdischarge after MCV on electromyography (EMG) measurements [3]. However, the variability of the myotonic phenomenon and the "warm-up" effect have made quantification of myotonia difficult. Often, the perception is one of a semi-quantitative evaluation which may not be sensitive enough to detect small changes or account for the variability.

We propose a protocol (Table 2) to determine whether quantitative muscle assessment can be considered a tool for the investigation of myotonia and thus be a good indicator of effective antimyotonic treatment for clinical and research purposes.

Table 1 Classification of myotonias

Inherited myotonia
Myotonic dystrophies
DM1 (myotonic dystrophy type 1, linked to chromosome 19q)
DM2/PROMM (myotonic dystrophy type 2/proximal myotonic myopathy on 3q-linked locus)
DMn (DM1-like phenotype unlinked to 3q-linked locus)
Drug-induced myotonia
Clofibrate
Chloroquine
Diazocholesterol
2,4 dichlorophenoxyacetate (2,3-D)
Pseudomyotonia
Acid maltase deficiency
Hypothyroidism

Table 2 Experimental protocol

Assessment of muscle strength
Quantitative muscle assessment (QMA), 11 muscles (maximum voluntary contraction, MVC)
Manual muscle strength testing (5-point MRC scale), 15 muscles (normal score, 150)
Assessment of myotonia
Subjective self-evaluation of severity (0, absent; 1, mild; 2, moderate; 3, severe)
Functional tests
Time to open a fist 10 times
Time to open and squeeze the eyes 10 times
Time to climb 10 steps starting from a seated position
Time to protrude the tongue 10 times
Time to step onto a chair 10 times
Measure of relaxation times by QMA
50% of maximum voluntary contraction
75% of maximum voluntary contraction
Measure of relaxation time by EMG

MRC, Medical Research Council [5]

Protocol design

Patient selection

Subjects with the following disorders are studied: hyperkalemic periodic paralysis with myotonia (HyperKPP), paramyotonia congenita (PC), myotonia congenita (MC), and mildly affected myotonic dystrophies (DM1, DM2, DMn) [1]. To avoid triggers, all subjects should be placed for 1 hour in a room at controlled temperature (22° C), and requested to remain completely relaxed for 30 minutes. In the days prior to the actual testing, the patients should avoid exercise and should follow a strict diet with low-carbohydrate intake and without foods very rich or very poor in potassium, according to the disease involved. For women, tests should not be performed during menses. Any myotonic treatment and any other treatment which is not life-saving should be discontinued at least one week before the test period.

Exclusion criteria reflect the degree of muscle weakness. If finger flexor strength scores are below 4 on MRC grading, patients should be eliminated for assessment of myotonia. Any patient scoring below 130 on MRC megascores should not be included in the experimental design.

Assessment of muscle strength

Strength is evaluated by manual muscle testing and by quantitative myometry. The accuracy and consistency of the data should be ensured by having the same person (ideally a trained physiotherapist) perform the test each time.

Quantitative muscle assessment (QMA). The QMA protocol measures: (i) the maximum force attained; (ii) rise time, i.e. the time taken for the rising edge of the data to go from 10% to 90% of the maximum; and (iii) sustain time, i.e. the time

the force remains above 70% of the maximum. Strength was tested in the following muscles: hand finger flexors, shoulder abductors and adductors, ankle dorsiflexors, and thigh and knee flexors and extensors.

Manual muscle strength (MRC). Strength is assessed in 10 muscles on the right and on the left in the upper limbs (scapular fixators, biceps, triceps, wrist flexors and extensors, short and long finger flexors, thumb opponent, and finger abductors and adductors) and in 5 muscles on the right and on the left in the lower limbs (ileopsoas, quadriceps, tibialis anterior, tibialis posterior and finger extensors). Muscle strength is quantified using the 0-5 MRC scale by summing the scores for each muscle group; a score of 5 indicates normal strength for all 15 muscles tested on the right and on the left and corresponds to 150 MRC megascore in normal subjects. Attention should be focused on finger flexors: finger flexor strength is quantified using a hand-held grip dynamometer. The patient is asked to exert the maximum possible force for 3 seconds and the maximum voluntary contraction (MVC) is calculated.

Assessment of myotonia

Assessment of myotonia includes:

(i) *Functional tests*: time to open a fist 10 times, time to open and squeeze the eyes 10 times, time to climb 10 steps starting from a seated position, time to protrude the tongue 10 times, and time to step onto a chair 10 times;
(ii) *Subjective measures*: self-evaluation of the severity of myotonia using an arbitrary 4-point scale (0, absent; 1, mild; 2, moderate; 3, severe);
(iii) *Objective measures*: assessment of myotonia from relaxation times (RTs) at the end of the 3-second MVC produced by hand grip. Relaxation times are the time for the MVC to decrease by 50% and 75% (referred to as 1/2 RT and 3/4 RT). Relaxation time values are accepted only if subjects exert the same degree of strength as measured in previous records of strength assessment with QMA. To avoid the influence of the warm-up phenomenon, we evaluate only the first grip and subsequent relaxation. When necessary, we repeat the test on the same subject, but not before 15 minutes have elapsed;
(iv) *EMG relaxation time* determined from the myotonic afterdischarge in the musculus opponens pollicis after MVC.

Conclusions

Pharmacological treatment of myotonia is a subject of controversy since a long list of various therapeutic agents have been tried in myotonic disorders [6-11]. The rational for treatment is dictated by the fact that many patients are disabled by their difficulty in relaxation after a maximum voluntary contraction to the extent their quality of life is impaired. On the other hand, the benefits of myotonia control must be weighed against the risk of antimyotonic agents. In other diseases, improvement of myotonia may unmask or worsen muscle weakness. In addition, there is no evidence that the prevention of myotonia, in those myotonic syndromes associated with myopathy or dystrophy, influences these features. However, in the majority of patients antimyotonic treatment is justified. Despite these considerations, there is still no standardised treatment regimen for myotonia and there have been relatively few randomized controlled trials for the quantification of myotonia.

Although preliminary, we present an experimental protocol for the quantification of myotonia. Any patient with a myotonic disorder can be studied as long as the inclusion criteria for the degree of muscle strength are considered as well as the other criteria mentioned. This allows for a large sampling size. We have included measures of muscle strength although the protocol focuses on measures of myotonia because we have often observed an inverse correlation between muscle strength and degree of myotonia. Moreover, several patients, especially those with myotonia congenita or with proximal myotonic myopathy, have reported increased weakness following antimyotonic therapy although the precise relationship between myotonic stiffness and weakness is unclear. Assessment of myotonia using this protocol design has emphasised a number of problems related to this phenomenon. There is an extreme variability of myotonia between patients with the same disease, but also within the same patient, from day to day and even within the same day. Factors affecting myotonia such as outside temperature, menses and exercise should be strictly controlled. Keeping the patients in a resting condition before testing and considering only the first grip to avoid the warm-up phenomenon may need further confirmation. The patient may not understand the test immediately and therefore give a partial result due to improper test position or system malfunctioning. We believe the patient should perform correctly because testing muscle strength uses the same apparatus so that the patient should be familiar with the hand-grip. Nonetheless, we have considered the possibility of error and believe that the 15-minute interval between one test and another one is sufficiently long to avoid warm-up. This implicates that testing may be repeated at specific intervals of time, although this makes testing lengthy and intolerable for the patient.

Although QMA seems to be a reliable tool to measure myotonia, there are still a number of unsolved issues. Further studies are needed to ensure the ability of QMA to quantify myotonia and to guarantee the reliability of the results for clinical research purposes.

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