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Muscle ultrasound measurements and functional muscle parameters in non-dystrophic myotonias suggest structural muscle changes

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ABSTRACT

Patients with non-dystrophic myotonias, including chloride (myotonia congenita) and sodium channelopathies (paramyotonia congenita/potassium aggravated myotonias), may show muscular hypertrophy in combination with some histopathological abnormalities. However, the extent of muscle changes has never been assessed objectively in a large group genetically confirmed patients. This study quantitatively determines echo intensities, thicknesses, ranges-of-motion and force of four skeletal muscles in 63 genetically confirmed patients. The main findings revealed elevated echo intensities in all muscles except the rectus femoris (+1.3–2.2 SD, $p < 0.0001$), and hypertrophy in the arms (+0.5–0.9 SD, $p < 0.01$). Muscle echo intensities were inversely correlated to the corresponding ranges-of-motion (biceps brachii: $r = -0.43$; $p < 0.001$, forearm flexors: $r = -0.47$; $p < 0.001$, rectus femoris: $r = -0.40$; $p = 0.001$, and tibial anterior: $r = -0.27$; $p = 0.04$) and correlated positively to age ($r = 0.22$; $p = 0.05$). The echo intensity of the forearm flexors was inversely correlated to their muscles' force ($r = -0.30$; $p = 0.02$). Together, these data suggest that non-dystrophic myotonias may lead to structural muscle changes.

1. Introduction

Non-dystrophic myotonias form a group of rare hereditary diseases, existing of either chloride (recessive and dominant myotonia congenita) or sodium channelopathies (paramyotonia congenita/potassium aggravated myotonias), that exclusively affect skeletal muscles [1–3]. The key symptom of non-dystrophic myotonias is myotonia, i.e., a delayed muscle relaxation after a voluntary or evoked contraction. The needle-electromyographies of non-dystrophic myotonias show myotonic discharges in almost all skeletal muscles, even at rest [4,5]. Both myotonia and myotonic discharges are the consequence of a hyperexcitable sarcolemma caused by a disturbed chloride or sodium conductance. Recently, the molecular basis of non-dystrophic myotonias was discovered allowing the diagnosis to be confirmed by genetic testing [6,7].

The term non-dystrophic myotonias by definition implies that, in contrast to myotonic dystrophy, non-dystrophic myotonias do not show dystrophy, and does not result in structural muscle changes. Muscle biopsies of non-dystrophic myotonias were initially described as normal or showing mild, non-specific abnormalities [8]. Subsequent investigations reported an absence of type 2B fibres in chloride channelopathies, while patients with paramyotonia congenita, a sodium channelopathy, were found to show intracellular large vacuoles and tubular aggregates [9–11]. However, the presence of muscle changes has never been systematically investigated in large group of genetically confirmed patients.

Clinically, muscle hypertrophy may be prominent in patients with non-dystrophic myotonias and is thought to be caused by repetitive and prolonged muscle contractions. Becker reported muscular hypertrophy in 71% of his patients with recessive myotonia congenita and in 25% of the patients with dominant myotonia congenita (both chloride channelopathies) [8]. In paramyotonia congenita muscular hypertrophy is reported to be rare (sodium channelopathy) [1]. Even so, these findings stem from the pre-genetic era and were all solely based on subjective, visual examinations.

Muscular ultrasound has been shown to be accurate in detecting the presence and extent of changes in muscle structure and muscle thickness [12–16]. Fibrosis and fatty infiltration as for example detected in abundance in muscular dystrophies are thought to account for the increased echo signal detected by muscle ultrasound [12,14,17,18]. Although, muscle ultrasound cannot determine the exact nature of changes, this technique is non-invasive and allows easy examination of multiple muscles, yielding a clear overview of the extent and distribution of the pathology within the patient's body [19].

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In order to determine whether and where in non-dystrophic myotonias muscle changes and muscular hypertrophy occur, we quantitatively measured the echo intensities and thicknesses of two proximal and two distal skeletal limb muscles in a large group of genetically confirmed patients. We, moreover, compared the outcomes for the chloride and sodium channelopathies and those of the male and female patients and, lastly, investigated whether the echo data were correlated to the corresponding ranges-of-motion, muscle force and age.

2. Patients and methods

2.1. Subjects

Between April 2005 and March 2006 a large cohort of non-dystrophic myotonia patients residing in the Netherlands participated in our comprehensive non-dystrophic myotonia study, 63 of whom took part in this investigation. Inclusion criteria were a minimum age of 18 years, a clinically and genetically confirmed diagnosis of non-dystrophic myotonia according to established clinical criteria [20], and needle electromyographic evidence of myotonic discharges. We distinguished chloride from sodium channelopathies and paramyotonia from other sodium channelopathies (potassium aggravated myotonias) by clinical criteria and DNA-analysis [20,21]. The study was approved by the local medical ethics committee and all patients gave their written informed consent prior to their participation.

2.2. Ultrasound measurements

The method of ultrasound scanning is described in detail in earlier reports [22,23]. In short, we examined four muscles in the transverse plane: left biceps brachii, right forearm flexors, right quadriceps femoris, and left tibialis anterior muscle. The apparatus used was a phased-array real-time scanner (Sonos 2000 Phased Array Imaging System; Hewlett-Packard Company, Andover, Massachusetts, USA), with a 7.5 MHz transducer. To enable us to use previously established normal values, all system parameters were equivalent to the ones we used in our previous study [22]. Mean muscle echo intensity was quantified using a computer-assisted grey-scale analysis. In each muscle a region of interest was selected according to our previous protocol and the mean grey value was calculated: 8-bit scale; black = 0; white = 255 [22]. These values are related to the amount of decibels that return to the transducer, which is incorporated in the hard- and software of the ultrasound device. A predefined look-up-table in the ultrasound machine converts the decibels to corresponding grey values. In our study (as in all studies on muscle ultrasound), this look-up-table was the same in every measurement, as a fixed preset (gain and compression) was used. As in severe neuromuscular disorders the outline of the vastus intermedius muscle may be difficult to delineate, we opted to use the rectus femoris in the quadriceps femoris muscle for our echo-intensity analysis [24].

Muscle thickness was measured with electronic callipers at predefined standardised locations in the ultrasound image [22]. To gauge differences in the dominant and non-dominant arm muscles we performed bilateral measurements in 38 patients (18 chloride channelopathies and 20 sodium channelopathies), with dominance having been established during the intake interview. All images were also independently evaluated visually by two investigators (J.T. and S.P.) to investigate if specific patterns of distribution or increased echo intensities were present either among different muscles or within the muscle, as has previously been described in certain congenital myopathies or anterior horn cell disorders [25].

2.3. Range-of-motion and muscle-force measurements

Active ranges-of-motion of the right wrist, left elbow, right knee and left ankle were measured in degrees using a transparent goniometer while adhering to Norkin and White's system with standardised positions for patients, examiner and goniometer [26].

The maximum isometric contraction values of elbow flexion, three-point grip, knee extension and ankle dorsiflexion were measured with a calibrated hand-held dynamometer (type CT 2001, C.I.T. Technics, Haren, The Netherlands) [27,28]. We used the 'make technique': the patients were instructed to take 1 or 2 s to reach maximum effort levels and subsequently contract their muscle as forcefully as possible. All measurements were conducted using standardised positions for patients, examiner and dynamometer [28]. All patients were tested in a temperature-controlled room (20 °C) at the same time of day and by the same investigator (JT) to reduce variations in testing.

2.4. Data analysis

The patients' ultrasound results were compared to previously established normal values (corrected for age and gender) [23] and transformed into z-scores, i.e., the number of standard deviations above or below normal [22,29]. In general, z-scores are constructed in such a way that in a healthy or reference population they lead to z-scores with an average of 0 and a standard deviation of 1. This 'normalisation' helps to interpret the outcome of a variable in a population that may otherwise be difficult to interpret (or changes with age). When the z-score in a diseased population is 0, the outcome is 'normal', while values above 2 and under −2 are 'abnormal' in the sense that they occur <5% of the healthy population.

Statistical analyses were performed using the SPSS package for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA). A one-sample *t*-test was used to assess whether the patients showed a significant increase in their echo intensity and muscle thickness z-scores compared with the normal population. An independent-sample *t*-test was used to compare the respective z-scores for the chloride and sodium channelopathies and male and female patients. We ran a paired-sample *t*-test to compare the absolute values of the echo intensities and thicknesses of the dominant and non-dominant arm muscles. Correlations between muscle echo intensities and the corresponding ranges-of-motion and muscle forces were calculated using Pearson's correlation coefficients, as were the correlations between muscle thickness and muscle force. Echo intensities and thicknesses were correlated to age for each muscle separately as well as for their sum scores. A p-value of <0.05 was considered to be significant.

3. Results

Table 1 shows the primary diseases and antropometric data of all 63 participating patients. In three patients the measurements for one muscle were excluded from further analysis: the left biceps muscle in one recessive chloride channelopathy due to a mechanical accident; the left tibialis anterior muscle in a sodium channelopathy because of chronic muscle weakness due to a previous lumbar disc hernia; the right rectus femoris muscle in a chloride channelopathy because the echo intensity could not be measured reliably as the rectus femoris was located at a depth of more than 3.5 cm and thus outside the maximum setting stipulated in the ultrasound protocol.