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Quantitative muscle ultrasound measures rapid declines over time in children with SMA type 1

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ABSTRACT

Muscles are small in spinal muscular atrophy (SMA). It is not known if muscle size changes over time in SMA type 1. We quantified changes over time in muscle size and echointensity during two repeated ultrasound examinations of unilateral proximal (biceps brachii/brachialis and quadriceps) and distal (anterior forearm flexors and tibialis anterior) muscles in three children with SMA type 1. We compared muscle thickness (MT) to body weight-dependent normal reference values. Children were 1, 6, and 11 months old at baseline and had 2, 2 and 4 months between ultrasound examinations, respectively. At baseline, MT was normal for weight in all muscles except an atrophic quadriceps in the oldest child. MT decreased and echointensity increased (worsened) over time. At follow up, MT was below normal for weight in the quadriceps in all three children, in the biceps/brachioradialis in two, and in the anterior forearm in one. Tibialis anterior MT remained normal for weight in all three children. Muscle echointensity increased over time in all muscles and, on average, more than doubled in two children. In children with SMA type 1, muscle atrophies and becomes hyperechoic over time. Quantitative muscle ultrasound measures disease progression in SMA type 1 that warrants additional study in more children.

1. Introduction

Spinal muscular atrophy (SMA) results from a loss of survival motor neuron 1 (SMN1) genes, has an estimated incidence of up to 1/6000 live births, and is the most common fatal neuromuscular disease of infancy [1]. The loss of survival motor neuron protein results in progressive muscle weakness from degeneration of the α-motor neurons in the anterior horn of the spinal cord and lower brain stem. A truncated survival motor neuron protein, produced by the survival motor neuron 2 (SMN2) gene, partially rescues the phenotype. The type of SMA is defined by the clinical severity and correlates with the number of SMN2 gene copies [2]. Children with SMA type 1 (Werdnig–Hoffmann) are most severely affected and never sit independently, those with type 2 achieve independent sitting, and those with type 3 walk. There are currently therapies in early clinical trials, such as antisense oligonucleotides, designed to lead to more functional SMN2-derived protein for patients with all types of SMA.

Reliable outcome measures that are easy to perform and do not require active patient participation are needed for clinical trials, particularly for the infants with SMA type 1 [3,4]. Motor unit number estimate (MUNE) and compound muscle action potential (CMAP) testing have been proposed to monitor the degeneration of motor neurons but are painful, require high levels of investigator training to achieve good reliability, and can be tedious to perform. Other techniques such as dual-energy X-ray absorptiometry (DEXA) or MRI have been proposed to monitor muscle size as a biomarker of disease in children with SMA [5–7]. MRI cannot be performed at the bedside and may require sedation. DEXA scanning exposes children to radiation.

Quantitative muscle ultrasound is a simple, painless, and rapid tool for measuring muscle pathology that can be performed at the bedside. Features of muscle measured with ultrasound include size (thickness or cross sectional area) and echointensity. Ultrasound and MRI yield highly correlated measurements of muscle size [8–10]. Both muscle size and echointensity can be quantified reliably using ultrasound by trained examiners [10–12]. Muscle size in children changes with growth and requires normalization for height and/or weight [13]. Muscle echointensity in children does not change with normal growth [13]. Muscle echointensity measured from the gray scale pixel levels in the ultrasound image will vary between different ultrasound systems and set-ups. Calibrated muscle backscatter (cMB) is a measure of echointensity that reduces the inter-system variability in gray scale pixel measurements by estimating the amplitudes of the sound waves scattered back to the ultrasound transducer and referencing values to a common phantom [14,15]. Both backscatter and gray scale measures of muscle echogenicity have high interrater reliability and similarly detect pathology [16]. cMB provides improved reliability over gray scale measurements for comparing images acquired using different ultrasound systems or configurations [15].

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Quantitative muscle ultrasound can measure neuromuscular disease progression even in very young children. For instance, in infants and young children with Duchenne muscular dystrophy, cMB increased 1.0–3.8 dB/year [17]. In children with SMA, muscle thickness is decreased [18] and muscle echointensity is increased and relates to disease severity [19–21]. In SMA types 2 and 3, muscle size does not change over time [5]. It is not known how muscle size or echointensity changes over time in children with the more severe SMA type 1 phenotype. In this study, we show how muscle size and echointensity (cMB) change over time in three infants with SMA type 1.

2. Methods

2.1. Patients

This study was approved by the institutional review board of Washington University, St. Louis and informed consent from parents/guardians was obtained. We evaluated 3 subjects between November 2013 and November 2014 with genetically confirmed SMA type 1. Each had an initial ultrasound examination and then a repeat examination at a subsequent clinic visit. All patients were followed in our neuromuscular clinic by neuromuscular neurologists, and charts were reviewed to determine patient demographics at the time of ultrasound examinations, including age, weight, and height. All 3 children were genetically confirmed SMA type 1 with 0 copies of the SMN1 gene, were severely weak, and did not achieve sitting independently as a motor milestone. Patient 1 had four copies of SMN2 and was able to achieve rolling over once very slowly and raise arms above the head but never achieved sitting. Patients 2 and 3 were more severely weak and had only 2 copies of the SMN2 gene.

2.2. Ultrasound

One investigator (C.M.Z.) obtained all ultrasound images and performed all ultrasound measurements. Ultrasound examinations were performed with a Philips iu22 ultrasound machine imaging system with an L12-5 linear-array probe. System settings were kept constant throughout every study. Ultrasound measurement protocol included 4 unilateral muscles in each child: two proximal arm/leg muscles (biceps brachii/brachialis and quadriceps) and two distal arm/leg muscles (anterior forearm flexors and tibialis anterior). The muscles were measured in the supine position, holding arms and legs extended with muscles relaxed. Arms were supinated, knees extended, and ankle in a neutral position. Transverse ultrasound images of the muscles were obtained at pre-defined anatomical locations that correspond to the maximal muscle diameter at the muscle belly. The biceps brachii/brachialis was measured at two-thirds of the distance from the acromion to the antecubital crease. The forearm flexors were measured at two-fifths of the distance from the antecubital crease to the distal end of the radius. The quadriceps femoris was measured halfway along the line from the anterior superior iliac spine to the superior aspect of the patella. The tibialis anterior was measured at one-quarter of the distance from the inferior aspect of the patella to the lateral malleolus. The transducer was placed perpendicular to the skin to avoid overestimation of muscle thickness, and oblique scanning was avoided by altering the angle of the transducer to achieve the best bone echo and thinnest appearance to the muscle. A liberal amount of transducer gel was applied and minimal pressure of the transducer was exerted on the skin.

2.3. Measurements

Muscle thickness (MT) was measured using electronic calipers. The thickness of the biceps brachii/brachialis was measured between the upper margin of the humerus and the lower boundary of the ventral fascia of the biceps brachii; the forearm flexor thickness was measured between the interosseous membrane next to the radius and the lower boundary of the ventral fascia of the most ventral flexors; the quadriceps femoris between the upper margin of the femoral bone and the lower boundary of the ventral fascia of the rectus femoris; and the thickness of the tibialis anterior was measured between the interosseous membrane next to the tibia and the lower boundary of the ventral fascia of the tibialis anterior. The rectus femoris had well defined circumferential margins and we therefore also measured the cross sectional area of this muscle using a free form polygon (QLAB®, Philips, Inc.). When muscle echogenicity was very abnormal, identification of the border between fascia and muscle was optimized by dynamic scanning along the length of the muscle prior to measurement.

Muscle gray scale levels were measured using QLAB® from a region of interest of the muscle drawn from the superficial fascia to the deep fascia or bone. cMB was measured from the biceps brachii/brachialis, rectus femoris, anterior forearm muscles, and tibialis anterior. Calibrated muscle backscatter decibel levels (cMB) were calculated from gray scale levels in 2 steps in concordance with a previous study [14]. First, the measured gray scale levels were converted to backscatter (decibels) using a previously identified conversion factor (4.54 gray scale levels/dB) for the ultrasound settings used in this study [15]. Second, muscle backscatter was calibrated to a reference phantom (Model 047; Computerized Imaging Reference Systems, Inc., Norfolk, VA, USA) by subtracting the backscatter measured from the phantom using a rectangular region of interest extending 5 cm deep (6.82 dB).

Average MT and cMB were defined as the average of measurements taken from the biceps brachii/brachialis, forearm flexors, quadriceps/rectus femoris, and tibialis anterior and were calculated for each subject. The difference in individual and average muscle size measurements between the initial and repeat ultrasound examination was calculated and expressed as a percentage of the baseline. Changes in cMB are reported as the difference between repeated measures. MT was also compared to body weight-dependent muscle-specific reference values [22]. Atrophic muscles were defined as a muscle thickness two standard deviations (<2.5 percentile) below the mean for weight in normals. We report the infant's weight percentile based on age referenced values for normal children [23]. Weight deceleration over time was defined as a weight percentile for age that crosses two major percentile lines on the growth chart.

3. Results

We studied 3 children aged 11.0, 1.2, and 5.5 months at baseline. The interval between the two ultrasound examinations was 4.1, 1.8, and 1.8 months, respectively. Patient age and weight are summarized in Table 1.

At baseline, only the quadriceps in the oldest child (#1) was atrophic and only the youngest child (#2) had qualitatively normal appearing muscle echointensity (Fig. 1). MT decreased over time in most muscles (Table 2). Proximal muscles atrophied over time more than distal muscles. At follow up, MT was below normal for weight in the quadriceps in all three children, in the biceps/brachioradialis in two, and in the anterior forearm in only one. MT in the tibialis anterior remained within normal limits for weight in all three children. Quadriceps and biceps

Table 1
Patient age and weight at time of ultrasound assessments.

Patient	Age at ultrasound (months)	Interval between ultrasound (months)	Weight (kg)	Weight percentile for age (%)
1	11.0	4.1	7.7	15.3
	15.1		9.5	45.7
2	1.2	1.8	4.8	57.6
	3.0		6.2	39.9
3	5.5	1.8	7.0	47.1
	7.3		7.4	38.1