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Heterogeneity of muscle fat infiltration in children with spina bifida

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Abstract

Children with spina bifida have well recognized functional deficits of muscle, but little is known about the associated changes in muscle anatomy and composition. This study used water-fat magnetic resonance imaging (MRI) to measure fat infiltration in the lower extremity muscles of 11 children with myelomeningocele, the most severe form of spina bifida. MRI measurements of muscle fat fraction (FF) were compared against manual muscle test (MMT) scores for muscle strength. The FF measurements were objective and reliable with mean inter-rater differences of <2% and intraclass correlation coefficients > 0.98. There was a significant inverse relationship between muscle FF and MMT scores ($P = 0.001$). Surprisingly, however, muscles with negligible strength (MMT 0–1) exhibited a bimodal distribution of FF with one group having FF > 70% and another group having FF < 20%. The MRI also revealed striking heterogeneity amongst individual muscles in the same muscle group (e.g., 4% fat in one participant's lateral gastrocnemius vs. 88% in her medial gastrocnemius), as well as significant asymmetry in FF in one participant with asymmetric strength and sensation. These results suggest that quantitative water-fat MRI may serve as a biomarker for muscle degeneration which may reveal subclinical changes useful for predicting functional potential and prognosis.

Keywords

Spina bifida; Myelomeningocele; Muscle fat fraction; Water-fat MRI

Spina bifida is a congenital disorder caused when the neural tube fails to close properly in utero. Myelomeningocele is the most severe type of spina bifida. In myelomeningocele, part of the spinal cord protrudes outside the spinal column in a fluid-filled sac, resulting in spinal cord damage and paralysis or weakness in muscles of the lower limbs. The current standard for clinical evaluation of lower extremity muscle function in spina bifida is manual muscle testing (MMT). However, MMT provides only a semi-quantitative assessment that can be dependent on the individual performing the evaluation and the effort exerted by the person

being tested. Physical assessment also has only limited ability to predict future function. Despite the well-recognized functional deficits of muscle in children with myelomeningocele, there is a lack of literature describing the associated changes in muscle anatomy and composition.

Magnetic resonance imaging (MRI) may be able to provide more quantitative and objective measurements of muscle integrity and detect subclinical changes that may be suggestive of future changes in function. MRI is non-invasive, does not involve ionizing radiation, and can provide rapid three-dimensional visualization of all muscles in the upper and lower legs, allowing for investigation of individual muscles. It is a recognized tool for quantifying muscle volume, fatty infiltration, and edema (Hollingsworth, de Sousa, Straub, & Carlier, 2012). In particular, recent developments in water-fat MRI techniques have advanced the accurate and precise quantification of fatty infiltration in skeletal muscles (Alizai et al., 2012; Bley, Wieben, Francois, Brittain, & Reeder, 2010; Karampinos, Yu, Shimakawa, Link, & Majumdar, 2011), and application of water-fat MRI in studies of Duchenne muscular dystrophy over the past decade has established a relationship between muscle fat fractions and disease progression (Kinali et al., 2011; Wokke et al., 2013; Wren, Bluml, Tseng-Ong, & Gilsanz, 2008). In addition to skeletal muscle, the utility of water-fat MRI in assessing fatty infiltration has been rigorously validated in abdominal organs, including the liver, heart, and pancreas, as well as in bone marrow (Alizai et al., 2012; Bley et al., 2010; Hu, Kim, Nayak, & Goran, 2010; Karampinos et al., 2011, 2013; Kellman et al., 2009; Reeder, Cruite, Hamilton, & Sirlin, 2011; Wokke et al., 2013).

The purpose of this preliminary study was to extend the application of water-fat MRI to a cohort of children with myelomeningocele. To the best of our knowledge, quantitative MRI assessment of skeletal muscle fat infiltration has not been reported in this population. First, we aimed to characterize and quantify the distribution of fat infiltration in multiple lower extremity muscles. Second, we examined the relationship between MRI-derived percent fat content in individual muscles and MMT-assessed functional strength. Finally, we evaluated the inter-rater reliability of measuring muscle fat content with water-fat MRI.

1. Materials and methods

Eleven children with myelomeningocele participated in this study after providing written assent and parental consent following institutional review board approval. There were 7 boys and 4 girls, all Hispanic whites, ages 7.1–15.8 years (Table 1). An experienced pediatric physical therapist performed a comprehensive physical examination including MMT to measure lower extremity muscle strength. Strength was graded on the standard 0–5 scale: 0 (no palpable contraction), 1 (trace contraction, no joint movement), 2 (poor, completes range of motion (ROM) with gravity eliminated), 3 (fair, completes ROM against gravity without resistance), 4 (good, completes ROM against gravity with moderate resistance), 5 (normal, completes ROM against gravity with maximal resistance; Kendall, Kendall, & Wadsworth, 1971). The muscles examined included the ankle dorsiflexors and plantarflexors, knee extensors and flexors, and hip adductors. Functional neurologic level was determined based on the MMT results following the International Myelodysplasia Study Group (IMSG) criteria (Wright, 2001). Muscles were also grouped in terms of strength: Negligible Strength Group = MMT of 0 or 1; High Strength Group = MMT score of 5 for the hamstrings and 4 or 5 for all other muscles; Intermediate Strength Group = all values in between, i.e., 2–4 for the hamstrings and 2–3 for all other muscles. A different cutoff was used for the hamstrings based on visual inspection of the data which may reflect differences in the recording of MMT scores for different muscle groups.

MRI examinations of the thighs and lower legs were performed on a 3T whole-body system (Achieva R3.2, Philips Healthcare, Cleveland, OH). A research version of the vendor's mDIXON water-fat pulse sequence was used (Eggers, Brendel, Duijndam, & Herigault, 2011). Participant setup and scan parameters for the 3D spoiled-gradient-echo sequence were: supine, feet first, axial acquisition, TR = 10 ms, first TE = 1.48 ms, Δ TE = 1.2 ms, 6 echoes, bipolar readouts, 1 mm voxels with 2 mm overlapping slices, flip angle = 3°, bandwidth = 1.3 kHz/pixel, and two-fold anterior-posterior parallel acceleration. Scan time was ~2 min for 125–170 contiguous slices. Four separate scans were performed in each child, one each for the right lower leg, the left lower leg, the right thigh, and the left thigh. The patient was repositioned as needed to obtain sufficient coverage of the desired anatomy. A 16-channel torso array was used. We were not able to obtain four scans in 3 children due to time constraints (one left lower leg, one right thigh, one left and right thigh); the analysis included data from all of the scans that were obtained. The subsequent image reconstruction of the water-fat MRI pulse sequence employed a seven-peak spectral model of fat based on previous spectroscopy data in bone marrow and subcutaneous adipose tissue (Ren, Dimitrov, Sherry, & Malloy, 2008) to generate voxel-wise muscle fat fraction (FF) maps. Such protocol has been shown to yield FF maps that accurately reflect the underlying tissue proton density ratios between fat and the sum of water and fat (Kinali et al., 2011; Wokke et al., 2013; Wren et al., 2008).

Two evaluators (one pediatric radiologist, one biomedical engineer) independently identified regions-of-interest encompassing individual muscles in each of the data sets after selecting image slices that provided optimal visualization of each muscle to be measured. Average FF values were measured for the region-of-interest in each of the following muscles using OsiriX imaging software (Pixmeo, Geneva, Switzerland): ankle plantarflexors (soleus, medial gastrocnemius, lateral gastrocnemius), ankle dorsiflexors (tibialis anterior), quadriceps (rectus femoris, vastus lateralis, vastus intermedius, vastus medialis), hamstrings (semitendinosus, semimembranosus, biceps femoris), and hip adductors (combined adductor magnus and longus).

Inter-rater reliability of the FF measurements was assessed using the difference between measurements, Pearson's correlation, and intraclass correlation coefficient (ICC). Muscle FF values were also compared to MMT strength scores using analysis of variance with Bonferroni post hoc tests. All statistical analysis was performed in Stata (version 12.1, StataCorp LP, College Station, Texas).

2. Results

The mean difference in muscle FF measurements between the two evaluators ranged from –0.2% to 1.6% and was dependent on the muscle being evaluated. The largest FF difference was 10.8%, with 203/220 measurements (92%) having a difference of less than 5%. The correlation and ICC between raters was very high for all muscles (all $r > 0.98$). Since the results were consistent between raters, subsequent results are presented using the average of the two fat fraction measurements.

In general, there was an inverse relationship between muscle strength and FF (Fig. 1). The relationship was stronger for the dorsiflexors and quadriceps and weaker for the plantarflexors and hamstrings. Examination of the High, Intermediate, and Negligible Strength Groups showed a significant inverse relationship between muscle strength and FF (Fig. 2). Strong muscles all had fat fractions below 20% with most under 10% (Fig. 3). This is in comparison to normal muscle fat fractions which are usually <8% (Ponrartana et al., 2013). Many muscles with intermediate strength also had fat fractions below 20%, but approximately half had higher fat fractions broadly distributed to over 90% (Fig. 3).

Interestingly, the muscles with negligible strength had a bimodal distribution of fat fractions. One group had high fat fraction over 70%, as expected, while another group had low fat fraction below 20% (Figs. 3 and 4).

In addition to these general findings, one clear advantage of MRI over MMT was its ability to examine and elucidate fat infiltration in individual muscles. Large differences in FF were sometimes observed between muscles in the same muscle group. For example, one child had 4% fat in the lateral gastrocnemius but 88% in the medial gastrocnemius (Fig. 5). Another had 11% fat in the semimembranosus, 30% in the semitendinosus, and 73% in the biceps femoris. Striking asymmetry was also observed in the hamstrings and plantarflexors of one participant, consistent with clinical asymmetry in strength and sensation (Fig. 6).

3. Discussion

To the best of our knowledge, this is the first study to specifically investigate muscle fat infiltration in children with spina bifida. Accurate quantification of muscle fat content and knowledge of which muscles are affected may enable better patient monitoring, titration of therapy, and functional prognosis. The results of the current study indicate that muscle fat content varies widely in children with spina bifida and generally reflects muscle strength and functional status. However, for reasons not yet known, fat fractions can remain low in some muscles with no observable contractile function, including in children who are non-ambulatory and may never have walked. With additional research, we believe quantitative water-fat MRI may improve clinical understanding of the pathophysiology and progression of skeletal muscle damage in children with spina bifida.

Our muscle fat fraction measurements demonstrated good inter-rater reliability in this pediatric population. This is consistent with a previous report showing good test-retest and inter-rater reliability of water-fat MRI measurements in children without disability (Ponrartana et al., 2013). The reliability of these measurements suggests that water-fat MRI can serve robustly as an objective and quantitative fat biomarker in muscles, as already established in a multi-center liver study (Mashhood et al., 2013). We found that the most difficult muscles to measure consistently were those with high intra-muscle heterogeneity due to sensitivity of the numerical measurement to the region-of-interest selected. These may be muscles in transition from a more intact to a more degenerated state. In fact, muscles with intermediate strength showed the broadest distribution of fat fractions, particularly in the triceps surae and hamstring muscles. MRI may be especially useful in detecting subclinical changes and predicting functional prognosis for these muscles.

One advantage of MRI is the ability to examine individual muscles. In some cases, fat fraction differs greatly among muscles in the same muscle group. Such differences are difficult to detect through physical examination since the muscles share the same function. Knowing which muscles have better tissue integrity may enable more appropriate customization of rehabilitation programs by indicating which muscles physical therapy should target. Examining the heterogeneity of muscle fat infiltration may also lead to future discoveries of how neurologic and mechanical inputs affect muscle development and adaptation.

The most provocative finding of this study is that on several occasions muscles seemed to be preserved despite long-term disuse, when they would be expected to atrophy and degenerate. Among muscles with MMT strength scores of 0 or 1, half had fat fractions below 20%. While this is slightly higher than the normal value of 3–8% (Ponrartana et al., 2013), it is much lower than the 70–90% fat fraction observed in other non-functional muscles. This finding raises intriguing questions regarding the causes and consequences of this unexpected muscle preservation. We hypothesize that these muscles receive some type of neurologic

stimuli which allow them to be preserved. While voluntary muscle activation is absent, there might be the possibility of activation through electrical stimulation. Another possibility is that the muscles may have a secondary non-contractile function such as involvement in metabolic regulation. These are open questions which the current study cannot answer. Additional research employing other strategies, including diffusion tensor imaging (Sinha & Sinha, 2011; Sinha, Sinha, & Edgerton, 2006; Williams et al., 2013), is needed to further explore these provocative questions.

Another possible use of this MRI muscle FF technique might be in early evaluation of patients where there is concern for tethered cord syndrome. Increased fat infiltration in muscles relative to a baseline examination might serve as an early indicator of symptomatic tethered cord and loss of muscle innervation. Suspicion of tethered cord currently depends on the manifestation of clinical symptoms such as atrophy, weakness, loss of sensation, worsening cavovarus foot deformity, or spasticity. By the time these symptoms appear, treatment with laminectomy and tethered cord release is often too late to achieve much restoration of function. MRI muscle FF measurements may be able to detect changes earlier, enabling closer monitoring and earlier, more effective neurosurgical intervention.

We note several limitations of this preliminary study. First, muscle composition and structure were not directly examined (e.g., biopsy). Although the degree of fat infiltration has been shown to correlate with muscle weakness in other patient populations (Johnson, Miller, Subramanian, & Modlesky, 2009; Kinali et al., 2011; Nordal, Dietrichson, Eldevik, & Gronseth, 1988; Wokke et al., 2013; Wren et al., 2008), it is possible that muscles which have a normal appearance and fat fraction on MRI may have other deficiencies not revealed by the water-fat imaging. Another limitation is the small sample size. Larger studies are needed to determine the generalizability of the results. In particular, we would like to confirm how common it is for muscle tissue to be preserved in non-functioning muscles. Finally, this study was cross-sectional with a single MRI examination for each participant. Longitudinal studies will be needed to fully understand the time course of muscle fat infiltration in spina bifida and how muscle fat fraction relates to changes in function.

4. Conclusions

In conclusion, quantitative water-fat MRI is a useful technique for measuring muscle fat fraction in children with spina bifida. The fat fraction values are objective and reliable. In this study, they were generally reflective of muscle strength, but also revealed interesting findings such as differences in tissue integrity between muscles with the same functional MMT score or, more surprisingly, low fat fraction in non-functional muscles. With the recent increase in commercial availability of water-fat MRI technology, this initial study should serve as a launching point for future research examining the determinants and functional implications of muscle fat infiltration or lack of fat infiltration in children with spina bifida.

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Fig. 1.
Muscle fat fraction as a function of muscle strength.

Fig. 2.

Muscle fat fraction differed significantly between muscles with negligible ($N = 74$), intermediate ($N = 59$), and high ($N = 87$) strength (all $P < 0.001$). Boxes indicate the 25th (lower quartile), 50th (median), and 75th (upper quartile) percentiles; whiskers indicate adjacent values within 1.5 times the interquartile range of the upper and lower quartiles.

Fig. 3. Histograms showing distribution of muscle fat fraction for muscles with high, intermediate, and negligible strength.

Fig. 4. MRI image showing preservation of muscle (9–35% fat) in a non-ambulatory thoracic level participant (left) compared with complete fatty infiltration (90–92% fat) in a non-ambulatory high lumbar level participant (right).

Fig. 5. MRI image showing a large difference in fat content between the medial (88% fat) and lateral (4% fat) gastrocnemius.

Fig. 6.
Asymmetric fat infiltration in a high sacral level participant.

Table 1

Participant characteristics.

Characteristic	Category/statistic	Count/value
Sex	Male	7
	Female	4
Age (years)	Mean $\pm$ SD (range)	12.5 $\pm$ 2.8 (7.1, 15.8)
Race	White Hispanic	11
IMSG level ^a	Sacral	5
	Low lumbar	1
	Mid lumbar	3
	High lumbar	1
	Thoracic	1

^aIMSG, International Myelodysplasia Study Group classification of functional level (Wright, 2001). Sacral level is the highest functioning with decreasing function to thoracic level, which is usually non-ambulatory.