

**Muscle ultrasound in children: normal values
and application to neuromuscular disorders.**

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Abstract

In this study, 105 healthy children (45 to 156 months old, 57 female) were examined using ultrasound (US) imaging to obtain reference values of muscle dimensional and aspect parameters. We measured biceps and quadriceps sizes and subcutaneous tissue thickness. To quantify muscle aspect, we calculated muscle density, inhomogeneity and white-area index by digital image analysis. Age-, weight- and gender-dependencies were discussed. We demonstrated earlier that the complete set of parameters allows for differentiation between myopathies and neuropathies in adults, with high sensitivity. In this study, we investigated if these parameters have additional value in the diagnostic evaluation of 36 children with proven neuromuscular disease (20 Duchenne muscular dystrophy, 16 neuropathies). We found that density analysis provides a sensitive method for distinguishing between healthy children and children with neuromuscular disorders. We have also found that more detailed aspect analysis is necessary to further distinguish between these types of neuromuscular disorders in children. In conclusion, this set of normal muscle parameters can be used to help diagnose neuromuscular disorders in children. It will also facilitate follow-up in disease progression and therapy.

Introduction

Imaging techniques such as computerised tomography,¹ magnetic resonance imaging² and ultrasonography³⁻⁵ have been used to evaluate possible muscle pathology and its progression, both in children and adults. None of these techniques is invasive, but ultrasound (US) imaging has the additional advantages of lack of ionising radiation and low cost. Moreover, in children, US does not demand anaesthetics to prevent movement artefact because of its rapid application. US can be used as a screening technique in outpatient clinics, for follow-up studies to evaluate the possible effects of treatment.

Muscle volume and cross-sectional area, as well as several qualitative measures of muscle aspect (or appearance) can easily be obtained, nearly independently of subcutaneous tissue thickness. Some studies, mostly in children,^{4,6-12} but also in adults^{13,14} or mixed populations,¹⁵ have shown that US can be used to distinguish between patients with neuromuscular disorders and healthy controls. In general, US images of myopathic muscles show increased overall echogenicity; whereas, muscles that are damaged due to a neuropathy (neuropathic muscles) show increased inhomogeneity due to pathological disruptions of muscle architecture^{2,12} and atrophy.

Only a limited number of studies have tried to distinguish between myopathies and neuropathies on the basis of US alone.^{13,15} Previously, we have shown that digital image analysis that includes newly defined aspect measures (muscle inhomogeneity and white-area index which measures the presence of patches of high echogenicity), as well as muscle echogenicity (or density),^{14,16-18} allows for differentiation between myopathies and neuropathies in adults, with high sensitivity.¹³ In combining quantitative parameters, muscle US imaging may also help in diagnosing neuromuscular disorders in children more accurately.

The purpose of the present study was to provide a complete set of quantitative normal values of biceps and quadriceps muscle dimension and aspects in healthy children. These values were applied to evaluate their additional value in children with proven neuromuscular disease.

Subjects

The biceps and quadriceps US characteristics were investigated in a group of 105 healthy children (48 boys, 57 female, 45-156 months old, further antropomorphic data in Table 1), after informed consent by their parents. All scans were made with an Aloka SSD-2000 US scanner using a 7,5 MHz linear probe.

To test the sensitivity and specificity of this set of normal values in differentiating

Table 1.

Antropomorphic variables. n = number of controls/patients; numbers given are median (interquartile range); BMI = body mass index (see text); m = male; f = female.

	Controls (m)	Controls (f)	DMD (m)	neuropathies (m)	neuropathies (f)
n	48	57	20	6	10
Age [months]	97,5 (41,5)	81,0 (38,0)	69,0 (28,0)	20,5 (28,3)	20,5 (69,0)
Weight [kg]	29,00 (11,75)	25,00 (10,50)	19,75 (5,38)	10,00 (8,75)	11,50 (8,75)
BMI [kg/m ²]	16,28 (2,34)	16,10 (2,26)	15,10 (1,73)	15,15 (0,58)	15,74 (3,30)

between neuromuscular disorders and healthy children, we selected 36 proven patients from our patient database. A total of twenty patients were diagnosed with Duchenne muscular dystrophy (DMD) between 1998 and 2002 (median age = 69 months, interquartile range (IQR) = 28 months) and 16 patients were diagnosed with neuropathies (13 spinal muscular atrophies (SMA) and 3 hereditary neuropathies) between 1995 and 2002 (median age = 20,5 months, IQR = 26 months). All patients underwent muscle ultrasonography during their diagnostic work-up in our outpatient clinic. Digital muscle images were available for 19 DMD and 5 neuropathy patients. The muscle size values were available for all patients.

Methods

Transverse and longitudinal US images were taken from the left elbow flexors and the left quadriceps muscle. For arm measurements, the probe was placed at the position of maximum circumference. For thigh measurements, the probe was positioned half-way between the lateral knee joint cleft and the major trochanter. If possible, the subjects lay supine with their trunk slightly flexed, the lower arm supinated and the legs slightly abducted and extended. Some very young children were scanned while sitting on their carer's lap. An excess of US gel was employed to prevent impression of the skin. To standardize the measurements, the probe was held perpendicular to the bone (judged by maximum bone echo). Gain and dynamic range were kept at fixed values (G75 and C04 for Aloka SSD-2000) and the image was focused at the muscle center for all measurements.

From the US images, subcutaneous tissue thickness (distance between skin and

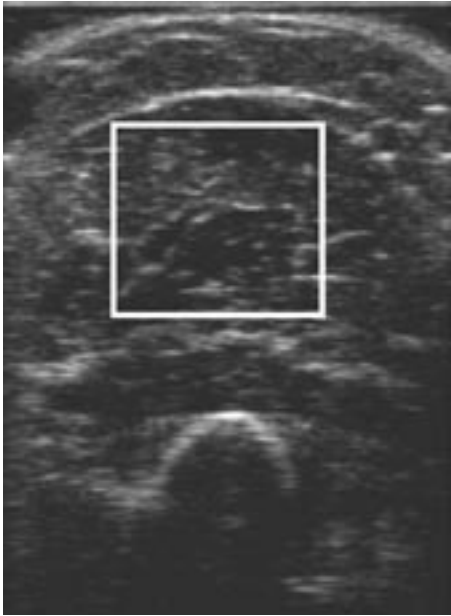


Figure 1. Typical transverse US image of normal biceps muscle (female, 30 years old) with selected rectangle for analysis indicated.

fascia in [mm]) and muscle thickness (distance between fascia and humerus or femur in [mm]) were determined. For the patients for whom no digitized US images were stored, the values that were used were those registered in our patient database at the time of measurement. These values were taken in the same way as the measurements on the digitised images. The quadriceps size was determined by the summed sizes of m. vastus intermedius and m. rectus femoris and the elbow flexor size was determined by the summed sizes of m. biceps brachii and m. brachialis. We will further use the term biceps to indicate the two elbow flexors and the term quadriceps to indicate the upper leg musculature. Anthropometric variables such as height [m], and weight [kg] were taken. The body mass index (BMI) was calculated as $\text{weight}/\text{height}^2$ (Table 1).

To quantify muscle aspect properties, we have developed new measures based on digital US image analysis. The methods that were defined by us earlier were chosen so that they complement the qualitative appearance of muscle US images in typical neuropathies and myopathies.¹³

Using Adobe Photoshop 4.0, (Abdobe, San Jose, CA) a representative rectangle of m. biceps brachii or m. rectus femoris was selected in the transverse US images (Figure 1), after calibration of the digitally stored echo image (768×576 pixels, 8-bit grey-value). Calibration was performed so that all grey-values are present in the image, knowing

Table 2.

Significant correlations in controls. Pearson r^2 values, *: $p < 0,05$; **: $p < 0.01$. STT = subcutaneous tissue thickness.

	age	height	weight	BMI
Male				
upper arm STT	-	-	-	0,616**
biceps muscle size	0,622**	0,649**	0,702**	0,375**
upper leg STT	-	-	0,294*	0,696**
quadriceps muscle size	0,610**	0,533**	0,695**	0,561**
biceps density	-	-	-	-
quadriceps density	-	-	-	-
biceps inhomogeneity	-	-	-	-
Female				
upper arm STT	-	-	-	0,465**
biceps muscle size	0,649**	0,652**	0,652**	0,381**
upper leg STT	-	-	0,336*	0,646**
quadriceps muscle size	0,528**	0,543**	0,650**	0,609**
biceps density	-	0,276*	0,273*	-
quadriceps density	0,333*	-	-	-
biceps inhomogeneity	0,311*	0,366**	0,333*	-

that the image background is pure black and the text is pure white. Care was taken not to select fascia or muscle-tendon transitions. Image-Pro Plus 3.0 (Media Cybernetics, Silver Spring, MD) was used for further digital image analysis.

To quantify muscle echogenicity, the average pixel value ('density') of the selection was determined. If this value is 0, the selection is pure black, if this value is 255, the selection is pure white.

For quantification of local or global pathological changes in the muscle, inhomogeneity was determined by first applying a Sobel filter, which extracts and enhances edges by expressing gradients (grey-value differences) between neighbouring pixels in a grey-value.¹³ If there was no difference between neighbouring pixels, the grey-value was set to 0 (black) but, if there was maximum difference, the grey-value was set to 255 (white). After filter application, white areas that were larger than $0,038 \times 0,019 \text{ cm}^2$ (area_{\min}) were counted. Area_{\min} is chosen so that it represents 2 pixels on the large Aloka (R08) calibration scale, which prevents counting 'noise'. The white areas were determined by all pixels with a value larger than 197, which corresponds to selecting visible contrasts. The inhomogeneity was then calculated as the number of counted

white areas divided by the area of the selection in cm². In this way, a high level of inhomogeneity corresponded to a visually observed high degree of inhomogeneity.

To quantify the ‘spottiness’ or presence of patches of high echogenicity in the muscle, all white areas (pixel value larger than 170: this corresponds to selecting visibly white areas or ‘spots’) larger than area_{min} were counted and their area summed. The white-area index (a fraction between 0 and 1) was calculated as the white area in the selection divided by the total area of the selection.

We have investigated possible correlations of all described measures with age, height, weight and BMI for healthy controls, for each gender. Weight- and BMI-related reference values (mean and SD, and appropriate percentile) were calculated per weight or BMI group, where the subgroup size depended on the total number of subjects per group. The weight groups were: less than 20 kg, 20-30, 30-40 and heavier than 40 kg. The BMI groups were: less than 16, 16-18 and more than 18 kg/m². Abnormal values were considered to be values above P90 for subcutaneous tissue thickness and all aspect measures, and below P10 for muscle size. We further used the term ‘atrophic’ for muscle sizes below P10.

Statistical analyses were performed using SPSS 10.0 (SPSS, Chicago, IL). Normality was tested by the Shapiro-Wilk test. Differences for genders were tested using the independent samples t-test.

Results

Correlations/regression

All correlations of muscle US parameters with age, weight, height and BMI were investigated for healthy controls. Significant correlations were found for both genders between upper arm subcutaneous tissue size and BMI, upper leg subcutaneous tissue size and weight and BMI and biceps and quadriceps muscle size and age, height, weight and BMI (Table 2). Significant correlations for muscle aspect measures were found only in girls for biceps density (with height and weight), quadriceps density (with age) and biceps inhomogeneity (with age, height and weight). First, all measures, except the quadriceps measures, were pooled for gender. Although normal values are typically given as a function of age, more sensitive parameters are obtained if classification is performed according to the most predictive variable. To find the main predictors, we subsequently employed linear regression analysis with stepwise inclusion of the independent variables that correlated significantly with the dependent variables. All subcutaneous tissue thicknesses were found to be best predicted by BMI, whereas all muscle sizes were best predicted by weight. All muscle aspect measures were found to be independent of age, height, weight or BMI.

Table 3.

Normal values (mean/SD in mm). STT = subcutaneous tissue thickness; BMI = body mass index (see text); m = male; f = female; n = number of subjects; SD = standard deviation; P10/P90 = relevant percentiles for abnormality. P90 for biceps size has been added because of abnormality in DMD. Significant differences between genders are indicated by ** p < 0,01 and * p < 0,05.

	n	Mean	SD	P10/P90
Upper arm STT (m/f)				
BMI < 16	47	4,61	1,01	/6,04
16 ≤ BMI < 18	44	5,69	1,20	/7,55
18 ≤ BMI	14	6,19	1,43	/8,60
Biceps muscle size (m/f)				
weight < 20 kg	14	11,60	1,45	9,10/13,90
20 ≤ weight < 30 kg	51	13,48	2,08	10,62/16,04
30 ≤ weight < 40 kg	27	15,99	2,02	13,70/18,92
40 ≤ weight	13	16,87	2,22	14,00/21,14
Upper leg STT (m)				
BMI < 16	20	7,70**	1,05	/9,18
16 ≤ BMI < 18	20	9,80*	1,86	/12,27
18 ≤ BMI	8	11,58	1,11	/13,70
Quadriceps muscle size (m)				
weight < 20 kg	3	-	-	18,50/
20 ≤ weight < 30 kg	21	24,67**	3,33	20,44/
30 ≤ weight < 40 kg	19	28,81*	3,68	24,00/
40 ≤ weight	5	31,72	3,20	27,40/
Upper leg STT (f)				
BMI < 16	27	8,93	1,61	/10,80
16 ≤ BMI < 18	24	11,08	1,94	/13,95
18 ≤ BMI	6	12,43	3,05	/16,70
Quadriceps muscle size (f)				
weight < 20 kg	11	23,93	2,45	19,80/
20 ≤ weight < 30 kg	30	27,25	3,42	23,59/
30 ≤ weight < 40 kg	8	32,01	3,69	27,10/
40 ≤ weight	8	31,44	5,03	26,00/

The normal values for upper arm and upper leg subcutaneous tissue thickness and biceps and quadriceps muscle size are given in Table 3. All values, except quadriceps muscle size in boys, were normally distributed; hence, means and SDs are given. Because girls quadriceps muscle size and upper leg subcutaneous tissue thickness

Table 4.

Muscle aspect normal values. The white-area index is constant = 0 in controls; SD = standard deviation; P90 = relevant percentile for abnormality; # mean; * median.

	mean/median	SD	P90
Biceps density	29,60 [#]	8,07	41,14
inhomogeneity	0,00 [*]	-	2,37
white-area index	0,00	-	0,00
Quadriceps density	27,46 [#]	7,00	37,68
inhomogeneity	0,00 [*]	-	1,19
white-area index	0,00	-	0,00

were generally larger than those of boys for comparable BMI and weight groups (see Table 3 for significant differences), these normal values were described separately for each gender. Inhomogeneity was not distributed normally; most controls had value zero. Furthermore, all controls had value zero for white-area index, which made any value deviant from zero abnormal in young children (Table 4).

Patients

In DMD patients, biceps muscle thickness was generally increased with respect to normal controls (Figure 2, Table 5). Atrophy of the biceps musculature (value < P10) was only found in 2 of 16 neuropathies. Notice, however, that these children were younger and weighed less than our controls. Quadriceps muscle thickness was below P10 in 6 of 20 DMD patients and in 4 of 6 neuropathy patients (Figure 3, Table 5). The upper arm subcutaneous tissue thickness was above P90 in 3 of 20 DMD patients and 10 of 16 neuropathy patients (Table 5). For the upper leg, the subcutaneous tissue thickness was above P90 in 6 of 20 DMD patients and 5 of 6 neuropathy patients (Table 5). Notice that 9 of the 16 neuropathy patients considered in our study were younger than 24 months old, whereas our normal controls were 45 months old and older. These young patients had relatively thick subcutaneous tissue layers. The results in these young patients will later be discussed in relation to available literature.

Muscle aspect values will only be discussed in detail for DMD patients. The results in neuropathy patients, although limited in number, will be discussed later with respect to our earlier obtained results in adult patients.¹³ Muscle density had a sensitivity

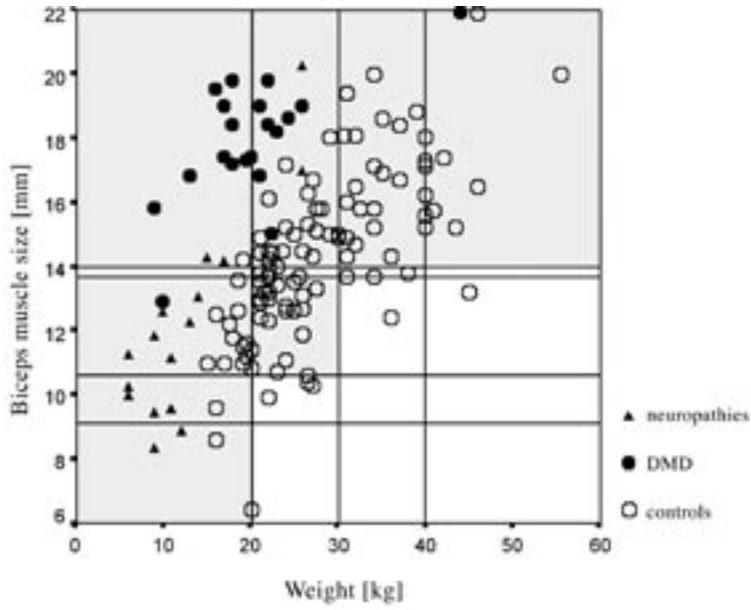


Figure 2. Scatter plot of biceps muscle size vs. weight for combined genders in 105 healthy children, 20 DMD patients and 16 neuropathies. Normal values based on P10 are indicated in grey.

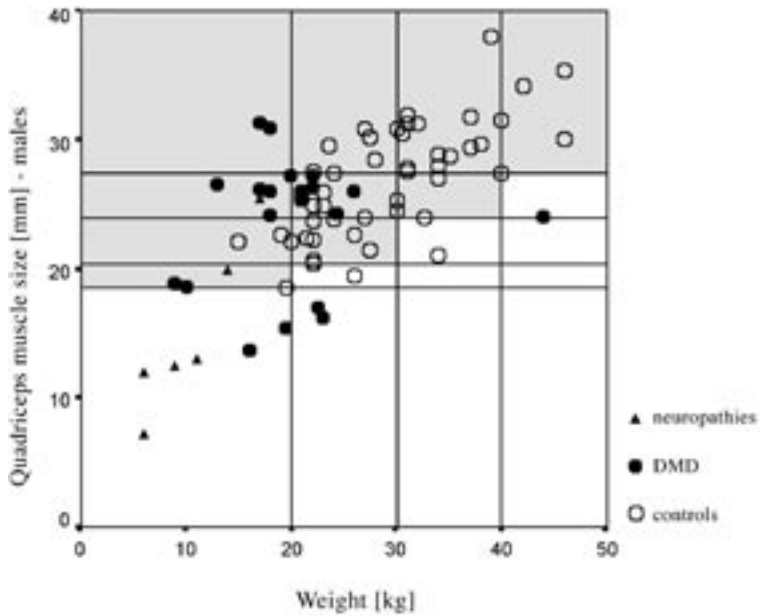


Figure 3. Scatter plot of quadriceps muscle size vs. weight for boys in 48 healthy children, 20 DMD patients and 6 neuropathies. Normal values based on P10 are indicated in grey.

Table 5.

% Specificity [(normal controls / all controls) x 100%] and sensitivity [(abnormal DMD / all DMD) x 100%] or [(abnormal neuropathies / all neuropathies) x 100%] of muscle aspect and dimensional parameters for a group of 20 DMD patients and 16 neuropathy patients compared to 105 healthy controls. Number between brackets = total number considered; STT = subcutaneous tissue thickness; *results from our previous study in adults.¹³

	Specificity	Sensitivity DMD	Sensitivity neuropathies	Sensitivity myopathies adults*
Biceps density	91%(105)	90%(19)	60%(5)	94%(17)
inhomogeneity	91%(105)	58%(19)	60%(5)	35%(17)
white-area index	100%(105)	26%(19)	20%(5)	82%(17)
muscle size	90%(105)	0%(20)	13%(16)	31%(17)
upper arm STT	91%(105)	15%(20)	63%(16)	-
Quadriceps density	91%(105)	90%(19)	100%(5)	56%(17)
inhomogeneity	91%(105)	74%(19)	80%(5)	50%(17)
white-area index	100%(105)	16%(19)	60%(5)	69%(17)
muscle size	88%(105)	30%(20)	67%(6)	73%(17)
upper leg STT	90%(105)	30%(20)	83%(6)	-

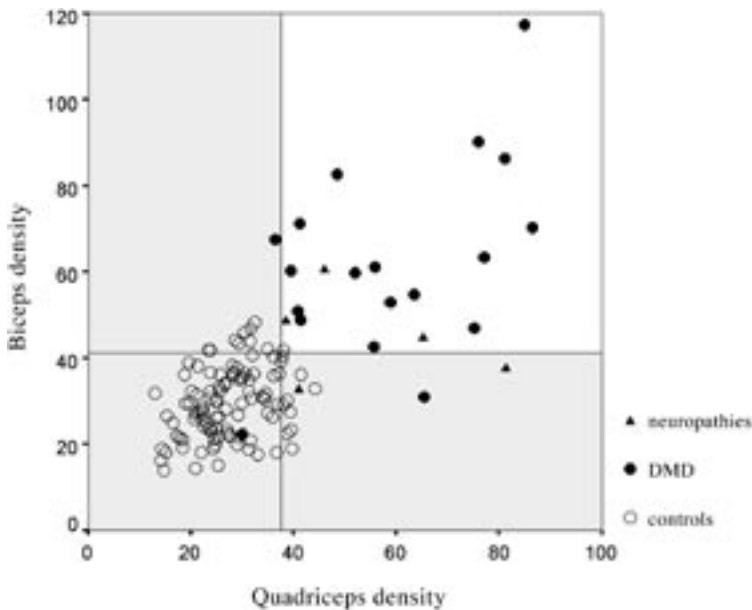


Figure 4. Scatter plot of biceps density vs. quadriceps density for combined genders in 105 healthy children, 19 DMD patients and 5 neuropathies. Normal values based on P90 are indicated in grey.

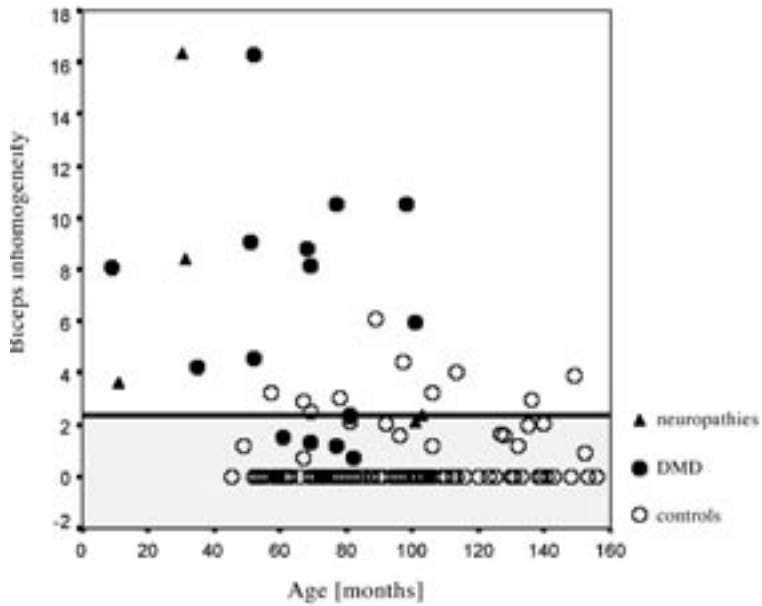


Figure 5. Scatter plot of biceps inhomogeneity vs. age for combined genders in 105 healthy children, 19 DMD patients and 5 neuropathies. Normal values based on P90 are indicated in grey.

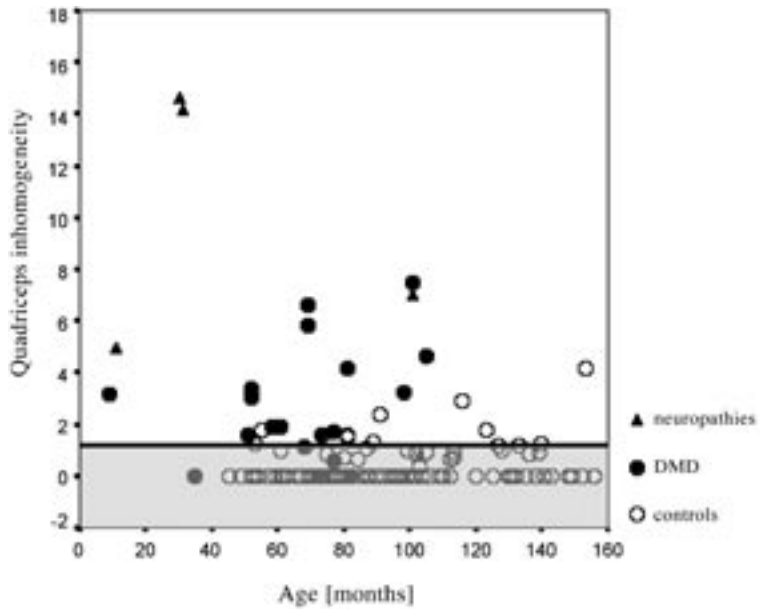


Figure 6. Scatter plot of quadriceps inhomogeneity vs. age for combined genders in 105 healthy children, 19 DMD patients and 5 neuropathies. Normal values based on P90 are indicated in grey.

of 90% in both biceps and quadriceps for DMD patients, with a specificity of 91% for both muscles (Table 5). If both densities were considered simultaneously, the specificity increased to 99% (only one control had abnormal biceps and quadriceps density) accompanied by a slight decrease in sensitivity to 84% (Figure 4). The biceps muscle was found to be abnormally inhomogeneous (value > P90) in 58% of DMD patients (Figure 5), whereas the quadriceps inhomogeneity (Figure 6) was above P90 in 74% of DMD patients (Table 5). The biceps white-area index was above P90 in 26% of DMD biceps muscle and 16% of DMD quadriceps muscle (Table 5).

Intra- and interobserver variability were already tested in our previous study in adults¹³ and were not repeated here because the densities observed in the adults were between 25 and 50 and, therefore, comparable to those of healthy children. Generally, the measurement error was below 3%, except for interobserver quadriceps density (7,4%).

Discussion

US muscle imaging is a non-invasive, safe and relatively cheap investigation technique to visualize skeletal muscles. US imaging can be very helpful in diagnosing neuromuscular disorders. Its sensitivity and specificity can be greatly enhanced if reference values are available.

In this study, we obtained a complete set of quantitative normal values of biceps and quadriceps muscle from 105 healthy children by US imaging. In addition to measuring muscle size and subcutaneous tissue thickness, we have also defined and calculated the aspect measures density, inhomogeneity and white-area index. We have shown previously that these measures allow for differentiation between myopathies and neuropathies in adults, with high sensitivity. We have investigated the additional value of these measures in the diagnostic evaluation of 36 children with proven neuromuscular disease. We have shown that, as in adults, the combined parameters could be used to quantify muscle atrophy and changes in muscle appearance.

Methods

Typically, normal values are expressed in regression lines with one SD for the whole group (see Scholten et al.¹⁹ for an example in children). In our study, the SD over the whole group was usually larger than the SD per subgroup. Furthermore, the subgroup analysis showed that the SD generally increased with increasing weight or

BMI (Table 3). The sensitivity and specificity of the US analysis method was, hence, increased by employing subgroups.

Several methods have been used to evaluate muscle US images. Heckmatt et al.⁴ visually graded the degree of scan change, based on the intensity of echo reflected from muscle and bone tissue, on a four-point scale. A major disadvantage of this scale is its subjectivity. Alternative scoring system of quantitative muscle changes were based on texture analysis methods,²⁰ the ratio of mean echo level in central and whole cross-sectional areas,²¹ or manual counting of perimysial septa per cm in children.²² Zuberi et al.¹² determined the sensitivity of US in detecting neuromuscular disorders by applying the criteria of Heckmatt and colleagues on muscle US images obtained from 100 children with various neuromuscular disorders. They reported a false-positive percentage in children aged < 3 years old of 21%, whereas this was 4,7% in children aged > 3 years old. Apparently this grading scale was less reliable in very young children. However, Kamala et al.,⁸ using the criteria of Heckmatt and colleagues, reported 100% sensitivity and specificity in a group of 20 children with progressive muscular dystrophy and 10 infants with infantile spinal muscular atrophy compared to 25 age-matched healthy controls. Those criteria have also been used to determine muscle atrophy as expressed in the ratio of muscle to subcutaneous tissue thickness.⁶ However, in obese children, the muscle-fat ratio is reduced due to an increase in subcutaneous tissue thickness, which incorrectly suggests muscle atrophy. Therefore, we have not provided normal values for the ratio of muscle size to subcutaneous tissue thickness.

The rationale of analyzing a representative rectangle of muscle US image instead of the whole muscle was explained earlier¹³ for adults. In obese children, it is not always possible to capture the whole muscle on an US image. Furthermore, inclusion of fascia and muscle-tendon transitions will increase density and inhomogeneity, as well as white-area index, which would make the method less sensitive and specific.

The normal values presented here depend on machine type and settings and should, therefore, be established separately for each type of machine. However, the principles of analysis described in this paper are of a general nature.

Results

We found that weight was the best predictor of muscle size. Both biceps and quadriceps muscle size increased with age, height and weight, as well as with BMI. However, adding another variable to the regression equation in addition to weight, typically gave less than 5% additional explanatory value. We, therefore, used one predictor for muscle size. The values that we found are comparable to other results in children

obtained by US imaging.^{19,23} Scholten et al.¹⁹ also found weight to be the best predictor for muscle size. For the same weight group, we found significant differences between boys and girls for quadriceps muscle size, which were not found in the studies by Heckmatt et al.²³ or Scholten et al.¹⁹ Heckmatt et al.²³ only studied age-dependence, and the group studied in Scholten et al.¹⁹ was much smaller, consisting of 59 children in a large age range (11 weeks-16 years).

BMI was the best predictor of subcutaneous tissue thickness. Upper arm and upper leg subcutaneous tissue thickness increased with BMI, both in girls and boys. However, at the same BMI, upper leg subcutaneous tissue thickness was larger in girls than in boys, which reflects gender-related differences in fat distribution. This was also found by Heckmatt et al.²³

Of our 16 neuropathy patients, 13 were younger than our youngest control. The muscle sizes in this group could not, therefore, be compared to our normal values. However, our results can be compared to an earlier US study of quadriceps musculature and upper leg subcutaneous tissue thickness in infants in their first year of life.¹¹ The authors found that the quadriceps muscle size increased from approximately 12 to 16 mm during the first year of life. If we employ their measure, 2 of our 16 neuropathy patients have atrophic quadriceps muscle.

By studying muscle size and subcutaneous tissue thickness separately we found that, in DMD patients, biceps muscle size was significantly increased compared to normal controls (weight group 10-30 kg, Student's *t*-test, $p < 0,001$). Of the 19 children in this DMD weight group, 17 had biceps muscle size $> P90$ (Table 5). As the children in our DMD group were between 9 months and 9 years old and still (or not yet) ambulatory, they were in an intermediate stage of their disease. Muscle atrophy is typically a feature of late stage DMD. The increased muscle size may be due to hypertrophy or pseudohypertrophy, which is known to be present in DMD for calf muscles²⁴ and sometimes in other (temporalis) muscles.²⁵ To our knowledge, it has not been observed before in upper arm musculature. A value larger than $P90$ for biceps muscle size may, therefore, be a useful indicator for DMD. For quadriceps, only four DMD patients have atrophic muscle, whereas most patients have normal or even increased quadriceps muscle size (Figure 3). This was also found in Heckmatt et al.²³ In Pillen et al.,¹⁰ where patients with different neuromuscular diseases were compared to patients with non-specific muscle complaints, quadriceps muscle thickness was found to be significantly decreased in neuromuscular disease. This seems to be mainly due to the inclusion of neuropathies.

The muscle aspect values density, inhomogeneity and white-area index were found to be constant in healthy children. In adults, we found that all values increased with age.¹³ The values that we found in children were slightly lower than the values in the youngest group of adults (20-30 years old), consistent with an increase in these values with age. The muscles in children were especially more homogeneous than those in

young adults. As far as we know, there are a limited number of studies of quantified normal muscle density values in children only.^{17,19} The values that were found in these studies are the same as respectively slightly higher (but with comparable SD) than in our study. The latter difference is most likely due to the inclusion of fascia and muscle-tendon transitions. Extended texture analysis was performed in Pohle et al.,¹⁵ using a neural network-type classification algorithm, but normal values were not explicitly given.

US imaging used in the assessment of neuromuscular disease typically employs muscle size and subcutaneous tissue thickness measurements, often complemented with density or gray value analysis. Previously, we have shown that inclusion of aspect values (inhomogeneity and white-area index) as well allowed for further distinction between neuropathic and myopathic disorders in adults.¹³ In adults, we found that all neuropathies had normal densities and white-area indices, but abnormally increased inhomogeneity, whereas almost all myopathies had increased densities, with often increased white-area indices and, sometimes, increased inhomogeneities (Table 5, last column for reference). In children, a different picture now arises.

All DMD patients, except one, showed either increased biceps density or quadriceps density. Both densities were increased for 16 of 19 patients. In contrast to the adult neuropathy patients, all 5 young neuropathy patients had increased quadriceps density and 3 of 5 had increased biceps density. Although normal aspect values were not available for this age group, they would certainly be lower than or similar to the values in the older control group. This difference between young and adult neuropathy patients was probably caused by the type of disease; in children, we considered hereditary diseases (mostly SMA) that are characterized by early and rapid muscle deterioration. In adults, we mainly considered amyotrophic lateral sclerosis. Heckmatt et al.¹⁷ reported 84% sensitivity based on density analysis in children with DMD, and Zuberi et al.¹² showed that, by using the qualitative criteria of Heckmatt et al.,⁴ a sensitivity of 91% could be reached in children older than 3 years with neuromuscular disorders. These values are comparable to our results. The most striking difference for aspect values between adults and children was found for inhomogeneity and white-area index in myopathies.

Whereas, the adult myopathy was characterized by high white-area index and rather low inhomogeneity, this was just the other way around in children with DMD. This difference is most likely due to the stage of the disease at which the US image was taken. A severe dystrophy, as it was mostly seen in the adult patients, is characterized by a homogeneous, dense image. The main histopathological features in DMD are those of myonecrosis with decreasingly effective regeneration as the disease progresses, and the replacement of muscle with fat and fibrous connective tissue,^{8,26} which strongly correlates with muscle echogenicity.²⁷ Because the pathologic changes in DMD are on the level of individual muscle fibres, a fine-grained inhomogeneous

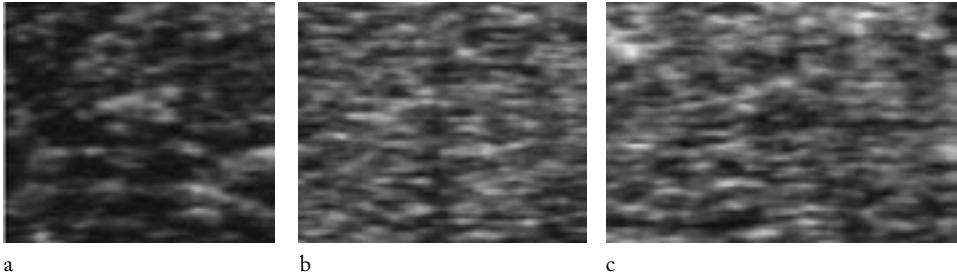


Figure 7. Examples of increasing biceps inhomogeneity in selections of muscle ultrasound images of DMD patients scaled to the same height. (a) Inhomogeneity = 0,00 (area 0,94 cm²), (b) Inhomogeneity = 4,58 (area 1,31 cm²), (c) Inhomogeneity = 16,27 (area 1,41 cm²)

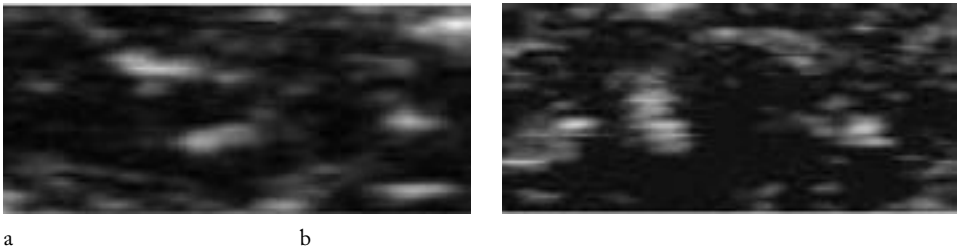


Figure 8. Examples of high quadriceps inhomogeneity in selections of muscle US images of neuropathy patients scaled to the same height. (a) Inhomogeneity = 14,10 (area 0,50 cm²), (b) Inhomogeneity = 14,57 (area 0,89 cm²).

US image results (Figure 7). In contrast, in neuropathies, all muscle fibers belonging to one motor unit are simultaneously affected, possibly after previous type grouping, leading to larger patches of increased density on US (Figure 8). Figures 7 and 8 illustrate, however, that similar values for inhomogeneity can reflect either typical DMD inhomogeneity or typical neuropathical inhomogeneity in children. A possible method of further distinction between fine-grained (DMD) and coarse-grained (neuropathies) inhomogeneities, inspired by the neural network classification parameters by Pohle et al.,¹⁵ could be to employ Sobel filters with larger ranges. These filters are currently used in the calculation of inhomogeneity. This will be further investigated in future research.

In conclusion, ultrasound imaging with quantitative analysis of muscle and subcutaneous tissue layer dimensions and quantitative muscle aspect parameters further enhances our understanding of changes in normal muscle in children. We found that all

analysed muscle dimensional parameters correlated best with either weight (muscle size) or BMI (subcutaneous tissue thickness). A value larger than P90 for biceps muscle size was found in 17 of 19 children with DMD and may, therefore, be a useful indicator for this disease. All muscle aspect parameters were found to be constant for the age group that was considered. The set of muscle parameters presented in this study provides a sensitive method for distinguishing healthy children and children with neuromuscular disorders. Although this method was shown to be sensitive for distinguishing myopathies and neuropathies in adults, more detailed texture analysis may be necessary to distinguish between these types of neuromuscular disorders in children. Hence, the proposed set of muscle parameters will support diagnostic use of ultrasound imaging in neuromuscular disorders and will facilitate follow-up in disease progression and therapy.

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