Duchenne muscular dystrophy quantification of muscular parameters and prednisone therapy

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Abstract

Duchenne muscular dystrophy (DMD) is clinically characterised by progressive muscle weakness and a gradual increase in the size of some affected muscles, especially calf muscles. The extent of calf enlargement is usually determined by subjective visual assessment. The purpose of this study was to determine the extent of calf muscle enlargement in DMD patients compared with healthy age matched boys by quantifying calf circumference. Calf circumference in the group of DMD patients is significantly increased. However, in individual patients calf enlargement can be feigned by a discrepancy between calf circumference and circumference of the upper leg and arm muscles as part of a general muscle atrophy.
Introduction

In 1868 Guillaume Benjamin Amand Duchenne described a disease which he named “pseudohypertrophic muscular paralysis.” This disease, which now bears his name, is characterised by progressive muscle weakness and a gradual increase in the size of some affected muscles, most prominently calf muscles, which is generally ascribed to muscle (pseudo) hypertrophy.

Hypertrophy of calf muscles is not specific for Duchenne muscular dystrophy (DMD). It has been described in various myopathic and neurogenic disorders, such as the autosomal recessive form of limb girdle muscular dystrophy, primary alfa- and gamma- sarcoglycanopathy, spinal muscular atrophy and in Charcot-Marie-Tooth disease type 1A. Muscle hypertrophy refers to an increase in the size of myofibres and, with this change, an increase in the size of (calf) muscles. There are, however, several other factors that may cause or contribute to calf enlargement such as an increase in subcutaneous fat, venous thrombosis, haemorrhage, focal myositis or a tumour in bone or muscle.

Various imaging techniques such as ultrasound, computer tomography and magnetic resonance imaging have been used to determine the thickness of the muscle and of the subcutaneous layer in neuromuscular disorders. The extent of calf enlargement in DMD patients is determined by subjective visual assessment. However, whether calf enlargement is found to be present in DMD patients, not only depends on calf appearance but also on bodyweight, height and atrophy of other muscles. These factors might feign the presence of calf enlargement.

In this study, the purpose was to determine the extent of calf enlargement in ambulant DMD patients compared with healthy controls by quantifying calf circumference with a tape measure.

Patients and Methods

In this study, calf circumference was measured in 19 ambulant DMD patients (age range 4-8 years, mean age 6.1 year SD 1.3) and in 59 healthy boys aged 4-10 years (mean age 7.0 year SD 2.1). The diagnosis of DMD had been confirmed by DNA-analysis and muscle biopsy. Maximal circumference of the upper arm and the upper leg as well as of the lower leg was determined on both sides in each subject in a supine position with shoulders 45° flexed, elbow 90° flexed, forearm pronated and hip and knee 45° flexed by shifting the tape measure.

In each subject gender, age, weight and height in underwear clothes without shoes were measured. Measurements were taken from the dominant as well as the non-
dominant side. The ratio of upper to lower leg circumference (leg-ratio = upper leg circumference / calf circumference) was also calculated.

In each age group, which comprises 1 year, at least 7 healthy boys were tested in a quiet room at school. None was under medical treatment. The procedure approximately took 15 minutes. All children and patients took part after informed consent given by their parents. All measurements were performed by the first author.

Statistics

Paired-sample t tests were used to determine differences between dominant and non-dominant sides for all bilaterally measured parameters. Significance was accepted if two-sided p-values were below 5%.

One-sample t test was used to determine differences in calf circumference, upper arm and upper leg circumference and leg-ratio between controls and patients. Multiple linear regression analysis (stepwise procedure) was used to predict calf circumference. Weight corrected normal scores (z-scores) were calculated in DMD patients for calf circumference, upper arm and upper leg circumference and leg-ratio. All statistical calculations were performed by using the SPSS 10.0 statistical program.

Results

Controls

Mean values for anthropometric variables in controls are presented in Table 1 for each age group.

<table>
<thead>
<tr>
<th>Age</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>109,0</td>
<td>117,0</td>
<td>128,0</td>
<td>127,0</td>
<td>136,0</td>
<td>139,0</td>
<td>140,0</td>
</tr>
<tr>
<td>(4,1)</td>
<td>(2,4)</td>
<td>(3,3)</td>
<td>(7,3)</td>
<td>(4,3)</td>
<td>(3,4)</td>
<td>(4,5)</td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>17,4</td>
<td>20,1</td>
<td>24,5</td>
<td>24,6</td>
<td>31,9</td>
<td>31,3</td>
<td>32,6</td>
</tr>
<tr>
<td>(1,0)</td>
<td>(2,0)</td>
<td>(2,6)</td>
<td>(4,5)</td>
<td>(5,3)</td>
<td>(5,1)</td>
<td>(5,7)</td>
<td></td>
</tr>
</tbody>
</table>
Paired-sample *t* test did not show significant differences between dominant and non-dominant sides for circumference of upper and lower extremities. Therefore, in all calculations, right sided values were used.

Multiple linear regression analysis showed that calf circumference in boys was best predicted by weight ($R^2 = 89.8$). Therefore weight corrected normal scores were calculated for upper and lower leg circumference as well as for upper arm circumference. Pearson correlation coefficient ($r$) between weight and calf circumference in healthy boys is 0.93 (Figure 1). Mean values for upper arm, upper leg and calf circumference for each weight group in boys are presented in Table 2.

**Table 2.**
Mean values and SD (in brackets) for upper arm and upper leg circumference as well as for calf circumference in healthy boys for each weight group.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Upper arm [cm]</td>
<td>17,4 (0,8)</td>
<td>18,4 (1,0)</td>
<td>19,5 (0,9)</td>
<td>22,0 (3,5)</td>
<td>22,4 (1,4)</td>
<td>23,5 (1,2)</td>
</tr>
<tr>
<td>Upper leg [cm]</td>
<td>30,6 (1,8)</td>
<td>32,3 (2,5)</td>
<td>36,6 (1,7)</td>
<td>40,0 (2,3)</td>
<td>41,2 (2,4)</td>
<td>44,2 (2,6)</td>
</tr>
<tr>
<td>Calf circumference [cm]</td>
<td>23,4 (1,0)</td>
<td>24,7 (1,3)</td>
<td>26,6 (1,0)</td>
<td>29,1 (1,7)</td>
<td>29,7 (1,0)</td>
<td>32,5 (1,0)</td>
</tr>
</tbody>
</table>

**DMD-patients**

In DMD patients, the Pearson correlation coefficient ($r$) between weight and calf circumference is 0.90 (Figure 1). The calf circumference in DMD patients is significantly increased compared with healthy controls (one-sample *t* test $p = 0.001$ 2-tailed). However, 12 of 19 (63%) patients had a normal score less than or equal to 2.0 SD (Figure 2). Calf circumference in DMD patients tend to deviate more from normal values with age although not significantly (linear regression $p = 0.077$) (Figure 2). Upper leg circumference and upper arm circumference tend to deviate more from normal values with age although not significantly (linear regression respectively $p = 0.052$ and $p = 0.133$). However, leg-ratio in DMD patients is significantly decreased compared with healthy controls (one-sample *t* test $p = 0.001$) (Figure 3).
Discussion

In this study, we quantified the extent of calf enlargement in ambulant DMD patients compared with healthy age matched boys by using a tape measure. In DMD patients, the mean circumference of the calves which was correlated best with weight just as muscle force, \(^{11}\) is significantly increased compared with weight matched healthy controls (Figure 2). This increase might be due to a real increase in muscle volume or to an increase in subcutaneous fat tissue or pseudohypertrophy. However, theoretically, calf enlargement can be feigned by a discrepancy between calf circumference and the aspect of other muscle groups, as part of a general atrophy.

The extent of subcutaneous fat tissue can be determined by ultrasonography. Heckmatt et al. \(^{12}\) failed to demonstrate an increase in subcutaneous fat in DMD patients by using this method. Discriminating between pseudo and real muscle hypertrophy is much more difficult. Muscle hypertrophy, which implies an increase in muscle fibre size without marked infiltration of collagen or fat tissue, is considered to be an important feature in DMD, and frequently appears in calf muscles and

![Figure 1. Weight [kg] versus calf circumference [cm] in normal boys (*) and in DMD patients (•). Pearson correlation coefficient (r) in healthy boys (straight line) is 0.93 and in DMD patients (dotted line) is 0.90. In healthy children calf circumference is best predicted by weight; for boys: calf circumference = 17.256 + 0.353 * weight.](image-url)
sometimes even in other (temporalis) muscles as well.\textsuperscript{13} Jones et al.\textsuperscript{14} reported the presence of hypertrophied muscle fibres in needle biopsy samples of calf muscle in DMD patients. Although these hypertrophied fibres were taken as characteristic for the first stage of the increase in muscle bulk,\textsuperscript{15} the extent of muscle fibre hypertrophy was not sufficient to contribute to the total calf muscle enlargement.\textsuperscript{14} Pseudohypertrophy, which is caused by replacement or infiltration of calf muscle by collagen and fat, might also contribute to an increase in calf circumference. Cros et al.\textsuperscript{16} reported in a biopsy experiment a percentage of 18-38\% of fat and fibrous tissue in the gastrocnemius muscle of DMD patients, whereas in controls this never exceeded 8\%.

However, the clinical impression of calf enlargement not only depends on the real extent of calf enlargement but also on factors such as the experience of the examiner and the physical constitution of the patient. It usually is determined by visual assessment. Pradhan et al.\textsuperscript{17} clinically examined 84 DMD patients for hypertrophy by inspection. They observed calf hypertrophy in 94\% of DMD patients.

On the contrary, in our study the normalised individual score for calf circumference was only significantly increased ($\geq$ 2.0 SD) in 7 of 19 (37\%) patients (Figure 2).

How can this difference between visual assessment and quantifying calf circumference be explained?

Theoretically, calf enlargement can be feigned by a discrepancy between calf circumference and the aspect of other muscle groups, as part of a general atrophy.

\textbf{Figure 2.} The relationship between age [months] and the normal score for calf circumference in DMD patients.
We suggest the relative atrophy of other muscle groups as a possible explanation for this discrepancy. In DMD patients, the upper leg circumference tends to decrease with age especially after the age of 7 years. This decrease might be caused by fibre atrophy of the upper leg muscles as was found by Cros et al.\textsuperscript{16} in quadriceps femoris biopsy. Muscle atrophy in DMD is not limited to the upper leg muscles, but can be found in upper arm muscles as well. The increases in calf circumference combined with a decrease of upper leg and upper arm circumference will both contribute to the visual disproportion between calf circumference and the general aspect of upper arm and leg muscles. This is also indicated by the significant decrease of leg-ratio in DMD patients (Figure 3). This suggests that the relative decrease of both upper arm and upper leg circumference together with a relative increase in calf circumference may even mimic calf enlargement in DMD patients. So subjective visual assessment is possibly a sensitive method to determine this discrepancy, but not sensitive to judge calf enlargement objectively. The absence of real or impression of calf hypertrophy on clinical examination does not rule out DMD and serum CK levels are indicated on clinical suspicion of DMD.

In conclusion, calf circumference in the group of DMD patients is significantly increased when compared with healthy boys. In individual patients however, calf enlargement can be feigned by a discrepancy between calf circumference and circumference of upper leg and arm muscles, as part of a general muscle atrophy. Mean values for upper and lower extremity length as well as for arm and leg circumference in boys and girls aged 4-10 years are available on request from the

\textbf{Figure 3.} The relationship between age [months] and the normal score for the leg-ratio in DMD patients.
first author.

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Reference List


