Duchenne muscular dystrophy quantification of muscular parameters and prednisone therapy
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CHAPTER 3

Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients.
Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients.

Submitted

Abstract

Neuromuscular disorders are characterised by progressive muscle weakness, which in time causes functional impairment. To quantify the extent of disease progression, two closely related parameters can be measured: muscle force and functional ability. Which of these parameters changes most depends on the disease stage. In a previous study we defined normal values for muscle force in children. In the present study we defined normal values for timed functional tests in healthy children aged 4 to 11 years. These values were applied in 16 ambulant Duchenne muscular dystrophy (DMD) patients aged 5 to 8 years to determine the extent of functional impairment. In ambulant DMD patients, we found that muscle function assessed by both timed functional tests (running 9 m and rising up from the floor) and muscle force testing was severely impaired. However, a small reduction of muscle force was accompanied by a large reduction in functional ability. Therefore, in our group of ambulant DMD patients, timed functional testing was the most sensitive parameter to determine the extent of disease progression. Timed functional testing may therefore be considered as an additional outcome measure in drug trials to evaluate the effects of therapy in intermediate stages of neuromuscular disorders.
Introduction

Neuromuscular disorders (NMD) are characterised by progressive muscle weakness, which can develop at any time from birth through adulthood. With progressing muscle weakness, functional ability will eventually become impaired. Muscle force and functional ability are often assessed respectively according to the Medical Research Council scale in which strength can be classified in a 6-point scale or by visual assessment of functional ability. As these parameters are of a qualitative nature, many centres nowadays also employ additional quantitative testing muscle force testing by dynamometry.\(^1\text{-}^4\) To determine muscle weakness and functional impairment objectively, normal values for muscle force and functional ability are needed. They can then be used to quantify possible functional impairment, to monitor the effects of therapy or to determine disease progression. Which of the parameters mentioned should preferably be used depends on the disease stage. A decrease in muscle force is often noticed only after the loss of muscle force is so extended that activities of daily living (ADL) become hampered. Typically, in the early stages of NMD, ADL function is still normal whereas, a dynamometry test would already indicate a decrease in muscle force. In the advanced stages of NMD most functional abilities will be lost, although some residual force may still be measured by dynamometry. In these two stages, dynamometry seems to be the most sensitive technique to measure disease progression.

We hypothesise that in the intermediate stages large changes in functional ability can be observed, whereas, muscle force, although severely affected, deteriorates only slightly. We previously established reference values for muscle force in normal children.\(^2\)

The purpose of this study was to gather normal values for timed functional tests in normal children aged 4-11 years. To study their value for determination of the extent of functional impairment, we applied the normal values in 16 ambulant Duchenne muscular dystrophy (DMD) patients aged 5-8 years and compared them to muscle force values to determine which parameter changes most during the ambulant period of DMD.

Subjects and methods

123 healthy children (66 boys), aged 4-11 years and 16 ambulant DMD patients, aged 5-8 years, who participated in a randomised controlled prednisone trial,\(^3\) were included in this study. In the DMD patients all parameters were measured in the first phase of the trial, before prednisone or placebo was given. Anthropometric measures (height and weight) were taken and timed functional testing (running 9 m and rising up from a supine position on the floor to a standing position as fast as possible) was
performed. All tests were carried out in underwear clothes and on bare feet. Timed tests were measured by using a stopwatch.

Maximum isometric muscle force was measured in nine different muscle groups by using handheld dynamometry (dynamometer type CT 3001 - C.I.T. Technics, Groningen, The Netherlands). The ‘break’ technique, in which the examiner gradually overcomes the muscle force and stops at the moment the extremity gives way was used. In bilaterally tested muscle groups, mean values were calculated to minimise the influence of left-right differences. To determine patterns of muscle weakness, individual muscles were grouped together to calculate clinically relevant summed scores. To prevent significant fatigue in DMD patients, less muscle groups were measured compared to healthy children. Therefore, our previously reported summed scores\(^2\) could not be used. We calculated new summed scores based on our reference values of individual muscle groups.

As we did not measure foot dorsal flexor muscles and neckflexor muscles in DMD patients, we could not directly use our reference summed scores for maximum isometric muscle force that we obtained earlier.\(^2\) Based on the reference values for individual muscle groups, we calculated new summed scores excluding foot dorsal flexors and neckflexors. New summed scores were obtained for total muscle force (all 9 muscle group scores), proximal muscle force (shoulder abductors, elbow flexors and extensors, hip flexors and abductors, knee flexors and extensors), distal muscle force (mean wrist extensors and mean three-point grip), arm muscle force (all arm muscle groups), and leg muscle force (all leg muscle groups). Measurements took place after informed consent of both parents and children.

**Statistics**

Differences between boys and girls for timed functional tests were calculated by using Student’s *t*-test or the non-parametric Mann-Whitney test for independent group samples when data were not distributed normally. Normality was tested by the Shapiro-Wilk test. Significance was accepted if two-sided p-values were below 5%. Pearson correlation coefficients (*r*) were calculated in healthy boys and girls to evaluate the association between timed functional tests and age, weight, height and body mass index (BMI) and timed functional tests and muscle force. Correlation was assumed to be significant at the two-tailed 5% level. Multiple regression analysis (forward method) was used in DMD patients to determine which summed muscle score best predicted timed functional test scores. All statistical calculations were performed by using the SPSS 10.0 statistical program.
Results

Healthy boys (mean age 7.4 year SD 2.3) and girls (mean age 7.4 year SD 2.2) were equally distributed over age groups of one year (Table 1). The mean age of the 16 DMD patients was 6.25 years (SD 0.93 years). Height and weight of the DMD patients was distributed normally and within normal range.

The number of boys and girls, as well as mean values for both timed functional tests are presented in Table 1. As values were not distributed normally we used the non-parametric Mann-Whitney test to test differences between genders. No significant differences between boys and girls for either timed functional test were found. As some neuromuscular disorders such as DMD are only found in boys, we did not pool the values for both genders despite the absence of differences between boys and girls.

The time needed to run correlated best with age in both boys and girls (Table 2). The time needed to rise up from the floor correlated best with age in boys and with BMI in girls. As age is the easiest parameter to work with in outpatient clinics and Pearson’s correlation coefficients were highly similar for age, weight, height and BMI, we chose to calculate mean values for both timed functional tests per age group, each comprising one year.

The time needed to rise decreased with age to a value of approximately 1 second at the age of 11 years (Table 1). There was a significant correlation between time needed to run 9 m and age both for healthy boys \(r = -0.63, p < 0.001\) and girls \(r = -0.54, p = <0.001\) (Table 2). Rising up from the floor correlated best with age in boys \(r = -0.60, p <0.001\) and BMI in girls \(r = 0.33, p = 0.006\) (Table 2).

### Table 1.

Age-related reference values (mean, (SD)) for timed functional tests in each age group in normal boys (b) and girls (g). SD = standard deviation, yr = year, sec. = seconds.

<table>
<thead>
<tr>
<th>Age [yr]</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>g</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Running [sec.]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>3.35 (0.48)</td>
<td>3.34 (0.34)</td>
<td>2.89 (0.35)</td>
<td>2.44 (0.30)</td>
<td>2.78 (0.27)</td>
<td>2.76 (0.25)</td>
<td>2.72 (0.28)</td>
<td>2.46 (0.28)</td>
</tr>
<tr>
<td>g</td>
<td>3.43 (0.25)</td>
<td>3.32 (0.39)</td>
<td>2.67 (0.47)</td>
<td>2.53 (0.35)</td>
<td>2.57 (0.24)</td>
<td>2.85 (0.12)</td>
<td>2.97 (0.26)</td>
<td>2.68 (0.33)</td>
</tr>
<tr>
<td>Rising [sec.]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>1.56 (0.56)</td>
<td>1.45 (0.16)</td>
<td>1.42 (0.29)</td>
<td>1.28 (0.33)</td>
<td>1.24 (0.24)</td>
<td>1.17 (0.24)</td>
<td>1.08 (0.25)</td>
<td>0.99 (0.14)</td>
</tr>
<tr>
<td>g</td>
<td>1.52 (0.43)</td>
<td>1.45 (0.21)</td>
<td>1.17 (0.19)</td>
<td>1.19 (0.27)</td>
<td>1.03 (0.20)</td>
<td>1.06 (0.21)</td>
<td>1.42 (0.39)</td>
<td>1.13 (0.27)</td>
</tr>
</tbody>
</table>
The time needed to run 9 m and the time needed to rise up from the floor from a supine to a standing position as a function of age are illustrated both for healthy boys and DMD patients in Figures 1 and 2. In general, the performance of the DMD patients declined with age, which was even more striking while normal children improved their performance with increasing age. At the age of 8 years the normal score for DMD patients was 3-4 for running 9m and 7-12 for rising up. In DMD, patients we found a significant negative correlation for the time needed to run 9 m with summed leg muscle force (r = -0.516 p = 0.041) and with summed proximal muscle force (r = -0.505 p = 0.046). Multiple regression analysis showed that the time needed to run 9 m was best predicted by summed leg muscle score. There was no significant correlation for the time needed to rise with any of the summed scores. Although two DMD patients performed within normal ranges on the timed functional test running, all DMD patients scored below the normal range (average ± 2SD) for muscle force, as can be seen in Figure 3 for total muscle force. The results for distal and leg muscle force were the same (results not shown). Again, the differences between healthy children and DMD patients become more apparent with increasing age, as normal children gain strength with age whereas, DMD children remain at the same strength level at best.

Table 2.
Pearson correlation coefficient (r) for timed tests against age, weight [kg], height [cm] and body mass index (BMI, [kg/m^2]) for healthy boys and girls. * p ≤ 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age</td>
<td>p</td>
<td>age</td>
<td>p</td>
</tr>
<tr>
<td>Running [sec.]</td>
<td>-0.632</td>
<td>&lt;0.001*</td>
<td>-0.542</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>weight</td>
<td>&lt;0.001*</td>
<td>-0.381</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>height</td>
<td>&lt;0.001*</td>
<td>-0.529</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.012*</td>
<td>-0.119</td>
<td>0.347</td>
</tr>
<tr>
<td>Rising [sec.]</td>
<td>-0.602</td>
<td>&lt;0.001*</td>
<td>-0.299</td>
<td>0.016*</td>
</tr>
<tr>
<td></td>
<td>weight</td>
<td>&lt;0.001*</td>
<td>0.026</td>
<td>0.835</td>
</tr>
<tr>
<td></td>
<td>height</td>
<td>&lt;0.001*</td>
<td>-0.277</td>
<td>0.025*</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.262</td>
<td>0.337</td>
<td>0.006*</td>
</tr>
</tbody>
</table>
Figure 1. Time needed to run 9 m versus age in healthy boys (*) and DMD patients (•).

Figure 2. Time needed to rise up versus age in healthy boys (*) and DMD patients (•).
Discussion

To quantify the extent of functional impairment in NMD muscle force or functional ability can be measured. Which of these parameters changes most depends on the degree of force loss. We hypothesised that in intermediate disease stages functional testing changes more than muscle force and therefore may be used as an additional parameter to quantify disease progression, as this is the stage where large changes in functional ability can be observed, whereas, muscle force, although severely affected, deteriorates only slightly. To test this hypothesis we first established a set of normal values for two timed functional tests in healthy children.

We then investigated a group of ambulant DMD patients and compared their performance on the functional tests to their maximum isometric muscle force as measured by a dynamometer.

In healthy children no differences in performance on both timed functional tests (running 9 m and rising up from a supine position on the floor to a standing position) were found between boys and girls. Differences may appear after puberty has set in. Although these changes were not observed as the oldest children in our study were 11 years old, we previously found that significant differences in muscle force become already apparent at age 10. Apparently, it takes some time before these changes in

![Figure 3. Total muscle force (Newton; [N]) versus age ([month]) in healthy boys (•) and DMD patients (•)](image-url)
muscle force are reflected in significantly different performances on functional tests, probably due to the changing relation between body dimension and muscle force. Both the time needed to run 9 m as well as the time needed to rise up from the floor, linearly decreased with age in healthy children for both genders. In normal children the time needed to run 9 m decreases with age until approximately 2.5 seconds at the age of 11 years. As junior athletes run 40 m in approximately 7-8 seconds and 60 m in 9-10 seconds, this time will probably not decrease much further in older children.

In the DMD patients we found no significant linear correlation between the time needed to run and age. This is in contrast with the results of Scott et al. who demonstrated a linear correlation for walking time against age in a group of 50 DMD patients. These differences may be due to the differences in group size and disease severity, as the Scott study included both ambulant and non-ambulant DMD patients.

The time to perform both timed functional tests increased with age in DMD patients in the present study, despite a small increase in force. Apparently, this force increase was not sufficient to compensate for the increase in weight and height with age. This was further illustrated by the negative correlation between the time needed to run 9 m and summed leg and proximal muscle force.

The mean running velocity in DMD patients in this study was 1.78 m/s which is faster than a mean value of 1.27 m/s measured by Hyde et al. in 27 ambulant DMD patients. The mean time in rising up from the floor was also much shorter in our patients (5.71 sec.) than in the group of patients studied by Hyde et al. (10.94 sec.). Although the mean age (6.65 years) of included patients was similar to the mean age in the present study (6.25 years) the spread in age was much larger in the Hyde et al. study (1.89 vs. 0.93 years), which may have caused the difference in time needed to execute timed tests.

Executing timed test such as rising up from the floor has been reported to be possible without help or external support in children with spinal muscular atrophy with an isometric muscle strength of only 15% of the reference value of knee extensors. This illustrates that functional ability can be maintained for a long time, even though muscle force may already be severely reduced.

In our ambulant DMD patients, the normal score for summed leg muscle force was maximally 7, whereas, this was up to 14 for the time needed to run 9m and 43 for the time needed to rise from the floor (results not shown). Thus, a small reduction in muscle force was accompanied by a relatively large deterioration in functional ability function. This indicates that in this group of DMD patients timed functional testing was more sensitive to disease progression, changes in functional impairment and effects of therapy than muscle force measurement.

In conclusion, these results indicate that timed functional tests such as running 9 m and rising up from the floor should also be considered as additional outcome measures in trials evaluating the effects of drug therapy in ambulant DMD patients.
Furthermore, we expect that the functional ability also changes more than muscle force in intermediate disease stages of other neuromuscular disorders.

Acknowledgements

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Reference List


