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Hip kinetics during gait are clinically meaningful outcomes in young boys with Duchenne muscular dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is an X-linked genetic neuromuscular disorder characterized by progressive proximal to distal muscle weakness. The success of randomized clinical trials for novel therapeutics depends on outcome measurements that are sensitive to change. As the development of motor skills may lead to functional improvements in young boys with DMD, their inclusion may potentially confound clinical trials. Three-dimensional gait analysis is an under-utilized approach that can quantify joint moments and powers, which reflect functional muscle strength. In this study, gait kinetics, kinematics, spatial-temporal parameters, and timed functional tests were quantified over a one-year period for 21 boys between 4 and 8 years old who were enrolled in a multisite natural history study. At baseline, hip moments and powers were inadequate. Between the two visits, 12 boys began a corticosteroid regimen (mean duration 10.8 ± 2.4 months) while 9 boys remained steroid-naïve. Significant between-group differences favoring steroid use were found for primary kinetic outcomes (peak hip extensor moments ($p = .007$), duration of hip extensor moments ($p = .007$), peak hip power generation ($p = .028$)), and spatial-temporal parameters (walking speed ($p = .016$) and cadence ($p = .021$)). Significant between-group differences were not found for kinematics or timed functional tests with the exception of the 10 m walk test ($p = .03$), which improves in typically developing children within this age range. These results indicate that hip joint kinetics can be used to identify weakness in young boys with DMD and are sensitive to corticosteroid intervention. Inclusion of gait analysis may enhance detection of a treatment effect in clinical trials particularly for young boys with more preserved muscle function.

1. Introduction

Duchenne muscular dystrophy (DMD) is a progressive X-linked genetic neuromuscular disorder that primarily affects males. Progressive proximal to distal muscle weakness due to disruption in the manufacturing of the dystrophin protein is a hallmark of this disease [1–3]. Young children with DMD develop subtle compensatory strategies to minimize demand on weak muscles during gait, which become substantially more pronounced and unstable with increasing age [4,5]. Corticosteroid treatment, a standard of care for boys with DMD, is generally initiated between 4 and 8 years of age [6,7], and initially preserves strength, maintains function, and prolongs ambulation [8–11]. Ultimately, ambulatory ability progressively deteriorates until walking ceases in the second decade of life.

More recently, novel therapeutics have been developed to target genetic pathways (e.g. exon skipping) and have curative potential [12,13]. Unfortunately, clinical trials have been met with difficulties in establishing efficacy [7,14,15]. Of paramount importance to the success of a randomized clinical trial is the use of outcome measurements that are sensitive to change, reliable, and clinically meaningful. In contrast to sophisticated techniques used to develop novel medications [16], clinical trials in neuromuscular disease typically utilize basic clinical measures such as timed and graded motor skills, manual muscle testing, and the 6-min walk test to establish therapeutic efficacy [17,18]. Current opinions from recent clinical trials suggest that these outcome measures may lack

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the sensitivity and specificity to detect significant improvements within the first 6-12 months of an intervention [14,19,20]. Outcomes that can detect more subtle changes in function and performance are needed.

Three-dimensional gait analysis offers a method of objectively quantifying changes in lower extremity function due to muscle weakness, and has been used extensively in the planning and assessment of treatments for gait pathologies, such as cerebral palsy [21]. The pathomechanics of gait in individuals with DMD, first described by Sutherland et al. [4], include postural compensations of lumbar lordosis, increased anterior pelvic tilt, reduced hip extension, and increased ankle plantar flexion. These strategies position the ground reaction force vector posterior to the hip joint and anterior to the knee, which reduces the demand on weaker hip and knee extensors. Cross-sectional studies have reported reduced peak and duration of hip extensor moments [22] and powers [22,23] as compared to children with typical development. Reduced peak knee extensor moments [22,24,25], plantar flexor moments [22,25], and ankle power generation have also been noted [22,23,25]. Cross-sectional studies have shown that boys with a history of corticosteroid use exhibited greater ankle power generation during gait as compared to boys who were steroid-naïve [23], but significant differences in kinematics were not found between these two groups [26]. These studies suggest that reduced moments and powers may be an important marker of gait pathology in boys with DMD. As proximal muscles are affected first [3], hip kinetics are most likely to be altered in early stages. To our knowledge, no longitudinal studies have utilized gait analysis to evaluate intervention efficacy in boys with DMD.

The purpose of this study was to determine the sensitivity of joint kinetics as indicators of early changes in muscle strength for young boys with DMD. Functional ability improves in children with and without DMD between the ages of 4–8 years [27–29]; therefore, investigators are cautious about the inclusion of this age group in clinical trials. In contrast to 10 m walk/run speed [29], joint kinetics do not appreciably change after three years of age for typically developing children [30]. In this study, we collected spatial-temporal data and quantified kinematics and kinetics at the hip, knee and ankle using three-dimensional gait analysis. Hip moments and powers are more likely to be subnormal because muscle weakness progresses from proximal to distal. We hypothesized that hip kinetics would be inadequate in young boys with DMD and would improve following initiation of corticosteroid intervention, as compared to a steroid-naïve group of boys who had not yet begun treatment. Timed functional tests commonly used in clinical trials were included for comparison.

2. Methods

2.1. Study population

The data used in this analysis were collected from participants that were enrolled in a larger longitudinal multicenter natural history study of gait and function which began in 2006. Inclusion criteria for the natural history study were a diagnosis of DMD determined by clinical evaluation and either a blood DNA study or muscle biopsy, the ability to walk independently for 10 min, and the ability to cognitively understand directions for testing procedures. Once all data had been collected, a subgroup was identified for the present analysis. Inclusion criteria consisted of two visits with gait analysis performed one year apart, age between 4 and 8 years, and no history of corticosteroid use at the baseline visit. Exclusion criteria consisted of significant medical events such as surgery, fractures, major illness, or casting one year prior to baseline or during the study period. Twenty-one boys were identified and included in the present analysis. Boys with a minimum of 3 months of a corticosteroid treatment prior to the post visit were identified as the Steroid group ($n = 12$). Boys with no corticosteroids were identified as the Naïve group ($n = 9$). The decision to initiate corticosteroid treatment was made as part of their separate individual clinical treatment plans and was reported via medical history form by the parents or guardians at each visit.

2.2. Gait analysis

Instrumented gait analysis was performed at 3 clinical gait laboratories using the Helen Hayes marker set. Reflective marker position data and ground reaction force data were collected at self-selected, preferred walking speeds while barefoot along a 15-m walkway using an 8-camera motion capture system (Vicon, Oxford, UK or Motion Analysis, Santa Rosa, CA, USA) and at least 2 forceplates (AMTI, Advanced Medical Technology, Watertown, Massachusetts, USA or Kistler, Kistler Instruments, Switzerland). Between 3–5 force plate strikes were collected for each limb of each participant. The clinical gait assessment was performed by trained evaluators and each assessment took approximately 45–60 min to complete. Spatial-temporal parameters, kinematics, and kinetics for all participants were calculated using Orthotrak (Motion Analysis, Santa Rosa, CA, USA). Kinematics and kinetics were time-normalized to percent of gait cycle. Moments and powers were normalized to body weight. Total support moment was calculated as the sum of hip, knee, and ankle moments at each percent in the gait cycle, with the convention of extensor moments as positive. The stride with the maximum peak hip extensor moment for each limb was identified and analyzed.

2.3. Timed functional tests

The time to perform standardized functional tasks was assessed using a stop watch. The times to walk or run 10 m (10 m Walk/Run), climb 4 stairs (4-Step Stair), and rise from a supine position to standing (Supine to Stand) were recorded.

2.4. Statistical analysis

The peak hip extensor moment during stance, the duration of the hip extensor moment through stance, and peak hip power generation during hip extension were primary outcome measures. Peak values for the left and right limbs were averaged for each participant. Changes in spatial-temporal parameters, key kinematic and kinetic variables, and timed functional tests were quantified within and between the two groups. Within-group changes were assessed using paired t-tests. Differences in the change scores between groups were assessed using independent t-tests. Data were assessed for normalcy using the Shapiro-Wilk test. Statistics were calculated using JMP Statistical Software Package (SAS Institute Inc, Cary, NC) with significance set at $p = 0.05$.

3. Results

Participant demographics are shown in Table 1. The two groups had similar ages, heights, weights, body mass indices (BMI), and time to follow-up. The average duration of corticosteroid use in the Steroid group prior to post testing was 10.8 ± 2.4 months (range 4–13 months). A statistically significant increase in BMI for the Steroid group as compared to the Naïve group was found. This is consistent with weight gain as a side effect of a corticosteroid intervention [6].

Average joint angles, moments, and powers at baseline and at follow-up for the Steroid and Naïve groups are shown in Fig. 1. Relative to published normative kinematics and kinetics for children [30], excessive hip flexion during swing was observed