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Progression and variation of fatty infiltration of the thigh muscles in Duchenne muscular dystrophy, a muscle magnetic resonance imaging study

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Abstract

The purpose of this study was to assess the progression and variation of fatty infiltration of the thigh muscles of Duchenne muscular dystrophy patients. Muscle magnetic resonance imaging was used to measure the degree of fatty infiltration of the thigh muscles of 171 boys with Duchenne muscular dystrophy (mean age, 6.09 ± 2.30 years). Fatty infiltration was assigned using a modified Mercuri's scale 0–5 (normal–severe). The gluteus maximus and adductor magnus were affected in patients less than two years old, followed by the biceps femoris. Quadriceps and semimembranosus were first affected at the age of five to six years; the sartorius, gracilis and adductor longus remained apparently unaffected until seven years of age. Fatty infiltration of all the thigh muscles developed rapidly after seven years of age. The standard deviation of the fatty infiltration scores ranged from 2.41 to 4.87 before five years old, and from 6.84 to 11.66 between six and ten years old. This study provides evidence of highly variable degrees of fatty infiltration in children of different ages with Duchenne muscular dystrophy, and indicates that fatty infiltration progresses more quickly after seven years of age. These findings may be beneficial for the selection of therapeutic regimens and the analysis of future clinical trials.

Keywords: Duchenne muscular dystrophy; Muscle magnetic resonance imaging; Fatty infiltration; Age

1. Introduction

Duchenne muscular dystrophy (DMD) is one of the most common muscular dystrophy diseases, with an incidence of 1 in 3500 male births [1]. It is an X-linked, recessive, hereditary disease caused by a genetic defect of the DMD gene [2]. DMD manifests as progressive muscle weakness starting before five years old [3,4], this is often concomitant with hypertrophy of the calf muscles. So far, muscle biopsy and genetic testing are still the gold standards for the diagnosis of DMD [5]. Early corticosteroid therapy can slow the progression of the disease [6].

Muscle MRI as a noninvasive method for evaluating muscle involvement in DMD is promising [7], practical and reproducible [8]. The main MRI change associated with DMD is fatty infiltration of the muscles [4,9]. The severity of fatty infiltration has been correlated with age [10] and muscle histopathology [11]. We have recently reported that fatty infiltration of the muscle in DMD is also correlated with the duration of the disease and the patient's body mass index [12]. There are currently no clear data on the variations in fatty infiltration between different age groups; however, this information is important for planning clinical trials. Therefore, using muscle MRI, we assessed the progression and variation of fatty infiltration of the thigh muscles in a large cohort of children with DMD ranging in age from one to ten years.

2. Materials and methods

2.1. Patients

One hundred seventy-one boys with DMD who presented to the Department of Neurology at Peking University First Hospital were enrolled in the study. They ranged from one to ten years old (mean: 6.09 years, SD: 2.30). All patients presented with progressive muscle weakness, especially in the thighs, before four years of age; the patients had difficulty in walking, climbing stairs, and rising from a supine position. One hundred twenty-four patients also presented with delayed motor milestones, including an inability to crawl (89 patients), and attaining the ability to walk independently at later than 15 months of age (91 patients). The disease duration ranged from

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0.3 to 8.5 years (mean: 3.66, SD: 1.87). Five of the patients had lost the ability to walk after seven years old. Physical examination revealed that their muscle strength was two to four grades lower than normal, and by a conversion formula of MRC [13], the strength of the proximal muscles of the lower limbs ranged from 38 to 100 (mean: 84.51, SD: 12.04). Serum CK levels ranged from 1600 IU/L to 43150 IU/L (normal 25–170 IU/L). All boys with DMD had their diagnosis established by either DNA testing or muscle biopsy, or both. One hundred forty cases had a confirmed mutation of the dystrophin gene; these included 114 cases of deletion mutation, 17 cases of duplication mutation, and 9 cases of point mutation. Seventy cases were confirmed by the lack of dystrophin in muscle biopsies. All patients underwent clinical assessments by two senior neurologists who were blind to the MR imaging findings.

The study was approved by the review board of the Peking University First Hospital. Written informed consent was obtained from the parents of all participants according to the Declaration of Helsinki.

2.2. Muscle MRI

Non-quantitative MRI was performed using a 1.5/3.0-T imaging system whole body scanner. T1-weighted sequences were performed with the following parameters (for 1.5 T or 3.0 T): repetition time = 450 ms or 480 ms, echo time = 12 ms or 14 ms, slice thickness = 5–8 mm or 2.8 mm, slice gap = 1–2 mm and field of view = 28–32 cm. The slice thickness of 2.8 mm was only used in one infant whose height was too short, but the signal-to-noise ratio of images was acceptable, thus this subject was enrolled. For the other subjects, the thickness of slices was 5–8 mm. Images were made bilaterally from the hips to the ankles of all 177 boys with DMD; axial and coronal images were obtained. None of the study participants had received previous corticosteroid treatment. To avoid the influences of exercise and activity, patients were requested to rest for at least one hour before the MRI examinations. The muscles were imaged in a non-contracted state. To avoid movement artifacts in some young infants and children, sedation (Chloral hydrate) at standard doses was administrated before the examination [14].

The MR images were assessed by two independent and experienced radiologists, who were blind to the clinical data. Using T1-weighted MR images, the degree of fatty infiltration was scored using a modified Mercuri's scale as follows [11,15,16]:

Score 0: Normal muscle signal intensity without fatty infiltration
Score 1: Occasional scattered areas of increased density
Score 2: Mild fatty infiltration with numerous discrete areas of increased signal and beginning confluence, affected areas comprise less than 30% of the individual muscle volume
Score 3: Moderate fatty infiltration with increased areas of confluent signal, affected areas comprise 30–60% of the individual muscle volume
Score 4: Severe fatty infiltration with increased confluent signal, affected areas comprise more than 60% of the individual muscle volume
Score 5: End-stage appearance, muscle entirely replaced by areas of confluent signal

Scores 0 and 1 reflect mild, scores 2 and 3 reflect moderate, and scores 4 and 5 reflect severe fatty infiltration of the muscle.

2.3. Statistical analysis

All values were calculated using the SPSS statistical package (Version 17.0J for Windows). Descriptive statistics were carried out when appropriate. Two scatter diagrams were analyzed using LOESS regression; one showed the correlation between the total scores for fatty infiltration and age, the other showed the correlation between CK levels and age.

3. Results

3.1. Severity of fatty infiltration in individual thigh muscles

For each age group, we calculated the percentages of each individual muscle in each score category (Table 1), and selected scores 4 and 5 as indicative of severe muscle involvement. The gluteus maximus and adductor magnus had the highest percentages of high scores in every age category. The biceps femoris and quadriceps femoris had the next highest percentages of high scores. These were followed by the semimembranosus and semitendinosus. The sartorius, gracilis and adductor longus muscles had the lowest percentages of high scores overall. (Table 1)

3.2. Age of onset of fatty infiltration in individual thigh muscles

Fatty infiltration of the thigh muscles began at as early as 1 to 2 years of age. The gluteus maximus and adductor magnus were affected before 2 years, and the biceps femoris was next affected. The vastus lateralis and rectus femoris were affected by 3 to 4 years of age. The quadriceps and hamstrings were both affected by 5 to 6 years of age. Severe fatty infiltration of all of the thigh muscles started after 7 years of age and included the sartorius, gracilis and adductor longus muscles (Table 1).

3.3. Correlation between total fatty infiltration scores and age

To explore the correlation between total scores for fatty infiltration of the thigh muscles and age, we created a scatter diagram and LOESS line. The LOESS line (Fig. 1A) showed a change in slope at the age of seven years old; indicating that the total scores of fatty infiltration increased slowly before, and quickly after, seven years of age. For comparison, we also plotted the serum CK levels versus age (Fig. 1B).

3.4. Variations in the severity of fatty infiltration in each age group

Before the age of five years, the standard deviation (SD) for fatty infiltration ranged from 2.41 to 4.87. In six-, seven-, eight-, nine- and ten-year-old patients the SDs for fatty