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Temporalis Muscle Hypertrophy and Reduced Skull Eccentricity in Duchenne Muscular Dystrophy

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Abstract

Muscle hypertrophy and muscle weakness are well known in Duchenne muscular dystrophy. Decreased muscle force can have secondary effects on skeletal growth and development such as facial and dental morphology changes. In this study, we quantified temporal muscle thickness, circumference, and eccentricity of the skull and the head on T1-weighted magnetic resonance imaging (MRI) scans of the head of 15 Duchenne muscular dystrophy patients and 15 controls. Average temporal muscle thickness was significantly increased in patients (12.9 $\pm$ 5.2 mm) compared to controls (6.8 $\pm$ 1.4 mm) ($P < .0001$), whereas the shape of the skull was significantly rounder compared to controls. Temporal muscle thickness and skull eccentricity were significantly negatively correlated in patients, and positively in controls. Hypertrophy of the temporal muscles and changes in skull eccentricity appear to occur early in the course of Duchenne muscular dystrophy. Further studies in younger patients are needed to confirm a causal relationship.

Keywords

muscular dystrophy, MRI, muscle disease, pediatric

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Duchenne muscular dystrophy is characterized by progressive weakness of skeletal, respiratory, and cardiac muscles due to the absence of dystrophin. Medical and supportive care have improved life expectancy from 20 up to 25 to 30 years. Muscle weakness in the legs usually manifests itself when a boy begins to walk on his toes and falls frequently. A prominent feature is calf hypertrophy, which in combination with a disturbed walking pattern and increased serum creatine kinase level suggests the clinical diagnosis of Duchenne muscular dystrophy.

Muscle hypertrophy in Duchenne muscular dystrophy is not restricted to the calf muscles, but has also been reported in other muscle groups. Specifically, the gracilis and sartorius muscles in the upper legs, deltoid and infraspinatus muscles in the shoulder region, and the tongue can be hypertrophic[1,2] One case report has described temporal muscle hypertrophy in Duchenne muscular dystrophy.[3]

It is likely that muscle hypertrophy in Duchenne muscular dystrophy is a response to dysfunction of weak skeletal muscles. It is currently not known if hypertrophy in Duchenne muscular dystrophy leads to an increase in muscle strength.[4,5] Mechanical forces exerted by skeletal muscles can influence bone structure[6] and, therefore, secondary effects of muscle weakness or hypertrophy could lead to differences in bone development. For example, decreased bite force has been suggested as related to skeletal changes in the oral-facial region.[7,8] Furthermore, dental malocclusion in Duchenne muscular dystrophy has been described as a result of imbalance of muscle strength in the orofacial region and developmental changes in jaw bones.[8] During an magnetic resonance imaging (MRI) study of the brain in Duchenne muscular dystrophy patients,

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we consistently observed temporal muscle hypertrophy and a different skull shape compared to healthy age-matched controls. The difference was so pronounced that given the knowledge of the impact that skeletal muscle force can have on bone, we choose to quantify and report our observations.

Methods

Subjects

Fifteen Caucasian Duchenne muscular dystrophy boys (8-16 years) and 15 age-matched healthy Caucasian (9-15 years) boys participated in the study. Patients were recruited from the Dutch dystrophinopathy database. Only patients with a genetically confirmed diagnosis were included. Controls were recruited from schools or sports clubs.

In patients using steroids (intermittent scheme, 10 days on, 10 days off) the scans were performed during the off-period. The study was approved by the institutional ethics committee. All participants and their parents gave informed consent.

Magnetic Resonance Imaging

Three-dimensional T1-weighted images (echo time [TE] = 4.6 ms, repetition time [TR] = 9.8 ms, voxel size = 1.17 × 1.17 × 1.2 mm, acquisition time = 4:56 minutes) of the head were obtained at 3 Tesla (Achieva, Philips Healthcare, Best, the Netherlands) using an 8-channel head coil. Quantitative determination of eccentricity and circumference of the skull (excluding muscles, fat, and skin) and the head (including muscles, fat, and skin) was performed by 2 independent observers. Transversal images from each boy were assessed from the anterior and posterior commissure (AC/PC) upwards (reconstructed to 10 slices, 1.5 mm thick, 2.0 mm slice gap). Regions of interest (ROIs) of skull and head were manually drawn in MIPAV (http://mipav.cit.nih.gov) and averaged for the 10 slices. MIPAV was also used to determine the largest cross-section of left and right temporal muscles.

Statistics

Differences in skull eccentricity, head eccentricity, temporal muscle thickness, skull circumference, and head circumference between Duchenne muscular dystrophy and controls were assessed. This was done using the values averaged for 2 independent observers by means of a Student *t* test with Welch correction where the variances were significantly different. Interobserver variability was computed using the intraclass correlation coefficient (ICC). Pearson correlation was computed between skull eccentricity and temporal muscle thickness, age and temporal muscle thickness, and between age and eccentricity. Statistical significance was set at $P < .05$. Statistical analyses were performed using SPSS (version 17.0, SPSS Inc, Chicago, IL).

Results

Descriptive data of the participants are shown in Table 1. On visual inspection of the images, hypertrophy of the temporal muscles was observed in all Duchenne muscular dystrophy patients as well as a rounder shape of the head compared to more ovoid shaped in healthy controls (Figure 1). The average cross-sectional temporal muscle size was 12.9 ± 5.2 mm in Duchenne muscular dystrophy compared to only 6.8 ± 1.4 mm in controls ($P < .001$; Figure 2A). In controls, a positive correlation between temporal muscle size and age was observed, whereas in Duchenne muscular dystrophy no such relation was observed (Figure 2B). The ICC for measurements of eccentricity and circumference of the skull and head was 0.994 ± 0.001. The circumference of skull and head showed no significant difference between Duchenne muscular dystrophy and controls. As a parameter for shape, eccentricity was calculated from ROIs drawn on head circumference and on skull circumference (Figure 1). Eccentricity ranges between 0 and 1, in which 0 represents a perfect circle and 1 a parabola. The average skull eccentricity in Duchenne muscular dystrophy (0.59 ± 0.05) was significantly different from skull eccentricity in controls (0.63 ± 0.05) ($P < .05$; Figure 2C). Boys with Duchenne muscular dystrophy had a rounder skull shape and controls had a more ovoid-shaped skull on transversal images. Skull eccentricity was not correlated with age.

Finally, a significant correlation between temporal muscle size and skull eccentricity was observed (Figure 2D). In Duchenne muscular dystrophy patients, thicker (hypertrophic) temporal muscles were related to a rounder shaped skull ($r = –0.54$, $P = .04$). In controls, thicker temporal muscles were correlated with an ovoid skull shape ($r = 0.55$, $P = .03$).

Table 1. Descriptive Data of the Participants.

	Duchenne muscular dystrophy (n = 15)	Controls (n = 15)
Age		
Mean ± SD	12.4 ± 2.7	12.4 ± 1.7
Median (range)	14.0 (8-16)	12.9 (9-15)
Use of steriods (n)		
Current use	12	0
Stopped >1 year	2	
Never used	1	
Wheelchair-bound (n)	9	0
Head circumference (cm)		
Mean ± SD	56.0 ± 2.8	55.5 ± 1.4
Range	52.5-60.0	53.0-58.5

Discussion

Our results show systematic temporal muscle hypertrophy in Duchenne muscular dystrophy patients, which is clearly apparent on transverse magnetic resonance images of the head. Additionally, in the transverse plane, the shape of the skull in Duchenne muscular dystrophy patients is rounder compared with healthy age-matched controls. Temporal muscle hypertrophy and skull eccentricity are significantly correlated in the boys with Duchenne muscular dystrophy, whereby a thicker muscle is associated with a rounder skull. On clinical examination, temporal hypertrophy is visible and palpable and should not be confused with a steroid-induced "moon face."

Hypertrophy of skeletal muscles is commonly observed after training and is associated with an increase in muscle strength. In Duchenne muscular dystrophy, however, hypertrophy of the leg muscles is not accompanied by an increase in strength but rather

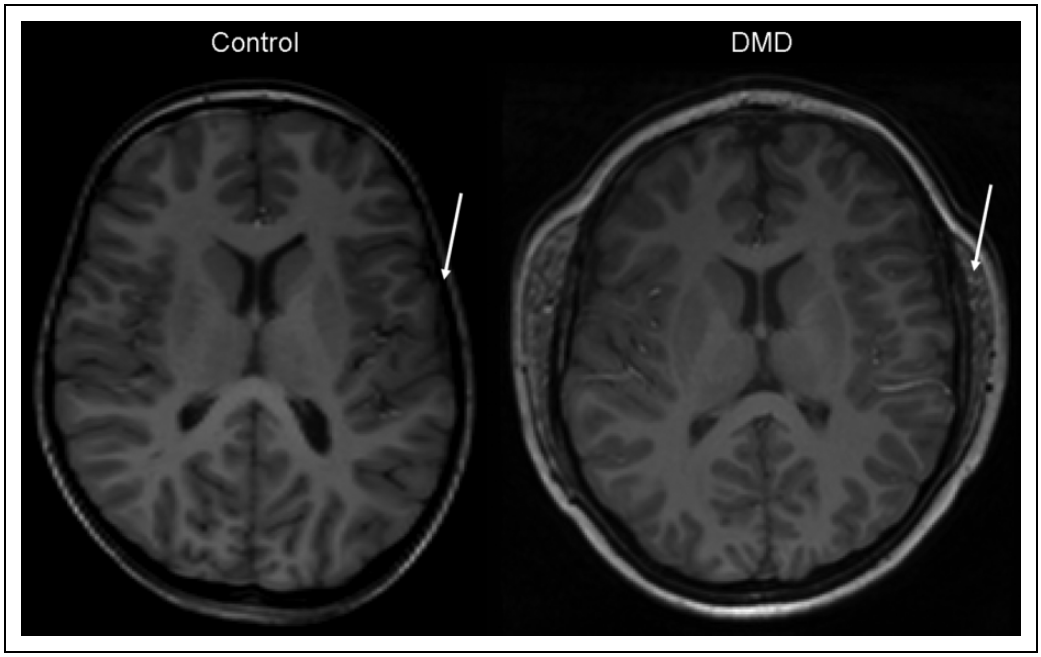

Figure 1. Transverse sections taken parallel to the anterior and posterior commissure (AC/PC) of a healthy 10-year-old boy (left) and a 10-year-old boy with Duchenne muscular dystrophy. The boy with Duchenne muscular dystrophy shows a rounder head and skull shape and bilateral temporal muscle hypertrophy (indicated by arrows).

by a decrease in strength, indicating a lower quality of the increased muscle mass.[4,5] It is unclear if the increased muscle mass of the temporalis muscles we observed results in an increased or decreased force, as we did not assess muscle strength of the temporalis muscles. Previous literature suggests that muscle force of the temporalis muscles decreases despite the hypertrophy, as bite force is known to be impaired in Duchenne muscular dystrophy patients above the age of 8.[7,9]

In addition, our results show that thicker temporal muscles are associated with a more ovoid skull shape in controls. Taken together, this could suggest that the weaker, hypertrophic cranial muscles, among which the temporal muscles, influences the development of the skull, resulting in a rounder shape. We did not observe a correlation of skull shape with age. Therefore, it is likely that the changes in skull shape are present at a young age. In support of this suggestion are data from 7-week-old dystrophic (dy/dyC57BL/6J) mice where the anatomic shape of the skull and mandible was different compared to control mice. This would suggest that bone development is affected early in muscular dystrophy.[10,11] Furthermore, histopathologic dystrophic features were already present in the temporal muscles in 7-week-old mdx mice.[12] An alternative hypothesis is that the observed skull shape is independent from temporal muscle hypertrophy, but generally related to bone differences such as short stature[13] and different bone mineral density[14] as recently described in Duchenne muscular dystrophy.

As the majority of the boys with Duchenne muscular dystrophy included in this study used long-term steroid treatment, this could have influenced the changes we observed. Though hypertrophic muscles due to anabolic steroids have been reported,[15] the current literature does not describe any relation between corticosteroid use and muscle hypertrophy. On the contrary, corticosteroid therapy is known to result in muscle wasting and type II muscle fibre atrophy.[16,17] In addition, Guillaime Duchenne described muscle hypertrophy in the 19th century[18] when corticosteroid therapy was not yet present. As corticosteroid therapy is usually not initiated in Duchenne muscular dystrophy before the age of 6 years, it is highly unlikely that steroid therapy is solely responsible for such a profound effect on skull morphology. Further studies in younger patients, preferably before they commence steroid treatment, could possibly clarify the pathophysiological mechanism of skull eccentricity and the relation to hypertrophy of the temporal muscles.

Improvement of muscle strength and function is the main goal for new treatment strategies in Duchenne muscular dystrophy. Future introduction of new therapies aimed at improving muscle strength will it is hoped improve long-term outcome and life expectancy in Duchenne muscular dystrophy. Irreversible skeletal changes may limit recovery of muscle function. Therefore, it is important to pay attention to both the evaluation of muscle function as to skeletal deformation, such as we have described for the skull in this report.

Author Contributions

CSMS: drafting the manuscript, study design, acquisition of data, analysis and interpretation of data. ND: acquisition of data, analysis and interpretation of data, statistical analysis, drafting the manuscript. BHAW, EMD and JCvdB: acquisition of data and revising the manuscript. MAvB: study design, revising the manuscript. JGMH: study design, obtaining of funding, revising the manuscript. JJGMV: study design, obtaining of funding, drafting/revising the manuscript. HEK:

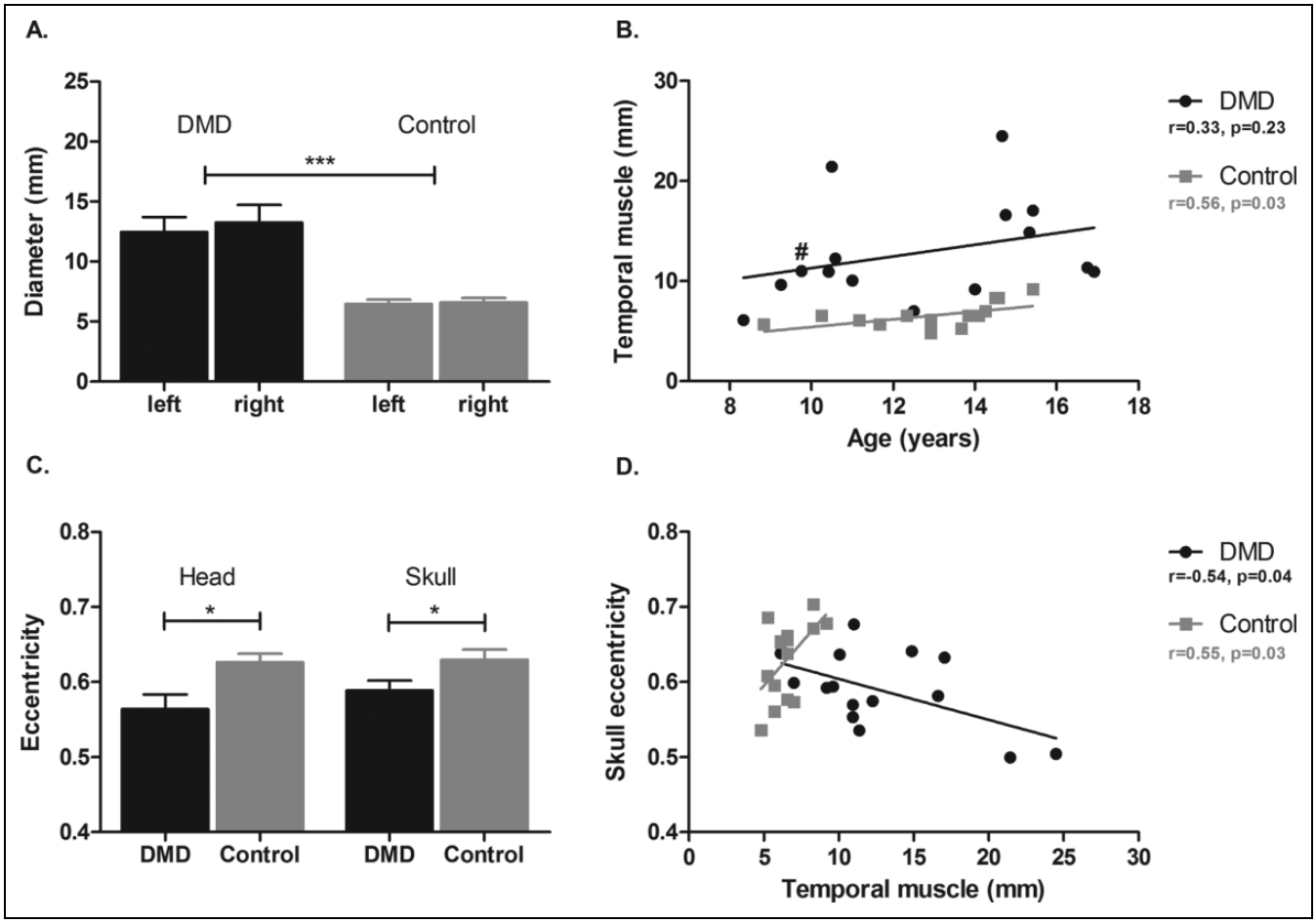

Figure 2. Temporal muscle thickness and skull morphology in Duchenne muscular dystrophy patients and healthy age-matched controls. In all images, Duchenne muscular dystrophy is depicted in black and control in grey. (A) Average thickness of left and right temporal muscles with standard error of the mean in Duchenne muscular dystrophy patients and in controls. (B) Correlation between temporal muscle thickness (averaged values for left and right) and age in Duchenne muscular dystrophy patients and in controls. Indicated by # is a Duchenne muscular dystrophy patient who has never used steroids. (C) Eccentricity (0 = perfect circle, 1 = parabola) of the head and the skull with standard error of the mean in Duchenne muscular dystrophy and in controls. (D) Correlation between temporal muscle thickness and skull eccentricity in Duchenne muscular dystrophy and controls. In Duchenne muscular dystrophy, larger temporal muscle size correlates to a rounder skull shape, but in controls larger temporal muscles correlate to a more ovoid shaped skull.
*$P < .05$, ***$P < .0001$.

study design, analysis and interpretation of data, study supervision, obtaining of funding, drafting/revising the manuscript.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CSMS reports to be involved in clinical trials for Duchenne muscular dystrophy for Santhera, GSK, and Prosensa. JJGMV reports to be involved in clinical trials for Duchenne muscular dystrophy for GSK, Prosensa, and Santhera. JJGMV is consultant for Prosensa on magnetic resonance imaging (MRI) studies, without receiving personal fees; all payments are made to the LUMC. HEK reports to be consultant for Prosensa on MRI studies, without receiving personal fees.

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Ethical Approval

The study was approved by the ethics committee of the Leiden University Medical Center (nr P09.121).

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