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Brothers with Becker muscular dystrophy show discordance in skeletal muscle computed tomography findings: A case report

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Abstract

Becker muscular dystrophy is caused by *DMD* mutations and is characterized by progressive muscle atrophy. The wide variations observed in muscle atrophy progression in Becker muscular dystrophy are considered multifactorial, including differences in mutations and environmental factors. In this case, two brothers, aged 2 and 3 years, had the identical *DMD* mutation, confirming their Becker muscular dystrophy diagnosis. They began using handrails when ascending and descending stairs at the age of 16 due to progressive muscular weakness. Over an 18-year follow-up, the older brother consistently had high serum creatine kinase levels, significantly over median levels. Muscle computed tomography finings revealed that the older brother's gluteus maximus and vastus femoris cross-sectional areas were only half and one-third of the younger brother's, respectively. The mean computed tomography values of gluteus maximus and vastus femoris were significantly lower in the older brother. Our report suggests that muscle atrophy in Becker muscular dystrophy cannot be solely explained by dystrophin mutation or environmental factors.

Keywords

Becker muscular dystrophy, creatine kinase, muscle computed tomography, gluteus maximus, vastus femoris, atrophy, urinary titin

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Introduction

Becker muscular dystrophy (BMD) is caused by dystrophin abnormalities resulting from *DMD* gene mutations. *DMD* mutations are associated with Duchenne muscular dystrophy (DMD), a fatal form of muscle atrophy, and the most common mutation involves exon deletions. In DMD, the deletion results in a shift of the amino acid reading frame and dystrophin loss. BMD is associated with an in-frame mutation that maintains the amino acid reading frame despite the exon deletion, producing a truncated dystrophin,[1] with some functionality. Thus, BMD is characterized by late onset and slowly progressive muscle atrophy. The clinical presentation of BMD is diverse, and asymptomatic cases have been reported.[2]

Treatment using antisense oligonucleotides to induce exon-skipping has been developed for DMD. Exon-skipping serves to restore the dystrophin reading frame in mRNA, consequently restoring dystrophin expression and converting the phenotype from DMD to BMD.[3] Four drugs have received regulatory approval and are used to treat DMD.[4] However, the improvement in motor function in genetically converted BMD is debated. The diversity in clinical BMD

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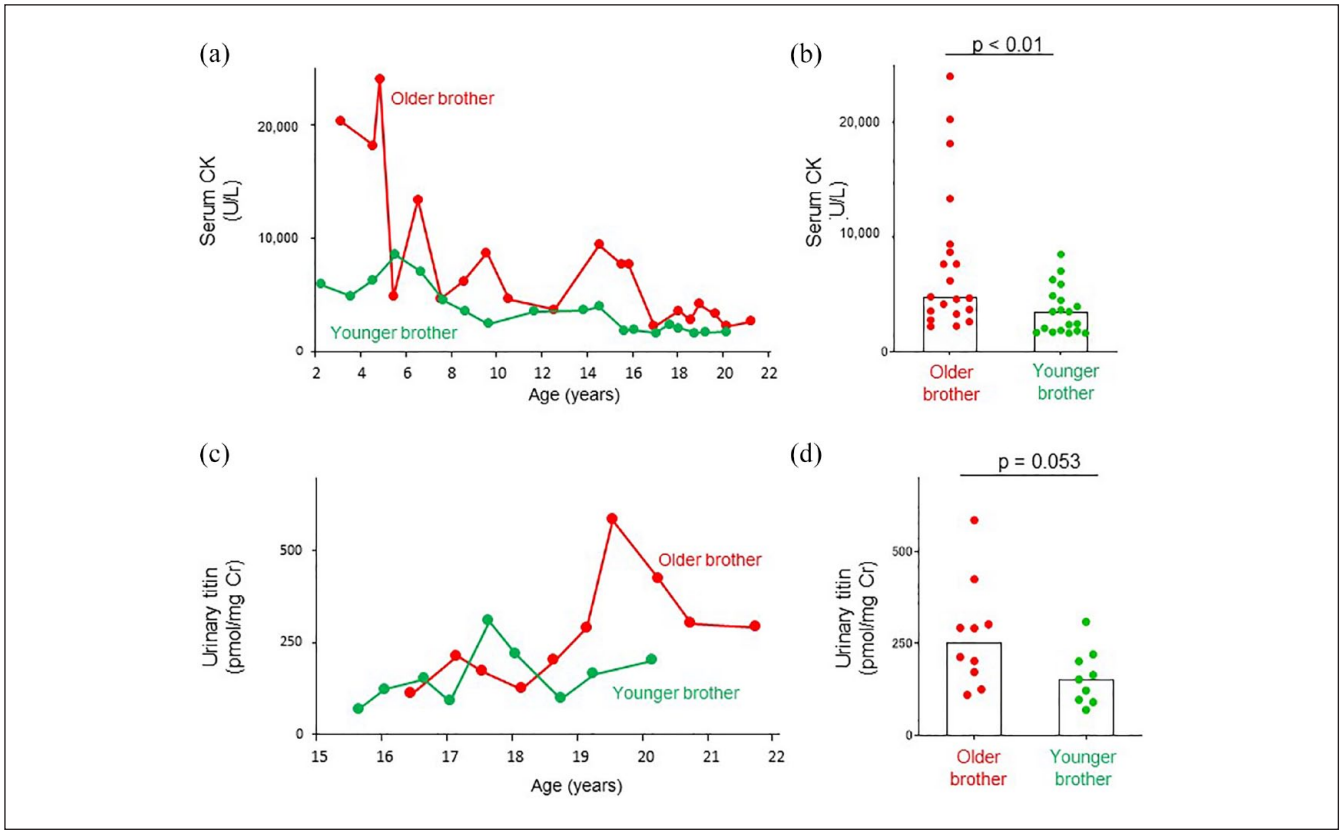

Figure 1. Comparison of serum CK and urinary titin levels between the brothers. The red and green dots indicate data from the older and younger brother, respectively. Values were compared using the Mann–Whitney *U*-test. Statistically significant differences were defined as $p < 0.05$. (a) Changes in serum CK levels over time; (b) Comparison of serum CK levels between the brothers. (c) Changes in urinary titin levels over time. (d) Comparison of urinary titin levels between the brothers. White bars represent the median values.

courses results from multifactorial influences, including variations in mutations and developmental environments. Herein, we illustrated how two brothers with BMD, with identical genotypes, a 1-year age gap, and similar upbringing, exhibited distinct findings of muscle atrophy examined using computed tomography (CT).

Case

The older brother was referred to our clinic at the age of 3 for a detailed examination of his increased creatine kinase (CK) levels. We suspected dystrophinopathy and performed *DMD* gene testing. We identified Δ45–47 mutation, an in-frame mutation, that confirmed BMD. His brother (1 year younger) was also suspected to have BMD and underwent blood tests at the age of 2.2 years. The tests revealed elevated serum CK levels (Figure 1(a)), and *DMD* gene testing revealed Δ45–47 mutation, confirming BMD. At age 16, the brothers began using handrails to ascend and descend stairs. While the older brother could not stand on one leg, the younger brother could. At the most recent visit (ages 21 and 20), both could walk independently and had no difficulty with daily living. No clinical findings that warranted consideration of other neuromuscular diseases were found. They had no history other than BMD, prolonged bed rest, and drug use that induced muscle atrophy. Blood test findings did not show any nutritional deficiencies.

The older brother had high serum CK levels from ages 2–20 years (Figure 1(a)). The median serum CK levels, including all measurements, of the older brother were approximately 1.4 times higher than those of the younger brother ($p < 0.01$) (Figure 1(b)). To examine age-dependent differences in serum CK levels, we compared the levels before and after the age of 10, and found that the older brother had significantly higher CK levels before and after 10 years (11,046 vs 4902 U/L, $p < 0.05$; 3638 vs 1864 U/L, $p < 0.01$, respectively). Degraded titin fragments excreted in urine are used as a biomarker of muscle degradation in BMD.[5] Therefore, urinary titin was measured to determine the muscle degradation degree (Figure 1(c)). The median value of urinary titin for the older brother was 1.7 times higher (252.5 vs 152.4 pmol/mg Cr) with no significance (Figure 1(d)). When differences in urinary titin levels were examined by age, the older brother had higher values ($p < 0.05$) only after 18.5 years.

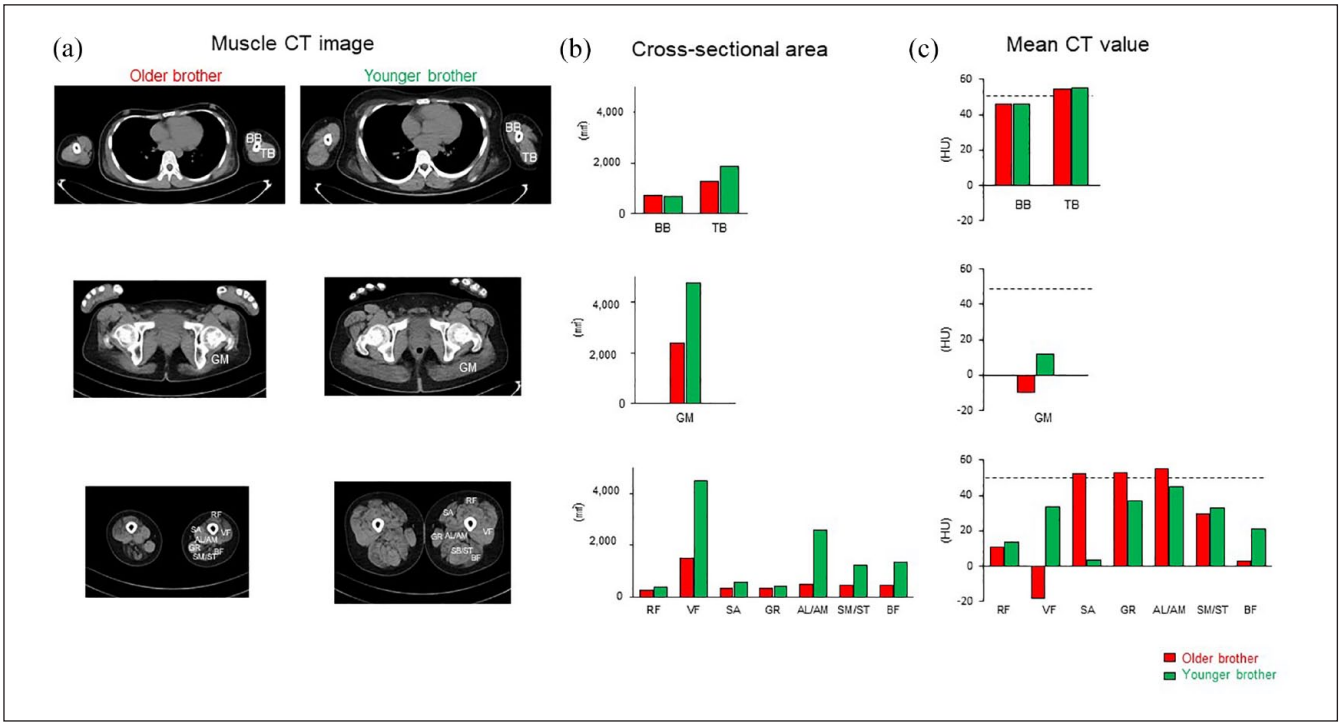

Figure 2. Muscle CT scan of the brothers. (a) A transaxial cross-sectional image was obtained at the mid-position of the upper arm, the proximal femoral head (gluteal), and the mid-position of the thigh from the top. The left and right images are from the older and younger brother, respectively. (b) CSAs and (c) CT values of the muscles are presented in the middle and right, respectively. The red and green bars indicate the values of the older and younger brothers, respectively. The dotted lines indicate the lower limit of the CT value found in healthy skeletal muscles.
BB: biceps brachii; TB: triceps brachii; GM: gluteus maximus; RF: rectus femoris; VF: vastus femoris; SA: sartorius; GR: gracilis; AL: adductor longus; AM: adductor magnus; SM: semimembranosus; ST: semitendinosus; BF: biceps femoris.

In adulthood, muscle degradation was worse in the older brother.

The brothers were aged 20 and 19 when the older brother had severe muscle degradation. Skeletal muscle CT was performed to evaluate the degree of skeletal muscle injury (Figure 2(a)). During examination, the heights and weights of the older and younger brothers were 171 cm and 52 kg and 169 cm and 76 kg, respectively. Moreover, the body mass indexes (BMIs) of the older and younger brothers were 17.7 and 26.5 kg/m^2, respectively. The cross-sectional areas (CSAs) of the triceps brachii (TB) in the upper arm of the older brother were smaller than that of the younger brother, indicating TB atrophy (Figure 2(b)). However, the mean CT values of the brothers did not differ in the TB (Figure 2(c)). The CSA of the gluteus maximus (GM) of the older brother (2380 mm^2) was half of that of the younger brother (4756 mm^2), indicating significant GM atrophy (Figure 2(b)). The CSA of seven different thigh muscles showed smaller values in the older brother. Particularly, the CSA values of the vastus femoris (VF) of the older brother were approximately one-third of that of the younger brother (1506 vs 4507 mm^2), indicating significant VF atrophy. Considering body size and comparing CSA divided by BMI for the GM and VF, there was greater atrophy in the older brother's muscles than those of his younger brother (Supplemental Figure 1). A comparison of mean CT values (Figure 2(c)) indicated that the pattern of fatty degeneration in each skeletal muscle differed between the brothers. Particularly, the mean CT values of GM (−9.9 vs 11.8 Hounsfield units (HUs)) and VF (−18.1 vs 33.5 HUs) were significantly lower in the older brother. Decreased CT values suggest fatty degeneration. Therefore, fatty degeneration in thigh muscles was more advanced in the older brother.

Discussion

This report contrasts with another report of twins with BMD and similar phenotypes.[6] Our cases exhibited differences in skeletal muscle atrophy and fatty degeneration. The etiology of these differences is unknown. We expected that some unknown modifying factors influenced the progression of BMD, causing the discordant phenotypes. However, it is very difficult to deny the presence of the secondary neuromuscular disorders in the elder brother. Fat degeneration was correlated with functional measures in BMD.[7] However, no marked difference was observed in their activities of daily living. Muscle atrophy can be caused by acquired factors, such as disuse, chronic disease, and steroid use.[8]

The brothers were only 1 year apart and shared a similar environment. Therefore, it is unlikely that environmental or acquired factors caused the condition. We could not investigate the possibility that one of the brothers may have possess other modifying factors identified in BMD,[9,10] which is a limitation of our study. We will continue to follow these brothers considering modifying factors or possible secondary neuromuscular disorders.

Serum CK level correlates with clinical severity in BMD.[11] Higher serum CK levels in the older brother at most ages may be related to the gluteal and thigh muscle injuries noted in adulthood. The elevated urinary titin levels in the older brother, suggesting active muscle degradation, may reflect the impairment of the gluteal muscle, which is the largest muscle. Accumulating more cases will elucidate these associations.

Muscle CT is the gold standard test for evaluating CSA,[12] and CT values can further quantify the degree of muscle degeneration.[13] The discrepancy in muscle CT findings in our cases demonstrated that the truncated dystrophin produced from genes with the same Δ45–47 mutation can cause differences in injured muscles and degree of injury. Whether the differences in affected muscles between the brothers are common to all BMD genotypes or limited to genotypes with Δ45–47 requires further investigation.

Exon-skipping drugs convert DMD to BMD, but their therapeutic efficacy varies between patients. Patients who are ambulatory before therapy remain ambulatory 4 years later, whereas others cannot walk a year later.[14] This indicates that patients who develop the BMD phenotype by exon-skipping therapy do not always have similar clinical symptoms. The Δ45–47 mutation involves deletions created by exon 45-skipping treatment for patients with DMD. The different phenotypes of the brothers with Δ45–47 may help explain divergent responses to exon 45-skipping therapy in treated patients.

Conclusion

Brothers with BMD having identical *DMD* mutations, a 1-year age difference, and an identical growing environment developed significant differences in GM and VF atrophy. This suggests that muscle atrophy in BMD cannot be solely explained by dystrophin mutation or environmental factors.

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Author contributions

YN, MM, and HA wrote the original draft. YN and HA collected and analyzed clinical data. TS and KO measured urinary titin concentration. TS, KO, HN, KN, and MM critically revised the article and approved the modified text.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MM is an advisor for JCR Pharma Co., Ltd., Japan and Daiichi Sankyo Co., Ltd., Japan. HA received lecture and advisory charges from Nippon Shinyaku Co., Ltd. and Chugai Pharmaceutical Co., Ltd., respectively. The other authors declare that they have no conflict of interest.

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Ethics approval

Ethical approval to report this case was obtained from Ethics Committee of Kobe University (No. 1534 and 1709).

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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Supplemental material

Supplemental material for this article is available online.

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