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Original article

Cardiac involvement in Fukuyama muscular dystrophy is less severe than in Duchenne muscular dystrophy

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Abstract

Background: One of the main complications in patients with muscular dystrophies is cardiac dysfunction. The literature on cardiac involvement in patients with Fukuyama congenital muscular dystrophy (FCMD) is limited.

Aim: To compare cardiac involvement between patients with FCMD and Duchenne muscular dystrophy (DMD).

Methods: We compared cardiac involvement between 30 patients with FCMD and 181 patients with DMD using echocardiography and serum biomarkers. All patients were receiving regular checkups at Kobe University Hospital. We used single regression analysis to compare echocardiographic parameters, age, and serum biomarkers.

Results: Almost all clinical and echocardiographic parameters were lower in patients with FCMD than DMD. The brain natriuretic peptide concentration in patients with FCMD showed no correlation with age or left ventricular ejection fraction ($r = 0.231$, $p = 0.22$ and $r = 0.058$, $p = 0.76$, respectively). A log-rank test revealed that the risk of left ventricular systolic dysfunction was lower in patients with FCMD than DMD ($p = 0.046$, hazard ratio = 0.348).

Conclusion: The clinical progression of cardiac dysfunction is significantly milder in patients with FCMD than DMD, while skeletal muscle involvement is significantly worse in patients with FCMD. These data suggest that the pathophysiological findings of FCMD can be explained by less severe cardiac dysfunction in FCMD than DMD.

Keywords: Fukuyama congenital muscular dystrophy; Natural history; Cardiac dysfunction; Duchenne muscular dystrophy; Echocardiography

1. Introduction

Fukuyama congenital muscular dystrophy (FCMD; MIM253800) and Duchenne muscular dystrophy (DMD; MIM310200) are two types of childhood-onset muscular dystrophy. FCMD is an autosomal recessive,

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severe muscular dystrophy associated with an anomaly of the brain [1,2]. It is the second most common childhood muscular dystrophy in Japanese populations, with an incidence of 3/100,000. One of 88 Japanese people is predicted to be a heterozygous carrier for FCMD [1,3]. Patients with FCMD have been recognized almost exclusively in Japan, but several populations outside of Japan, such as in China and Korea, have been recently reported [4]. Mutation of the *fukutin* gene on chromosome 9q31 has been shown to be responsible for FCMD [3,5,6]. FCMD has also been shown to be the first human disease resulting from the ancestral insertion of a SINE-VNTR-*Alu* (SVA) retrotransposal element into a causative gene. This insertion originated in an ancestor of Japanese ethnicity 100 generations ago [7,8]. FCMD was recently reported as a splicing disease [9]. FCMD is also known as alpha-dystroglycanopathy, indicating a deficiency in the glycosylation of *O*-mannose-type glycan [10]. The glycosylation of alpha-dystroglycan is severely reduced in the skeletal muscle of patients with FCMD. The *fukutin* gene has recently been described as an enzyme that catalyzes cytidine 5′-diphosphate (CDP)-ribitol [11].

Clinically, functional disabilities are more serious in patients with FCMD than in those with DMD; typically, the maximum motor function achievements consist only of unassisted sitting or sliding on the buttocks, and 90% of patients never gain walking ability [2]. However, although patients with DMD manifest clinical signs such as Gower's sign at around 3 years of age, they usually gain walking ability. Almost all patients with DMD develop cardiomyopathy with left ventricular (LV) dilatation. Therefore, we previously emphasized the importance of the prediction of cardiac involvement in patients with DMD at an early stage [12–14]. Furthermore, the myocardial pathology of FCMD was extensively investigated in a review by Fukuyama et al. [2]. The authors found that little had been reported on cardiac abnormalities in patients with FCMD because previous studies identified almost normal cardiac muscle during autopsy of patients with FCMD. Myocardial fibrosis and a low heart weight were also described in several reports [2]. However, other authors have speculated that LV systolic dysfunction in FCMD is similar to that in DMD [15], although the genotypical variation and motor capacities of patients with FCMD were not fully characterized in that study. Ishigaki [16] reported in a review that LV function decreases after the age of 15 years in patients with FCMD. In the present report, cardiac dysfunction of patients with FCMD at our hospital was investigated by assessment of LV function and some serum biomarkers. Comparative studies between patients with FCMD and those with DMD in our institution were also analyzed.

2. Materials and methods

2.1. Study population

The study group comprised 30 consecutive patients with FCMD and 160 age-matched consecutive patients with DMD who had been receiving regular outpatient physical checkups at the Department of Pediatrics of Kobe University Hospital from August 2007 to May 2016. The diagnosis of FCMD and DMD was confirmed by genetic analysis in all patients. All patients with FCMD had an SVA mutation in one allele. The heterozygous mutations in patients with FCMD included a nonsense mutation in exon 3 [17] in two patients and a deep intronic splicing mutation in intron 5 [18] in three patients. The remaining patient had a compound heterozygous splicing mutation in exon 9 (unpublished data). The genetic backgrounds of patients with DMD, were as follows: deletion mutation (88/160, 55%), nonsense mutation (34/160, 21%), small insertion/deletion mutation (20/160, 13%), duplication mutation (12/160, 8%), splice site mutation (4/160, 3%), and other mutations (2/160, 1%). Other mutations included chromosomal rearrangement and unknown mutations. Motor function was assessed by an orthopedic doctor specialized in rehabilitation. All patients with FCMD who were found to have asynergy by cardiac echocardiography underwent treatment with a cardioprotective agent. This study was approved by the local ethics committee of Kobe University (Clinical research number 1653), and written informed consent was obtained from all patients and their families after they had been provided with a full explanation of the procedures to be undertaken.

2.2. Serum and echocardiographic examinations

Serum laboratory tests such as measurement of the brain natriuretic peptide (BNP), creatine kinase, and aldolase concentrations were performed in both patients with DMD and FCMD. A commercially available echocardiographic system (Aplio XG; Toshiba Medical Systems, Tochigi, Japan) was used for all echocardiographic studies. Digital routine grayscale two-dimensional cine loops from three consecutive beats were obtained from the parasternal long-axis, mid-LV short-axis, and standard apical views. The parasternal long-axis view was used to obtain the LV end-diastolic dimension, LV end-systolic dimension, left atrial dimension, intraventricular septal thickness, LV posterior wall thickness, and aortic root dimension. The LV ejection fraction (LVEF) was assessed using the modified Simpson method. All chamber sizes were divided by the body surface area (index). Pulsed-wave Doppler-derived transmitral velocities were obtained from the apical