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Prognostic impact of left ventricular noncompaction in patients with Duchenne/Becker muscular dystrophy — Prospective multicenter cohort study☆,☆☆

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ABSTRACT

Background: The reported prevalence of left ventricular noncompaction (LVNC) varies widely and its prognostic impact remains controversial. We sought to clarify the prevalence and prognostic impact of LVNC in patients with Duchenne/Becker muscular dystrophy (DMD/BMD).
Methods: We evaluated the presence of LNVC in patients with DMD/BMD aged 4–64 years old at the study entry (from July 2007 to December 2008) and prospectively followed-up their subsequent courses (n = 186). The study endpoint was all-cause death and the presence of LVNC was blinded until the end of the study (median follow-up: 46 months; interquartile range: 41–48 months).
Results: There were no significant differences in baseline characteristics between patients with LVNC (n = 35) and control patients without LVNC (n = 151), with the exception of LV function. Patients with LVNC showed, in comparison with patients without LVNC, a significant negative correlation between age and LVEF (R = −0.7 vs. R = −0.4) at baseline; and showed a significantly greater decrease in absolute LVEF (−8.6 ± 4.6 vs. −4.3 ± 4.5, $p<0.001$) during the follow-up. A worse prognosis was observed in patients with LVNC (13/35 died) than in patients without LVNC (22/151 died, Log-rank $p<0.001$). Multivariate Cox analysis revealed that LVNC is an independent prognostic factor (relative hazard 2.67 [95% CI: 1.19–5.96]).
Conclusion: LVNC was prevalent in patients with DMD/BMD. The presence of LVNC is significantly associated with a rapid deterioration in LV function and higher mortality. Neurologists and cardiologists should pay more careful attention to the presence of LVNC.

1. Introduction

Left ventricular (LV) noncompaction (LVNC) is a rare cardiomyopathy that is characterized by the presence of persistent trabecular meshwork and deep intertrabecular recesses, which are secondary to the arrest of myocardial maturation [1–4]. The World Health Organization listed LVNC as an unclassified cardiomyopathy in 1995, and The American Heart Association classified the condition into a genetic cardiomyopathy in 2006 [5,6]. Increased awareness of LVNC among cardiologists, as well as improved imaging technologies, has led this previously poorly recognized condition to become a widely recognized cardiomyopathy [7].

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Although knowledge concerning LVNC continues to increase, the reported prevalence varies widely and its prognostic impact remains controversial since most studies conducted to date have been retrospective and lacked adequate controls [4,8]. On the other hand, studies have shown that neuromuscular diseases are most frequently (reported prevalence of neuromuscular diseases was 66% and 82%) associated with LVNC [3,8–10].

Dystrophin defects cause Duchenne muscular dystrophy (DMD) and its milder variant, Becker muscular dystrophy (BMD). These X-linked recessive myopathies are caused by mutations in the dystrophin gene that lead to a fragile cytoskeleton of muscle cells [11]. Patients with DMD/BMD develop progressive systemic muscle weakness, which leads to a premature death that is primarily caused by its cardiac involvement [12]. The objective of the current multicenter cohort study was to clarify the prevalence and prognostic impact of LVNC in common neuromuscular diseases (DMD/BMD) without intervention bias.

2. Methods

2.1. Study design and patients

A total of 224 male patients with DMD/BMD from 4 neuromuscular centers; namely, Niigata National Hospital (Niigata, Japan), Shimoshizu National Hospital (Chiba, Japan), Hakone National Hospital (Kanagawa, Japan), and The University of Tokyo Hospital (Tokyo, Japan) were invited to participate. Experienced neurologists diagnosed DMD/BMD following the assessment of clinical manifestations, physical examinations, family history, increase in serum creatine kinase, muscle pathology, and dystrophin analyses using combinations of immunofluorescence staining, Western blotting, and/or genetic analysis [13]. Six patients diagnosed as BMD without any confirmation of dystrophin deficiency were excluded from the study; however, there were no other exclusion criteria. From July 2007 to December 2008, 186 of 218 patients (ages 4 to 64 years old), consisting of 164 patients with DMD and 22 patients with BMD, gave consent for participation in the study.

The prognosis from the date of study entry (date of baseline echocardiography) until the end of the study (February 2012) was determined through hospital visits or telephone contact. It is difficult to define onset of the disease because the dystrophin defect is present at birth and the musculoskeletal manifestations gradually progress from childhood in DMD and between adolescence to midlife in BMD. It is often difficult to identify the exact cause of death because respiratory failure and heart failure occur concurrently in most patients. Hence, the current cohort study adopted death (all-cause mortality) as the study endpoint. The institutional review boards from the participating centers approved the study and written consent was obtained from the patients and/or their relatives.

2.2. Diagnosis of LVNC

LVNC was diagnosed based on echocardiographic images that fulfilled all the diagnostic criteria described by Chin et al. [1], Jenni et al. [2,14], and Stöllberger et al. [3]. These criteria include the presence of a bilayered myocardium, consisting of a thin compacted layer (C) and a significantly thicker noncompacted layer (NC) with multiple (more than 3) trabeculations: C/(NC + C) is less than 0.5 at end-diastole; NC/C is greater than 2 at end-systole; predominant localization of trabeculations in the mid-lateral, apical, or mid-inferior regions of the LV; and the presence of deep-perfused intertrabecular recesses demonstrated by color Doppler imaging (Fig. 1).

Echocardiography was performed twice at each hospital by experienced cardiologists, once at the time of study entry (from July 2007 to December 2008) and again at the follow-up evaluation (from April 2011 to February 2012) according to the standardized methods described in guidelines of the American Society of Echocardiography [15]. Artida, AplioXG, and AplioMX digital ultrasound systems (Toshiba Medical Systems, Tochigi, Japan) were used to obtain echocardiographic images. Images were reviewed at The University of Tokyo by 2 readers independently; a diagnosis of LVNC was made when the images fulfilled all the aforementioned criteria. Images from the follow-up echocardiograms were also reviewed to reconfirm the presence of LVNC. The presence of LVNC was blinded to the primary doctors who determined the treatment regimens until the end of study. However, the best available treatments were provided for each patient.

After the end of the study, patients with LVNC were also invited to undergo magnetic resonance imaging using an Achieva 1.5 T dual-gradient MR scanner (Philips Healthcare, Best, The Netherlands). A standard cardiac magnetic resonance imaging protocol was used and the presence of LVNC was confirmed according to the reported criteria; NC/C is greater than 2.3 in diastole [16].

2.3. Statistics

Data are presented as the mean ± standard deviation (SD) for continuous variables, and as percentage for categorical variables. To compare the values at baseline and LV ejection fraction (EF) changes during follow-up, independent *t*-tests were used to analyze continuous data, and Chi-square tests were used for nominal data. Linear regression analysis was used to study the relationship between the age of the patients and LVEF. The Kaplan–Meier test with log-rank statistical analysis was conducted for the period from the time of study entry to study completion.

Multivariate Cox proportional hazards regression analysis was used to estimate the relative hazard risk of the independent relationship between death and LVNC. Because most patients with DMD/BMD died from heart failure and/or respiratory failure, adjusted baseline variables for multivariate Cox analysis were: 1) age, 2) heart failure -related factors (blood pressure, heart rate, and LV dysfunction), and 3) respiratory failure -related factors (ventilator use and oxygen use). Because baseline LVEF, LV end-diastolic diameter (LVEDD), and age were strongly correlated to each other, it was difficult to include all these variables into the Cox model. LVEDD not only contains the problem of multi-collinearity, but it also changes from childhood to adolescence. We did not use corrected LVEDD because there is strong individual variation of physical appearance (abnormally low weight with variation of height) in patients with DMD/BMD. Hence, we included age and LV dysfunction (defined as an LVEF less than 50%) as mentioned above. Statistical analysis was performed using IBM SPSS Statistics software (version 20.0.0, IBM, NY). p values less than 0.05 were considered significant.

3. Results

3.1. Baseline characteristics and the diagnosis of LVNC

LVNC was diagnosed in 19% (35 of 186) of the patients. Although some patients showed limited image quality, the echocardiographic variables and the presence of LVNC could be evaluated by expert echocardiologists in all patients. There were no significant baseline differences in the distributions of DMD/BMD type, age, blood pressure, heart rate, ventilator use, oxygen use, and medications administered between patients with and without LVNC (Table 1). However, echocardiographic findings, including LVEF, were already different at the baseline evaluation. There were no significant differences in the baseline distributions of patients, therapies, or mortalities among the institutions. One patient

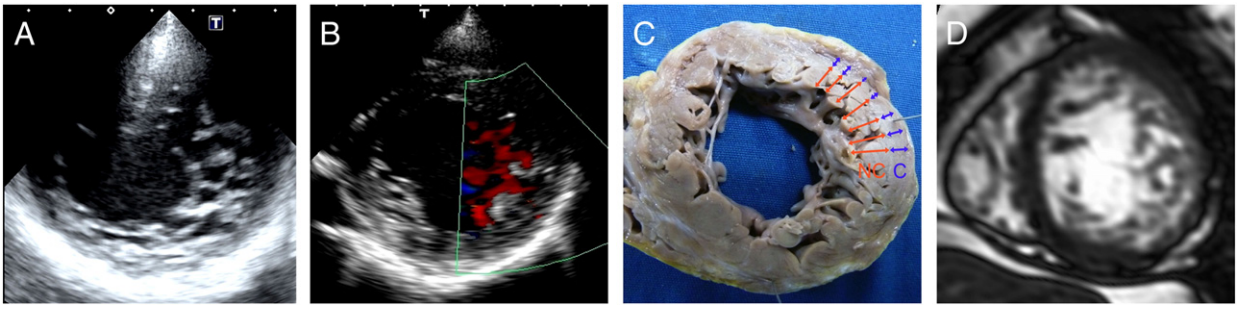

Fig. 1. Representative images of left ventricular noncompaction (LVNC). [Panel A] Echocardiogram of a 25-year-old patient with Duchenne muscular dystrophy (DMD) shows the presence of multiple trabecular meshwork with predominant localization in mid-apical lateral wall. [Panel B] Deep-perfused intertrabecular recesses are shown by color Doppler imaging in a 19-year-old patient with DMD. [Panel C] An autopsy specimen of the left ventricle from a 39-year-old patient with DMD. The myocardium fulfills the LVNC criteria; the presence of a compacted layer (C) and a noncompacted layer (NC), C/(NC + C) of less than 0.5 and NC/C greater than 2. [Panel D] A cardiac magnetic resonance image of a 37-year-old patient with Becker muscular dystrophy (BMD) fulfills the criterion of NC/C greater than 2.3.