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Letters to the Editor

Left ventricular noncompaction cardiomyopathy: Recent update on genetics, usefulness of biomarker, and speckle imaging

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Left ventricular noncompaction cardiomyopathy (LVNC) is an emerging form of predominantly genetically mediated cardiomyopathy characterized by failure of intrauterine compaction of the myocardium leading to the formation of two distinct layers of myocardium, an outer compacted thinner epicardial layer and an inner hypertrophied non compacted endocardial layer interspersed by blood-filled intertrabecular recess.

We read with great interest the review article by Ikeda et al. [1] titled ``Isolated left ventricular non-compaction cardiomyopathy in adults'' giving a comprehensive overview of this emerging form of cardiomyopathy. LVNC is a relatively rare form of cardiomyopathy and listed under the category of genetic cardiomyopathies by the American Heart Association. With the improvement in diagnostic modalities the incidence of LVNC has increased in clinical practice, however, still there is lack of familiarity among clinicians about this form of cardiomyopathy. The pathogenesis of LVNC is characterized by a deviation from normal embryological development in which there is involution of trabeculations and formation of the compact myocardium in ventricles and transformation of the intertrabecular recess into capillaries with the development of coronary vessels by 12–18 weeks of gestation. However, in LVNC, the embryological spongy appearance of myocardium persists after birth and results in the formation of two distinct layers of the myocardium. LVNC may occur in isolation or may be associated with other cardiac anomalies like Ebstein anomaly [2]. Clinical presentation of LVNC varies across the spectrum from a severe prenatal form of systolic heart failure to asymptomatic adults. Classically it is characterized by the triad of systolic heart failure, arrhythmia, and thromboembolic phenomena.

In a recently published study, van Waning et al. [3] studied the correlation of genetics with clinical features and outcomes among children and adults diagnosed with LVNC. In most families, LVNC is characterized by the autosomal dominant pattern of inheritance with variable penetration. They showed that nearly one-third of LVNC patients had a mutation in cardiomyopathy gene. MYH7, MYBPC3, and TTN mutations were the most common mutations (71%) found in genetic LVNC. Children with a genetic form of cardiomyopathy were diagnosed at an earlier age, had lower left ventricular ejection fraction and suffered more major adverse cardiovascular events (MACE) than children with a sporadic form of the disease. Among adults, no difference in MACE was observed between genetic, possibly genetic, and sporadic form of the disease. LV systolic dysfunction was mainly mediated by the presence of multiple mutations and TTN mutation and correlated with MACE among adults with a genetic form of the disease as compared to sporadic form. The MYH7 mutation was protective against MACE.

Although the management of LVNC is tailored toward the management of clinical manifestations, given the rare occurrence of this form of cardiomyopathy we do not have robust data regarding risk stratification and prognostication. In an interesting largest studied cohort of LVNC patients, Stämpfli et al. [4] described the prognostic utility of N-terminal of pro-brain natriuretic peptide (NT-pro BNP) in comparison to left ventricular ejection fraction (LVEF), New York Heart Association class and exercise capacity. It is interesting to note that NT-pro BNP is a stronger prognostic factor than LVEF in predicting the death and the need for cardiac transplantation.

The diagnosis of LVNC depends on morphologic criteria of myocardium and rests predominantly on two-dimensional echocardiography supplemented by cardiac magnetic resonance imaging. However, given the lack of a universally accepted definition and consensus on most recommendable diagnostic criteria, the false positive rates are considerably high leading to overdiagnosis of LVNC in individuals with physiological trabeculations such as athletes, individuals of Afro-Caribbean origin, patients with sickle cell anemia, and pregnant women. Cortés et al. [5] in their study involving speckle imaging demonstrated that presence of an anomalous rotation in which the base and apex of the left ventricle rotate in the same direction also known as rigid body rotation offers the potential for differentiation of LVNC from physiological states and other forms of cardiomyopathies. Thus with increasing awareness of this form of cardiomyopathy with increasing insight into genetics coupled with the use of genetic counseling, the use of a multidisciplinary approach is expected to improve the diagnosis and outcomes.

Conflict of interest

None.

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Left ventricular noncompaction cardiomyopathy: Recent update on genetics, usefulness of biomarkers, and speckle imaging

We appreciate Dr Bandyopadhyay's letter concerning our article [1] on isolated left ventricular noncompaction cardiomyopathy (LVNC) in adults. LVNC refers to a myocardial phenotype with excessive trabeculations of the LV myocardium and severe thickening of the endocardial noncompacted layer compared with the epicardial compacted layer. LVNC is the morphological expression of an underlying cardiomyopathy (primary or secondary), and debate continues over whether LVNC is a distinct cardiomyopathy/trait or the myocardial phenotype of a different underlying disease. Indeed, LVNC is listed as a genetic cardiomyopathy by the American Heart Association, whereas it is classified as an unclassified cardiomyopathy by the World Health Organization and European Society of Cardiology.

Owing to the use of high quality cardiovascular (CV) imaging modalities and low threshold for screening patients with nonspecific symptoms for underlying cardiac disease, an increasing number of subjects meet the diagnostic criteria of LVNC. It is challenging to distinguish patients with the myocardial phenotype of LVNC, who have an underlying cardiomyopathy, from healthy individuals with excessive trabeculations as a normal variant. The lack of universally accepted diagnostic criteria sometimes leads to over-diagnosis of LVNC in subjects with physiologic, reversible remodeling of the LV myocardium with excessive trabeculations such as pregnant women and athletes. Kohli et al. reported that 30 patients (15%) fulfilled Jenni's echocardiographic criteria for LVNC out of 199 patients with LV systolic dysfunction in a single center [2]. Similarly, we reported 23 patients (7.7%) who fulfilled Jenni's echocardiographic criteria for LVNC among 300 consecutive adult patients with LV systolic dysfunction. We found that LV trabeculations of 9 patients (39%) visibly reduced in association with improvement of LV contractility after optimal heart failure therapy [3]. These observations suggest that it is possible to misclassify a transient deformation of the myocardium with excessive trabeculations as LVNC using the current morphological criteria alone.

As you mentioned that we do not have robust data regarding risk stratification and prognostication for LVNC, identifying higher risk patients for future CV events and who need regular follow-up is critical. Therefore, genetic assessment, along with biomarkers and new CV imaging modalities, may improve diagnostic accuracy. Van Waning et al. highlighted the knowledge gap in the mechanisms of LVNC with its marked genetic heterogeneity and sarcomere gene mutations shared with other myocardial disorders [4]. There were significantly more genetic mutations in children (45%) than in adults (30%), and LV systolic dysfunction was a risk factor for CV events in carriers of a mutation. They emphasized the importance of routine genetic testing to establish a genotype–phenotype correlation. We conducted a nationwide survey and retrospectively evaluated adult patients with morphologic LVNC including congenital, acquired, or significant valvular heart disease, neuro-muscular disease, or secondary cardiomyopathy in Japan (unpublished data). A total of 310 patients (232 male, 74.8%) were registered from 60 institutions in Japan. The median age and LV ejection fraction were 55 years and 35.0%, respectively. Half of the patients (148 cases, 47.7%) had underlying cardiac diseases (dilated cardiomyopathy, 23.2%; adult congenital heart diseases, 5.2%; valvular heart diseases, 4.5%; hypertrophic cardiomyopathy, 4.2%) and only 7 patients (2.5%) had a family history of LVNC. We evaluated 272 patients, who were followed-up for more than 30 days for the incidence of CV events, including all-cause death, hospitalization for worsening heart failure, ventricular arrhythmia, and systemic thromboembolism. Over a 3.6-year median follow-up period, all-cause death ($n = 22$, 8.1%), CV death ($n = 16$, 5.9%), hospitalization for heart failure ($n = 59$, 21.7%), ventricular arrhythmia ($n = 28$, 10.3%), and systemic thromboembolism ($n = 7$, 2.6%) were observed. There was no difference in the incidence of CV events between patients with underlying cardiac diseases ($n = 134$) and those without (i.e. isolated LVNC) ($n = 138$) (CV events rate at 5 years: 30.3% vs. 31.1%, $p = 0.58$). We found that hospitalization for heart failure was the most common cause of CV events and such events did not appear to be influenced by the etiology of CV diseases in this patient population.

LVNC is increasingly being diagnosed in clinical practice, although there are still many unanswered clinical questions with regard to this condition. An international registry including a larger number of subjects with excessive trabeculations with a prospective follow-up and a multidisciplinary, international collaboration of clinicians, pathologists, geneticists, imaging specialists, and epidemiologists may aid in resolving several questions [5]. This larger study should be considered to elucidate the real prevalence assessment of LVNC, clarify the useful prognostic factors for patient management, and determine appropriate therapeutic interventions for these patients.

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