Congenital Heart Disease and Noncompaction Cardiomyopathy

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Introduction

Although noncompaction cardiomyopathy (NCCM) often occurs in an isolated feature, it may also be present in various types of congenital heart disease (CHD) [1]. In the majority of patients, NCCM is diagnosed in adulthood, similar to hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), which are rarely congenital [2]. In some cases, NCCM detected in adult patients were already present from birth on, but remained unnoticed until symptoms developed and high-resolution cardiac imaging techniques were applied [3]. Recently, the association of NCCM with other cardiac abnormalities has been reported. The pathogenetic mechanism(s) of sarcomere defects in cardiomyopathies are not fully understood. It is possible that the pathological myocardial changes in the adult onset sarcomere related cardiomyopathies are caused by a compensatory response to impaired myocyte function resulting from mutations in the sarcomere genes [4]. However, sarcomere gene mutations found in patients with NCCM were similar to mutations in patients with Ebstein anomaly, but there is no clear genotype-fenotype association [5]. This suggests that sarcomere gene mutations may cause both structural congenital heart disease and NCCM. Longitudinal studies of unaffected carriers of pathogenic mutations are necessary to provide insight whether noncompaction may develop later in life.

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Prevalence

With a prevalence of approximately 0.14%, NCCM is a relatively common genetic cardiomyopathy [6]. Although, the original diagnosis of NCCM could only be made in the absence of other structural heart disease, the association of NCCM with other diseases as metabolic diseases, genetic disorders are often reported. Moreover, NCCM is associated with congenital heart disease [7]. Stähli et al. reported the association between NCCM and various forms of congenital malformations [6]. The prevalence of NCCM in patients with CHD differs between the congenital malformations. The most common CHD associated with NCCM were various forms of Ebstein anomaly (15%), aortic coarctation (3%), Tetralogy of Fallot (2%) and bicuspid aortic valve (1%) [6]. In Fig. 4.1, the distribution of NCCM in patients with CHD is shown. Increasingly, congenital cardiac malformations as septal defects, Ebstein anomaly, patent ductus arteriosus, Fallot's tetralogy, aortic coarctation, and aortic aneurysms are being reported in familial cardiomyopathies (HCM, DCM, and NCCM) linked to sarcomere mutations, suggesting that these specific sarcomere defects may have been involved in cardiac morphogenesis. Of note is the congenitally corrected transposition of the great arteries, where the heart twists abnormally during fetal development, and the ventricles are reversed. The heavily trabeculated right ventricle in the left ventricularposition could be confused for a NCCM, a good example of pseudo-NCCM (see Fig. 4.2).

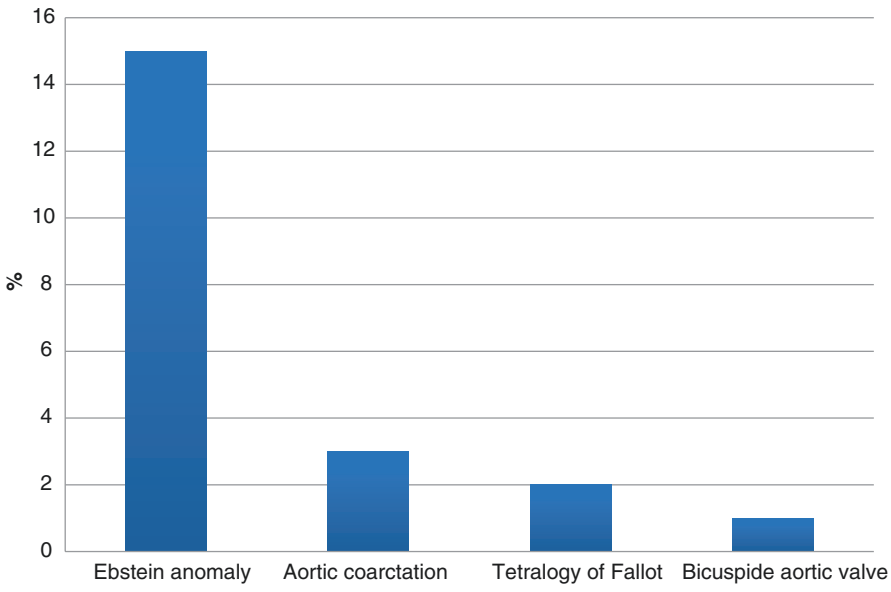

Fig. 4.1 The most common congenital heart disease associated with NCCM

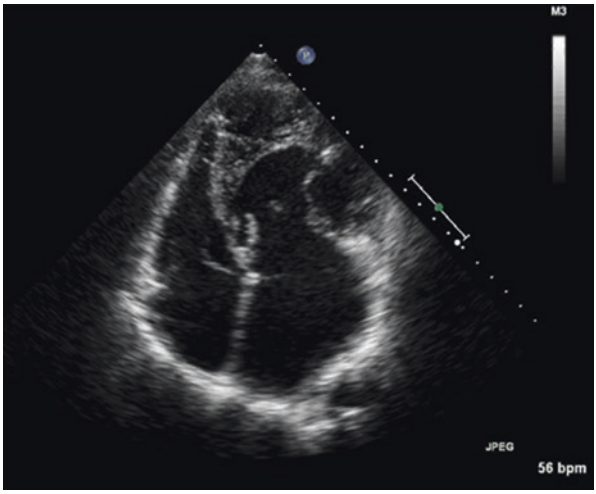

Fig. 4.2 Image of a patient with congenital corrected Transposition of the Great Arteries (ccTGA). The heavily trabeculation of the right ventricle can easily be confused for NCCM

Ebstein Anomaly Associated with Left Ventricular Noncompaction

The most prevalent congenital heart disease associated with left ventricular noncompaction cardiomyopathy is Ebstein anomaly [6]. In the past decade, several reports of Ebstein anomaly associated with noncompaction cardiomyopathy have been described [7–10]. Ebstein anomaly is a rare type of congenital heart disease and has an incidence of approximately 1 in 200,000 live births [9]. Ebstein anomaly is a malformation of the tricuspid valve defined the displacement of the origin of the tricuspid leaflets more apically and rotated to the right ventricular outflow tract. This displacement is accompanied by varying degrees of valvar dysplasia and abnormal attachments, which leads to atrialization of part of the right ventricle with diminished right ventricular size and function. The tricuspid valve itself is usually regurgitant, but may be also stenotic or even imperforate. Transthoracic echocardiography is the main diagnostic modality to confirm the diagnosis of Ebstein anomaly (Figs. 4.3 and 4.4). Late complication as cyanosis, right-sided heart failure, arrhythmias, and sudden cardiac death are reported, although many patients may remain asymptomatic [9]. Therefore, regular cardiologic evaluation is warranted to diagnose early signs of right-heart failure, progressive cardiomegaly with RV dilation, or RV dysfunction. Additionally, rhythm abnormalities as (concealed) accessory pathways, which can lead to Wolff–Parkinson White syndrome are described and other congenital malformation such as atrial septal defect, ventricular septal defect, bicuspid aortic valve or pulmonary stenosis, may also be present. Chronic symptoms in Ebstein anomaly are mainly related to right heart morphology and function. When a patients with Ebstein anomaly and NCCM, the non-compacted myocardium may alter a patient's prognosis because of the high likelihood of ventricular arrhythmia or cardiac arrest [11]. The etiology of Ebstein anomaly is

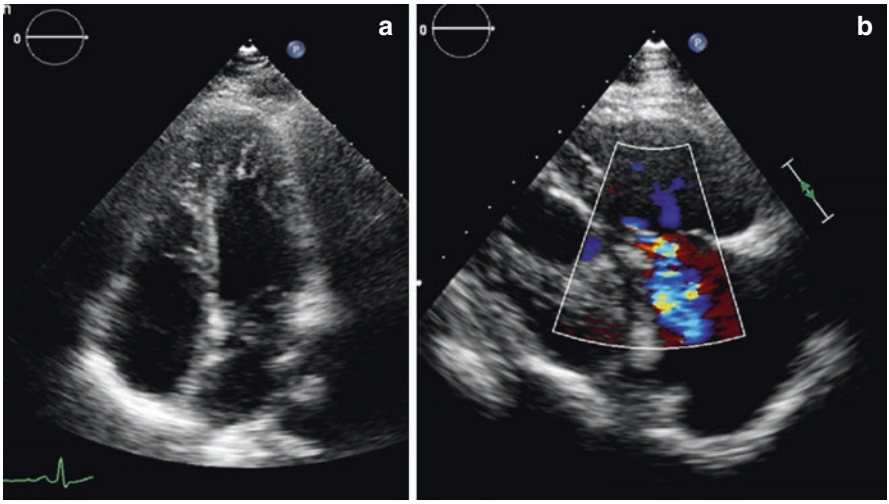

Fig. 4.3 Images of a 32-year-old woman with Ebstein anomaly and left ventricular noncompaction cardiomyopathy. She is asymptomatic and identified as a mutation carrier of MYH7-mutation by family screening. (**a**) Echocardiographic images, apical 4-chamber view; Ebstein anomaly and LVNC are evident. (**b**) Color Doppler image, showing tricuspid valve regurgitation

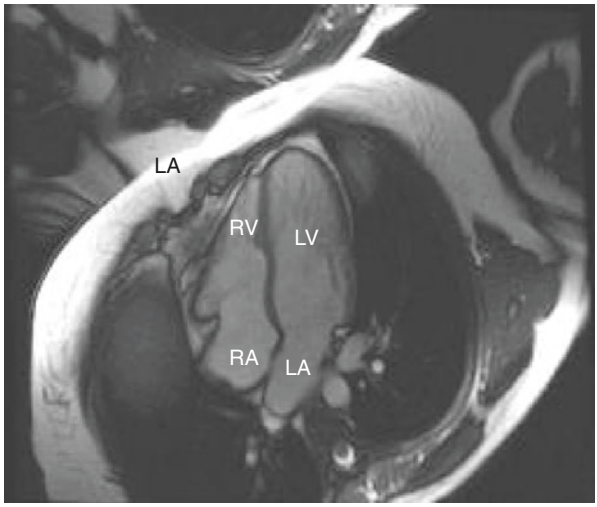

Fig. 4.4 MRI image, 4-chamber view; Ebstein anomaly is present (shown by apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve), as well as LVNC. *LV* left atrium, *LA* left atrium, *RV* right ventricle, *RA* right atrium

unknown, but families with Ebstein anomaly have been described. The association of Ebstein anomaly and NCCM has been reported similar sarcomeric gene mutations have been found [5]. This suggests that a similar genetic predisposition may lead to both, defective right and left ventricular myocardial differentiation with different morphologic–phenotypic manifestations. Comparable mechanisms may play a role in patients with conotruncal defects in whom the outflow tract of both, the right and left ventricles, and thus differentiation of right and left ventricular

myocardial mass may be abnormal. Many reports of NCCM in combination with Ebstein anomaly might describe a specific subtype of Ebstein anomaly, which has an inheritance pattern. Mutations in MYH7 have been reported in sporadic patients as well as families with NCCM and Ebstein anomaly [4]. Therefor, careful screening of patients with Ebstein anomaly for NCCM is preferable. In these patients with confirmed NCCM, further familial and genetic screening are needed with an extra attention for eventual concomitant cardiomyopathy.

Left Ventricular Outflow Tract Abnormalities in Combination with NCCM

Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, occurring in 1–2% of the general population [12, 13]. BAV is often associated with other common congenital malformations as patent ductus arteriosus, ventricular septal defect, and aortic arch obstruction. However BAV is strongly associated with coarctation of the aorta as well as aortic dilation, aneurysm, and dissection [12, 13]. (Figs. 4.5 and 4.6). Recently, the association of NCCM with less complex CHD, such as LV outflow tract abnormalities, was recognized. Isolated cases of BAV along with NCCM have been described in the literature [14]. Agarwal et al. reported an incidence of up to 11% NCCM in their BAV population [12]. This highlights the need of awareness among clinicians and sonographers aware of the possible presence of NCCM in patients diagnosed with BAV. However, the true incidence of this combination is unknown, and future large-scale studies are needed to understand its true incidence and clinical sequelae. It can be expected that BAV patients with concomitant NCCM are at increased risk for cardiac adverse events. Like concomitant

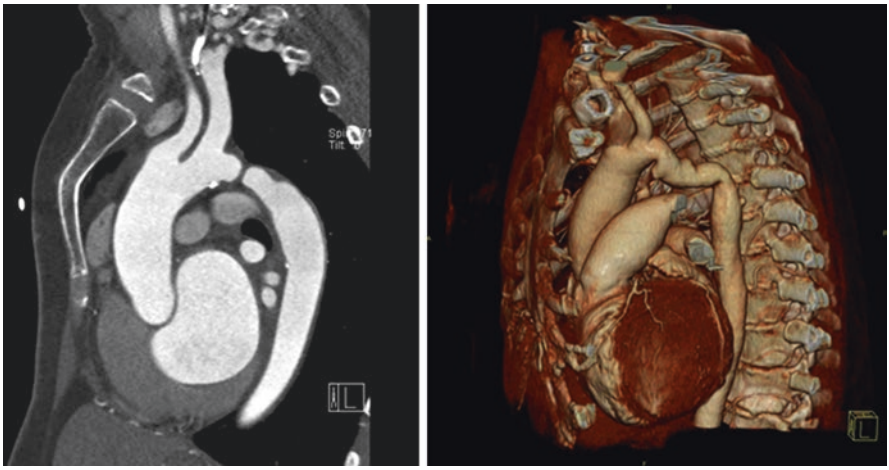

Fig. 4.5 Various forms of aorta coarctation CT images of a patient with aorta coarctation. These images demonstrate the different morphology in aorta coarctation from discrete stenosis to tubular hypoplastic segment, complex 3D turtuous anatomy

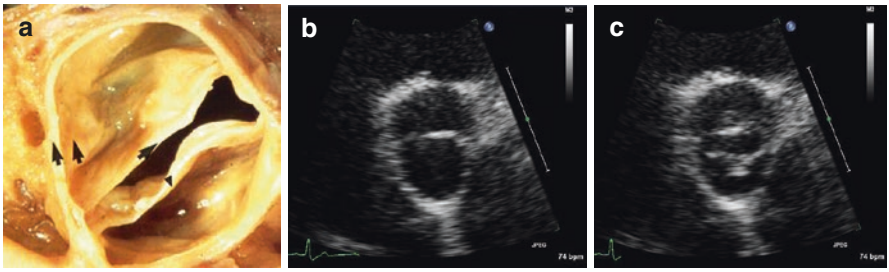

Fig. 4.6 Bicuspid aortic valve (**a**) Anatomic image of a bicuspid aortic valve, (**b** and **c**) Echocardiographic image (parasternal short-axis) from a bicuspid aortic valve in diastole (**b**) and systole (**c**)

aortic valve disease increases the risk for aortic valve stenosis and/or regurgitation and BAV-associated aortopathy for aortic root dissection, concomitant NCCM will increase the risk for heart failure, atrial and ventricular arrhythmias, thromboembolic events, and sudden cardiac death.

Clinical Features

Diagnosis of NCCM relies on non-invasive imaging studies, usually echocardiography and MRI. Transthoracic echocardiography remains the most common diagnostic strategy, largely because of its widespread availability, ease of interpretability, and low cost. The most common diagnostic method is based on a ratio of the thickness of the non-compacted layer to that of the compacted layer, with a ratio of greater than 2:1 at the end of diastole deemed diagnostic as in details described in Chap. 3 [15]. Advanced echocardiographic techniques, such as strain, strain rate, and torsion, are now being used to assist diagnosis of NCCM [16]. In patients with CHD, echocardiography is the first choice for diagnosis and follow-up. However, the awareness to look for NCCM in patients with CHD is not daily practice. Cardiac MRI is now increasingly used in patients with CHD; this might help additionally in identifying additional lesions as NCCM. The MRI diagnostic criteria for NCCM are also based on the ratio of the thickness of the non-compacted layer to that of the compacted layer, with a ratio of greater than > 2.3, given the typically used measurements at the end of diastole [17].

Heart failure is among the most frequent presentations of NCCM, followed by supraventricular and ventricular arrhythmias, including sudden cardiac death, and thrombo-embolic events. However, as in other cardiomyopathies, there is a great variability in clinical presentation, even within families, ranging from a fully asymptomatic course to severe heart failure necessitating cardiac transplantation. Patients with CHD are often diagnosed at childhood and follow for many years. Because the age of presentation of NCCM is highly variable varying, medical and surgical teams caring for patients with CHD should be aware that NCCM can be associated with

all forms of CHD and may be associated with poor postoperative outcomes and prolonged lengths of hospital stay [14, 18]. Therefore, patients with NCCM-CHD represent a high-risk population that requires additional attention at the time of preoperative screening, parental counseling and prophylactic drug treatment. Further prospective studies should be performed to further delineate the increased risk associated CHD surgery in children with NCCM.

Therapy and Follow-Up

Current guidelines for heart failure, arrhythmias, cardiac resynchronization therapy, and ICD implantation for primary and secondary prevention are applied for NCCM. For a detailed overview, we refer to the Chaps. 5, 6, and 9. However, the patients with CHD or NCCM have not been included in the landmark trials of ICDs. Also, the patients with CHD face a lot of challenges, because of the multiple previous surgical interventions to address the anatomic malformations, followed by the potential of heart failure and life-threatening arrhythmias. In the study of Gleva, they found that the in-hospital complication rate of ICD procedures in patients with CHD and patients with NCCM were low. However, the CHD patients with Ebstein anomaly, had the greatest all-cause complication rate. In patients with NCCM, beta-blockers and angiotensin-converting enzyme (ACE) – inhibitors are the cornerstones of the treatment in the presence of LV dysfunction and/or arrhythmias. However, clear-cut evidence-based clinical guidelines for this disorder, with or without CHD, are missing due to the lack of data and clinical trials.

An important issue is the use of prophylactic anticoagulants, in view of frequent thrombo-embolic events in NCCM. The early case reports and case series emphasized the high risk of thrombo-embolism and advised routine anticoagulation therapy. However, a review of 22 publications addressing the issue concluded that thromboembolic events are rare in NCCM. Fazio et al. came to the same conclusion. Currently, anticoagulation therapy is advised only in patients with an ejection fraction less than 40% (cut off empirical/arbitrary), paroxysmal or persistent atrial fibrillation, and/or previous thrombo-embolic events. The cardiologic follow-up depends on individual symptoms and cardiac abnormalities. In asymptomatic patients with preserved LV function, annual or biannual cardiologic follow-up is recommended, including ECG and echocardiography. If necessary, these could be extended with 24 h-Holter monitoring and exercise-testing for eventual spontaneous or exercise-induced (non)sustained ventricular tachyarrhythmias.

Conclusion

Various forms of congenital heart disease are associated with NCCM, particularly Ebstein anomaly, left ventricular outflow tract obstruction and tetralogy of Fallot. Medical and surgical teams caring for patients with CHD should be aware that NCCM can be associated with all forms of CHD and may be associated with poor

outcomes and increased cardiac events. Further prospective studies should be performed to further delineate the increased risk of patients with CHD in association with NCCM and appropriate management.

Conflict of Interest None declared.

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