Genetics, clinical features and long-term outcome of noncompaction cardiomyopathy: A Dutch multicenter study

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Abstract

Background Clinical outcome of noncompaction cardiomyopathy (NCCM) ranges from asymptomatic to heart failure, arrhythmias, and sudden cardiac death. Genetics plays an important role in NCCM.

Objective This study investigated the correlations between genetics, clinical features and outcome in adults and children diagnosed with NCCM.

Methods In a multicenter study from four cardiogenetic centers in the Netherlands 327 unrelated NCCM patients were classified into 1) "genetic", with a mutation 32% (81 adults; 23 children), 2) "probably genetic", familial cardiomyopathy without a mutation 16% (45 adults; 8 children), or 3) "sporadic", no family history, and no mutation (149 adults; 21 children). Clinical features and major adverse cardiac events (MACE) during follow-up were compared across the three groups of patients.

Results: Mutations in *MYH7*, *MYBPC3* and *TTN* explained 71% of genetic NCCM. Older patients were more likely to have sporadic NCCM (OR 0.983 per year; CI 95% 0.97-0.99; p=0.01). Genetic NCCM, in particular with multiple mutations, was more frequent in children (p=0.04). At long-term follow-up (median 27 months), MACE was related to LV dysfunction (HR 2; p=0.01), presentation before one year (HR 3; p=0.05), and multiple mutations in *MYBPC3* (HR 5; p=0.01). Patients with *MYH7* mutations had low risk for MACE (p=0.03).

Conclusions:

Genetics, age and LV function were important predictors for outcome of NCCM. This highlights the importance of genetic testing and family history for prognosis of NCCM. Mutations were

more frequent in early onset NCCM, suggesting different mechanisms in genetic and adult, mostly sporadic, patients.

Condensed abstract

Children were more likely to have a mutation, whereas the majority of the patients diagnosed in adulthood were 'sporadic' cases without a mutation or familial disease. In carriers of mutations risk of major adverse events was related to left ventricular function. In contrast, in sporadic cases risk of complications was not dependent on left ventricular function. The most prevalent genetic cause, *MYH7* mutations, carried low risk for MACE. These findings highlight that genetic testing and taking family histories of cardiomyopathies have important implications for the management and prognosis of NCCM patients and their relatives.

Introduction: Noncompaction cardiomyopathy (NCCM), also known as left ventricular noncompaction (LVNC), has been classified as a distinct cardiomyopathy with excessive trabeculations of predominantly the left ventricle.[1] NCCM is characterized by a more than twofold thickening of the endocardial noncompacted (NC) layer compared to the epicardial compacted (C) layer of the myocardium(NC/C>2).[2] Initially referred to as sponge heart,[3] NCCM has gained attention with the improvements in cardiac imaging allowing more detailed visualization and increasing clinical awareness.[4, 5] Clinical symptoms range from severe prenatal manifestations to asymptomatic cardiomyopathy presenting at adult age.[6, 7]

Genetics play an important role in NCCM since 17-50%[8, 9] of the patients have a family member with a cardiomyopathy and the yield of DNA testing ranges from 17 to 41% depending on patient selection and the number of genes screened.[7, 10] In most families, an autosomal dominant pattern of inheritance is observed with variable penetrance.[11] The majority of the genetic defects associated with NCCM have also been reported in hypertrophic (HCM) and dilated cardiomyopathy (DCM).[7, 12] In NCCM, pathogenic variants in the sarcomere, in particular in *MYH7* are the most common cause.[7, 10] However, the role of the sarcomere gene defects in the development of the cardiac hypertrabeculation has not been established yet. When Genetic testing identifies the genetic cause, relatives at risk can be identified accurately and cardiac family screening can be directed to carriers. As NCCM is not as common as HCM and DCM, associations between mutations in cardiomyopathy genes, family history and the age of onset, left ventricular function and long term outcome have not been investigated in detail before.

We conducted a large multicenter study in four cardiogenetics centers in the Netherlands to investigate the role of genetics in NCCM. The focus to investigate the relationship between clinical and cardiologic features at diagnosis, the risk of left ventricular dysfunction and occurrence of major adverse cardiac events (MACE) during follow-up in NCCM patients diagnosed in childhood or adulthood. These insights may help to improve management of NCCM patients and their families.

Methods

Study Population

The study population consisted of 327 unrelated NCCM patients referred to the Departments of Clinical Genetics of the Erasmus Medical Center Rotterdam (EMC), the University Medical Center Groningen (UMCG), the University Medical Center Utrecht (UMCU) and the Amsterdam Medical Center (AMC) for genetic counseling and DNA testing (with informed consent) between January 2005 and January 2016. Diagnosis of NCCM was based on evaluation of echocardiographic images according to the Jenni criteria by the referring cardiologist, confirmed with re-evaluation by JVW.[13] For the patients of which images of echocardiographic exams were missing or inconclusive (n=78), MRI data were used for cardiologic diagnosis according to the criteria proposed by Petersen.[5] One patient was diagnosed at autopsy. NCCM patients who refused DNA testing (n=22) were excluded from this study.

Specifics on the genes tested and methods of classification of variants are described in detail in the online methods. The core-panel of tested cardiomyopathy genes included 45 cardiomyopathy genes: *ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CALR3, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, EMD, GLA, JPH2, JUP, LAMA4, LAMP2, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYPN, MYOZ1, MYOZ2,LDB3, PKP2, PLN, PRKAG2, RBM20, RYR2, SCN5A, SGCD, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN* and *VCL*. All variants were evaluated by current Dutch guidelines and classification of each variant was achieved with consensus of all participating centers. The yield of the genetic testing is presented in online figure 1. Variants were classified as (likely) pathogenic mutations classes 4 and 5 (online table 1a, 2a, 1b and 2b). Variants of unknown clinical significance (class 3) were reported in table S5. Patients were classified as genetic if they had a (likely) pathogenic mutation. Patients with only variants of unknown clinical significance were not classified as genetic because these variants have not been proven to be pathogenic. Patients were classified as probably genetic if they had a family history of cardiomyopathy and DNA testing did not identify a mutation. Patients were classified as sporadic if patients o mutation or family history of cardiomyopathy (figure 1).

Clinical data

Clinical data were retrieved from the medical records, including age, gender, cardiac diagnosis, ECG, echocardiography and cardiac magnetic resonance imaging (MRI) when available. In case

the images of the first echocardiographic examination were unavailable, more recent echocardiographic imaging was used (table 1).

Ventricular function

LV systolic dysfunction was defined as fractional shortening < 19% in men and < 21% in women on echocardiography or an LV ejection fraction < 45% on MRI. Abnormal right ventricular (RV) function was defined as a tricuspid annular plane systolic excursion (TAPSE) <17 mm on echo or RV ejection fraction <45% on MRI. For children we classified the dimensions of the ventricles as abnormal if they were more than two standard deviations from reference range.[14, 15]

Adverse events

Clinical events at follow-up were retrieved from the medical records. We used a combined end-point for our hazard models, because of low incidence of death. The occurrence of cardiac death, implantation of a left ventricular assistance device (LVAD), heart transplantation, (aborted) sudden cardiac death, appropriate ICD shock, or stroke were classified as major adverse cardiac events (MACE).

Family history

Family histories were ascertained at the departments of Clinical Genetics. Patients were classified as familial, if at least one first-degree or two second- degree relatives were reported with a cardiomyopathy there were no patients with only one second degree affected relative. Medical records confirmed the diagnosis of 82% of the relatives reported to have a cardiomyopathy; in 18% of the affected relatives, no medical records were available. The

occurrence of (aborted) sudden cardiac death (SCD) at age <50 years in the family of the index patients was recorded. In families with multiple cases of NCCM, one case per family, the index case which was the first case diagnosed with NCCM, was included as the index in the study. Relatives of these index patient were excluded from this study.

Statistical analysis

Categorical data were compared with Pearson Chi-Squared test or Fisher's exact test. For continuous variables, unpaired t-tests were used for two groups and ANOVA tests for more than two groups. Logistic regression was used to find associations between genetic status and left ventricular dysfunction at baseline. Kaplan–Meier survival curves were estimated and differences between groups were assessed by the log-rank test, using time at diagnosis as time zero. To identify risk factors for MACE, cox proportional hazards regression analysis was used. Patients lost to follow-up were considered at risk until the date of last contact, at which time-point they were censored. All patients were checked for survival via the municipal personal records database. Analysis was performed with SPSS statistical software, version 21.0 (SPSS Inc., Chicago, IL).

Results

NCCM genetics

The 327 NCCM patients were categorized into the three groups; genetic in 104 (32%) (81 adults, 23 children), probably genetic in 53 (16%)(45 adults, 8 children) and sporadic in 164 (52%) (149 adults, 21 children; table 1, figure 2). The online tables 1a, 2a and online figure 1 present

the complete list of mutations identified in children and adult NCCM patients with reference to previous reported variants and the reported cardiomyopathy (NCCM, HCM or DCM) and the yield per tested gene (Online figure 2). In addition, we present the list of 192 variants of unknown clinical significance in cardiomyopathy genes identified in 111 patients (Online table 3), of which 13 (12%) had also a (likely) pathogenic variant in (another) gene. Of the patients without a mutation 98 (30%) had a class 3 variant. Seventy-one (41%) of the sporadic cases had a class 3 variant.

From the 104 genetic cases, 82% had a mutation in a sarcomere gene (figure 2), the majority (71%) had a mutation in *MYH7*, *MYBPC3* or *TTN* and 11% in *ACTC1*, *ACTN2*, *MYL2*, *TNNC1*, *TNNT2* or *TPM1*. *MYH7* was the most frequently mutated gene; in 19% (n=10) of children and 11% (n=29) of adult patients. *TTN* mutations were an important cause in adults (7%, n=18), while none of the patients diagnosed in childhood had a *TTN* mutation. Non-sarcomere gene mutations were detected in *DES, DSP, FKTN, HCN4, KCNQ1, LAMP2, LMNA, MIB1, NOTCH1, PLN, RYR2, SCN5A* and *TAZ.* One patient classified as genetic had an 1p36 deletion. Mutations occurred more frequently in female patients irrespective of age at diagnosis (male 27% vs female 38%, p=0,039).

Complex genotypes

Complex genotypes (multiple mutations in one patient) in cardiomyopathy genes were more prevalent in children (10%) than in adult NCCM patients (3%) (p=0.038; table1, online Tables 1b and 2b). Three children had complex *MYBPC3* mutations presenting with severe clinical phenotypes but none of the adults had a complex *MYBPC3* genotype. Four adult patients in this

Dutch study population had the same two *MYH7* mutation in cis (c.1633G>A and c.2863G>A) were not considered a complex genotype, and are expected to have a common ancestor. Three adult patients had the combination of a *MIB1* and a *TTN* mutation. One patient had three pathogenic mutations in three different genes; *FKTN*, *RBM20* and *HCN4*. This patient was 53 years old when he was first admitted to the hospital for bradycardia. He had no structural heart defect and did experience serious adverse effects at end of follow-up (58 years).

De novo mutations

De novo mutations involving *DES* and *PLN* were observed in two children and *PRDM16* and *MYH7* in two adult patients. The children had a severe heart failure requiring necessitating a heart transplantation at young age (the *DES* patient at the age of 10 years, the *PLN* patient at age 17 years). In contrast, the adult patients with a *de novo* mutation had a mild course of the disease without severe complications.

Family history

Family history of cardiomyopathy was present in 40% (n=21) of the children and 36% (n=99) of the adults (table 1). Of the 120 familial cases, 56% (n=67) had a (likely) pathogenic mutation. Of the 207 patients without a family history of cardiomyopathy 18% (n=37) had a mutation. Overall, NCCM was the most frequent cardiomyopathy with 23% (n=76) among affected relatives of NCCM index patients. In 12% (n=39) of the families DCM was reported, in 3% (n=11) HCM, and in one family a relative was diagnosed with Arrhythmogenic Cardiomyopathy (ACM). Sudden death (SD) of a relative below the age of 50 was reported by 7% (n=23) of the

patients; in 8% (n=21) of the families of adult index cases and 4% (n=2) of the families of pediatric index cases.

Age at diagnosis

The study population included 16% (n=52) pediatric NCCM patients diagnosed before the age of 18 years, and 84% (n=275) adult patients. Figure 3 illustrates the distribution of age at diagnosis. Overall, the median age at diagnosis of NCCM was 41 years (range 0-79 year, IQR 27-54 years), 44 years (range 18-79 IQR 33-56) for adult patients and 8 years (range 0-17 IQR 0-14) for children (table 1). Thirty percent (n=16) of the 52 children were diagnosed before the age of 1 year. Mutations were found more frequently in children than in adults (43% children, 29% adults, p=0.036, table 1). Age at diagnosis was inversely associated with the probability of finding a mutation (OR 0.983 per year; CI 95% 0.97-0.99; p=0.01).

Congenital heart defect (CHD)

CHD was observed in 9% of the NCCM patients (n=28). In particular children (p=0.027; table 1) had more f ASD (p=0.005) and VSD (p<0.001). Six of the 16 NCCM patients diagnosed before the age of one year also had a congenital heart defect. Four families (2 children and 2 adults) had Ebstein's anomaly and an *MYH7* mutation (figure 4). Familial segregation of NCCM and Ebstein's anomaly was observed in a family with one adult patient and one child. *MYH7* was the only sarcomere gene associated with CHD. Two children with a CHD had a chromosomal defect: a 1p36 deletion syndrome patient with an ASD, multiple VSD's and an open ductus arteriosus and in a trisomy 21 patient with an ASD and a VSD and an *MYH7* mutation. The other

congenital heart defects were observed in patients with defects in non-sarcomere genes in the probably genetic and sporadic cases categories.

Clinical features

Heart failure (27%) and arrhythmias (26%) were the most common reason for presentation in pediatric and adult patients (online figure 2). In 4% (n=14) of the patients the primary presentation was a cardiac arrest. Thrombo-embolic events were the first sign of NCCM in 3% (n=10) of the patients, three of them had a CHD. Thirty patients, of which 16 with a mutation, were identified through family screening for other conditions than NCCM. In these cases, a relative was diagnosed with a cardiac condition for which cardiologic family screening was recommended, i.e. HCM, DCM, SCD, familial hypertension, hemochromatosis. Medical screening identified 42 patients, of which 12 had a mutation, who had a cardiologic examination for another medical condition. Thirty-four percent (n=24) of the patients identified by family- and medical screening were asymptomatic, seven had a mutation.

Hypertension was frequently observed in adult patients (n=62 (23%)), and was more frequent observed in patients without a mutation (p=0.047, table 1). Also a left bundle branch block (LBBB) was significantly more common in sporadic adult NCCM patients (27%) compared to the adult genetic (10%) and probably genetic cases (11%, p=0.01; table 1). The online table 4 presents further information on echocardiographic, ECG and CMR parameters of the NCCM patients.

Reduced ventricular function

The risk of having a reduced left ventricular function was higher for genetic patients compared to the probably genetic and sporadic cases (p=0.024), with highest risk for patients with multiple mutations and *TTN* mutations (table 3 and in figure 4). Overall, dysfunction of the left ventricle was observed more often than dysfunction of the right ventricle (RV 14% and LV 53 %). The right ventricular function was measured in 31 of the 52 pediatric NCCM patients (12 genetic, 5 probably genetic, and 14 sporadic) at admission, detecting reduced RV function in four genetic cases (with a *DES de novo*, *PLN de novo*, homozygous *MYL2*, and *MYH7* defect) which also had a reduced LV function and in one sporadic patient with a normal LV function. The risk for having a reduced right ventricular function was increased for genetic patients (p=0.008). Risk for having a reduced right ventricular function was decreased in sporadic patients (p=0.024).

Major adverse cardiac events (MACE)

During median follow-up (FU) of 60 months (IQR 18-113), MACE occurred in 14 (27%) children, vs 58 (21%) of the adult during a median FU of 25 months (IQR 4-58 months; table 2). An increased risk for MACE was observed for children classified as probably genetic (p=0.025; figure 5A), including children diagnosed before the age of 1 year (HR 2.1; 95% CI 1.0-4.4; p=0.048; table 4) and with multiple mutations in *MYBPC3* (HR 5.2; 95% CI 1.62-16.5; p=0.006). In sporadic pediatric cases, the risk for adverse events was reduced (HR 0.1; 95% CI 0.02-0.93; p=0.043). No difference in risk for MACE was observed between adults with genetic, probably genetic and sporadic NCCM (Figure 5B).

Univariate analysis showed that a reduced LV function was associated with increased risk for MACE (HR 1.7; 95% CI 1.1-2.8; p=0.028). In line with these observations, genetic patients

with a good left ventricular function had low risk of adverse events (p=0.002; figure 5C). For patients with an *MYH7* mutation, low risk for MACE was observed (HR 0.17; 95% CI 0.04-0.69; p=0.013; table 4 and figure 4). In sporadic patients risk for MACE was not related to LV function (figure 5D); in patients without a mutation with a normal LV-function risk of MACE was almost the same risk of MACE in patients with LV-dysfunction.

Cardiac arrest occurred significantly more in female patients than in male patients (11%, vs 2%, p=0,003). Significantly more adult females had a cerebrovascular accident (CVA) than males (9%, vs 3%, p=0,045). Patients with congenital heart defects were more often associated with CVA's (without CHD 5%, with CHD 56%, p=0,001).

Discussion

In this large cohort of NCCM patients we investigated the correlations between genetics,, clinical presentation and the long-term outcome. We showed that nearly one third of the NCCM patients had a mutation in a cardiomyopathy gene. In this heterogeneous cardiomyopathy, age at diagnosis, left ventricle dysfunction and risk of MACE were linked to the genetic status. Children diagnosed with NCCM had more often a genetic cause than adults. Furthermore, left ventricular dysfunction at presentation and long-term outcome were related to genetic causes.

Approximately half (48%) of the NCCM patients had a genetic cause; in 32% of the patients, DNA testing detected the cause of the disease and 16% of the patients had familial disease without a mutation, in line with previous reports.[7] The mutations in *MYH7*, *TTN* and *MYBPC3* were the most important genetic causes for NCCM. Among these, the *MYH7* gene was

the most common genetic cause for NCCM, as described previously.[7,10] The risk for MACE (5%) was lower in *MYH7* patients. *MYH7* was the only sarcomere gene associated with CHD, four patients had a *MYH7* mutation and Ebstein's anomaly. *TTN* defects were not observed in the pediatric cases in this study. As far as we know, there are no reports of children with *TTN* related NCCM. A high prevalence of *TTN* mutations in peripartum cardiomyopathy and possibly also in chemotherapy induced cardiomyopathy suggest that *TTN* defects may be associated with onset of cardiomyopathy symptoms later in life.[16-18]

Three of the 22 different cardiomyopathy genes involved in NCCM were not reported previously in NCCM, expanding the genetic spectrum of NCCM with the *DES*, *PLN* and *RBM20* genes.[19, 20] One third of the mutations were found in patients who did not report relatives with a cardiomyopathy, i.e. when family history was negative. This illustrates that DNA testing should not be restricted to cases with a positive family history, and that DNA testing of patients without a family history is as important as testing patients with a family history.

The proportion of genetic patients is expected to be higher than 50% because some patients had incomplete DNA tests. Thirty percent of the patients without a mutation, had Sanger sequencing of a small number of cardiomyopathy genes instead of the current cardiomyopathy panel of >45 genes. These cases may have a mutation in a cardiomyopathy gene that was not tested. In addition 71 (41%) of the sporadic cases had a variants of unknown clinical significance that may be reclassified in the future as likely pathogenic or pathogenic variant when additional genetic and/or functional evidence will become available. Moreover, patients may carry

mutations in NCCM genes that have not been identified yet. Similarly, sporadic cases may still have unknown novel genetic causes.

Children diagnosed before the age of 1 year, were mostly associated with one or more mutations, had severe LV dysfunction and a high risk for MACE. These findings are consistent with earlier reports of severe cardiac dysfunction in cases with a perinatal diagnosis of NCCM and in HCM with bi-allelic *MYBPC3* mutations.[21] In contrast, children with sporadic NCCM were diagnosed incidentally and had normal cardiac function with low risk for MACE.

In adults, the majority was sporadic and had no mutation and no family history of cardiomyopathies. In the patients without a mutation the risk of MACE was not related to LV dysfunction. The risk for MACE was higher in the sporadic patients with a normal cardiac function than in genetic patients with a normal cardiac function, indicating alternative risk factors for MACE in the sporadic cases. These insights may help in predicting the risk for major adverse cardiac events in long-term and can be used to determine management and intensity of follow-up for specific groups of patients. Reduced right ventricular function was observed more frequently in adult patients with genetic NCCM, suggesting that in genetic NCCM pathology may not be limited to the left ventricle.[22, 23]

The compaction of the myocardium starts in gestational week eight and occurs from base to apex. If the compaction process is not completed, (mostly)the apex is affected by noncompacted myocardium.[24] Assuming that all NCCM is caused by an arrest of normal compaction of the endocardium in early cardiogenesis, the diagnosis shortly after birth or in childhood would be expected to be higher than the observed 16% of childhood cases in our

cohort. Late onset NCCM may be explained by an enhancement of a latent asymptomatic congenital defect by disruptions of the cardiac homeostasis later in life. Recent studies showed that an increased cardiac preload was associated with hypertrabeculation and with the morphologic features of NCCM. Conditions with an increased cardiac preload which are associated with hypertrabeculation included sickle cell anemia, pregnancy and intensive sports.[25-27] Our observation that LBBB was more prevalent in adults with sporadic NCCM underscores such role of increased cardiac preload in the development of NCCM features. Since hypertension was more common in sporadic NCCM patients than in patients with genetic defects, the role of hypertension in NCCM may be mediated through activation of similar mechanisms as genetic defects in (non)sarcomere genes or lead to cardiac remodeling. For instance, like in HCM where hypertension may cause cardiac muscle hypertrophy mimicking HCM caused by genetic defects and associated with an impairment of the contractile functions.

Study Limitations

Our patient population was a selection of the patients referred for DNA testing, therefore we cannot exclude a selection bias of more severe cases. Consequently, asymptomatic or mildly affected cases may have been underrepresented leading to an overestimation of severe clinical features. Moreover, to control for overrepresentation of genetic causes, only index patients were included in the study and not the affected relatives. We may have underestimated the role of genetic causes for NCCM because not all patients were tested for the complete genetic cardio-panel (~45 genes). Many variants of unknown significance were found, some of which were rare and may in the future be reclassified as likely pathogenic when additional evidence of the effect

of the variant becomes available. Adult patients were more often classified as sporadic than children. There might be an underestimate of asymptomatic familial disease in adults, because family screening may be more difficult, since elder relatives of adults may not be available for screening. It was a retrospective study and therefor some clinical data were missing.

Conclusion

Almost half the studied NCCM patients were (probably) genetic, with a high prevalence of pathogenic mutations in *MYH7*, *MYBPC3* and *TTN* gene. Age, mutations and family history were important predictors for outcome of NCCM, highlighting the role of genetic testing and a detailed family history in management and clinical surveillance of NCCM. Mutations were more frequent in children and were associated with worse outcome. In contrast, adults were more likely to have sporadic (non-genetic) origins of NCCM. Mutations and LV function were correlated and determined together the risk for MACE. In patients without a mutation the risk of MACE was not related to LV dysfunction. These observations endorse the heterogeneity of NCCM and the importance of genetics, simultaneously evoking questions on different etiologies for NCCM in children and adults.

Perspectives

Competency in medical knowledge: NCCM is heterogeneous and genetics play a more important role in children than in adults**.** Genetic information may complement cardiologic management and help predict prognosis of NCCM patients and their relatives. In carriers of mutations risk of major adverse events was related to left ventricular function. In contrast, in

sporadic cases risk of complications was not dependent on left ventricular function. Hence, showing the importance of DNA testing and taking family histories.

Translational outlook: Prospective large follow up studies are needed confirm the genotype-phenotype correlations, determine the effects of risk related follow-up strategies and design gene tailored management of NCCM patients and their families.

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