Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: A study from the Pediatric Cardiomyopathy Registry

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Background Studies of cardiomyopathy in children with Noonan syndrome (NS) have been primarily small case series or cross-sectional studies with small or no comparison groups.

Methods We used the Pediatric Cardiomyopathy Registry database to compare the survival experience of children with NS and hypertrophic cardiomyopathy (HCM) with children with idiopathic or familial HCM and to identify clinical and echocardiographic predictors of clinical outcomes.

Results Longitudinal data in 74 children with NS and HCM and 792 children with idiopathic or familial isolated HCM were compared. Children with NS were diagnosed with HCM before 6 months old more often (51%) than children with HCM (28%) and were more likely to present with congestive heart failure (CHF) (24% vs 9%). The NS cohort had lower crude survival than the group with other HCM ($P = .03$), but survival did not differ after adjustment for CHF and age at diagnosis. Within the NS cohort (1-year survival 78%), a diagnosis of HCM before age 6 months with CHF resulted in 31% 1-year survival. Lower height-for-age z score (hazard ratio 0.26, $P = .005$) in place of CHF and lower left ventricular fractional shortening z score (hazard ratio 0.79, $P = .04$) also independently predicted mortality.

Conclusions Patients with NS with HCM have a worse risk profile at presentation compared with other children with HCM, resulting in significant early mortality (22% at 1 year). Decreased height-for-age and lower, although still supranormal, left ventricular fractional shortening z score are independent predictors of mortality in patients with NS with HCM. Such patients should have an aggressive therapeutic approach including potential listing for cardiac transplantation. (Am Heart J 2012;164:442-8.)

Outcomes for children with hypertrophic cardiomyopathy (HCM) who present in the first year of life are substantially worse than when HCM is diagnosed after the first year of life.[1-4] A greater understanding of infantile HCM is needed not only because this age group has worse clinical outcomes but also because the incidence of infantile HCM is >10-fold greater than the incidence of pediatric HCM presenting after the first year of life.[1]

The leading genetic cause of infantile HCM is the Noonan syndrome (NS).[5] The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500 live births,[6,7] and congenital cardiovascular malformations (CCVMs) have been reported in as many as 80% of patients with NS.[5,8-11] Hypertrophic cardiomyopathy is reported in 20% to 30% of all NS cases.[5,7,12]

Studies of patients with NS with HCM have generally been small case series or retrospective or cross-sectional studies with small or no comparison groups, although there are exceptions.[2,3] These reports describe the distribution of cardiac abnormalities in NS, including HCM, but rarely have compared the outcomes of children with NS with those of other children with HCM. Reports regarding whether the outcomes for children are better or worse than children with other causes of HCM are

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inconsistent.[1,2,10,13-15] Cardiac transplantation is rarely reported for patients with NS with HCM.[4,10,14]

Using data from the National Heart, Lung, and Blood Institute–funded Pediatric Cardiomyopathy Registry (PCMR), we compared the long-term survival of patients with NS with HCM with that of children with HCM from other causes. Furthermore, we examined patient characteristics and serial measurements of growth and left ventricular (LV) size and function to determine if they predicted mortality in patients with NS.

Methods

The patients in this study were identified from the PCMR between January 1990 and February 2009 at nearly 100 participating centers in the United States and Canada. The PCMR design and implementation are described in detail elsewhere.[16,17] Briefly, patients aged <18 years, newly diagnosed with cardiomyopathy at participating centers, were eligible for inclusion in the PCMR. Children with specific secondary causes of ventricular hypertrophy such as pulmonary parenchymal or vascular disease, endocrine disease, rheumatic disease, immunologic disease, cardiotoxic exposures, or CCVMs that occur independently of a malformation syndrome were excluded. All participating centers obtained institutional review board approval.

Each HCM case in the PCMR was classified morphologically using the following specific criteria[16,17]: (1) septal or LV posterior wall thickness exceeding 2 SDs for body surface area compared with a normal population of infants, children, and adolescents[18]; or (2) the presence of localized LV hypertrophy. The patients with NS in this study were diagnosed clinically by phenotype because genotyping was not commonly performed in the period of this study. Children with idiopathic and familial HCM are hereafter referred to "other" forms of HCM.

Demographic, family history, vital and transplant status, and clinical data relevant to cardiomyopathy, including echocardiographic measurements, were collected at diagnosis and annually thereafter.

Statistical methods

A Fisher exact test was used to compare the frequencies of categorical variables by the presence or absence of NS. Student *t* test (for normally distributed variables) and the Wilcoxon rank sum test (for variables with other continuous distributions) were also used to evaluate differences by the presence or absence of NS. Echocardiographic *z* scores relative to body surface area (LV end-diastolic and end-systolic dimension and LV end-diastolic posterior and septal thicknesses and LV mass) or relative to age (LV fractional shortening)[18] were assessed at the diagnosis of cardiomyopathy for statistical differences from normal (*z* score = 0) using Student 1-sample *t* test.

The Kaplan-Meier method was used to estimate survival after cardiomyopathy diagnosis with censoring at the time of heart transplantation. A Wald test was used to compare 1- and 3-year survival rates for the NS and other HCM groups. Random effects mixed modeling was used to assess changes in LV size and function over time. Univariate Cox proportional hazards regressions using the Wald test and the log-rank statistic were used to assess subgroup differences in survival. Multivariable Cox proportional hazards regression modeling was used to identify independent correlates of survival for the cohort with NS. The association between longitudinal echocardiographic measurements and survival was analyzed using a Cox regression model with time-dependent covariates. Echocardiographic variables were modeled as linear covariates as well as dichotomous variables based on median values. Hazard ratios (HRs) are reported with 95% CIs. All tests were 2 tailed. Analyses were conducted using the Statistical Analysis System version 9.1 (SAS Institute, Cary, NC) and S-PLUS version 6.1 (Insightful Corporation, Seattle, WA).

Table I. Characteristics at diagnosis of cardiomyopathy for children with NS compared with children with idiopathic or familial (other) HCM

Characteristic at the time of diagnosis	NS + HCM (n = 74)		Other HCM (n = 792)		*P*
Male, n (%)	38	(51)	548	(69)	.003
Median age (y), (Q1, Q3)	0.4 (0.02, 2.1)		8.0 (0.3, 13.4)		<.001
Age <6 m, n (%)	38	(51)	222	(28)	<.001
Race, n (%)					.61
White	47	(64)	531	(69)	
Black	8	(11)	95	(12)	
Hispanic	15	(21)	114	(15)	
Other	3	(4)	34	(4)	
Unknown	1	–	18	–	
CHF, n (%)	18	(24)	72	(9)	<.001
Family history of*					
Genetic syndromes	6	(10)	16	(2)	.005
CCVM	5	(8)	45	(6)	.58
Cardiomyopathy	3	(5)	208	(29)	<.001
Sudden death	3	(5)	81	(11)	.14
Arrhythmia	1	(2)	27	(4)	.72

*Maximum n = 63 and 729, NS vs other HCM.

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Results

The NS cohort consisted of 74 children who were diagnosed with HCM, and the comparison group consisted of 792 children with idiopathic or familial isolated HCM, excluding patients with storage diseases, mitochondrial disease, or other metabolic or syndromic diseases.

Characteristics at diagnosis

The NS cohort was 51% male, and 64% were non-Hispanic whites (Table I). The median age at diagnosis of cardiomyopathy was 4.6 months (interquartile range 0.2-24.6 months). More than half (51%) of all NS children were diagnosed with cardiomyopathy before 6 months old. Noonan syndrome was diagnosed before or at HCM

Table II. Echocardiographic characteristics at diagnosis of HCM for children with NS and children with idiopathic or familial HCM

Characteristic at the time of diagnosis	NS + HCM (n = 74)	Other HCM (n = 792)	*P*
Mean *z* scores (maximum n = 52 and 607)			
LV EDD	−3.28 ± 2.6	−1.93 ± 2.81	.001
LV ESD	−4.99 ± 2.45	−3.14 ± 3.26	<.001
LV FS	5.50 ± 3.78	3.68 ± 4.88	.01
LV EDPWT	2.13 ± 2.51	1.82 ± 2.75	.44
EDST	2.58 ± 2.18	3.41 ± 2.51	.02
LV mass	0.52 ± 2.70	1.87 ± 2.52	<.001
Height-for-age	−1.80 ± 1.63	−0.12 ± 1.52	<.001
Weight-for-age	−1.02 ± 1.44	0.35 ± 1.74	<.001

EDPWT, End-diastolic posterior wall thickness; *EDD*, end-diastolic dimension; *EDST*, end-diastolic septal thickness; *ESD*, end-systolic dimension; *FS*, fractional shortening.

Table III. Congenital cardiovascular malformations in 17 of 74 children with NS and HCM

Structural anomaly	n (%)*
Mitral valve abnormality	5 (7)
Aortic valve–ascending aorta abnormality including coarctation of the aorta	4 (5)
Pulmonary valve stenosis/insufficiency	8 (11)
Pulmonary artery stenosis/hypoplasia	3 (4)
Atrioventricular canal defect	1 (1)
Atrial septal defect	5 (7)
Ventricular septal defect	1 (1)
Coronary artery anomalies	0 (0)
Left or right ventricular outflow tract obstruction	1 (1)

* Percentage is based on total sample of 74 cases; number of CCVMs does not equal number of patients because some patients have multiple CCVMs.

diagnosis in 73%, and congestive heart failure (CHF) symptoms were present at the time of diagnosis of HCM in 24%.

All mean echocardiographic *z* scores were statistically different from normal (*z* score = 0), except for LV mass. Mean LV fractional shortening *z* score was 5.5 SDs above the norm, and the median LV end-diastolic posterior wall thickness *z* score to LV end-diastolic dimension *z* score ratio was 4.7 SDs above the norm ($P = .007$) (Table II). Of the 74 children, 17 (23%) had at least 1 CCVM (Table III).

Comparison of NS and other HCM at diagnosis

The NS cohort differed from other children with HCM in many respects (Tables I and II). They were younger, more likely to have CHF at diagnosis, more likely to have a family history of genetic syndromes, less likely to have a family history of cardiomyopathy, and had a smaller length/height *z* score. At diagnosis, LV fractional shortening (percentage) was higher (52.0 ± 8.9 vs 45.1 ± 8.9, $P < .001$), mean LV mass *z* score was smaller (mean ± SD 0.52 ± 2.70 vs 1.87 ± 2.52, $P < .001$), and the median ratio of LV end-diastolic posterior wall thickness to LV end-diastolic dimension was higher (0.32 vs 0.28, $P = .007$) in NS children than in other children with HCM. *Asymmetric septal hypertrophy*, defined as an end-diastolic septal thickness to LV posterior wall thickness ratio *z* score >2, was noted in 35% of NS compared with 42% of other children with HCM ($P = .31$). Left ventricular outflow obstruction was more often present in patients with NS compared with other HCM (30% vs 9%, respectively, $P = .01$), but these data were only available for 20 patients with NS. Noting that left-sided lesions (mitral or LV outflow abnormalities) might have affected LV dimension or function during fetal life, we also compared the NS cohort after exclusion of cases with left-sided lesions to the other HCM group. The inferences were similar, implying that the smaller LV size and mass of the NS group is not attributable to the cases of left-sided lesions.

Longitudinal changes in LV size and function in NS

Longitudinal analysis of LV size and function in the NS cohort revealed significant increases in LV end-diastolic and systolic dimension *z* scores over time (0.25 SD units per year for both, $P < .001$) but no change in the LV fractional shortening *z* score over time. The ratio of LV end-diastolic posterior wall thickness to LV end-diastolic dimension decreased over time (0.013 decrease per year, $P < .001$). There were no changes in weight-for-age but a significant decrease in height-for-age (0.09 drop in *z* score per year, $P = .004$).

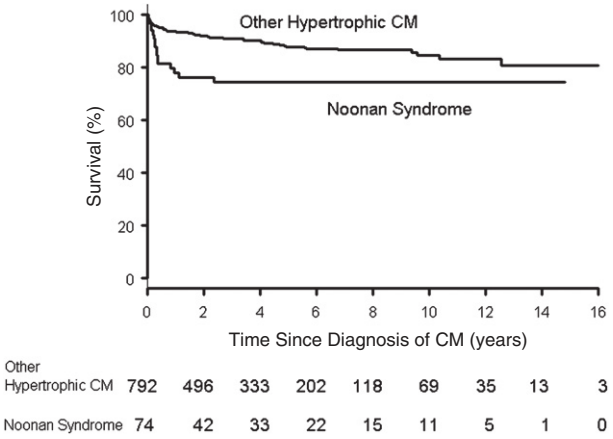
Survival for NS and HCM compared with other HCM

The 2 groups had a similar duration of follow-up (median 4.7 years for NS and 3.6 years for other HCM, $P = .27$) among nontransplanted survivors, with one-quarter of the patients with NS and patients with other HCM followed up for at least 9.6 and 6.7 years, respectively, after cardiomyopathy diagnosis. No patients with NS underwent cardiac transplantation; 3 patients with NS were listed for cardiac transplant during follow-up but died before receiving a transplant. Patients with NS had higher mortality (HR 1.81, $P = .03$) than did the 792 patients with other types of HCM (3-year death rates 26% vs 11%) (Figure 1). This difference was partly explained by the younger age and higher prevalence of CHF at diagnosis in the NS group (median age 0.4 years, 24% with CHF) compared with that of the remaining patients with HCM (median age 8.0 years, 9% with CHF). The age- and CHF-adjusted HR for mortality for NS versus other patients with HCM was 1.21 ($P = .49$).

Risk factors for mortality in NS

Of the 16 deaths in the NS group, 15 occurred in those diagnosed with HCM before 6 months of age; thus, survival was lower in this subgroup compared with those diagnosed at 6 months of age or older (log-rank $P < .001$, 1-year survival 64% vs 96% and 5-year survival 58% and

Figure 1



Survival since diagnosis of HCM in children with and without NS. Estimated survival since diagnosis of HCM in children with (n = 74) and without (n = 792) NS. Log-rank $P = .03$. The size of the risk set is shown below the x-axis. CM indicates cardiomyopathy.

96%, respectively). The presence of CHF was also a risk factor. Survival was lower when CHF was present at HCM diagnosis than if CHF was not present (log-rank $P < .001$) with 1-year survival rates after cardiomyopathy diagnosis of 34% and 90%, respectively (Table IV).

Survival rates did not differ between the 17 patients with NS with CCVMs and those without such defects (log-rank $P = .82$, 5-year survival 73% vs 74%, respectively) and did not differ by sex, race/ethnicity, or family history (Table IV). Furthermore, survival rates did not differ between the 9 patients with NS with a left-sided CCVM and the patients with NS who did not have a left-sided CCVM (log-rank, $P = .66$, 5-year survival rate 83% vs 74%, respectively). An LV fractional shortening z score at presentation that was at or above the median of 6.35 was associated with better survival ($P = .02$) (Figure 2).

We also sought to determine whether serial LV and growth measurements predicted mortality in patients with NS. Echocardiographic measurements (1-13 measurements per patient) were used as time-dependent covariates. In univariate analyses (Table IV), CHF, LV end-systolic dimension, LV fractional shortening, end-diastolic septal thickness, LV mass, height-for-age, and weight-for-age z score were associated with poorer outcome.

Multivariable Cox regression modeling was used to identify independent predictors of death. Age at diagnosis of HCM and the presence of CHF were first examined as clinical factors without accounting for quantitative echocardiographic measurements. In this 2-factor model, both HCM diagnosis before 6 months old and the presence of CHF at diagnosis were independent predictors of death (Figure 3) ($P < .05$). In patients with

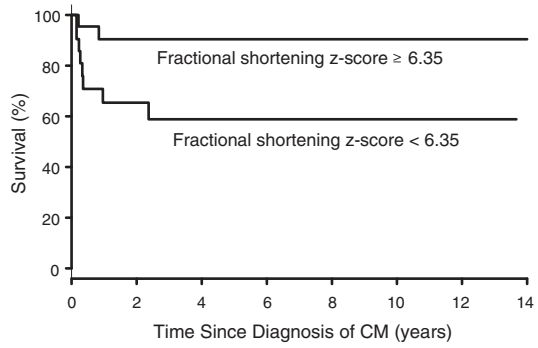
Table IV. Univariate Cox regression modeling of time to death in 74 patients with HCM and NS

Covariate	n	HR (95% CI)	P
Age at diagnosis of HCM (<6 vs ≥6 months)	74	14.7 (1.9-111.3)	<.001
CHF at diagnosis of HCM (present vs absent)	74	7.7 (2.8-21.1)	<.001
Gender (male vs female)	74	1.4 (0.5-4.0)	.48
Race (white vs black vs Hispanic vs other) (3 *df*)	73		.70
Black vs white		1.2 (0.3-5.8)	
Hispanic vs white		2.0 (0.6-5.8)	
Other vs white		Not estimable	–
Family history			
Cardiomyopathy (present vs absent)	62	Not estimable	–
Sudden death (present vs absent)	63	1.4 (0.2-10.4)	.77
CCVM (present vs absent)	60	3.3 (0.7-15.3)	.13
Genetic syndromes (present vs absent)	61	0.6 (0.1-4.8)	.65
Arrhythmia (present vs absent)*	62	Not estimable	–
Serial echocardiographic data (time-varying covariate)			
LV EDPWT to LV EDD ratio ≥0.32 vs <0.32	61	2.79 (0.85-9.11)	.09
EDST to LV EDPWT ratio ≥1.28 vs <1.28	63	1.67 (0.49-5.73)	.41
LV EDD z score	61	0.94 (0.74-1.20)	.63
LV EDD z score ≥−3.03 vs <−3.03	61	1.51 (0.49-4.64)	.47
LV ESD z score	56	1.28 (0.99-1.66)	.06
LV ESD z score ≥−5.00 vs <−5.00	56	4.75 (1.02-22.11)	.047
LV FS z score	60	0.84 (0.73-0.96)	.011
LV FS z score dichotomized ≥6.35 vs <6.35	60	0.39 (0.11-1.35)	.14
LV EDPWT z score	63	1.17 (0.96-1.43)	.13
LV EDPWT z score ≥2.01 vs <2.01	63	2.71 (0.83-8.82)	.10
EDST z score	63	1.65 (1.23-2.20)	<.001
EDST z score ≥2.11 vs <2.11	63	8.59 (1.11-66.8)	.04
LV mass z score	60	1.21 (1.02-1.44)	.03
LV mass z score ≥0.36 vs <0.36	60	2.87 (0.79-10.46)	.11
Height-for-age z score	61	0.50 (0.32-0.76)	.001
Height-for-age z score ≥−2.1 vs <−2.1	61	0.38 (0.10-1.42)	.15
Weight-for-age z score	65	0.48 (0.30-0.77)	.001
Weight-for-age z score ≥−1.1 vs <−1.1	65	0.08 (0.01-0.62)	.02

HR, Hazard ratio.
* Family history of arrhythmia was present in only 1 patient; therefore, no modeling was performed.

CHF who were diagnosed before age 6 months, 1-year survival was only 31%. In multivariable modeling, however, age at diagnosis was not a significant independent risk factor because of its collinearity with LV fractional shortening (mean z score 4.2 vs 6.7 for those diagnosed at age <6 months vs ≥6 months). Congestive heart failure at diagnosis, time-dependent LV fractional shortening z score, and time-dependent height-for-age z score were all important predictors (2 roughly equivalent models). Risk factors in the first model (n = 61) were lower, although still supranormal, LV fractional

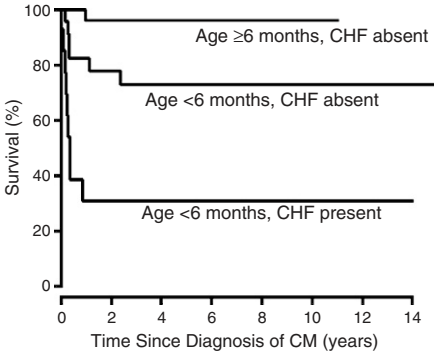
Figure 2



FS z-score < 6.35	24	11	8	5	4	3	2	0
FS z-score ≥ 6.35	24	17	13	9	5	3	1	0

Survival by LV fractional shortening *z* score in children with NS and HCM. Estimated survival since diagnosis of HCM in 48 children with NS by LV fractional shortening *z* score at the time of HCM diagnosis (<6.35 vs ≥6.35 to where 6.35 is the median). Log-rank $P = .02$. Five-year survival is 59% for children with a *z* score <6.35 and 90% for children with a *z* score ≥6.35. The size of the risk set is shown below the x-axis. FS indicates fractional shortening.

Figure 3



Age≥6 mo, CHF absent	33	23	18	12	8	5	0	0
Age<6 mo, CHF absent	23	16	12	8	6	5	4	1
Age<6 mo, CHF present	15	3	3	2	1	1	1	0

Survival by age and CHF in children with NS and HCM. Estimated survival since diagnosis of HCM in 74 children with NS by age and CHF status at the time of HCM diagnosis. Log-rank $P < .001$. The size of the risk set is shown below the x-axis. The subgroup of 3 cases with CHF who were diagnosed at age ≥6 months is not shown (one known to survive 5.5 months postdiagnosis, and 2 were not seen after diagnosis).

shortening *z* score (HR 0.79 per unit *z* score increase, 95% CI 0.63-0.98, $P = .04$) and a lower height-for-age *z* score (HR 0.26 per unit *z* score increase, 95% CI 0.10-0.67, $P = .005$). Risk factors in the alternative model (n = 74) were lower LV fractional shortening *z* score (HR 0.85 per unit *z* score increase, 95% CI 0.74-0.98, $P = .02$) and CHF at diagnosis (HR 0.20, 95% CI 0.06-0.69, $P = .01$).

Cause of death in NS

The cause of death was established for 11 of the 16 children with NS who died. There were no discernible patterns, although "severe" HCM (presumably cardiac), CHF, and kidney failure were noted for several children. Information explicitly recorded about sudden death was available for only 8 children, and none were classified as sudden.

Discussion

The crude mortality rate of children with NS-associated HCM was worse than that of infants and children with other causes of HCM, consistent with some earlier reports.[3,19] However, the NS cohort differed from patients with other HCM in several ways, and multivariable analysis revealed no survival difference—the higher mortality of patients with NS is associated with younger age and higher prevalence of CHF at the time of HCM diagnosis. A recent report noted that survival of 30 patients with NS with HCM (recruited from 1966 to 2007) was similar to that of 120 patients with no NS with HCM in the first decade after diagnosis.[15] However, lack of specifics regarding the clinical or echocardiographic characteristics of these patients and the 40-year duration needed to acquire this cohort makes comparison with our results challenging.

The rapid early mortality in our NS cohort is particularly striking: 26% at 3 years. There were no deaths in the NS cohort 2.5 years after the diagnosis of HCM. An increased risk of mortality in NS-associated HCM was associated univariately with presentation at younger age, CHF, lower LV fractional shortening *z* score, impaired somatic growth, and greater septal thickness *z* score and LV mass *z* score. The presence of a CCVM or a positive family history of HCM was not associated with higher mortality.

Our findings confirm those of others[3,4] that CHF is an important risk factor for mortality in NS children with HCM (HR 7.7). Furthermore, when CHF was present in children diagnosed with HCM in the first 6 months of life, mortality was 69% in the first year after HCM diagnosis. Given that the mean LV fractional shortening *z* score in patients with NS was almost 6 SDs above normal, it appears that CHF was a result of LV diastolic dysfunction. The severe hypertrophy leads to pulmonary edema and lower cardiac output. A young infant with NS who demonstrates symptoms of CHF merits close monitoring, and consideration for early listing for cardiac transplantation may be warranted, given the 1-year mortality rate of 69%.

Two easily measured, serial factors were independent predictors of death: *z* scores indicating below average height, and lower, although still supranormal, LV fractional shortening. Although many children with NS

have impaired height, marked and persistent linear growth retardation indicates a poor prognosis. This leads one to believe that weight, which was not an independent predictor of death, is likely to be associated with LV dysfunction, whereas height might relate to some intrinsic disease properties in NS.

Consistent with our finding that outcomes for HCM children with NS, after adjustment for age and CHF, did not significantly differ from those of children with HCM from other causes, histologic findings of myocardial disarray and patterns of LV hypertrophy have been found to be similar in the 2 groups.[12,14,19] Mutations in 9 genes have been identified in patients with NS.[20] However, the relation of specific genotypes to clinical outcomes in children with NS and HCM has yet to be described.

Study limitations

The PCMR is the largest study of children with HCM, executed at nearly 100 North American centers, and its cohort of 74 NS cases is a relatively large contemporary sample. Furthermore, most studies of NS are based on children who are still alive at an older age, which may bias in results. A strength of the PCMR design is its more comprehensive capture of cases, with a median age of 4.6 months. However, our report has several limitations. Multivariable modeling included only 61 cases and therefore rendered wide CIs for some risk estimates. Nevertheless, numerous clinically relevant associations were found. In addition, information on CCVMs was not explicitly collected but was provided as free text. Centralized echocardiographic readings were not conducted for this study, and explicit collection of LV outflow tract obstruction occurred for only a subset of cases. Genotyping data were not available for our patients, most of whom were diagnosed before the first report of an NS-associated mutation in 2002. However, to date, no NS-HCM mutations predictive of clinical course have been reported, and NS is still primarily diagnosed phenotypically. We believe that our series of patients is representative of the clinical presentation faced by most physicians.

Conclusions

Children with NS present with HCM at an earlier age and more often with CHF than children with familial or idiopathic HCM, leading to high mortality: 22% at 1 year. The hazard of death is greatest in the first 6 months of life, particularly if CHF is present. Therefore, infants presenting with HCM should be evaluated for NS because the phenotype may be more difficult to recognize in this age group. Conversely, infants diagnosed with NS should be evaluated immediately for the presence of HCM and CCVMs. Decreased, although still supranormal, fractional shortening z score and impaired vertical growth were independent predictors of mortality. Serial measurement of ventricular state and somatic growth of NS children will result in individual evidence-based counseling and management, including consideration for early listing for cardiac transplantation.

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Disclosures

The authors have reported that they have no relationships to disclose.

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