

# Noonan syndrome and cardiomyopathy: outcome predictors.

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Pediatric Cardiomyopathy Registry

## ABSTRACT

In an effort to provide counseling for families, we reviewed long term data on patients with Noonan syndrome (NS) and cardiomyopathy (CM) focusing on the association between survival and age at diagnosis, congestive heart failure (CHF) at CM diagnosis, gender, and race/ethnicity. The Pediatric Cardiomyopathy Registry (PCMR), sponsored by a grant from the NHLBI, has 62 patients with NS diagnosed with CM between 1990 and 2002. All had hypertrophic CM. Annual follow-up data was collected from the time of diagnosis until death, transplant, transfer to a non-participating institution or discharge from follow-up. Of the 62 cases, 39% were retrospective (diagnosed 1990-1995) and 61% were prospective (1996-2002). Forty-seven (76%) had an etiology of NS at the time of diagnosis. Half of the NS patients were diagnosed with CM at <6 months of age, 27% had CHF at the time of diagnosis, and 52% were male. The racial/ethnic breakdown was 64% white, 11% black, 20% Hispanic and 5% other. The median follow-up time for these patients was 3.7 years with 15 deceased (24%). Of the deceased, 33% were diagnosed with CM at <6 months of age compared to 36% of those alive. One-year survival since the diagnosis of CM was lower in those diagnosed at <6 months of age than those diagnosed at ≥6 months of age (50% vs. 95% respectively, log-rank p-value <0.001). If CHF was present at the time of diagnosis of CM, one-year survival was lower than if CHF was not present (39% vs. 67%, log-rank p-value <0.001). One-year survival was similar for males and females (74% vs. 76%, log-rank p-value = 0.767). One-year survival also did not differ by race (white 50%, black 71%, Hispanic 50% and other 100%, log-rank p-value = 0.181). Therefore, age of <6 months and CHF at the time of diagnosis are associated with poor outcomes in patients with NS and CM.

## INTRODUCTION

Noonan syndrome was first described in 1963 by Drs. Noonan and Ehrlke. It has since been determined to be an autosomal dominant condition with variable expression. Clinical characteristics include distinctive facial features, short stature, skeletal anomalies, usually mild developmental disabilities, bleeding diatheses and heart defects.<sup>(1-3)</sup> Congenital heart disease (CHD) has been reported in as many as 90% of patients.<sup>(1,7)</sup> The two most common heart lesions seen are pulmonic stenosis (PS) and hypertrophic cardiomyopathy (HCM). Engle and Ehlers (1972) first described cardiomyopathy in patients with Noonan syndrome. In 1975, Nora et al described cardiac lesions in 45 of 81 patients, 8 with HCM. Hirsch et al reported 2 cases of rapidly progressive obstructive cardiomyopathy. These individuals died at 23 months and 9 months with congestive heart failure. The older of the two had a sibling who died at 2 weeks of age also from heart failure. It had been suggested that individuals with NS and HCM die at a younger age and from CHF as opposed to individuals with isolated HCM who die older and at an increased risk for sudden death.<sup>(3)</sup> Few studies are longitudinal. Skinner et al (1997) presented their findings from a 25-year study of patients with HCM from infancy. Eight of their patients also had Noonan syndrome. Of these, there were 2 deaths from CHF, one at 11 months of age and the other at 7 months of age. Few studies have large cohorts of individuals with NS and HCM. The Pediatric Cardiomyopathy Registry (PCMR) is sponsored by a grant from the National Heart, Lung and Blood Institute (NHLBI). The PCMR was designed to describe the epidemiologic characteristics and clinical course of selected cardiomyopathies in patients 18 years old or younger and promote the development of etiology-specific prevention and treatment strategies.<sup>(8)</sup> The large cohort size and population-based design addresses limitations of sample size and ethnically homogeneous samples in other studies.<sup>(8)</sup>

## CASE STUDIES

Authors	N	Deaths	Sudden Deaths
Engle and Ehlers, 1972	12	1	1
Phornphutkul et al, 1973	1	1	1
Nora et al, 1974	8	2	2
Hirsch et al, 1975	2	2	2
Zubeida et al, 1987	3	3	3
Sharland et al, 1991	30	30	30
Burch et al, 1992	4	4	4
Burch et al, 1993	29	29	29
Ishizawa et al, 1996	11	2	2
Nishikawa et al, 1996	13	1	1
Skinner et al, 1997	8	2	2
Marino et al, 1999	13	13	13
Salbert et al, 2003	62	15	1

## METHODS

The PCMR enrolled 62 patients who were diagnosed with hypertrophic cardiomyopathy between 1996 and 2002 at 19 participating sites with an etiology of Noonan syndrome. Etiologic assessment of Noonan syndrome occurred prior to or at CM diagnosis (n=47, 76%) or on annual follow-up (n=15, 24%). Median follow-up available for NS patients was 3.7 years with 15 deaths occurring during that period.

## RESULTS

Table 1. Characteristics at CM Diagnosis in Noonan syndrome (N=62)

Characteristic	n	(%)
Region		
New England	13	(21%)
Central Southwest	18	(29%)
Non-regional	31	(50%)
Gender		
Male	32	(52%)
Female	30	(48%)
Median Age at CM diagnosis	5.6 mos.	
Less than 6 mos.	31	(50%)
Greater than or equal to 6 mos.	31	(50%)
Race		
White	39	(64%)
Black	17	(11%)
Hispanic	12	(20%)
Other	3	(5%)
Unknown	1	—
CHF at CM diagnosis		
Present	17	(27%)
Absent	45	(73%)
Echocardiographic 2 scores (max n=40)		
End-Diastolic Dimension	-3.34 ± 2.38	
End-Systolic Dimension	-4.00 ± 1.85	
Fractional Shortening	6.20 ± 3.74	
End-Diastolic Posterior Wall Thickness	2.14 ± 2.62	
End-Diastolic Septal Wall Thickness	2.62 ± 2.29	
Left Ventricular Mass	0.36 ± 2.91	
Family History (max n=54)		
CM	3	(6%)
Sudden Death	3	(8%)
Congenital Structural Heart Disease	5	(9%)
Arrhythmia	1	(2%)
Genetic Syndromes	5	(8%)

Table 2. One-year Survival Estimates

Group	1-year Survival (95% CI)	Log-rank P-value
Age at CM diagnosis		
< 6 mos.	59% (41% to 77%)	<0.001
≥ 6 mos.	95% (85% to 100%)	
CHF at CM diagnosis		
Present	39% (11% to 66%)	<0.001
Absent	67% (76% to 98%)	
Gender		
Male	74% (57% to 91%)	0.767
Female	76% (59% to 93%)	
Race		
White	80% (66% to 93%)	0.181
Black	71% (38% to 100%)	
Hispanic	50% (15% to 85%)	
Other	100% (— to —)	

Survival since the diagnosis of CM was significantly lower in those diagnosed at <6 months of age than those diagnosed at ≥6 months of age (see Figure 1). If CHF was present at diagnosis of CM, survival was significantly lower than if CHF was not present (see Figure 2). Survival was similar for males and females. Survival also did not differ by race.

Figure 1. Survival by Age at CM Diagnosis

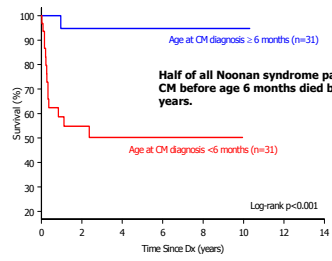
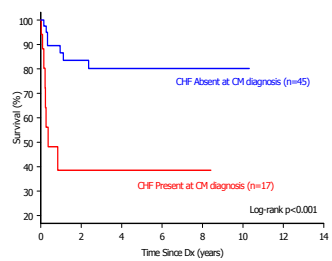


Figure 2. Survival by CHF at CM Diagnosis



## DISCUSSION

Since the first descriptions by Drs. Noonan and Ehrlke, the cardiovascular anomalies found in patients with NS have been well described. Although the CM is usually hypertrophic, progressive and distinctive, the natural history and risk factors have not been well described in a large sample of patients. The discovery of asymptomatic HCM in patients with Noonan syndrome raises the question of long-term management strategies. Although uncommon, reports of sudden death heighten the need for early recognition and intervention in high-risk groups. The problem is defining who is at high risk.

Mapping of the gene for NS to the long arm of chromosome 12 followed by the association of mutations in PTPN22 in more than 50% of patients evaluated with Noonan syndrome suggests that genotype-phenotype correlations could assist in counseling and managing patients with NS.<sup>(10)</sup> Non-allelic genetic heterogeneity has been described.<sup>(9)</sup> It may be that specific genotypes correlate with the development of complications including early onset CHF, rapidly progressing CHF, or sudden death.

We reviewed our data to categorize sub-groups of patients at risk. Analysis of our data revealed that none of our patients had been transplanted and 15 had died. One-year survival since the diagnosis of CM was significantly lower in those diagnosed at <6 months of age than those diagnosed at ≥6 months of age. If CHF was present at the time of diagnosis of CM, one-year survival was significantly lower than if CHF was not present. One-year survival was similar for males and females and one-year survival also did not differ by race.

Maron et al (1982) published the clinical features and natural history of HCM in infants. A total of 20 cases were reviewed. The cohort included four patients with genetic syndrome including: lentiginosis with deafness (LEOPARD syndrome), Noonan syndrome, tuberous sclerosis and Pierre-Robin syndrome. Current knowledge would suggest that based on echocardiographic findings, there were several other patients in that cohort with Noonan syndrome. A one month old with PS, CHF and RVH died suddenly at one month of age. A 2 month old died suddenly with HCM and CHF; RVH was described on ECG. An 8 month old with valvular PS and CHF died post operatively. The ECG showed RVH with "strain." In this same cohort, a 12 year old was described with PS and RVH with "strain" on ECG as well. There were 4 other survivors with HCM and RVH. Two other infants that died showed RVH on their ECG. One had congenital NS. The other had TGF.<sup>(11)</sup> The data did not indicate which four patients were diagnosed with the genetic syndromes mentioned.

In an era of possible genotype correlation leading to specific intervention, splitting sub-groups and identifying specific phenotypes is imperative. This review has led to multiple new areas of interest.

**Areas of Future Investigation:**

- Does having PS or other structural CHD in conjunction with HCM in NS increase the risk for complications and death?
- Is sudden death more or less common in individuals with HCM and Noonan syndrome compared to those with isolated HCM?
- Is it possible to determine by phenotype, which individuals are at increased risk for sudden death?
- How do we counsel families with a newborn with Noonan syndrome regarding life expectancy?
- What is the natural history of the HCM by echocardiogram and can a certain profile be predicted?
- Can genotype-phenotype correlations be made to determine a management plan?
  - a. Who should be recommended for transplant?
  - b. Who would benefit from an AICD?
  - c. Should every patient suspected of having Noonan syndrome have a Pediatric Cardiology evaluation including echocardiogram?

## CONCLUSIONS

- Age less than 6 months is significantly associated with poor outcome in patients with both NS and CM. Half of all NS patients diagnosed with CM before age 6 months died by age 2.4 years.
- CHF at CM diagnosis is significantly associated with poor outcome in patients with both NS and CM.
- Survival does not differ by gender or race in patients with both NS and CM.