Cardiac Findings in Noonan Syndrome on Long-term Follow-up

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ABSTRACT

Objective. Noonan syndrome (NS) is the second most common genetic syndrome associated with cardiac abnormalities, including, most notably, pulmonary stenosis (PS) and hypertrophic cardiomyopathy (HCM). Little is known about the natural history of heart disease in this unique subset of patients. We sought to contribute information on the natural history of NS by looking at how the cardiac disease progresses with time.

Design. This is a retrospective review of the medical records of patients with NS seen at our institution between 1963 and 2011.

Results. Records were available for 113 patients. Average length of follow-up was 14.16 years (2 months to 44 years, median 12.5 years). Sixty-six percent (75/113) of our patients had PS; within this subset, 57% (43) were classified as mild, 9% (7) moderate, and 33% (25) severe. None of the cases of mild PS worsened with time. All of the severe cases had an intervention, as did some moderate cases. Fourteen percent (16/113) of our patients had HCM; 56% (9/16) were mild, diagnosed at an average age of 3.8 years. Seven of these were stable with time, while one did progress. Forty-four percent (7/16) of cases were classified as severe, diagnosed at an average age of 4.2 months, and all were managed medically, surgically, or both. Our cohort had seven deaths (ages 6 months and 6, 10, 20, 40, 49, and 50 years).

Conclusion. Mild PS in patients with NS is nonprogressive. Severe, and in some cases moderate, PS will invariably require a therapeutic intervention. It is uncommon for HCM to progress or have new onset beyond early childhood. Prognosis of heart disease in NS is influenced most by the findings on presentation.

Key Words. Noonan Syndrome; Pulmonary Stenosis; Hypertrophic Cardiomyopathy; Natural History

Introduction

Over 50 years ago in 1962, at a Midwest Society of Pediatric Research meeting, Dr. Jacqueline Noonan reported on nine patients with a shared phenotype of pulmonary valve stenosis, short stature, and characteristic facies.[1] Six years later, she published a description of an additional 10 patients.[2] Geneticist John Opitz, recognizing this was a distinct syndrome occurring in both males and females with normal chromosomes and possessing a tendency for heritability, suggested the eponym "Noonan syndrome" (NS).[3] It firmly entered the medical lexicon after Dr. Victor McKusick listed it as a hereditary congenital disorder of the cardiovascular system in the early 1970s.

NS is currently recognized as the second most common genetic syndrome associated with cardiac abnormalities, with an incidence of 1:1000–2500.[4] It remains primarily a clinical diagnosis prompted by well-characterized facial, musculoskeletal, and/or cardiac abnormalities. In 2001, the first molecular cause (*PTPN11* gene mutation) was identified.[5] Presently, seven identified genes constitute approximately 75% of cases, and it is classified within the "RASopathies," a family of related developmental syndromes caused by upregulation of RAS signaling.[6]

The literature describes a broad spectrum of associated cardiac abnormalities, though particular notoriety is given to pulmonary stenosis (PS) and hypertrophic cardiomyopathy (HCM), the two most common associated defects.[7,8] The standard of care is to follow up these patients periodically, but little has been published on the natural history of heart disease in this unique subset of patients. We sought to contribute information on the natural history of NS by looking at how the cardiac disease progresses with time.

Methods

We retrospectively reviewed the medical records of patients with NS who were seen at our institution between 1963 and 2011. One hundred forty-eight patients were identified as having a clinical diagnosis of NS, based on previously described phenotypical features. Patients suspected of having a clinically related but alternate diagnosis, such as cardiofaciocutaneous syndrome, LEOPARD syndrome, and Costello syndrome, were excluded. The authors abstracted from the medical record the following information: patient's age at diagnosis, cardiac diagnoses, echocardiogram and catheterization data (where available), date and type of surgery (if applicable), number of years of follow-up, and age at and cause of death (if applicable). Follow-up data were subsequently compared with the data from first presentation. All of the collected data were based on chart notation; we did not recharacterize or otherwise classify lesions beyond what was documented. A survival curve was calculated using Kaplan-Meier principles. This study was approved by our institutional review board.

Results

One hundred forty-eight patients were identified as meeting inclusion criteria. Medical records were available for 113 patients, and follow-up data existed for 98 of these patients. Patient characteristics are presented in Table 1. Length of follow-up for the entire group averaged 14.16 years (2 months to 44 years, median 12.5 years). Seven patients died during the study interval (7%). There were 64 men and 49 women. Mean age at diagnosis was 4.8 years (newborn to 49 years). Forty-two patients were diagnosed at less than 1 year of age, many in early infancy; 42 patients were 1–10 years old at diagnosis, 6 were adolescents, and 8 were adults. Consistent with prior studies,[8–11] the distribution of cardiac anomalies was varied, with PS and HCM being represented most commonly (Figure 1). Eleven patients (10%) did not have heart disease.

Table 1. Demographic Characteristics of the Patients Studied

Male/Female, n (%)	64/49 (57/43)
Number of patients, n	113
Number of patients with follow-up, n (% of 113)	98 (87)
Age at diagnosis	4.8 (neonate to 49)
Age ≤1 y, n (%)	42 (43)
Age >1 and ≤10 y, n (%)	42 (43)
Age >10 and ≤18 y, n (%)	6 (6)
Age >18, n (%)	8 (8)
Length of follow-up, y	14.16 (0.17–44, median 12.5)
No heart disease, n (% of 113)	11 (10)
ASD/PFO, n (% of 113)	5 (4)
VSD, n (% of 113)	3 (3)
PDA, n (% of 113)	3 (3)
Subaortic stenosis, n (% of 113)	2 (2)
Tetralogy of Fallot, n (% of 113)	2 (2)
Dysplastic mitral valve, n (% of 113)	2 (2)
Dysplastic aortic valve, n (% of 113)	1 (1)
Deaths, n (% of 98)	7 (7)
Elapsed time from diagnosis to death, y	19.4 (0.5–44)
Pulmonary stenosis, n (% of 113)	75 (66)
Mild, n (% of 75)	43 (57)
Age at diagnosis, y	2.8 (neonate to 32)
Length of follow-up, y	11.32 (0.17–41, median 10)
Moderate, n (% of 75)	7 (9)
Age at diagnosis, y	2.2 (neonate to 7)
Length of follow-up, y	13.7 (2–44, median 7)
Severe, n (% of 75)	25 (33)
Age at diagnosis, y	6.26 (neonate to 49)
Length of follow-up, y	17.2 (2–44, median 14)
Hypertrophic cardiomyopathy, n (% of 113)	16 (14)
Mild, n (% of 16)	9 (56)
Age at diagnosis, y	3.8 (neonate to 18)
Length of follow-up, y	13.2 (2–27, median 7)
Severe, n (% of 16)	7 (44)
Age at diagnosis, y	0.35 (neonate to 1.17)
Length of follow-up, y	16.1 (0.5–36, median 10)

ASD, atrial septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

Pulmonary Stenosis

Seventy-five patients (66%) had PS of varying severity—43 (57%) mild, 7 (9%) moderate, and 25 (33%) severe.

Mild

Average age at diagnosis for patients with mild PS was 2.8 years (1 month to 32 years, median 1 year), with 11.32 years (2 months to 41 years, median 10 years) of follow-up. All cases of mild pulmonary stenosis with follow-up were nonprogressive, and none of our patients required a procedure on their pulmonary valve. About half of the cases of mild PS were isolated, though some had another coexisting lesion, including atrial septal defect/patent foramen ovale (ASD/PFO) (8) (two were closed surgically), ventricular septal defect (VSD) (3) (all closed spontaneously), patent ductus arteriosus (2) (one was ligated), dysplastic aortic valve (2), mitral valve prolapse (3), and peripheral pulmonary artery stenosis (2). Six patients had associated mild HCM.

Moderate

Average age at diagnosis for patients with moderate PS was 2.2 years (1 month to 7 years,

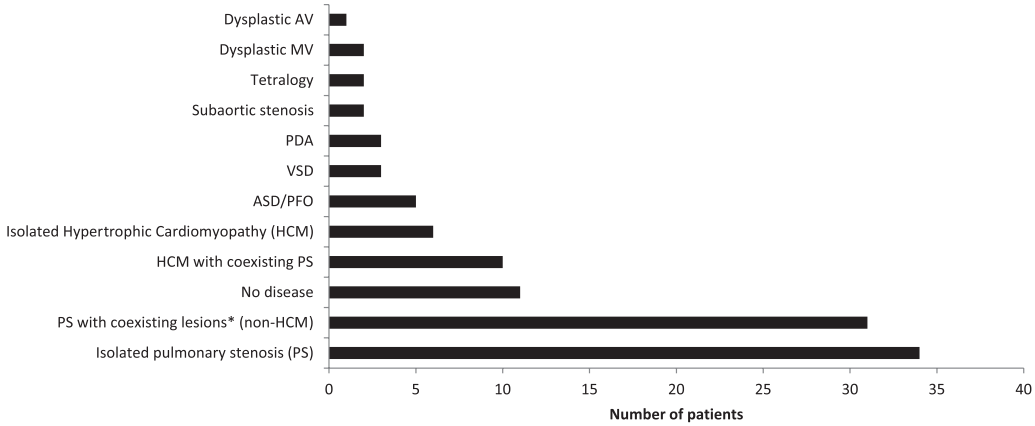

Figure 1. Distribution of cardiac disease in Noonan syndrome. *Coexisting lesions are common, and include ASD/PFO (15), VSD (4), mitral valve (MV) prolapse (3), dysplastic aortic valve (AV) (2), patent ductus arteriosus (2), peripheral pulmonary artery stenosis (2), subaortic stenosis (2), and bicuspid aortic valve (1). ASD, atrial septal defect; PFO, patent foramen ovale; VSD, ventricular septal defect.

median 1.13 years), with 13.7 years (2–44, median 7) of follow-up. Three of the patients went on to have a procedure, on average 12.5 years after diagnosis. (Two patients had balloon valvuloplasty; 1 had a valvectomy.) Three patients were stable with time and one was lost to follow-up. Four patients had isolated pulmonary valve disease, with associated ASD (closed at surgery), VSD, and mild HCM seen in the other three, respectively.

Severe

Average age at diagnosis for patients with severe PS was 6.26 years (shortly after birth—49 years, median 3 years), with 17.2 years (2–44, median 14) of follow-up. All patients had a therapeutic procedure (3 valvuloplasties, 10 valvectomies, 12 valvotomies), an average of 2.1 years after diagnosis (at time of diagnosis to 16 years, median 5 months). Again, many patients had isolated pulmonary valve disease. When present, coexisting lesions included ASD/PFO (6) (all closed surgically), bicuspid aortic valve (1), subaortic stenosis (2), and three cases of HCM.

Hypertrophic Cardiomyopathy

Sixteen patients (14%) carried a diagnosis of HCM, 9 (56%) mild and 7 (44%) severe.

Mild

Average age at diagnosis for the nine patients was 3.8 years (birth to 18 years), with 13.2 years of follow-up (2–27 years, median 7). Seven patients followed up did not show evidence of progression; two of these patients had been on chronic beta-blocker therapy. One patient had mild disease diagnosed at age 5 that 17 years later was classified as moderate. One patient had mild HCM associated with moderate PS, who, after balloon valvuloplasty, demonstrated resolution of septal hypertrophy. Seven of nine patients had documented associated pulmonary valve disease (6 mild, 1 moderate).

Severe

Average age at diagnosis for the seven patients was 4.2 months (shortly after birth to 14 months), with 16.1 years of follow-up (range 6 months to 36 years, median 10 years). Five patients were on chronic beta-blocker therapy. One of these patients had an ablation and implantable cardioverter-defibrillator (ICD) placed for non-sustained ventricular tachycardia 20 years after diagnosis; two of these patients had associated severe PS at diagnosis and underwent valvuloplasty; one had a myectomy 5 months after diagnosis but died 1 month later (age 6 months) secondary to heart failure. Another patient underwent a myectomy 12 years after diagnosis, developed atrial fibrillation 12 years later, then experienced an aborted sudden death and placement of an ICD 6 years later (32 years after original diagnosis). Another patient, who had associated severe PS treated by valvotomy at 1 year of age, died unexpectedly at 10, presumably of an arrhythmia.

Table 2. Deaths

Diagnosis at Presentation	Age at Presentation	Age at Death	Cause of Death
Severe HCM	Neonate	6 mo	Heart failure
Severe PS	4 y	6 y	At surgery
Severe HCM and severe PS	Neonate	10 y	Presumable arrhythmia
Severe PS	6 y	28 y	Car accident
Tetralogy of Fallot	Neonate	40 y	Presumable arrhythmia
Severe PS	5 y	49 y	Arrhythmia
Severe PS	33 y	50 y	Stroke

HCM, hypertrophic cardiomyopathy; PS, pulmonary stenosis.

Other Cardiac Abnormalities

As shown in Table 1 and Figure 1, there are a number of less common, isolated lesions seen in NS. Nearly half of the left-to-right shunting lesions (5/11), including ASD (2/5), VSD (1/3), and patent ductus arteriosus (2/3), required surgical repair. Both patients with subaortic stenosis underwent resection; one of these patients subsequently suffered from recurrent ventricular tachycardia, and the other patient required repeat myectomy 3 years later. Both patients with tetralogy of Fallot, after multiple surgeries, had late complications due to arrhythmias. The patient with a dysplastic aortic valve had frequent premature ventricular contractions on late follow-up.

Deaths

Among the 98 patients with follow-up data, there were seven deaths (see Table 2). Elapsed time from diagnosis to death averaged 19.4 years (6 months to 44 years). One patient with severe HCM died at 6 months secondary to heart failure. A 6-year-old with severe PS died at surgery. A 10-year-old who had undergone successful surgery for severe PS also had known HCM; he died suddenly, and severe HCM was present at autopsy. A patient with a history of valvotomy for severe PS died at 28 in an automobile accident. Another, with a history of tetralogy of Fallot repair at age 5, conduit replacement and ICD placement at 35, and cardioverted atrial fibrillation at 36, died suddenly at age 40, presumably of an arrhythmia. A patient with severe PS, valvuloplasty at 16, and valvectomy at 28 died at 49 secondary to an arrhythmia. A patient first seen at our institution at age 33 and diagnosed with severe PS with subsequent valvotomy had atrial fibrillation on follow-up 6 years later, then 1 year later underwent tricuspid valve replacement; this patient died at 50 secondary to a cerebral-vascular accident.

Discussion

There is a paucity of information on the long-term cardiac outcomes in NS. A recent cross-sectional study on 35 patients with NS, ages 16–68, reported that cardiac disease was stable and nonprogressive with time, though the data were self-reported.[12] Even for individuals without heart disease, current recommendations state that they should have cardiac reevaluation every 5 years.[11] Our study compared follow-up data with presentation data. We had 113 patients included in our cohort, 98 of whom had at least 1 follow-up visit. Most patients had multiple visits over many years. Thus, we had data for 87% with an average follow-up of over 14 years.

NS is recognized as a risk factor for progression of pulmonary stenosis because of the high prevalence of valve dysplasia.[13,14] Prior work showed that patients with dysplasia were more likely to need an intervention and were less likely to have a satisfactory result.[8] Establishing which patients are at risk has important prognostic implications. Our study included 75 patients with pulmonary stenosis, followed up for an average of 13.6 years. Those designated as having mild PS comprised the majority, and they were stable over the study period without progression. These findings are consistent with studies of isolated mild pulmonary valve stenosis, which seldom progresses beyond early infancy and is generally regarded as a static lesion beyond 6 months of life.[15–17]

Severe pulmonary valve dysplasia is a distinct marker of NS, being uncommonly found in nonsyndromic patients with PS.[18] Thirty-seven percent (28/75) of our patients with PS had a procedure to relieve stenosis, including all 25 of our severe patients. Another study[19] on NS reported that 42% of patients with PS who were followed for an average of 12 years needed a procedure to relieve stenosis, but a lack of specifics with regard to initial diagnosis and time to procedure from diagnosis makes comparison with our results chal-

lenging. Reviewing the average ages at diagnosis of the varying degrees of PS, it is interesting that the severe subgroup had the latest age at 6.26 years, largely owing to two individuals who were diagnosed well into adulthood (at 33 and 49 years). There were 11 in 25 patients diagnosed at less than 1 year of age, while 10 in 25 were diagnosed in preschool and as school-aged children.

The timing, course, and prognosis of NS-associated HCM is variable and not well understood.[10] Symptomatic HCM in infancy, of which NS is the leading genetic cause,[9] carries a poor prognosis and is associated with significant mortality.[20,21] Studies focusing on HCM outcomes in NS compared with nonsyndromic HCM have shown varying results.[20–23] Nugent et al. did not find a difference in freedom from death or transplantation between 23 children with NS and those without.[23] Others, however, reported a worse outcome in NS-associated HCM compared with nonsyndromic HCM.[21,22] Our study included 16 subjects with HCM followed up for an average of 14.6 years. Two patients (12.5%) died within that time period; 14 (87.5%) had good late survival, but two of these patients required ICD placement an average of 26 years after presentation. Mild HCM was nonprogressive with the exception of one patient who showed an interval increase in hypertrophy over a 17-year period; as a group, though, these patients did well. Mild HCM was diagnosed later in childhood compared with severe HCM, which typically manifests in early infancy through the first year of life. Beyond this time, we did not have patients present with severe HCM. Furthermore, of the 82 patients who did not have HCM on presentation, none had new-onset HCM on reassessment. We conclude that it is unlikely for HCM to progress or have new onset beyond infancy and early childhood, but acknowledge the need for ongoing surveillance until more is definitively known.

Finally, since originally described, and for most of its history, NS was a clinical diagnosis. Yet the past decade has seen an impressive advance in molecular genetics, and genetic testing is now available to aid in establishing a diagnosis in up to 75% of cases.[6] Along with these diagnostic capabilities, genotype–phenotype associations are beginning to be understood. *PTPN11*, the most common genetic mutation, is positively associated with pulmonary stenosis and atrial septal defects but negatively associated with HCM, which is overrepresented in *RAF1* mutations.[24] Most of our cohort's data predate the modern era of available genotyping. Only four patients had an identified gene documented in their medical record: one with *PTPN11* who had severe PS, two with *SOS1* (both with mild PS, one with an associated small ASD), and one with *SHOC2* who had a dysplastic mitral valve.

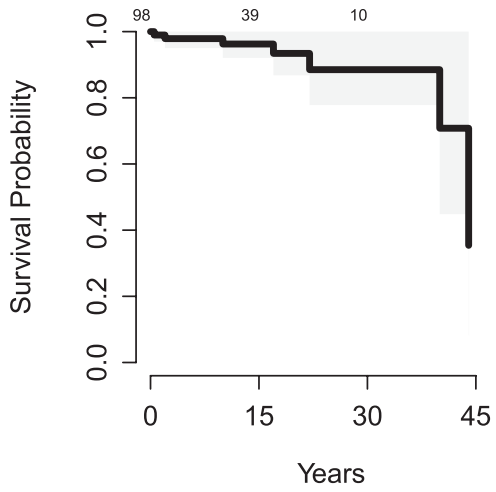

Figure 2. Survival to death from time of presentation in Noonan syndrome. All patients with follow-up (n = 98) included.

Limitations

This is the experience of a single institution. HCM is rare, and our cohort of 16 patients is a small sample size, which limits its generalizability. We were unable to retrieve all records, and other records were incomplete. Diagnoses were clinical, and most did not have formal genetic testing, which only recently has been available. This favors selection of individuals with more recognizable phenotypes. Further, the RASopathies resemble each other in infancy. Additionally, some patients did not have echocardiogram or catheterization data to compare, which restricts quantitative analysis. Finally, remarkable advances in cardiac diagnosis and management have occurred in the five decades spanned by this study. This introduces errors that we are unable to adjust for.

Conclusion

Our study demonstrates that the majority of patients with NS have stable cardiac disease with time, and prognosis depends primarily on the severity of disease at presentation. Overall late survival is good (Figure 2). Severe disease, typically

symptomatic in the form of severe PS and/or severe HCM, usually presents early in life, and these patients are at greatest risk for long-term morbidities. Mild pulmonary valve disease, in isolation or with coexisting lesions, portends a very favorable prognosis, though associated septal defects, if present, may require repair. Moderate pulmonary stenosis can progress to the point that a corrective procedure is necessary, but this can be years after presentation. Patients with mild HCM do relatively well over time without worsening of hypertrophy. It is rare to have new-onset HCM beyond early childhood.

This study adds information on the natural history of the two most common cardiac defects seen in NS. A strength of this study is the amount and length of longitudinal data acquired (>14 years). Prospective studies will be needed to confirm our findings and enable better prognostication. With the advent of molecular genetics, it will be interesting to see a more thorough accounting of genotype–phenotype associations and if certain mutations are predictive of clinical course.

Author Contributions

John L. Colquitt, MD: conception and design, data acquisition, data analysis and interpretation, manuscript authorship, approval of article.

Jacqueline A. Noonan, MD: conception and design, direction and supervision of the project, data acquisition, data analysis and interpretation, critical revision of article, approval of article.

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