Cardiac Findings in Noonan Syndrome

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Noonan Syndrome Seminar
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Cardiac findings in Noonan Syndrome

- Brief Overview
- Review of cardiac investigations
- Structural heart disease
- Functional heart disease
- Outcome data
- Current management & Future directions
- Summary

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Overview

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Noonan Syndrome

- Multisystem disorder
- Autosomal dominant inheritance
- Incidence 1:1000-2500
- Second most common genetic syndrome associated with cardiac abnormalities
  - Pulmonary stenosis (60%)
  - Hypertrophic Cardiomyopathy (20%)
  - Atrial septal defect (5-10%)
- Cardiac involvement can range from mild through to significant morbidity

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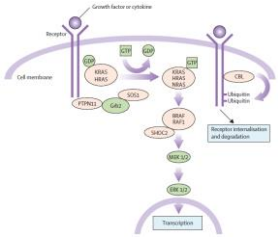
RAS-MAPK pathway



Important signal transduction pathway.
Stimulate cell proliferation
Genes implicated with NS usually enhance signal through this pathway

PTPN11	(50%)
SOS1	(10%)
RAF1	(10%)
KRAS	(<2%)
NRAS	(<1%)

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www.thelancet.com Vol 381 January 26, 2013

Genotype and phenotype correlation

	Cardiovascular	Growth	Developmental
PTPN11 (roughly 50%)	More pulmonary stenosis; less hypertrophic cardiomyopathy, and atrial septal defect (ostium secundum type)	More short stature; lower IGF1 concentrations	Patients with N308D and N308S have little or no intellectual disability
SOS1 (roughly 10%)	Less atrial septal defect	Less short stature	Less intellectual disability, language delays
RAF1 (roughly 10%)	More hypertrophic cardiomyopathy	--	--
KRAS (<2%)	--	--	More severe cognitive delay
NRAS (<1%)	--	--	--

Percentages in parentheses are the proportion of patients with Noonan syndrome who have the mutation.

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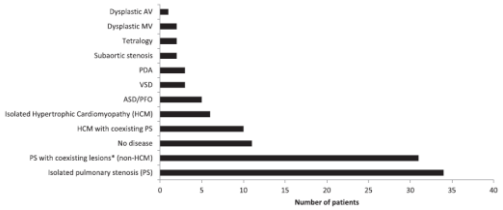
Distribution of cardiac involvement



Congenit Heart Dis. 2014;9:144–150

Cardiology

Patient pathway for cardiology

Fetal
- ⟸ High Risk Screening
- ⟸ Abnormal anomaly scan
- ⟸ Fetal arrhythmia

Neonatal
- ⟸ NICU/Prematurity
- ⟸ Undiagnosed CHD
- ⟸ Genetic/metabolic condition

Paediatric
- ⟸ Acquired Heart disease: Oncology, Infective & inflammatory disease
- ⟸ Screening Fhx Cardiomyopathy, CT disorders
- ⟸ Arrhythmia
- ⟸ Screening – high performance athletes

Adult

Cardiology service

- Increasing role of fetal cardiology screening
- Screening is possible from around 18 weeks
- Main presentation to service is in neonatal period
- Transition from paediatric to adult congenital service
- Some terminology
  - Echocardiogram (Echo)
  - Electrocardiogram (ECG)
  - Cardiac magnetic resonance imaging (CMRI)
  - Cardiac catheterisation

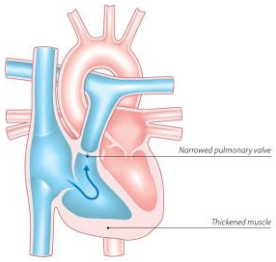
Structural heart disease

Pulmonary Stenosis

Narrowing of the valve from the RV to the pulmonary artery

Typically there is a thickening of the valve leaflets – dysplastic

A narrow valve leads to increased RV pressure



Presentation

- Severe PS may present with cyanosis or collapse in neonatal period
- Usual presentation – asymptomatic murmur in childhood
- Possible reduction in exercise capacity
- Clinically there is a murmur & ejection click, ESM at ULSE
- ECG normal or RVH
- CXR normal or dilated MPA
- Echo is used to grade the severity of the obstruction
  - Mild <40mmHg
  - Moderate 40-60mmHg
  - Severe >60mmHg

Pulmonary stenosis

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

John L. Colquitt, MD,* and Jacqueline A. Noonan, MD†

Followed 113 patients for an average 14years (2 months-44 yrs)

75 patients had PS (66%)
43 patients had mild PS (57%)
7 patients had moderate PS (9%)
25 patients had severe PS (33%)

All mild were non-progressive
3 patients with Moderate PS had a procedure (average 12 years after Dx)
All severe PS had a procedure (average 2 yrs after diagnosis)

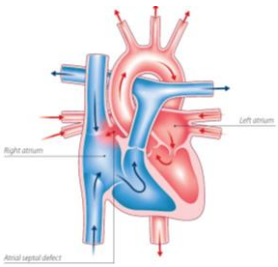
Congenit Heart Dis. 2014;9:144–150

Pulmonary Stenosis

- Pulmonary valve often dysplastic
- Response to balloon valvuloplasty is variable
- May require surgical valvotomy
- The result often exchanges stenosis for regurgitation
- Generally PR is well tolerated
- May have a reduced exercise tolerance
- With time may develop a dilated RV
- Investigated with CMRI
- Pulmonary valve replacement may be needed.

Atrial Septal Defect (secundum)

- usually asymptomatic murmur
- occasionally with symptoms of cardiac failure
- Precordial hyperactivity
- Possible RV+
- Fixed split S2
- Grade 2-3/6 ESM ULSE
- Tricuspid diastolic flow murmur (if large L→R shunt)



ASD - Prognosis

- Small defects may close spontaneously
- Large defects, long term risk of
  - Right heart failure
  - pulmonary hypertension
  - atrial arrhythmias
  - paradoxical embolism
- ASD closure usually recommended for large defects

ASD Closure

Surgical patch closure
- Large defects
- Inadeqaute margins

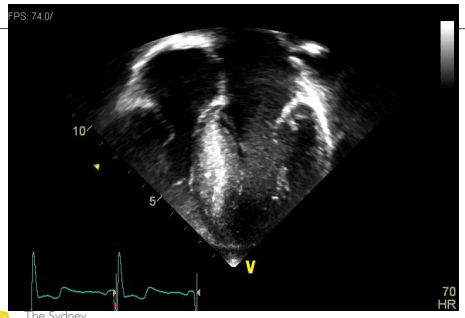
Transcatheter closure
- Smaller defects with good margins

Results
- Surgical outcome is excellent, mortality <1% but requires sternotomy
- Transcatheter closure under evaluation, excellent results but unknown long term risk of erosion (very low risk)

Functional Heart Disease

Hypertrophic Cardiomyopathy

- Hypertrophy means enlargement
- Cardiomyopathy means impaired function
- Present in approx. 20% of NS patients
- More commonly seen SOS1 mutation
- Less common in PTPN11
- Can be mild-severe
- Symptoms are related to impaired diastolic function (relaxation)
- Hypertrophy may cause outflow tract obstruction
- Risk of arrhythmia (abnormal heart rhythms)
- Diagnosis is with Echo and CMRI.



Presentation

Survival Implications: Hypertrophic Cardiomyopathy in Noonan Syndrome

Edward J. Hickey, MD, FRCS(C),* Rohit Mehta, MD,† Maryam Elmi, MD,* Kentaro Asoh, MD,† Brian W. McCrindle, MD, FRCP(C),† William G. Williams, MD, FRCS(C),* Cedric Manlhiot, MD,† and Lee Benson, MD, FRCP(C)†

Table 1. Noonan syndrome-HCM vs. nonsyndromic HCM

	Noonan syndrome-HCM (n = 30)		Nonsyndromic HCM (n = 120)		
Variable	Median	Range	Median	Range	*P* value
Age at diagnosis (years)	0.42	0 to 14.7	7.2	0.02–17.9	.001
Interventricular septum *z*-score	+6.9	2 to 13.6	+6.8	2 to +32.7	.43
LV posterior wall *z*-score	+2.4	−0.6 to 12.5	+1.7	−0.6 to +11.0	.27
LV end-diastolic volume *z*-score	−2.0	−11.2 to 0.6	−1.8	−7.2 to +1.9	.11
LV end-systolic volume *z*-score	−2.7	−5.2 to 1.6	−2.6	−7.2 to +2.1	.20
LVOT peak gradient (mmHg)	32.1	3 to 100	21	0 to 125	.78

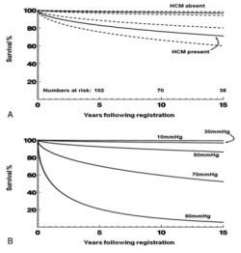
HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract.

Congenit Heart Dis. 2011;6:41–47

Management

- Management is directed at managing diastolic impairment
- Beta blockade is mainstay of therapy
- Hypertrophy may lead to obstructive outflow gradients from the left heart
- In significant cases a myectomy may be necessary
- Hypertrophy is a risk for ventricular arrhythmia
- Some patients require placement of an ICD (defibrillator)
- If there is failure of medical therapy (+myectomy) then transplantation may be considered

At risk group



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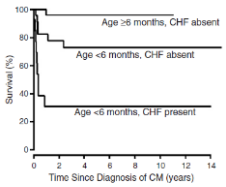

American Heart Journal
Volume 164, Number 3

At Risk

- Earlier presentation (at <6 months of age)
- Signs of heart failure at presentation
- Development of left ventricular outflow obstruction
- A greater degree of hypertrophy increases risk of arrhythmia

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Longterm Outcome

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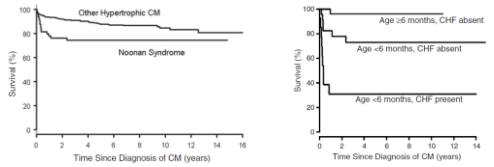
Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: A study from the Pediatric Cardiomyopathy Registry

James D. Wilkinson, MD, MPH,[a,g] April M. Lowe, MS,[b,g] Bonnie A. Salbert, DO,[c,g] Lynn A. Sleeper, ScD,[b,g] Steven D. Colan, MD,[d,g] Gerald F. Cox, MD, PhD,[e,g] Jeffrey A. Towbin, MD,[f,g] David M. Connuck, MD,[c,g] Jane E. Messere, RN,[a,g] and Steven E. Lipshultz, MD[a,g] *Miami, FL; Watertown, Boston, and Cambridge, MA; Danville, PA; and Cincinnati, OH*



Children present at an earlier age with HCM ass NS
Greatest risk in first 6 months
Recommend early assessment

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The natural history of Noonan syndrome: a long-term follow-up study

A C Shaw, K Kalidas, A H Crosby, S Jeffery, M A Patton

Arch Dis Child 2007;92:128–132. doi: 10.1136/adc.2006.104547

Results: Data are presented for 112 individuals with Noonan syndrome (mean age 25.3 (range 12–71) years), who were followed up for a mean of 12.02 years. Mutations in *PTPN11* were identified in 35% of probands. Ten subjects died during the study interval; three of these deaths were secondary to heart failure associated with hypertrophic cardiomyopathy. Pulmonary stenosis affected 73 (65%) subjects; 42 (58%) required no intervention, nine underwent balloon pulmonary valvuloplasty (three requiring further intervention) and 22 surgical valvuloplasty (three requiring further intervention). Hypertrophic cardiomyopathy affected 21 (19%) patients, which had remitted in two cases, but one subject required cardiac transplant. No subjects died suddenly or had symptoms suggestive of arrhythmia. The mean final adult height

Approx. 1/3 required intervention on the pulmonary valve
Outside of early childhood HCM appears stable with low risk of arrhythmia

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

John L. Colquitt, MD,* and Jacqueline A. Noonan, MD†

*Department of Pediatrics and †Division of Pediatric Cardiology, Department of Pediatrics, University of Kentucky College of Medicine, Lexington, Ken, USA

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.

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Current practice and future direction

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Current

- Early screening of infants suspected of having NS
- Looking for early identification of HCM
- Genotype/phenotype correlation is important
- Prognosis and treatment is very dependent on age and severity of symptoms
- HCM management is related to diastolic failure, outflow obstruction and risk of arrhythmia
- For Pulmonary stenosis approx. 1/3 patients will require intervention
- Outside of the early period HCM appears to run a stable course
- Most children will require serial echocardiography screening (annual)
- If HCM present then MRI may be necessary to quantify but generally reserved for older children

Future

- Targeted therapy?
- Research directed at targeting RAS mediated pathways
- Immunosuppresive therapy may ability to inhibit or dampen pathway
- Rampamycin - mouse model with HCM in LEOPARD syndrome
- Levostatin decrease RAS signalling
- Concerns regarding the safety of long-term use of these medications

Summary

Summary

- Noonan syndrome has a high incidence of cardiac involvement
- Strong genotype-phenotype association
- Approx. 1/3 patients will require intervention for Pulmonary stenosis
- HCM present in 20% of patient
- Greatest risk is with early and syptomatic presentation (<6 months)
- Important for early cardiac review in all patients with NS
- Conversely important to consider NS in all infants presenting with HCM
- Outside of the early childhood period the course of HCM is often stable

Thank You