FACTSHEET #5
CARDIOLOGY (heart issues)

Noonan Syndrome Association

Cardiac or heart abnormalities are often associated with Noonan Syndrome. These can include problems with the heart valves, holes in the walls separating the chambers of the heart, and thickening of the heart muscle.

People with Noonan Syndrome can be affected by a wide range of heart-related disease, which fall into two main categories:

- Congenital heart disease affects about 80% of patients
- Thickened heart muscle (hypertrophic cardiomyopathy) is found in about 20% of patients.

Heart problems in Noonan Syndrome

COMMON	Description
Pulmonary valve stenosis	The pulmonary valve (the valve between the right ventricle and the pulmonary artery that goes to the lungs) is too small, narrow, or stiff.
MODERATE RISK	
Hypertrophic cardiomyopathy	The heart muscle becomes abnormally thick (hypertrophied).
RARE	
Atrial septal defect	A hole in the wall (septum) that divides the upper chambers (atria) of the heart.
Ventricular septal defect	A hole in the wall (septum) that separates the two lower chambers (ventricles) of the heart
Atrioventricular septal defect	A large defect in the centre of the heart that can be a combination of: • atrial septal defect • ventricular septal defect • abnormalities of the valves, often resulting in one large valve instead of two separate valves
Mitral abnormalities	A problem with the valve located between the left heart chambers (left atrium and left ventricle)
Aortic coarctation	Part of the aorta – the large artery that carries oxygen-rich blood to the rest of the body – is narrower than usual.
Patent ductus arteriosus	A persistent opening between the two major blood vessels leading from the heart. The opening, a normal part of a baby's circulatory system in the womb, usually closes shortly after birth.
Tetralogy of Fallot	Complex abnormality with four defects of the heart: • Ventricular septal defect; • Pulmonary stenosis; • Enlarged and abnormal aortic valve; • Ventricular hypertrophy – the muscular wall of the lower right chamber of the heart (right ventricle) is thicker than normal.

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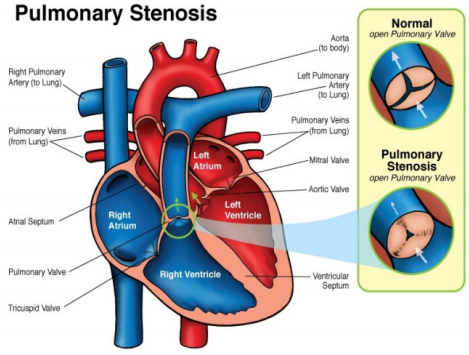
Pulmonary valve stenosis

Affecting about 40% of people with Noonan syndrome, pulmonary valve stenosis is the most common heart problem. It occurs when the pulmonary valve (the valve between the right ventricle and the pulmonary artery that goes to the lungs) is too small, narrow, or stiff.

The severity varies:

- Mild cases (about 60%): these cases are similar to patients with pulmonary valve stenosis who do not have Noonan syndrome – the stenosis tends not to progress (and often improves without treatment) and may not need surgical treatment. However, in some cases there may be an additional heart problem such as an atrial septal defect.
- Moderate (about 10%) or severe (about 30%) cases: in these cases, the rates of surgical treatment are higher – about 50% and 100%, respectively.



Atrioventricular septal defects

An atrioventricular septal defect (AVSD) is a large defect in the centre of the heart that can be a combination of:

- atrial septal defect
- ventricular septal defect
- abnormalities of the valves, often resulting in one large valve instead of two separate valves

A partial atrioventricular septal defect is the most common form of this problem, but complete defects, while rare, do occur.

Hypertrophic cardiomyopathy

About 10 - 20% of people with Noonan syndrome suffer from hypertrophic cardiomyopathy, where the heart muscle becomes abnormally thick (hypertrophied). This can become evident early in life, with more than half diagnosed by six months of age (much earlier than other childhood forms of hypertrophic cardiomyopathy, which on average become evident at the age of 8 years). Obstructions of the outflow from the left ventricle are common, and children with Noonan syndrome and hypertrophic cardiomyopathy are more likely to have congestive heart failure than other children with hypertrophic cardiomyopathy.

Genetics

A mutation in the PTPN11 gene is the most common cause of Noonan syndrome but there are now up to 15 genes which may be involved. The gene affected can also influence the likelihood and type of congenital heart disease.

PTPN11 mutation

- More likely to have pulmonary valve stenosis or an atrial septal defect
- Less likely to have hypertrophic cardiomyopathy

RAF1 mutation

- Less likely to have pulmonary valve stenosis
- More likely to have hypertrophic cardiomyopathy

RIT1 mutation

- More likely to have hypertrophic cardiomyopathy and valve abnormalities

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SOS1 mutation

- More likely to have pulmonary valve stenosis

Treatment

About a third of patients with pulmonary stenosis needed surgery or a repeat procedure.

A balloon can be used to open a stiff valve, through a procedure termed 'percutaneous balloon valvuloplasty'. If this fails or is deemed not feasible, surgical valvotomy – an open-heart procedure to open up a valve – can be carried out.

Other structural heart defects may require invasive treatment. Some may be amenable to catheter intervention (e.g. percutaneous balloon valvuloplasty, stent insertion or device closure) but others may require cardiac surgery. Treatment of other structural heart defects – these may require cardiac surgery

Treatment of hypertrophic cardiomyopathy is primarily directed at treating symptoms. This is usually with medication (e.g. beta blockers), although rarely cardiac surgery to relieve left ventricular outflow tract obstruction or to repair or replace the mitral valve may be required.

Very rarely, individuals with Noonan syndrome and hypertrophic cardiomyopathy may be at an increased risk of potentially life-threatening abnormal heart rhythms and treatment with an implantable cardioverter-defibrillator (ICD) may be recommended.

More recently, a new class of drugs (MEK inhibitors such as trametinib) has been reported to improve the features and symptoms of hypertrophic cardiomyopathy in some children with Noonan syndrome and related conditions presenting with very severe forms in the first few months of life.

Further studies to investigate the use of these drugs are ongoing.

REFERENCES/FURTHER READING

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New review with Kaski and Bruce Gelb submitted for publication – included later