Congenital Heart Diseases in Noonan's Syndrome – Mitral Valve Anomalies: Important Cause of Left Ventricular Outflow Tract Obstruction

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Background: Noonan's Syndrome (NS) is a common genetic disorder associated with congenital heart disease. It is an autosomal dominant. Cardiac defects are found in 50-60% of cases of this syndrome. Ventricular outflow obstruction in the form of pulmonary valvular stenosis and hypertrophic cardiomyopathy (HOCM) is the most common congenital heart condition. Apart from HOCM, mitral valve anomalies are also associated with left ventricular outflow obstruction.

Objective: To identify congenital heart diseases associated with Noonan's syndrome.

Design: A Retrospective Study.

Setting: Pediatric Cardiac Outpatient Service, Bahrain Defence Force Hospital, Bahrain.

Method: All patients with confirmed Noonan's syndrome from 2005 to 2018 were included in the study. Cardiac evaluation was performed by chest X-ray, ECG, 2D echocardiography and cardiac catheterization. Personal characteristics were documented: age at diagnosis, sex and consanguinity. Morphologic types of congenital heart diseases (CHD) and outcomes were analyzed.

Result: Twenty-nine children with Noonan's syndrome; 15 (52%) males and 14 (48%) females were included in the study from 2005 to 2018. Pulmonary valvular stenosis, 21 (72%), was the most common cardiac anomaly followed by HOCM, 5 (17%). Mitral valve tissue was found in two (7%) patients. Severe obstruction to the left ventricular outflow by accessory mitral tissue was identified in one (3%) patient which required surgery.

Conclusion: Cardiac defects are common in NS. Left outflow tract obstruction due to accessory mitral valve tissue is rare; however, it is a significant anomaly and if not specifically looked for on echocardiography, it could be missed.

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Noonan's syndrome (NS) is an autosomal dominant genetic disorder characterized by short stature, webbed neck, facial features of low set ears, hypertelorism, epicanthic folds, ptosis, chest deformity and mental retardation (NS, OMIM 163950).

The syndrome is named after pediatric cardiologist, Dr. Jacqueline Noonan, who described it in nine patients with pulmonary stenosis, hypertelorism, webbed neck, low set ears and chest deformity[1]. The incidence of NS worldwide is 1 in 1,000-2500 live births[2]. Genetic mutations in as many as 9 genes (PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1, and CBL) have been identified. These genes code for proteins in the RAS-mitogen-activated protein kinases (MAPK) pathway, involved in growth and differentiation. "RASopathies" (neuro-cardio-facial-cutaneous disorders, such as Neurofibromatosis type-1, Costello, LEOPARD, and Legius syndrome), are a group of syndromes with similar genetic mutations and pathogenesis pathways with varied phenotype[3,4].

Diagnosis of NS is based mainly on clinical features. In neonates, excessive nuchal fold and lymphedema of limbs is a soft marker for NS. In non-neonates, typical facial features aid in the diagnosis. However, patients may have varied phenotypic presentation and can pose a challenge for accurate diagnosis. Duncan et al and Ineke van der Burgt have described comprehensive scoring systems which aid in the clinical diagnosis of NS[5,6]. Only 75% patients of NS can be diagnosed by molecular studies.

NS is a multisystem disorder and cardiac diseases are common. Valvular pulmonary stenosis (PS) is the most common cardiac defect followed by HOCM, atrial septal defects (ASD),

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atrioventricular septal defects (AVSD), Tetralogy of Fallot (ToF) and left-sided obstructive lesions[7-11].

Left-sided valvular abnormalities, such as mitral valve prolapse, abnormal insertion of papillary muscles, accessory mitral valve tissue and aortic valve abnormalities have been detected by various studies. Some of these can cause severe left ventricular outflow obstruction requiring intervention[12-14].

The aim of this study is to identify congenital heart diseases associated with Noonan's syndrome.

METHOD

All patients with confirmed Noonan's syndrome from 2005 to 2018 were included in the study. Cardiac evaluation was performed by Chest X-ray, ECG, 2D echocardiography and cardiac catheterization. Personal characteristics were documented: age at diagnosis, sex and consanguinity. Morphologic types of congenital heart diseases (CHD) and outcomes were analyzed.

RESULT

Twenty-nine patients were diagnosed with NS, 15 (52%) males and 14 (48%) females. Age at diagnosis was 6 months to 12 years, mean of 72 months. Ten (34.5%) patients had second-degree consanguinity.

Twenty-one (72%) patients had PS, 11 (38%) had isolated PS and 10 (35%) had PS associated with cardiac defects; 3 (10%) patients of the isolated PS had dysplastic thickened pulmonary valve and severe valvar PS with mean right ventricular to pulmonary artery gradient of >70mmHg (range 110-85mmHg), moderate PS was diagnosed in 5 (17%) patients with mean gradient of 45mmHg (range 50-35mmHg) see table 1. Five (17%) patients with isolated PS underwent successful percutaneous balloon dilatation of pulmonary valve. One patient with severe dysplasia of the pulmonary valve required a second percutaneous dilatation of the pulmonary valve, see table 2. Of the 10 patients with non-isolated PS; four had an associated small secundum ASD, three had mitral valve anomalies, two had HOCM and one had VSD.

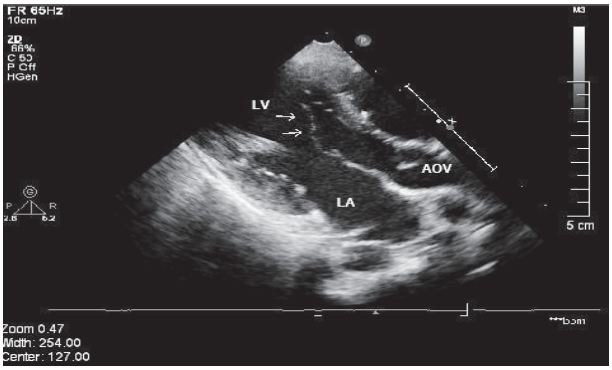
Table 1: Congenital Heart Diseases in Noonan's Patients

Main Cardiac Abnormalities	n (%)	Associated Cardiac and Non-Cardiac Abnormalities	Intervention
Isolated PS	11 (38%)	Microcephaly, Temporal lobe epilepsy in 1	Percutaneous balloon dilation in 5
PS with ASD	4 (13.7%)	-	Percutaneous balloon dilation in 1
PS with VSD	1 (3.4%)	-	Surgical correction
PS with mitral valve anomalies	3 (10.3%)	Accessory mitral valve tissue in 2, Myxomatous mitral valve with MVP in 1	Resection of obstructive accessory mitral valve tissue in 1
HOCM	5 (17%)	ASD in 2, Mild PS in 2, Aortic valvular regurgitation, abnormal papillary muscle with fibrotic myocardium in 1	None
Isolated ASD	3 (10.3%)	-	Percutaneous device closure in one, surgical closure in 2
Isolated VSD	1 (3.4%)	Pulmonary Hypertension	Surgical closure in one
Tetralogy of Fallot	1 (3.4%)	Atrio-Ventricular Septal Defect	Surgical correction in one
Total	**29 (100%)**		**12 (41%)**

Table 2: Outcomes of Isolated Pulmonary Valve Stenosis

Severity of Pulmonary Valve Stenosis	Valve Morphology Number (%)	RVOT & PA Gradient mmHg (mean)	Balloon Dilation Outcome
Severe	Dysplastic 3 (10.3)	110 -85 (70)	Success (2), redo dilation (1)
Moderate	Doming 5 (17)	50-65 (45)	Success (3), no intervention (2)
Mild	Doming 3 (10.3)	20-35 (25)	No intervention

Three (10.3%) of the four patients with PS and associated ASD's had only mild valvular pulmonary stenosis. Only one (3.4%) with severe PS required percutaneous balloon dilatation of the pulmonary valve. Of the three patients with PS and associated mitral valve abnormalities, two (7%) had accessory mitral valve tissues, see figure 1. One (3.4%) had severe left ventricular outflow tract obstruction and underwent surgical resection, see figure 2 and 3. The remaining patient demonstrated myxomatous mitral valve with mitral valve prolapse and mild regurgitation requiring no intervention.



LA= left atrium, LV= left ventricle, AOV= aortic valve

Figure 1: 2D Echocardiography Showing Accessory Mitral Valve Tissue (White Arrows)

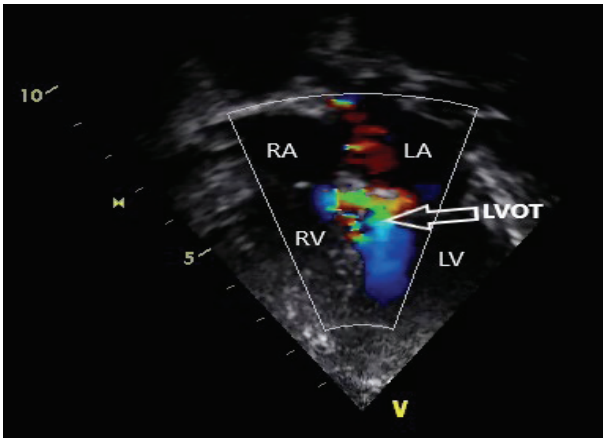


Figure 2: 2D Color Doppler (Apical 4 Chamber) Showing Turbulence (Arrow) Across Left Ventricular Outflow due to Accessory Mitral Valve Tissue

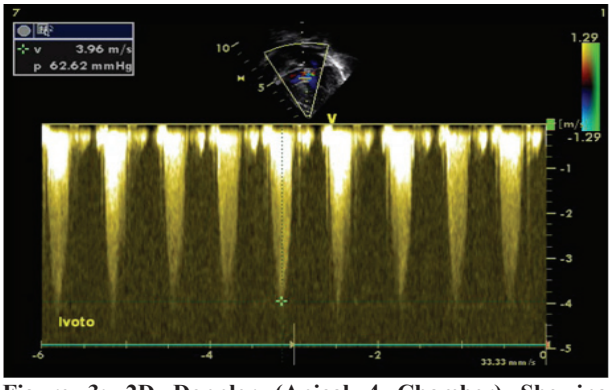


Figure 3: 2D Doppler (Apical 4 Chamber) Showing Severe Left Ventricular Outflow Obstruction (Peak Gradient>62mmHg) due to Accessory Mitral Tissue

The second most common cardiac anomaly in our study was HOCM diagnosed in 5 (17%) patients. All five had associated cardiac defects; none required intervention. Small secundum ASD's was seen in two (7%) patients with HOCM. Two (7%) neonates referred as cardiac murmur showed biventricular hypertrophy with mild pulmonary valvular stenosis. Both these neonates on follow-up showed complete resolution of ventricular hypertrophy but persistent mild valvular pulmonary stenosis. One (3.4%) patient with HOCM had fibrotic myocardium, abnormal papillary muscle and mild aortic valvular regurgitation with good left ventricular systolic function. No intervention was required.

Three (10.3%) patients had isolated large secundum ASD. One (3.4%) underwent percutaneous device closure using Amplatzer septal occluders and the other two (7%) required surgical closure as anatomy was not suitable for device closure. An isolated large peri-membranous VSD was detected in one (3.4%) infant which required early surgical closure due to pulmonary hypertension. One (3.4%) infant had ToF with an atrioventricular septal defect which required surgical correction.

DISCUSSION

In this study, pulmonary valve stenosis was the most common cardiac anomaly, which is similar to other studies. Dysplastic pulmonary valves with severe stenosis were confirmed by 2D echocardiography in 10.3% patients as compared to 7% in a study by Burch et al[15]. We obtained positive outcomes in two patients, while the third patient required a second procedure of balloon dilation with optimal result. Studies by Prendiville et al and Ishizawa et al have shown a high re-intervention rate for severely dysplastic pulmonary valves[16,17].

Hypertrophic cardiomyopathy incidence was 20% cases in NS[18]. It was documented in 5 (17%) of our patients. None of the patients required intervention and in two neonates, the ventricular hypertrophic cardiomyopathy regressed without treatment. Associated lesions were secundum atrial septal defect, valvular pulmonary stenosis and mild valvular aortic regurgitation.

In this study, accessory mitral valve tissues (AMV) were found in two patients. A study by Prifiti et al reported accessory mitral tissue in 12% of all mitral valve anomalies in NS patients[19]. Accessory mitral valve tissue could have varied morphology, such as balloon parachute, sail and leaflet. In addition, AMV tissue has been classified on the basis of intraoperative anatomy. Type I AMV, defined as a fixed mass, could be nodular (type IA) or membranous (type IB). Type II AMV occurs as a mobile mass and is classified as pedunculated (type IIA) or leaflet-type (type IIB). Type IIB AMVs are further divided into those with rudimentary chorda tendinea (type IIB1) or well-developed chorda tendinee (type IIB2). Type IIB has been the most frequent presentation reported.

In our study, the AMV was Type IIB membranous leaflet type. Children with moderate to severe LVOT obstruction require early surgery. Surgical outcomes of accessory mitral tissue in children have been satisfactory[20].

CONCLUSION

Noonan's syndrome has high incidence of major cardiac anomalies. Mitral valve anomalies like accessory valve tissue, although rare in general population, are often present in Noonan's syndrome and cause significant left ventricular outflow obstruction and should be carefully looked for in echocardiography.

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REFERENCE

1. Noonan JA. Hypertelorism with Turner Phenotype. A New Syndrome with Associated Congenital Heart Disease. Am J Dis Child 1968; 116 (4):373-80.
2. Nora JJ, Nora AH, Sinha AK, et al. The Ullrich-Noonan Syndrome (Turner Phenotype). Am J Dis Child 1974; 127(1):48-55.
3. Bentires-Alj M, Kontaridis MI, Neel BG. Stops along the RAS Pathway in Human Genetic Disease. Nat Med 2006; 12(3):283-5.
4. Tidyman WE, Rauen KA. The RASopathies: Developmental Syndromes of RAS/MAPK Pathway Dysregulation. Curr Opin Genet Dev 2009; 19:230–236.
5. Duncan WJ, Fowler RS, Farkas LG, et al. A Comprehensive Scoring System for Evaluating Noonan Syndrome. Am J Med Genet 1981; 10(1):37-50.
6. Ineke van der Burgt. Noonan Syndrome. Orphanet Journal of Rare Diseases 2007; 2:4.
7. Nora JJ, Torres FG, Sinha AK, et al. Characteristic Cardiovascular Anomalies of XO Turner Syndrome, XX and XY Phenotype, and XO/XX Turner Mosai. Am J Cardiol 1970; 25:639-641.
8. Van der Hauwaert LG, Fryns JP, Dumoulin M, et al. Cardiovascular Malformations in Turner's and Noonan's Syndrome. Br Heart J 1978; 40:500–509.
9. Digilio MC, Marino B, Giannotti A, et al. Noonan Syndrome with Cardiac Left-Sided Obstructive Lesions. Hum Genet 1997; 99:289.
10. Marino B, Digilio MC, Toscano A, et al. Congenital Heart Diseases in Children with Noonan Syndrome: An Expanded Cardiac Spectrum with High Prevalence of Atrioventricular Canal. J Pediatr 1999; 135:703–706.
11. Hirsch HD, Gelband H, Garcia O, et al. Rapidly Progressive Obstructive Cardiomyopathy in Infants with Noonan's Syndrome. Circulation 1975; 52:1161–1165.
12. Marino B, Gagliardi MG, Digilio MC, et al. Noonan Syndrome: Structural Abnormalities of the Mitral Valve Causing Subaortic Obstruction. Eur J Pediatr 1995; 154:949–952.

13. Klues HG, Roberts WC, Maron BJ. Anomalous Insertion of Papillary Muscle Directly into Anterior Mitral Leaflet in Hypertrophic Cardiomyopathy. Significance in Producing Left Ventricular Outflow Obstruction. Circulation 1991; 84:1188–1197.
14. Klues HG, Maron BJ, Dollar AL, et al. Diversity of Structural Mitral Valve Alterations in Hypertrophic Cardiomyopathy. Circulation 1992; 85:1651–1660.
15. Burch M, Harland M, Shinebourne E, et al. Cardiologic Abnormalities in Noonan Syndrome: Phenotypic Diagnosis and Echocardiographic Assessment of 118 Patients. JACC 1993l; 22(4):1189-1192.
16. Prendiville TW, Gauvreau K, Tworog-Dube E, et al. Cardiovascular Disease in Noonan Syndrome. Archives of Disease in Childhood 2014; 99(7):629-34.
17. Ishizawa A, Oho SI, Dodo H, et al. Cardiovascular Abnormalities in Noonan Syndrome: The Clinical Findings and Treatments. Acta Pediatr Jpn 1996; 38: 84-90.
18. Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan Syndrome and the other RASopathies: Prog Pediatr Cardiol 2015; 39(1): 13–19.
19. Prifti E, Frati G, Bonacchi M, et al. Accessory Mitral Valve Tissue Causing Left Ventricular Outflow Tract Obstruction: Case Reports and Literature Review. J Heart Valve Dis 2001; 10(6):774-8.
20. Eiriksson H, Midgley FM, Karr SS, et al. Role of Echocardiography in the Diagnosis and Surgical Management of Accessory Mitral Valve Tissue Causing Left Ventricular Outflow Tract Obstruction. J Am Soc Echocardiogr 1995; 8(1):105-7.