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A Case Series

Childhood Noonan Syndrome Presenting with Severe Pulmonary Stenosis: A Rare Case Report

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Abstract:
Noonan syndrome [NS] is an autosomal dominant inherited condition that can be passed down through families. The incidence of NS is estimated to be between 1:1000 and 1:2500 live births. It causes abnormal development in many parts of the body. It is used to be called Turner-like syndrome. Though most of the cases are autosomally inherited some cases may be sporadic. We report a case of 13 year old male child presented to us with features of short stature, dysmorphic facies and severe pulmonary valvular stenosis without any family history of similar illness.
Keywords: Noonan Syndrome, Pulmonary valvular stenosis.

Introduction

Noonan syndrome (NS) is a common autosomal-dominant condition that is associated with short stature and congenital heart disease (CHD), most often pulmonic stenosis. It is clinically and genetically heterogeneous. Although initial descriptions focused on characteristic facial features as part of the clinical picture, the availability of genetic testing has demonstrated a highly variable clinical presentation in which behavioral and emotional features may be more prominent. Hypertrophic cardiomyopathy (HCM) is present in approximately 20 percent of patients, although the proportion of patients with this varies greatly according to the gene mutated [1].

The prevalence of NS is widely quoted as 1 in 1000 to 1 in 2500 [1]. However, the true prevalence remains unknown. The features of NS change with age [2], and it is not uncommon for a parent to be diagnosed only after the birth of a more severely affected child. NS affects males and females equally but may be more recognizable in boys since they can present with cryptorchidism. NS occurs across all ethnic groups [3]. NS is associated with advanced paternal age, similar to several other conditions with dominant inheritance [4].

Genetics

NS is nearly always an autosomal-dominant condition, and two-thirds of patients are the

first affected person in their family due to a de novo pathogenic variant [4].

Approximately 50 percent of patients have a pathogenic variant in protein tyrosine phosphatase, nonreceptor type *11 (PTPN11),* with clustering of variants in specific codons. The PTPN11 gene encodes the protein Src homology region 2 domain- containing phosphatase 2 (SHP2), a dual-specificity phosphatase [4]. The genetic basis in the remainder of patients is usually a pathogenic variant in one of many other genes encoding a protein of the Ras-mitogen-activated protein kinase (Ras-MAPK) pathway (Figure 1).

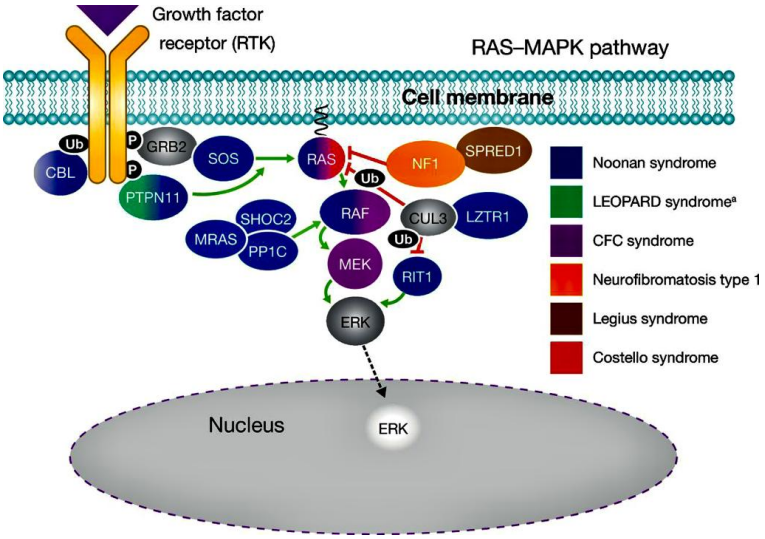

Figure 1: Clinical features of Noonan Syndrome.

Variants in some of these genes are associated with particular clinical characteristics (Figure 2).

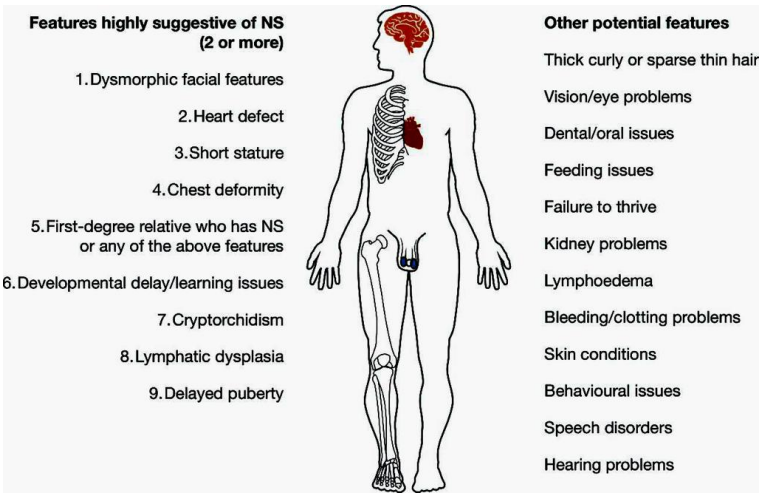

Figure 2: *The RAS—MAPK signalling pathway showing mutations that may lead to diseases such asNoonan syndrome. Some of the pathway components exist in multiple isoforms (eg, RAS: KRAS, HRAS, NRAS, RRAS; RAF: RAF1, BRAF; SOS: S0S1, S0S2, etc). CFC, cardiofaciocutaneous; MAPK, mitogen-activated protein kinase; P, proline; RTK, receptor tyrosine kinase enzyme; Ub, ubiquitin.*

Pathogenic variants in leucine zipper-like transcription regulator 1 *(LZTR1)* may underpin approximately 10 percent of NS, and these may show either autosomal-dominant or

autosomal-recessive inheritance, with consequent implications for recurrence risk in future pregnancies in the family [5].

Approximately 10 percent of patients tested do not have an identifiable pathogenic variant in any of the known genes, suggesting that additional genes are involved [6]. A number of candidate genes for NS have been identified using high-throughput technologies such as exome sequencing and are awaiting further evaluation before their role in NS can be confirmed [6].

We are presenting a rare case report of Noonan Syndrome in a 13 year old male child having multiple features of NS including short stature, dysmorphic facies, skeletal anomalies and severe pulmonary valvular stenosis.

Case Report

A 13 year male child was brought to us by his parents for cardiac evaluation. The parents informed us that the child was suffering from gradually increasing dyspnea and fatigue on effort for last 10 years. The child was born at full term, delivered at a hospital by caesarean section. The family history and vaccination status of mother and child were unremarkable. There was no history of cyanosis, palpitation, chest pain, syncope or heart failure.

On clinical examination the child was having a short stature: height 136cm with a weight of 23 Kg, BP 80/50 mmHg in the right upper extremity, Pulse rate 93/min and SPO2 95% at room air. The facies of the child revealed multiple dysmorphic features (Figure3).

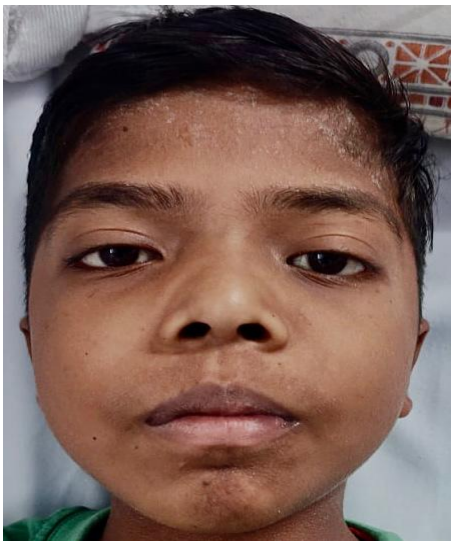

Figure 3: Dysmorphic facies

(i) Small forehead
(ii) Wide set eyes -hypertelorism
(iii) Bilateral epicanthal folds
(iv) Sunken nasal bridge
(v) Wide nostrils
(vi) Large philtrum
(vii) Thick Lips
(viii) low-set ears
(ix) high-arched palate
(x) Low hairline

Besides the above, there was presence of pectus carinatum deformity of the sternum (Figure 4).

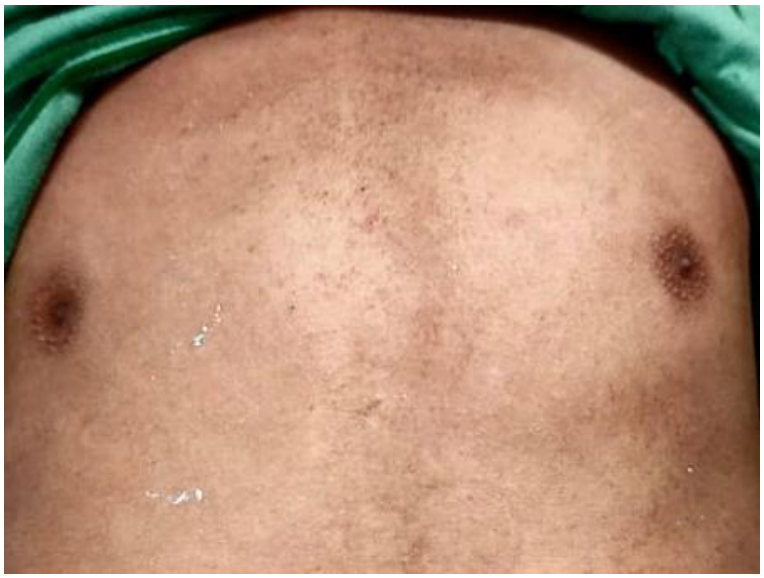

Figure 4: prominent protruding chest with pectus carinatum deformity.

On cardiovascular e xamination a Grade IV/VI ejection systolic murmur was widely audible over precordium, best heard in the left 2nd Intercostal space, at the left sternal edge. The P_2 component of the 2nd heart sound was soft. All the peripheral pulses were normal and there was no radio-femoral delay. The resting ECG showed sinus tachycardia with a ventricular rate of 113/min with gross right ventricular hypertrophy, right atrial enlargement and right axis deviation (Figure 5).

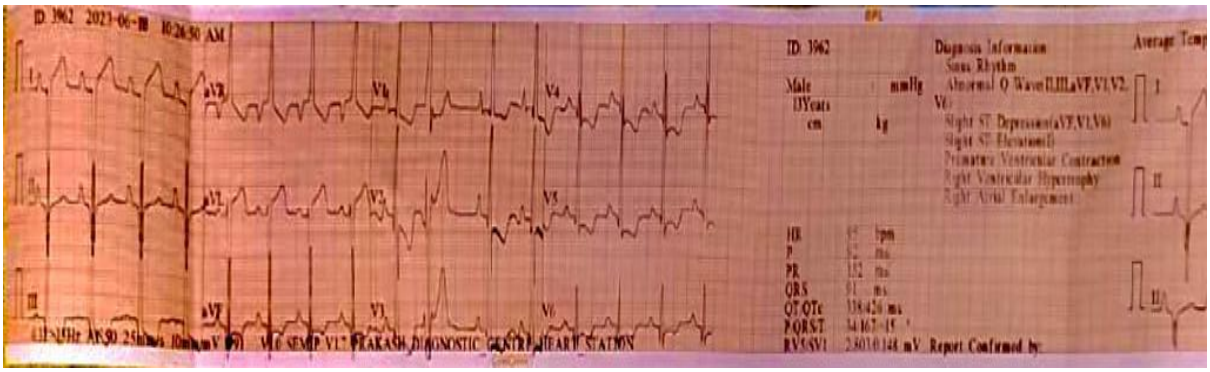

Figure 5: Resting ECG demonstrates: right ventricular hypertrophy, right atrial enlargement, right axis deviation and normal sinus rhythm.

X ray chest (PA) identified the presence of cardiomegaly, with dilated main and left pulmonary artery. There was distinctive presence of peripheral pruning of pulmonary vasculature (Figure 6).

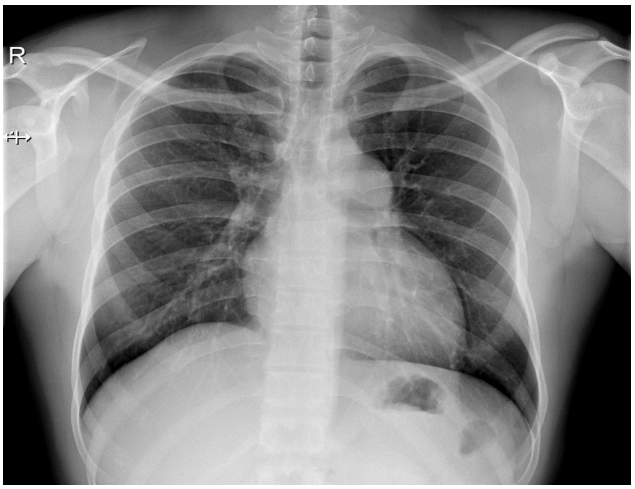

Figure 6: X-ray Chest PA view shows cardiomegaly, dilatation of main and left pulmonary artery. Peripheral pruning of pulmonary vasculature is conspicuously present.

Transthoracic Echocardiography (TTE)

TTE was performed by the author in supine and left lateral decubitis positions. Imaging was done in long axis (LX), short axis (SX), apical 4-chamber (4CH), apical 5 chamber (5CH) and suprasternal views. There was levocardia, situs- solitus, AV concordance, VA concordance, concordant-d-bulbo-ventricular loop, normally related great arteries, left aortic arch, normal systemic and pulmonary venous drainage.

In the subcostal view (Figure 7), an intact interatrial septum with a dilated right atrium was visible. In the parasternal short axis view at the level of papillary muscle (Figure 8), a dilated right ventricle with a small left ventricle (LV) was identified with a D-shaped LV and a flat ventricular septum, suggesting a significant systolic overload of the right ventricle. On imaging further in the short axis view at the level of aortic valve (Figure 9), a domed non calcific pulmonary valve is delineated with hypoplastic pulmonary valve annulus and past stenotic dilatation of main, left and right pulmonary arteries. Pulmonary valve annulus (D) was 11.2 mm, main pulmonary artery (D) was 23.2 mm, left pulmonary artery (D) was 17.2 mm and right pulmonary artery (D) was 15.2 mm.

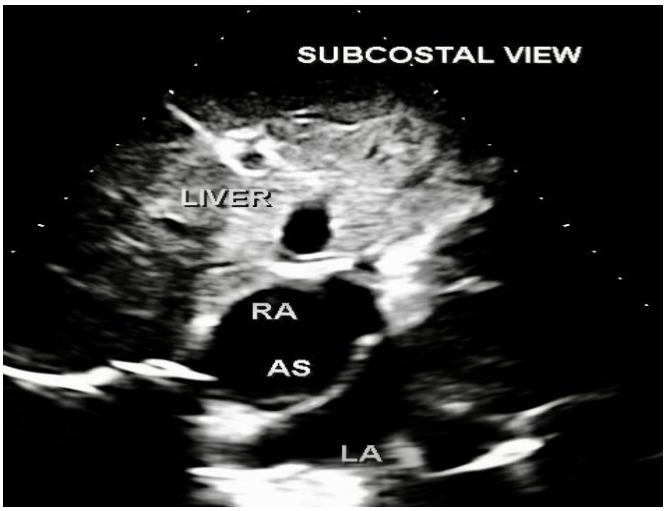

Figure 7: In the subcostal view Intact interatrial septum is visualised.

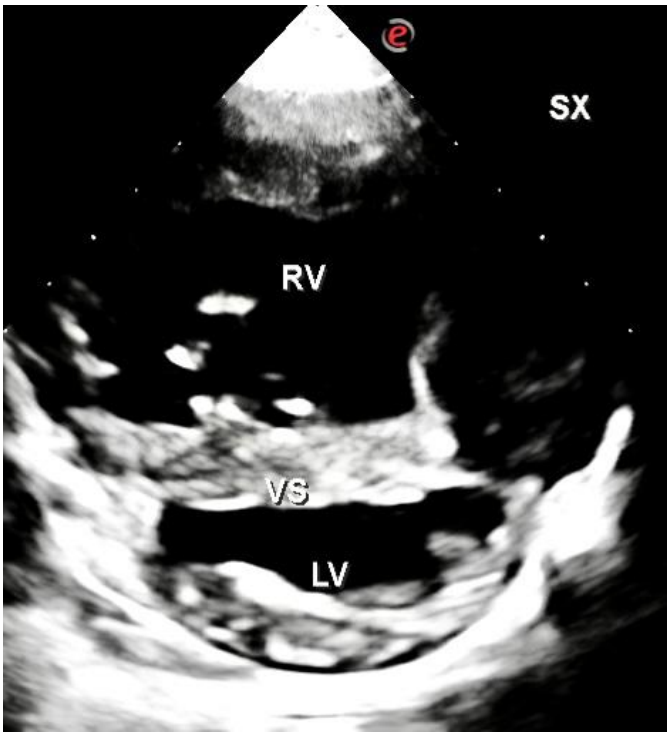

Figure 8: In the short axis view

(SX) a dilated right ventricle with small left ventricle is identified with a
D- Shaped left ventricle and a flat ventricle septum, suggesting a significantly elevated right ventricular systolic pressure resulting in systolic overload of right ventricle.

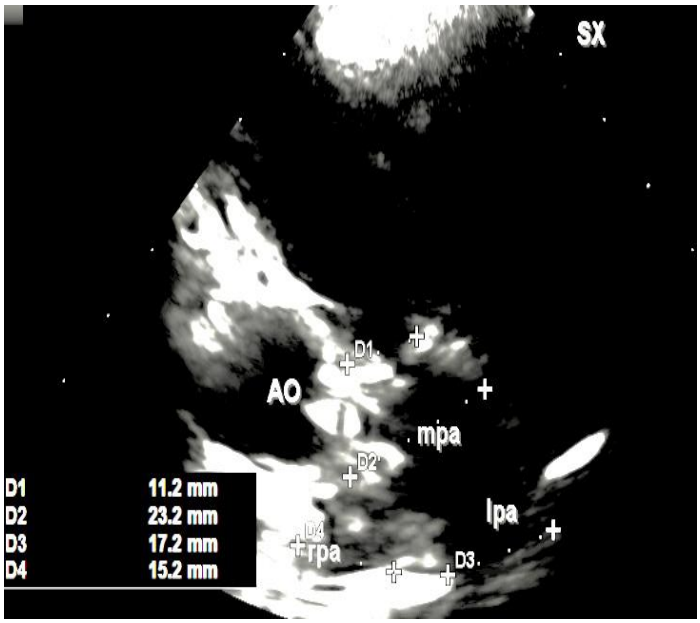

Figure 9: *In the SX view at the level of aortic valve, a domed non calcific pulmonary valve is delineated with hypoplastic pulmonary valve annulus and post stenotic dilatation of main, left and right pulmonary arteries. pv annulus (D) 11.2 mm, mpa (D) 23.2 mm, lpa (D) 17.2 mm, rpa (D), 15.2 mm.*

mpa, main pulmonary artery, lpa, left pulmonary artery, rpa,right pulmonary artery.

On color flow mapping (Figure 10) across the pulmonary valve, a highly turbulent mosaic pattern flow was distinctly recognised, suggesting a severe obstruction at the level of pulmonary valve. On continuous wave doppler analysis across the pulmonary valve (Figure 11), a severely obstructive jet was outlined with a peak/mean gradient of 138.1/89.9 mmHg, consistent with severe pulmonary valvular stenosis.

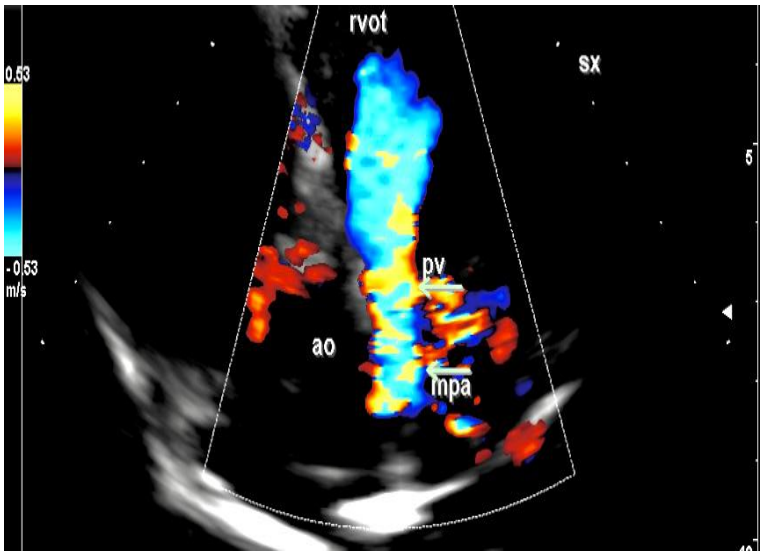

Figure 10: *On Color flow mapping across the pulmonary valve in the SX view, a highly turbulent mosaic pattern flow was distinctly outlined, suggesting a severe obstruction at the level of pulmonary valve*

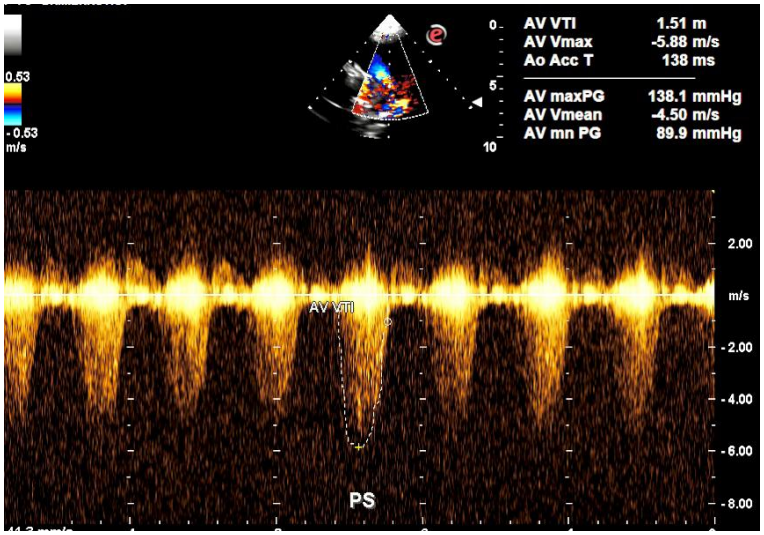

Figure 11: *On Continuous wave Doppler analysis a high intensity systolic jet is discerned with a peak and mean gradient of 138.1/89.9 mmhg, consistent with severe pulmonary valvular stenosis.*

On performing the color flow mapping in the 4CH view (Figure 12), a characteristic central and severe tricuspid regurgitation jet was demonstrated with a large jet area of 9.38 cm, occupying nearly 50 % right atrial area. Furthermore, the tricuspid valve was thickened with dilatation of

right atrium (Figure 13). The right ventricle was also dilated alongwith significant concentric hypertrophy. Interatrial septum was intact with small left atrial and left ventricular cavities, even though the biventricular systolic functions were normal. The LVEF was 75 %.

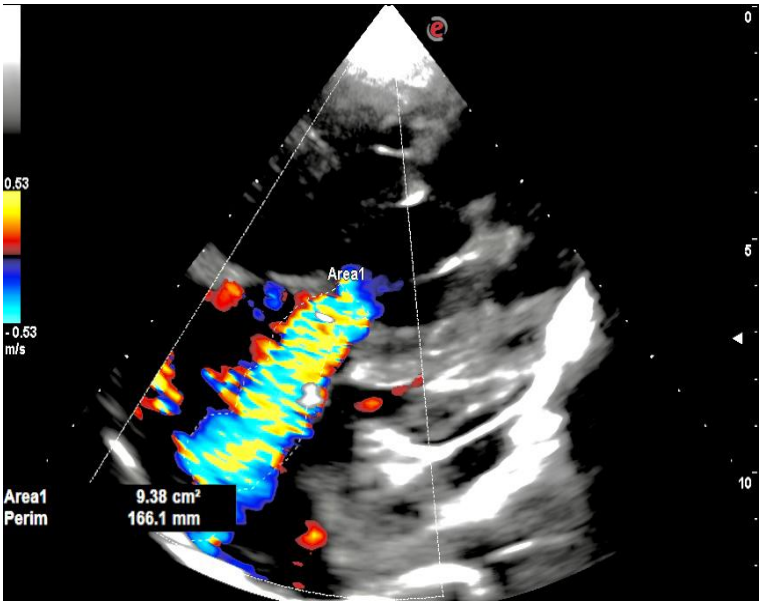

Figure 12: *In the 4CH View, on color flow mapping a characteristic central and severe tricuspid regurgitation jet was seen with a jet area of 9.38 cm2.*

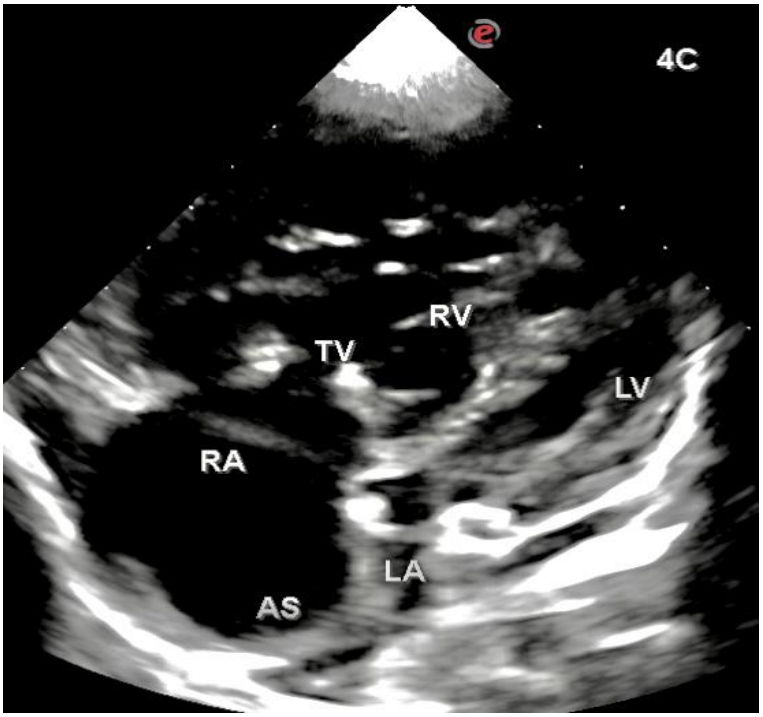

Figure 13: *In the 4CH View a dilated right ventricle with concentric hypertrophy, thickened tricuspid valve, dilated right atrium and intact interatrial septum was envisaged.*

There was no evidence of any additional congenital defects – ASD, VSD, PDA, COA or Aortic stenosis.

Discussion

Noonan Syndrome is an autosomal dominant disorder characterised by short stature, typical face dysmorphology and congenital heart defects. NS is a clinical diagnosis and establishing the diagnosis can be very difficult, especially in adulthood. There is a great variability in expression and the phenotype becomes less pronounced with increasing age [7]. Several scoring systems have been devised to help the diagnostic process. The most recent scoring system was developed in 1994 by Van der Burgt et al [8] (Figure 14).

Figure 14: Scoring System for Noonan Syndrome

FEATURES	A-MAJOR	B-MINOR
1. FACIAL	Typical face dysmorphology	Suggestive face dysmorphology
2. CARDIAC	PV stenosis, HOCM, ECG typical of NS	Other defect
3. HEIGHT	<P3	<P10
4. CHEST WALL	Pectus carinatum/excavatum	Broad thorax
5. OTHER	Mental retardation, cryptorchidism and lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

HOCM: hypertrophic obstructive cardiomyopathy;
**P3 and P10 refer to percentile lines for height according to age, with the normal range of variation defined as P3-P97 inclusive*

Definitive NS: "A" plus one other major sign or two minor signs; "B" plus two major signs or three minor signs

In our patient there was presence of two major features of NS:

(i) Severe pulmonary valvular stenosis with ECG typical of NS
(ii) Pectum carinatum anomaly of the chest

And two minor features:

(i) Suggestive facial dysmorphology and
(ii) Height being less than 10^{th} percentile.

The above features are definitive of NS, according to the scoring system.

Common features of NS include: Characteristic facial features that change with age. In the postnatal period the forehead is broad and high, there is hypertelorism, epicanthic folds and downward slanting palpebral fissures, low-set posteriorly rotated ears with a thick helix, high arched palate, micrognathia, and a short neck with excess nuchal skin and a low posterior hairline [2, 7]. The facial features can be subtle, especially at old age.

The most common congenital heart defect is pulmonary valve stenosis with dysplastic leaflets (50%-62%) [9]. Hypertrophic obstructive cardiomyopathy (HOCM) with asymmetrical septum hypertrophy is present in 20% of patients. Atrial septal defects occur in 6%-10% of cases, ventricular septal defects occur in 5% of cases and persistent ductus arteriosus occurs in 3% of cases. Other congenital heart defects more often seen in NS are atrioventricular canal defect (AVCD) associated with subaortic obstruction and structural anomalies of the mitral valve. Characteristic chest deformities consist of pectus carinatum superiorly and pectus excavatum inferiorly. These sternal abnormalities are present in 70%-95% of cases. Common orthopaedic features include cubitus valgus (50%), radioulnar synostosis (2%), clinobrachydactyly (30%), joint

hyperextensibility (50%) and talipes equinovarus (12%) [2, 10].

Undescended testicles at birth are common in male patients (77%). Urinary tract malformations are present in 10% of cases, mostly pyelo-ureteric stenosis and/or hydronephrosis. Increased bruising or bleeding is frequent, especially in childhood. Up to 55% of cases have a mild-to-moderate bleeding tendency. Severe haemorrhage occurs in 3% of cases [2].

Abnormalities of pigmentation in NS include pigmented naevi (25%), *cafe-au-lait* spots (10%) and lentigines (3%). Acute leukaemia and myeloproliferative disorders (MPD) have been described in some patients. Lymphatic vessel dysplasia, hypoplasia, or aplasia are common findings in NS (20%). Hearing loss due to otitis media is a frequent complication (15%-40%). Hepatosplenomegaly unrelated to cardiac failure is often present in infancy (26%-51%) [11].

Our patient had characteristic facial features, chest deformity, cardiac abnormalities and short stature. There are a number of conditions with phenotypes strikingly similar to NS. The first to mention is Turner syndrome (45, X0), a well known chromosomal abnormality in girls. Moreover, there are a group of distinct syndromes with partially overlapping phenotypes in which causative mutations are found in genes of the RAS-MAPK pathway. These include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1) and LEOPARD syndrome [12].

Severe pulmonic stenosis most often presents in childhood with right ventricular failure and cyanosis. Adults are usually treated early in life with either surgical or balloon valvotomy, in significantly symptomatic patient [13]. The prognosis continues to be good after successful treatment [14].

In our case the presence of markedly symptomatic severe pulmonary valvular stenosis prompted us to immediately refer the child to a tertiary care pediatric cardio-vascular institute for possible balloon valvulotomy of the pulmonary stenosis.

Conclusion

Noonan Syndrome is a rare inherited disorder that can occur sporadically in small number of cases. It is clinically diagnosed based on scoring of characteristic facial dysmorphism, cardiac abnormalities and other deformities. Though confirmation needs demonstration of characteristic mutations, scoring systems can help the diagnostic process.

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