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ORIGINAL RESEARCH

# Noonan Syndrome: A Case Report

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**Summary**

The clinical findings and treatment options of cardiovascular abnormalities in a 20-year old male patient with Noonan syndrome are described with literature review. The classical clinical features of Noonan syndrome, which were identified included short stature, abnormalities of ear and eye, low posterior hair line, cubitus valgus and webbed neck. The major cardiovascular abnormalities included pulmonary valvular stenosis and hypertrophic cardiomyopathy. A comparison with Leopard syndrome is made and the overlapping features between the two rare genetic disorders are discussed.

*Key words: Hypertrophic Cardiomyopathy, Leopard syndrome, Noonan Syndrome, Pulmonary stenosis, Ptosis*

## Introduction

Noonan Syndrome is a congenital, autosomal dominant disorder with a wide spectrum of phenotype expression. [1] In 1962, at a Midwest Society of Paediatric Research meeting, Dr. Jacqueline Noonan described nine patients with a shared phenotype of pulmonary valve stenosis, short stature and characteristic facies. [2] A severe form of the disease known as Noonan syndrome is typically characterized by severe pulmonary stenosis (50-60%) and severe hypertrophic cardiomyopathy (20-30%) [3] which are usually present early in life; indeed one child reportedly had mild, non-obstructive hypertrophic cardiomyopathy at the age of 3.5 years [4] and such patients are at higher risk of long-term morbidities such as decreased exercise tolerance and shortness of breath. [5] On the other hand, mild pulmonary valve disease in isolation or with co-existing lesions, portend a very favorable prognosis, although associated septal defects, may require surgical repair.

Some of the recognizable features of Noonan syndrome could be the consequence of lymphatic obstruction or dysfunction during development; these features include webbing of the neck and prominence of the trapezius muscles, cryptorchidism, widely spaced nipples, low-set and posteriorly rotated ears, hypertelorism and ptosis. [6] Affected individuals have characteristic facial features comprising down slanting palpebral fissures, epicanthal folds, a short and broad nose with a depressed root and upturned tip, deeply grooved philtrum with high, wide peaks of the vermilion, high palate and micrognathia. The prominent components of the disease include short stature, a chest deformity and a cardiac abnormality.

The diagnosis of Noonan syndrome presently rests solely on clinical criteria. [4] Some other syndromes manifesting with heart and skin disorders,

described as cardio-facio-cutaneous syndromes [7] include Watson syndrome [8] and LEOPARD syndrome. [9] In the teenage years and during young adulthood, the facial features are sharper with the thin and high nasal bridge. The older adult has prominent nasolabial folds, high anterior hairline and transparent wrinkled skin. Short stature is present in over 80% of cases and is often the reason for referral. In general, there is a two- year delay between bone age and chronological age. Undescended testes, either one or both are present in about half of affected males. Noonan syndrome has been linked to one of four genes (*PTPN11, KRAS, SOS1,* and *RAF1*), three of which encode components of the Tyrosine kinase signal-transduction pathway. [10] In a report by Lee, hypertelorism was present in 74%, ptosis in 48%, epicanthal folds in 48% and an anti-mongoloid slant in 38% of Noonan syndrome cases. [11] The majority of children with Noonan syndrome who have significant pulmonary stenosis will require surgical treatment. We describe in this report an adult male with Noonan syndrome who presented with features of pulmonary stenosis. This report is meant to heighten the clinical suspicion index of researchers and diagnosticians in order to facilitate early diagnosis of the syndrome and prevent the complications later in life.

## Case Presentation

A 20-year old male, Pakhtoon caste Pakistani, presented to the Cardiology Department of the Civil Hospital, Karachi, Pakistan on 20th March 2017 with complaints of recurrent shortness of breath since birth. The shortness of breath was exertional and also occurred at rest and it was associated with platypnoea, orthopnoea and paroxysmal dyspnoea. There was associated palpitation and easy fatigability. As a child, he was not very active and never participated in sports. He also suffered from episodic chest pain. He was a product of consanguineous marriage. He was admitted to school in childhood, but he dropped out because his parents felt he was a slow learner. There was no other family member with similar phenotype.

General examination revealed an afebrile, short stature (130 cm) and the height centile was less than the 5th compared to 176cm which corresponds to the 50th centile for the age. He also had low set ears, anti-mongoloid palpebral slant, high arched palate and ptosis in the left eye. The blood pressure was 120/70mmHg with a pulse rate of 98 beats per minute; and the jugular venous pressure was normal. There was Grade IV digital clubbing but without cyanosis, pedal oedema or pallor. Apical impulse was located on the mid-clavicular line at the fourth intercostal space and was described as heaving in character but without a thrill. However, there was a parasternal edge heave. On auscultation, the first heart sound was normal while the second heart sound was inaudible. However, there was a grade 3/6 pan-systolic murmur in the tricuspid and mitral areas but there was no ejection click or fourth heart sound.

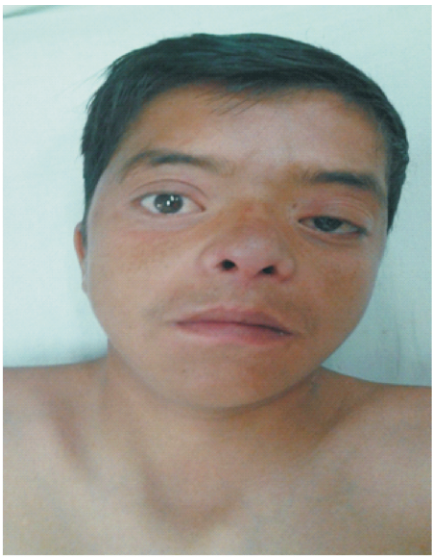

**Figure1: Noonan Syndrome patient with anti-mongoloid palpebral slant and ptosis in left eye.**
(Authors obtained the permission of the patient's parent for the use of his image in this report)

There was no testicular abnormality and the physical findings on the other systems were normal. Complete blood picture, serum urea, creatinine and electrolytes were normal.

The electrocardiogram (Figure 2) showed normal sinus rhythm and extreme right axis deviation, right ventricular hypertrophy with right bundle branch block and T wave inversions in $V_1$, $V_2$, $V_3$ and $V_4$.

Echocardiography (Figure 3) and colour flow imaging (Figure 4) showed a thickened pulmonary valve, dilated right ventricle with dysfunction, and dilated right atrium .Other chambers and valves were normal. The colour doppler study showed mild pericardial effusion

The chest radiograph was normal. Echocardiography and color flow imaging showed enlarged right ventricular dysfunction with severe pulmonary stenosis and severe tricuspid regurgitation associated with enlarged right atrium. Although the inter-ventricular septum was intact, it was pushed to the left side. The remaining chambers and valves were normal.

The final diagnosis made by the cardiologists was Noonan Syndrome The patient had valvuloplasty and he is currently on follow-up care.

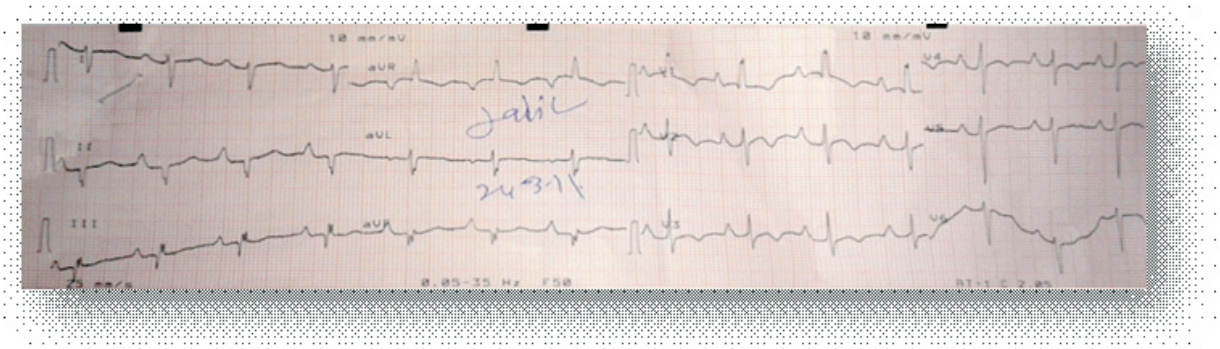

**Figure 2: Electrocardiogram showing right axis deviation, right ventricular hypertrophy with right bundle branch block.**

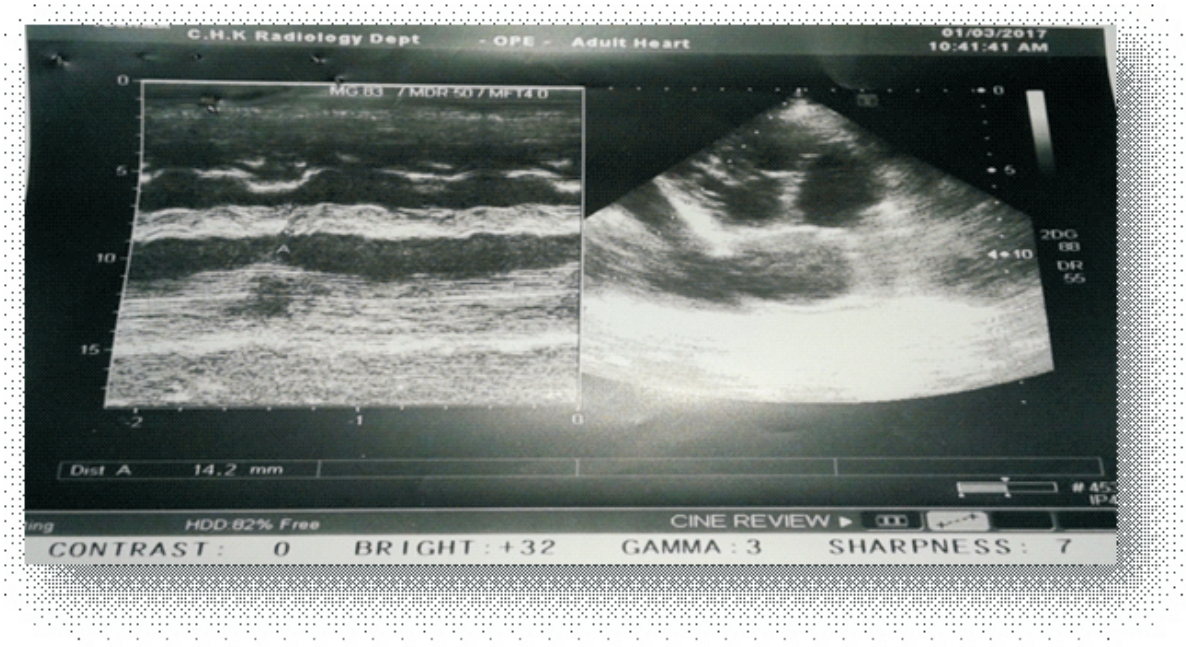


**Figure: 3 2D Echocardiogram (Parasternal long axis view) showing stenotic pulmonary valve.**

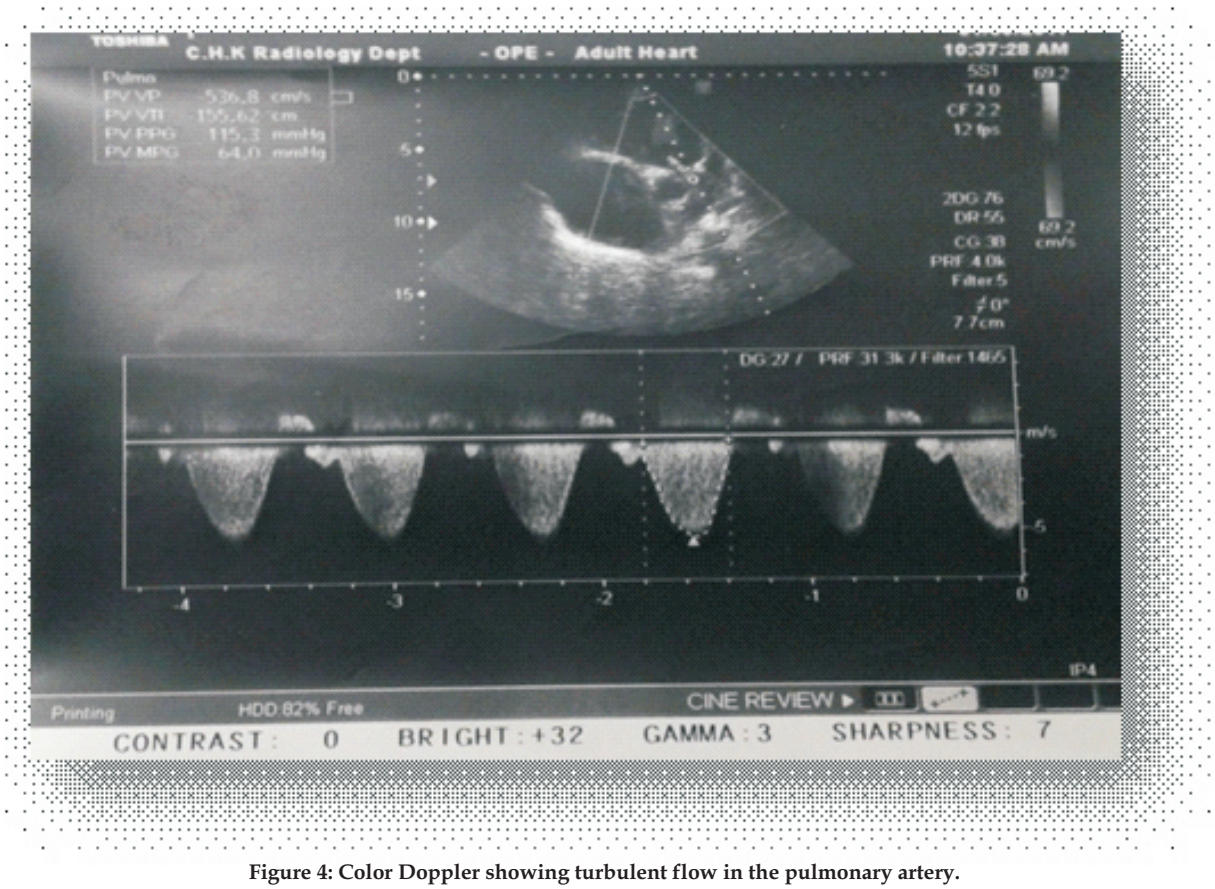


**Figure 4: Color Doppler showing turbulent flow in the pulmonary artery.**

## Discussion

Noonan Syndrome is a rare, autosomal dominant disorder characterized by short stature, facial abnormalities, congenital heart defects and urogenital malformations. Ocular changes occur in 95% of patients and these usually include hypertelorism, ptosis, refractive errors, strabismus, amblyopia, rarely nystagmus, colobomas, cataracts and optic nerve drusen. [1] The diagnostic criteria [12] include four or more cardinal features with a normal karyotype 46 XY. The differential diagnoses of girls with short stature include Noonan syndrome, [13] the clinical pictures, of which include a number of dysmorphic signs typically associated with Turner Syndrome. Like Turner syndrome, there is also the possibility of mental or learning disabilities depending on its severity as suggested by the history of slow learning in the index patient. [3]

In consonance with the cardinal features, the index patient had short stature, ptosis, pulmonary stenosis and facial dysmorphism. A karyotype could not be done because of the poor socioeconomic background of the patient. However, he appeared to be a sporadic case of Noonan syndrome as the other members of the family were phenotypically normal. In approximately 50% of Noonan syndrome cases, there is a mutation of PTPN11 gene on chromosome 12. Noonan syndrome mostly occurs on a sporadic basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission. [14,15]

LEOPARD syndrome, another very rare inherited disorder has many features similar to Noonan syndrome. The acronym stands for lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and deafness. [3, 8] The skin may distinguish LEOPARD Syndrome from Noonan Syndrome in classic cases when multiple lentigines are present in Leopard syndrome. Lentigines classically develop during

childhood and increase in number until puberty. Increased hyperpigmentation and café-au-lait spots are present in the first months of life in about 75% of the patients. In contrast, patients with Noonan Syndrome present with cafe-au-lait spots in only about 10% of the cases with lentigines in 2%. [16] However, the diagnostic clues of LEOPARD Syndrome are the cutaneous manifestations hypertrophic cardiomyopathy and deafness. It is important to note that the index patient had no cutaneous manifestations such as lentigines or signs of deafness. These are clear distinctions from LEOPARD syndrome.

## Conclusion

Noonan syndrome is a rare genetic disorder, but the diagnosis should be made early in life so that subsequent morbidities can be prevented or minimized. However, the clinical presentation may be mild and the typical facial features may recede with age, hence the diagnosis might be missed. The details of follow-up care of the index patient were sparse since he was referred from the cardiology unit to the cardiothoracic surgery unit for valvuloplasty. Since Noonan syndrome is a multi-systemic disorder, early diagnosis, especially in the third world countries where diagnostic facilities are sparse, targeted pharmacogenomic efforts should be developed.

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**References**

1. Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, Lyonnet S, Vidaud M, Le Bouc Y. Noonan syndrome: relationships between genotype, growth, and growth factors. J Clin Endocrinol Metab 2006; 91(1): 300-306.
2. Noonan JA. Associated non-cardiac malformations in children with congenital heart disease. J Pediatr 1963; 63: 468-470.
3. Burt J, Ramirez A, Limback J, Derrick E, Agha A, Varich L. Unusual Vascular Manifestations of Noonan Syndrome. J Cardiovasc Dis Res 2017; 8(3): 101-103.
4. Noonan J, O'Connor WI. Noonan syndrome: a clinical description emphasizing the cardiac findings. Pediatr Int 1996; 38(1): 76-83.
5. Colquitt JL, Noonan JA. Cardiac findings in Noonan Syndrome on Long-term Follow-up. Congenital Heart Dis 2014; 9(2): 104-05.
6. Allanson JE. Noonan syndrome. Am J Med Genet C Semin Med Genet 2007; 145: 274–279.
7. Fryer AE, Holt PJ, Hughes HE. The cardio-facio-cutaneous (CFC) syndrome and Noonan syndrome: Are they the same? Am J Med Gen Part A. 1991; 38(4): 548-551.
8. Gorlin RJ, Anderson RC, Blaw M. Multiple lentigenes syndrome: complex comprising multiple lentigenes, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, sensorineural deafness, and autosomal dominant hereditary pattern. Am J Dis Child 1969; 117(6): 652-662.
9. Watson GH. Pulmonary stenosis, café-au-lait spots, and dull intelligence. Arch Dis Child 1967; 42(223): 303.
10. Gelb BD, Tartaglia M. Noonan syndrome and related disorders: dysregulated RAS-mitogen activated protein kinase signal transduction. Hum Mol Genet 2006; 15(Suppl_2): R220-226.
11. Lee NB, Kelly L, Sharland M. Ocular manifestations of Noonan syndrome. Eye 1992; 6(3): 328-334.
12. Piplani S, Kumar P. Noonan syndrome: Case Report. Med J Armed Forces India 1998; 54(4): 363-364.
13. Halac I, Zimmerman D. Evaluating short stature in children. Pediatr Ann 2004; 33(3): 170-176.
14. Tartaglia M, Cordeddu V, Chang H, Shaw A, Kalidas K, Crosby A, *et al*. Paternal germline origin and sex-ratio distortion in transmission of PTPN11 mutations in Noonan syndrome. Am J Hum Genet 2004; 75(3):492-7.

15. Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. Ann Rev Genomics Hum Genet. 2005; 6: 45-68.

16. Digilio M, Sarkozy A, de Zorzi A, Pacileo G, Limongelli G, Mingarelli R, *et al*. LEOPARD syndrome: Clinical diagnosis in the first year of life. American Journal of Medical Genetics Part A. 2006; 140A(7): 740-746.