

Case Report

NOONAN SYNDROME – 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 11 year old male child presented to the hospital with features of cardiac failure and morphologic features of NS who has no similar history in the family.

Keywords: Noonan Syndrome, Sporadic, Turner like Syndrome

INTRODUCTION

Noonan syndrome was first recognized as a unique entity in 1963 when Noonan and Ehmke described a series of patients with unusual facies and multiple malformations, including congenital heart disease (Noonan and Ehmke 1963). The incidence of NS is estimated to be between 1:1000 and 1:2500 live births (Allanson, 1978; Sharland *et al.*, 1992).

The cardinal features of Noonan syndrome include unusual facies (ie, hypertelorism, down-slanting eyes, and webbed neck), congenital heart disease (in 50%), short stature, and chest deformity. Approximately 25% of individuals with Noonan syndrome have mental retardation. Bleeding diathesis is present in as many as half of all patients with Noonan syndrome. Skeletal, neurologic, genitourinary, lymphatic, eye, and skin findings may be present to varying degrees.

The pathophysiology of Noonan syndrome is not fully understood. Four disease-causing genes (*PTPN11*, *SOS1*, *RAF1*, and *KRAS*) have been identified. All 4 genes are part of the RAS/RAF/MEK/ERK signal transduction pathway, which is an important regulator of cell growth. Mutations in the RAS-MAPK signaling pathway are responsible for Noonan syndrome (Zenker 2009; Bertelloni *et al.*, 2013; Roberts *et al.*, 2013).

CASES

An eleven years old male child born of non-consanguineous marriage residing at Pondicherry (union territory, India), presented with history of fatigue, breathlessness which was aggravated on exertion, short stature and facial dysmorphism. Antenatal period was uneventful and no similar history in the family. He was diagnosed to have congenital heart disease and has past history of cardiac catheterization done 5 years back. On examination, pulse rate was 82 beats/min, blood pressure was 120/80 mmHg and body temperature was 98.6 degree F. His height was 116cm (Expected is 144cms) and weight was 16kg (Expected is 37.4kg). He had coarse facial features with hypertelorism, depressed nasal bridge, low set ears, deformed left ear with microtia, high arched palate, and webbed neck (Figure 1). There was thoracic scoliosis, pectus carinatum, cubitus valgus with clinodactyly. On CVS examination there was pansystolic murmur and loud P2. Due to monitory constraints only few relevant investigations were carried out which revealed the following: Hemoglobin 13.6 gm/dl, Total leukocyte count 10,900/mm³, MCV -86 Fl, MCH - 26 pg with normocytic and normochromic red blood cells on peripheral blood smear. Platelet count was 2.7 lakhs/cmm. USG scrotum revealed bilateral undescended testis Echocardiogram revealed MID Muscular Ventricular Septal Defect with Eisenmengers Syndrome, Pulmonary Hypertension and Patent

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Ductus Arteriosus. Child was treated symptomatically with anti-failure drugs. There was improvement in symptoms and regression of cardiac manifestations.

IMAGING FINDINGS



Figure 1(a,b): Photograph of 11 year old boy showing typical facial dysmorphism, deformed left ear, webbed neck and chest wall deformity



Figure 2(a): Photograph shows mild thoracic scoliosis and webbed neck with prominence of scapula. (b) Chest radiograph AP View shows mild thoracic scoliosis with convexity towards right and rib deformity with synostosis of left upper ribs

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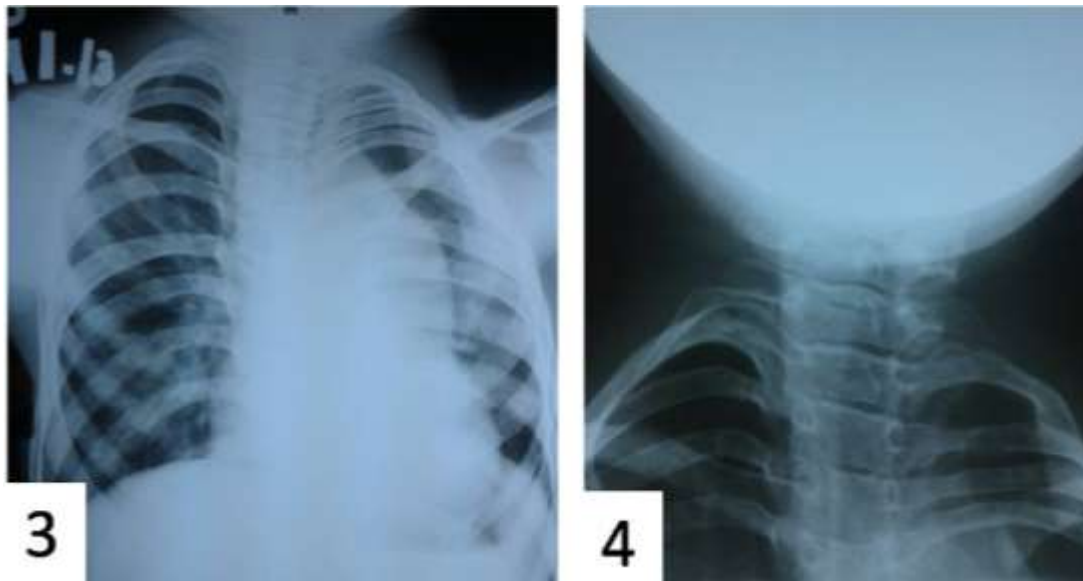


Figure 3: Chest radiograph PA view shows enlarged pulmonary conus suggestive of pulmonary hypertension.

Figure 4: Elevated Right scapula with upward orientation of upper right cervico thoracic ribs



Figure 4: Dorsolumbar spine radiograph showing mild scoliosis.

Figure 5: Pelvis radiograph shows partial agenesis of sacrum

DISCUSSION

Noonan Syndrome is an autosomal dominant disorder characterised by short stature, typical face dysmorphology and congenital heart defects. NS is a clinical diagnosis. 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 (Allanson *et al.*, 1985). Several scoring systems have been devised to help the diagnostic process. The most recent scoring system was developed in 1994 (Van der Burgt *et al.*, 1994) (Table 1).

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Table 1: 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: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs

This patient has 4 major features with a) typical facial dysmorphology, b) cardiac manifestations, c) height being less than 3rd percentile and d) Pectus carinatum and 1 minor feature with bilateral cryptorchidism which is definitive of Noonans syndrome 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 (Sharland *et al.*, 1992; Allanson *et al.*, 1985). 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%) (Pernot *et al.*, 1987). 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%) (Allanson 1987; Sharland *et al.*, 1992).

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 (Sharland *et al.*, 1992).

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%). This patient had characteristic facial features, chest deformities, cardiac abnormalities and undecended testis diagnostic of NS.

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. Then 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 (Preus, 1984).

As the syndrome has a wide spectrum of disorders, patients with Noonan syndrome have to undergo the following lab studies and investigations:

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- Hematological investigations (Total blood count, coagulation profile and measurement of factor XI level at the minimum)
- Karyotyping and mutation analysis
- Cardiac investigations (ECG, echocardiogram and consultation with a pediatric cardiologist)
- Assessment of development (IQ, Identify any delays, mental retardation)
- Audiologic evaluation

Antenatal diagnosis includes a DNA test for mutation analysis carried out on blood, chorionic villi and amniotic fluid samples. NS should be considered in all fetuses with polyhydramnios, pleural effusions, oedema and increased nuchal fold with a normal karyotype.

Asokan *et al.*, reported a case of 13 year old child with facial, oral and cardiac features of NS (Asokan *et al.*, 2007). Nirmal *et al.*, reported a case of a 4-year-old male child with Noonan syndrome (Nirmal *et al.*, 2001). Lee and Cooper *et al.*, reported a case of multiple giant cell lesions of the mandible that occurred in a nine year old female child with phenotypic features of Noonan syndrome (Lee and Cooper, 2007).

With special care and counseling, the majority of children with NS will grow up and function normally in the adult world. Management should address feeding problems in early childhood, evaluation of cardiac function and assessment of growth and motor development. Physiotherapy and/or speech therapy should be offered if indicated.

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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