

## **Case report**

### **Noonan's Syndrome of a 25 years old female**

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#### **Abstract**

Noonan's syndrome is an autosomal dominant disorder with a webbed neck that mimics Turner syndrome. However, the syndrome has also been found to be genetically heterogeneous. Noonan syndrome is characterized by short stature, hyperkeratosis of skin, distinct facial features, lymphoreticular abnormalities, nail dystrophy. No abnormality in chromosome number has so far been reported. Here we present a 25 year old female who came to Bangladesh Medical College Hospital in May'08, with generalized skin eruptions and left leg swelling.

**Key words:** Noonan's syndrome, genetic disorders

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#### **Introduction**

The syndrome is named after Dr Jacqueline Noonan. Noonan syndrome is a genetic disorder that prevents normal development in various parts of the body. It is a relatively common genetic condition which affects both males and females. It used to be referred to as the male version of Turner's syndrome; however, the genetic causes of Noonan syndrome and Turner syndrome are distinct. Noonan Syndrome occurring about 1 in 1,000 - 2,500 live births world wide. It is one of the most common genetic syndromes associated with congenital heart disease, similar in frequency to Down syndrome. The syndrome is not always identified at an early age<sup>1</sup>.

#### **Case History**

A 25 years old female from Mohammadpur, Dhaka attended the Dermatology Out-patient department, Bangladesh Medical College Hospital in May '08. She presented with generalized skin eruptions for 25 days and heavy left leg since childhood. On examination it was observed that eruptions were hyperkeratotic scaly, bilaterally, symmetrically distributed over erythematous base. The lesions were scaly over dorsum of hands and also trunk and neck. The lesions were also pruritic but less severe. The left leg was found to be edematous; edema 2-plus, localized and pitting type.

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## Noonan's Syndrome of a 25 years old female

The patient also had complaints of occasional central, continuous, non-radiating chest pain. She, however, also complained of occasional palpitation. Regarding her past illness nothing was contributory. She did not reveal any history of taking drug and exposure to excess sunlight or any chemicals prior to her skin eruptions. General and systemic examinations patient found to be moderately anemic. All of her family members are in good health. Through investigation was carried out. Her Hb level was 9.9 g/dl and ESR 30 mm in 1st hr. Differential blood count revealed eosinophilic leucocytosis. All other cell counts were within normal limits. Urine routine and microscopic examination showed trace amounts of albumin with normal number of epithelial cell and pus cell. Serum IgE was raised with the level being 268 IU/ml. ICT for Filaria & Antinuclear antibody (ANA) was negative. The thyroid function test was normal. Echo-Doppler revealed trivial TR, normal chamber dimension, good LV systolic function (LVEF 73% at rest). Lymphoscintigraphy revealed chronic lymphatic channel obstruction in right lower limb and normal lymphatic flow in the left lower limb.

The patient was treated with 5% Crotamiton cream and combination of Hydrocortisone and Fusidic acid ointment which were mixed together and applied locally over the lesions thrice daily, Tab Desloratadine (5 mg) twice daily, Tab Normanal (500 mg) twice daily for 15 days and antibiotic Azythromycin (500 mg) once daily dose for 5 days.

### **Discussion**

Noonan syndrome is characterized by short stature; congenital heart defect; broad or webbed neck; unusual chest shape with superior pectus carinatum,



**Fig:** Short stature (1a), lymphedema (1b), Plethoric face (1c), Skin lesions (1d)

N.B: Informed Consent was taken from the concerned patient about publication if this report

inferior pectus excavatum, and apparently low-set nipples, developmental delay of variable degree; cryptorchidism, and characteristic facies. Coagulation defects and lymphatic dysplasias are frequently observed. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect, found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals which may be present at birth or appear later life. Other structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Length at birth is usually normal. Final adult height approaches to the lower limit of the normal. Mild mental retardation is seen in up to one-third of individuals. Ocular abnormalities,

including strabismus, refractive errors, amblyopia, and nystagmus, occur in up to 95% of individuals.

The cause is a mutation in the *PTPN11* (12q24.1), *SOS1* (2p22-p21), *RAF1* (3p25) and *KRAS* (12p12.1) genes. The mutation(s) can be inherited from affected parents (autosomal dominant), or can occur during development in genetically predisposed children<sup>2</sup>. About 50% of cases diagnosed with Noonan syndrome found to have mutation(s) of tyrosine phosphatase nonreceptor type 11 (*PTPN11*) genes. The gene encodes protein termed tyrosine phosphatase, nonreceptor type 11, also called SHP-2 which has important role in the development of heart, blood cells, bones and other tissues during fetal life. Mutations in *PTPN11* gene results in synthesis of variant protein which lacks its switching 'on - off' response to different other signals rather always stays on. It is postulated that this results in uncoordinated cell division and growth which occur in Noonan syndrome<sup>3</sup>.

Mutations so far identified in the *KRAS* gene are Val14, Thr58, Val152 and Asp153. Mutant *KRAS* suggested to be reducing RAS inactivation resulting in increased RAS signaling which is thought to disrupt normal growth and maturation of various tissues giving rise to Noonan syndrome.

Noonan syndrome has also been found with another condition called neurofibromatosis 1 which suggests present of mutation in the neurofibromin 1 (*NF1*) gene. *NF1* gene encodes a protein termed neurofibromin which acts as a tumor suppressor and helps keep cells from growing too fast or in an uncontrolled way.

Characteristic facial features are the key of clinical diagnosis of case of Noonan

syndrome. These features, however, may vary depending on the age of the patient. A baby less than one month old may have wide-set and down-slanting eyes, low-set ears, a deep groove and wide peaks in the upper lip, a short neck and a low hairline on the back of the head. An infant may have prominent eyes with a downward slant and thickened lids, and a depressed root of the nose with a wide base and bulbous tip. An adolescent's face is typically wide at the forehead tapering to a pointed chin, the facial features become sharper and the eyes are less prominent, the neck lengthens to reveal skin webbing or prominent neck (trapezius) muscles. In adulthood, the crease that runs from the edge of the nose to the corner of the mouth becomes prominent and skin appears transparent and wrinkled. Clinical features in combination with congenital heart diseases of different forms are cardinal for diagnosis of Noonan's syndrome.

Detection of NS associated *PTPN11*, *SOS1*, or *KRAS* gene mutations may confirm the diagnosis of the syndrome. However, absence of mutation(s) will not exclude the diagnosis as there are more as yet undiscovered genes that cause Noonan Syndrome.

Treatment of patients with Noonan's syndrome must be multidisciplinary approach. Once diagnosis of Noonan's syndrome is confirmed plan of treatment depends on the age of the patients, and nature and gravity of clinical conditions. In patients of younger age near normal growth usually is the main target. In case of adult usually treatment plan is to maintain near normal life and to avoid complications. Severe cardiac complications sometimes corrected by surgery. Attention is usually paid to boys to take measures for undescended testes and testosterone supplementation initiated

for attainment of growth and near normal life.

Since the condition is not uncommon physicians need to remain vigilant to fall short in diagnosing these cases. It may be also mentioned that patient with Noonan's

Syndrome need special and coordinated attention for their treatment of specific complication and maintain near normal life.

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### **References**

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