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NOONAN SYNDROME-CASE REPORT

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ABSTRACT
Noonan syndrome is a common genetic disorder with multiple congenital abnormalities. It is characterized by congenital heart disease, short stature, a broad and webbed neck, sternal deformity, variable degree of developmental delay, cryptor-chidism, increased bleeding tendency, and characteristic facial features that evolve with age. Molecular genetic testing can confirm the diagnosis in most cases, which has important implications for genetic counseling and management. Physicians should know how to diagnose Noonan syndrome because patients who have it require monitoring for a large number of potential health conditions.[1] **Discussion:** A 23 year old male patient is a known case of lower respiratory tract infection and cardiomyopathy since 8years and came with complaints of cough with sputum, shortness of breath Grade-3 progressive in male general medicine dapartment. On third day, Webbed neck, small mouth, upturned neck, thin long slender was noticed. During the treatment on the eighth day, the patient developed high grade fever associated with chills and rigors, headache, bodypain for which treatment was given. The patient also developed mild rashes over the back for which no treatment was given. **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.

KEYWORDS: Webbed neck, sternal deformity, bleeding tendency, developmentel delays, molecular genetic testing.

INTRODUCTION
Noonan syndrome is a disorder that involves unusual facial characteristics, short stature, heart defects present at birth, bleeding problems, developmental delays and malformations of the bones of the rib cage. Noonan syndrome is caused by changes in one of several autosomal dominant genes. A person who has Noonan syndrome may have inherited an altered (mutated) gene from one of his/her parents, or the gene changes may be a new change due to an error carried by the egg or sperm or occurring at conception. Alteration in four genes – PTPN11, SOS1, RAF1 and KRAS have been identified.Noonan syndrome is present about 1 in 1000 to 1 in 2500 population.[2]

The clinical features of Noonan syndrome includes
Cardiovascular: Hypertrophic cardiomyopathy, pulmonary stenosis, often with a dysplastic value. Dental / Oral: Articulation difficulty, high arched palate, Malocclusion, and Micrognathia.
Dysmorphic Facial Features:

- **New born:** Large head compared to face, tall forehead with narrow temples, widespread eyes, downward slat of palpebral fissures, epicanthal folds, short, broad nose with depressed root and full tip deeply grooved philtrum, small chin and short neck, oral shaped, low set, posteriorly rotated earn with thick helix, excess nuchal skin, swollen edematous dorsum of hand and feet.
- **Infant:** Wispy hair, thickly hooded prominent eyes, wide-based, depressed nose with bulbous, upturned tip and cupid low appearance of upper lip.
- **Child/ adolescent:** Inverted triangle- shaped head, coarse facial features, curly / wooly hair, wide forehead, neck skin webbing, small chin, pectus sternal deformity, cubitus valgus, widely spaced nipples.
- **Adult:** High anterior hairline, Triangle-shaped head, Transparent, Wrinkled skin, prominent nasolabial folds.[3]

Ears: Hearing loss. Eyes: Anterior segment problems, nystagmus, ptosis, Hypertelorism and epicanthal folds, refractive error, strabismus. Gastrointestinal tract: Feeding difficulty. **Genitourinary:** Cryptorchidism, female fertility is normal, males have fertility issues, malformations, puberty can be delayed in both sexes. Growth: Birth weight and length are normal, failure to

thrive and short stature, mean final adult height is 63 to 66 inches (160–68cm) in males and 59 to 61 inches (150-155cm) in female. Hematological: Increased bleeding tendency, leukemia and myeloproliferative disorder. Lymphatic: lymphedema. Neurological: behavioral conditions, CNS malformations, early motor milestones delay, learning difficulties, mild individuals have normal intelligences, speech disorders. Skeletal: cubitus valgus, spinal abnormality, sternal deformities. Skin conditions: dystrophic nails, extra prominence on pads of fingers and toes, follicular keratosis, hyper-elastic skin, moles, multiple lentiginous, thick curly hair or thin sparse hair.

Diagnostic parameters[4]

Feature	A=major	B = minor
1) Facial	Typical facial dysmorphology	Suggestive facial dysmorphology
2) Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or ECG results typical of Noonan syndrome	Other defect
3) Height	< 3rd percentile	< 10th percentile
4) Chest wall	Pectus carinatum/excavatum	Broad thorax
5) Family history	First-degree relative with definite Noonan syndrome	First-degree relative with suggestive Noonan syndrome
6) Others	All of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia	one of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia
Note: Noonan syndrome is considered present if the patient has typical facial dysmorphology plus one feature from categories 2A through 6A or two categories from features 2B through 6B, or has suggestive facial dysmorphology plus two features from categories 2A through 6A or three features from categories 2B through 6B.		

Diagnosis was made solely on the basis of clinical features, but molecular genetic testing can provide confirmation in 70% of cases.

CASE PRESENTATION

A 23 year old male patient was admitted in the general medicine ward with chief complaints of cough with sputum, shortness of breath Grade-3 progressive. Webbed neck, small mouth, upturned neck, thin long slender fingers was noticed.On examination, patient was conscious and coherent, plus rate was 78bpm, BP was 100/80mmhg.He has a past history of lower respiratory tract infection since 8yrs and cardiomyopathy since 7yrs.He was investigated for complete blood picture, biochemistry, thyroid test, serum creatinine, Random blood glucose and blood urea. RBC count-5.45cells/mm(3.8-4.8) and Blood urea- 29.25mg/dl(7-20) was found to be higher than normal.2D Echo was performed which shows dilated LA/RA, LVH, Biventricular hypertrophy. He had coarse facial features with hypertelorism, depressed nasal bridge, low set ears, deformed left ear with microtia, high arched palate, and webbed neck. There was thoracic scoliosis, pectus carinatum, cubitus valgus with clinodactyly. On CVS examination there was pansystolic murmur. 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/mm, MCV-86 Fl, MCH-26pg with normocytic and normochromic red blood cells on peripheral blood smear. Platelet count was 2.7 lakhs/cmm. USG scrotum revealed bilateral undescended testis.Few days later, patient developed high grade fever associated with chills and rigor, headache, bodypain and rashes.The patient was not prescribed with medication for rashes.

DISCUSSION

Noonan syndrome is a developmental disorder characterised by facial dysmorphia, short stature, cardiac defects and skeletal malformations. Recently, PTPN11 which encodes the non-receptor protein tyrosine phosphatase SHP-2 (src homology region 2-domain phosphatase-2) was identified as the defective gene.SHP-2 is a member of a small family of cytosolic protein tyrophosphatases (PTP). These proteins exhibit high degree of homology in amino acid sequence and are essential during development. SHP-2 is the key molecule in the cellular response to growth factors, hormones, cytokines and cell adhesion molecules. It is required for activation of the mitogen activated protein (MAP) kinase cascade induced by epidermal, fibroblast and hepatocyte growth factors. It is involved in mesodermal patterning, limb development, hematopoetic cell differentiation and semilunar valvulogenesis.

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

- 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

Treatment focuses on the problems that occur and is usually multidisciplinary as in most other syndromes. The expected outcome depends on the extent and severity of symptoms that are present. Activities of the child may be limited depending on cardiac status and the presence of hematologic abnormalities. Certain types of congenital heart lesions are amenable to surgical correction. Patients with bleeding disorders must be advised against the use of aspirin and aspirin containing products or other medications that may interfere with coagulation or platelet function. Growth hormone has been used to accelerate growth in some patients with this syndrome. All patients require continuous developmental, audiologic and ophthalmologic follow-up.[5]

CONCLUSION

Patients with Noonan syndrome often exhibit alteration of the stomatognathic apparatus. For these subjects dental care is necessary starting from the first years of age, in order to prevent problems that could become irreversible and difficult to manage in day hospital. Therefore, either a primary or a secondary prevention are recommended, with customised protocols that should also envisage a rehabilitation process aimed at the normalisation of the musculature of the lower third of the face, which is compromised by the syndrome.[6]

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