Noonan Syndrome – A Case Report

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Abstract
Noonan syndrome is an autosomal dominant multisystem disorder, associated with cardiac anomalies and a distinctive facial appearance, characterized by genetic heterogeneity. Noonan syndrome affects both females and males, and has an estimated incidence of 1 per 1,000-2,500 live births. The present report aims at presenting the oro-facial findings in a case of Noonan syndrome in a 16 year-old male.

Keywords: Noonan Syndrome (NS), Webbed neck, Short stature, Pectus excavatum.

Introduction
Noonan syndrome (NS) is an autosomal dominant, variably expressed, multisystem disorder.[1] It’s first description was made in 1883 by Kobylinski.[2] However studies on the NS had been first conducted in 1963 by Jaqueline Noonan and Ehmke.[2,3,4]
NS is also called Webbed neck syndrome, Pseudo-Ullrich Turner syndrome, Female Pseudo-Turner syndrome or Turner-like syndrome.[5]
The incidence is one in 1,000 to 2,500 live births for severe phenotype, but mild cases may be as common as one in 100 live births. Familial recurrence is consistent with an autosomal dominant mode of inheritance, but de novo mutations are more common, accounting for 60% of cases.[6]
Tartaglia et al. in 2001 reported the molecular basis of this syndrome: mutation in the PTPN11 (protein tyrosine phosphatase non-receptor type 11) gene on chromosome number 12, in about 50% of the individuals with NS.[5]
To date, many cases have been reported, but there have been few descriptions of the cranio-dento-facial features. Therefore, the present paper is intended to describe the oro-facial findings in a case of NS.

Case Report
A16-years old male patient came to the department of Oral Medicine & Radiology with chief complain of unaesthetic appearance of teeth. There was no relevant medical or family history. Patient had slurred speech and showed poor school records i.e. he had failed thrice in the 7th grade and so was dropped out from school.
On general examination, patient was of short stature i.e., 4 feet and 8 inches and showed facial
dimorphism, with facial shape of an inverted triangle (Figure 1). Physical examination revealed webbing of neck/ ptergium colli (this was the most dominant feature), pectus excavatum and wide spaced nipples which appeared to be low-set (Figure 2 and 3). Also features like thickly hooded prominent eyes with mild hypertelorism, multiple lentigines on nose, epicanthic folds and deeply grooved philtrum were present (Figure 1). Moreover he had a tendency for lip incompetence and he reported the habit of mouth breathing.

On intra oral examination multiple retained deciduous teeth and multiple missing permanent teeth was found. On panoramic radiograph multiple over retained deciduous teeth in relation to 55, 63, 73, 75 & 83 and multiple unerupted permanent teeth in relation to 15, 23, 33, 35 and 43 were seen ( Figure 4).

Based on clinical and radiographic features observed a provisional diagnosis of Noonan’s syndrome was established. Comprehensive treatment was planned which included extraction of retained deciduous teeth and orthodontic treatment.

**Figure 1:** Extraoral features showing facial dimorphism, facial shape of an inverted triangle, multiple lentigines on nose, epicanthic folds and deeply grooved philtrum.

**Figure 2:** Webbing of neck

**Figure 3:** Pectus excavatum with wide spaced nipples.

**Figure 4:** Panoramic radiograph showing: multiple retained deciduous teeth in relation to 55, 63, 73, 75, 83 and multiple unerupted permanent teeth in relation to 15, 23, 33, 35, 43.
Table 1:

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>A-MAJOR</th>
<th>B-MINOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Facial</td>
<td>Typical facial dysmorphology*</td>
<td>Suggestive facial dysmorphology</td>
</tr>
<tr>
<td>2. Cardiac</td>
<td>Pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or electrocardiographic results typical of Noonan syndrome</td>
<td>Other defect</td>
</tr>
<tr>
<td>3. Height</td>
<td>&lt;3rd percentile</td>
<td>&lt;10th percentile*</td>
</tr>
<tr>
<td>4. Chest wall</td>
<td>Pectus carinatum/excavatum*</td>
<td>Broad thorax</td>
</tr>
<tr>
<td>5. Family history</td>
<td>First-degree relative with definite Noonan syndrome</td>
<td>First-degree relative with suggestive Noonan syndrome</td>
</tr>
<tr>
<td>6. Other features</td>
<td>All of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia</td>
<td>One of the following: intellectual disability*, cryptorchidism, and lymphatic vessel dysplasia</td>
</tr>
</tbody>
</table>

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.

*: Features present in our case.

Table 2:

<table>
<thead>
<tr>
<th>Features of NS</th>
<th>Expected</th>
<th>In Present Case</th>
</tr>
</thead>
</table>
| Cardiovascular | Pulmonary valvular stenosis  
Hypertrrophic cardiomyopathy  
Patent ductus arteriosus  
Arterial septal defect  
Ventricular septal defect  
Mitril insufficiency | No abnormality was detected on clinical examination and on reported by physician. |
| Growth | Short stature  
Birth weight and length normal | Short stature |
| Skeletal | Sternal deformity: Pectus carinatum, Pectus excavatum  
Spinal abnormality | Pectus excavatum |
| Dysmorphic facial features (changes with age) | • Newborn: Hypertelorism, downward slant of palpbral fissure, Short neck, Low set posteriorly rotated ears with thick helix, Short broad nose, Large head compared to face, Swollen edematous dorsum of hands and feet  
• Infant: Wispy hair, Thickly hooded prominent eyes, Wide-based, depressed nose, Cupid bow appearance of upper lip  
• Adolescent: Inverted triangle shaped head, Neck skin webbing, Pectus sternal deformity, Small chin, Widely spaced nipples, Curly / wooly hair, Nose has a pinched root and a thin high bridge  
• Adult: Prominent naso-labial folds, High anterior hair line, Transparent and wrinkled skin | NA  
Inverted triangle shaped head  
Neck skin webbing  
Pectus sterna deformity  
Prominent naso labial folds  
Deeply grooved philtrum  
Widely spaced nipples  
NA |
<p>| Neurologic | Learning difficulties | Learning difficulties |</p>
<table>
<thead>
<tr>
<th>Skin and Hairs</th>
<th>Mild intellectual disability</th>
<th>Speech difficulties</th>
<th>Mild intellectual disability</th>
<th>Speech difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigines</td>
<td></td>
<td>Cafe-au-lait spots</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thick curly or thin sparse hairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Cryptorchidism</td>
<td>Males can have fertility issues</td>
<td>No relevant history</td>
<td></td>
</tr>
<tr>
<td>Puberty can be delayed in both genders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>Hypertelorism</td>
<td>Posis of eyelids</td>
<td>Mild hypertelorism</td>
<td></td>
</tr>
<tr>
<td>Epicanthelc folds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down slanting palpbral fissures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ears</td>
<td>Low set posteriorly rotated Hearing loss</td>
<td>Not present</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>Feeding difficulties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Increased bleeding tendency: Factor deficiency, Platelet defect</td>
<td>No relevant history</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra oral</td>
<td>High arched palate</td>
<td>Delayed eruption</td>
<td>High arched palate</td>
<td></td>
</tr>
<tr>
<td>Malocclusion</td>
<td></td>
<td></td>
<td>Delayed eruption</td>
<td></td>
</tr>
<tr>
<td>Articulation difficulty</td>
<td></td>
<td></td>
<td>Malocclusion</td>
<td></td>
</tr>
<tr>
<td>Micrognathia</td>
<td></td>
<td></td>
<td>Retained deciduous teeth</td>
<td></td>
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</table>

**Discussion**

NS is a multisystem disease with a wide spectrum of heterogeneity regarding the genetic and clinical characteristics.\(^7\) The eponym “Noonan syndrome” was adopted in recognition of Dr Noonan, because she was the first to indicate that this condition occurred in both genders, was associated with normal chromosomes, included congenital heart defects, and could be familial.\(^8\)

The characteristic abnormalities resemble those in Turner syndrome, which only affects females and so NS was used to be called as “Male Turner syndrome”. This term is no longer used because NS can affect females also. The observation that patients with NS have normal karyotypes (46XY) was important in allowing the distinction to be made between the Turner and Noonan syndromes.\(^5\)

Autosomal dominant abnormalities are the results of germline mutations in the intracellular retrovirus associated DNA sequences (RAS) / mitogen-activated protein kinase (MAPK) pathway which can lead to NS and the associated abnormalities.\(^8\) NS has been linked to the chromosomal band 12q24.1. Also studies suggest that 50% of cases of NS are caused by missense, gain-of-function mutations in PTPN11.\(^1\)

As it is an autosomal dominant anomaly, any person affected has up to a 50% chance of transmitting it to their children.\(^3\) However in the present case there was no such family history, makes it more likely to be of mutation possibility. A scoring system given in Table - 1 by van der Burgt et al in 1994 has been devised to help diagnose patients with the condition.\(^6\)

Thus it confirms with the diagnosis of NS. Cardiovascular abnormalities are common in patient with NS and it includes pulmonary valvular stenosis, hypertrophic cardiomyopathy, patent ductus arterious, arterial septal defect, ventricular septal defect and mitral insufficiency.\(^5,6,7\) Though birth weight and length are normal, they generally have short stature.\(^6\) Pectus excavatum is commonly seen though other skeletal deformities like pectus carinatum, spinal abnormality and cubitus valgus can occur.\(^6\)

Facial features often changes with age. In newborns large head compared to face, hypertelorism, downward slant of palpbral fissure, short neck, low set posteriorly rotated ears with thick helix, short broad nose, Swollen edematous dorsum of hands and feet are seen. In Infants features like wispy hair, thickly hooded prominent eyes, wide-based depressed nose and
cupid bow appearance of upper lip occurs. Adolescents present typically with inverted triangle shaped head, small chin, neck skin webbing, pectus sternal deformity, widely spaced nipples and curly / wooly hairs. Adults with NS have prominent naso-labial folds, high anterior hair line and transparent and wrinkled skin.\textsuperscript{[6]}

Patient may have learning and speech difficulties and may present with mild intellectual disability.\textsuperscript{[6]} Lentigines, café-au-lait spots and pigmented nevi can be the skin manifestations of NS.\textsuperscript{[5]} Males can have fertility issues and cryptorchidism but puberty can be delayed in both genders. Patient may have feeding difficulties.\textsuperscript{[6]}

Intra oral manifestations of NS includes high arched palate, delayed eruption, malocclusion, articulation difficulty and micrognathia.\textsuperscript{[5,6]}

Moreover these patients may have increased bleeding tendency due to factor deficiency and platelet defects.\textsuperscript{[6]}

Details regarding expected features in this syndrome and that which were present in our case are listed in Table – 2.\textsuperscript{[5,6,7]}

The syndromes that should be differentiated with NS includes LEOPARD syndrome ( acronym stands for lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness), Cardiofaciocutaneous syndrome, Costello syndrome, Turner syndrome, Fetal alcohol syndrome, Aarskog syndrome, Baraitser-Winter syndrome and Neurofibromatosis type 1.\textsuperscript{[1,8]}

All individuals with NS require detailed and regular follow up for ongoing developmental, audiologic, ophthalmologic, cardiac, neurologic and other associated problems. Because bleeding anomalies and blood clotting disorders have been reported, a full hematologic workup must be performed before any dental surgery.\textsuperscript{[9]}

**Conclusion**

With a prevalence of one in 1000–2500, NS is a disorder that dentist may encounter during their career. Because presentation can be mild and the typical facial features recede with age, the diagnosis might be overlooked. No confirmatory testing for NS is available. This entity remains a strictly clinical diagnosis because of characteristic dental and skeletal structures and dentists can play a major role in the diagnosis of this syndrome. Regular detailed follow-up with a multidisciplinary approach is often needed to address the medical and developmental complications of NS.

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**References**
