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CASE REPORT

TOE WALK IN NOONAN SYNDROME- A CASE REPORT

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ABSTRACT

Noonan syndrome (NS) is a rare genetic disorder, which may occur as sporadic or inherited as autosomal dominant or recessive trait. It is a multifactorial condition that is characterized by a series of congenital malformations including facial anomalies, post-natal growth development, webbing of neck, pulmonary stenosis and undescended testicles in boys. NS can be confirmed genetically by the presence of any of the known mutations. However, despite identification of fourteen causative genes, the absence of a known mutation will not exclude the diagnosis, as there are more undiscovered genes that cause NS. Thus, the diagnosis of NS is still based on clinical features. The present report describes a case of this syndrome without cardiac abnormalities but with characteristic bilateral toe walking.

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INTRODUCTION

The eponym "Noonan syndrome" (NS) was first recognized by a paediatric cardiologist Dr JacqelineNoona in 1962 (Opitz, 1985). Though it is an autosomal dominant disorder there is evidence for a rare autosomal recessive form. It can occur in both genders with normal number of chromosomes. The estimated prevalence of this genetic disorder is 1 in 1000 to 1 in 2500 live births (Noonan and Ehmke, 1963). Germ line mutations (Carta, 2006) in genes in Ras/MAPK pathway which is a critical pathway for cell growth to cell death have been linked to NS in 61% of cases. In 2001 Tartaglia *et al*. (2001) discovered PTPN11, the first gene for NS which encodes SPH-2, a non-membranous protein tyrosine phosphatase with largely positive regulatory roles in signal transduction for many cytokines, hormones and many growth factors. PTPN 11 mutations account for more than 50% of NS cases. Gene mutations can also occur in KRAS, SOSI, RAFI, $SHOC_2$, NRAS genes.

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The characteristic features are short distinctive facial features, chest deformity, and congenital heart diseases. Though the diagnosis is based solely on clinical findings, establishing the diagnosis can be very difficult in adulthood due to great variability in expression and the phenotype becomes less pronounced with increasing age. But definitive diagnosis can be made by one major sign or two minor signs or 2 minor signs or 3 major signs. (Table 1) This is a case report of a 10-year-old Asian boy with NS showing multiple congenital anomalies but without cardiac and karyotyping abnormalities who was referred by a general dental practitioner for management.

Case presentation

We present a case of 10-year- old Asian boy, reported along parents with chief complaints of pain and bleeding gums since 10 days. History revealed that the child had delayed mile stones, learning disability, speech problems and had undergone or chiding for left testis 5yrs back and surgery for webbed neck three years ago. Family history was non-contributory and child is third in birth order and was born full term. Other siblings, two sisters were normal.

Table 1. Scoring system for diagnosis of NS

Present changes	A=major	B=minor
Face	Typical face dysmorphology	Suggestive face dysmorphology
Heart	Pulmonary valve stenosis, cardiomyopathy	Other defect
Body height	<P3*	<P10*
Thorax	Pectuscarinatun/excavatum	Broad thorax
Family history	First degree relative with definite NS	First degree relative with suggestive NS
Others	Other Mental retardation, cryptorchidism and lymphatic dysplasia	Milder forms of these changes

* P3 and P10-related measures height by age (normal range P3-P97)

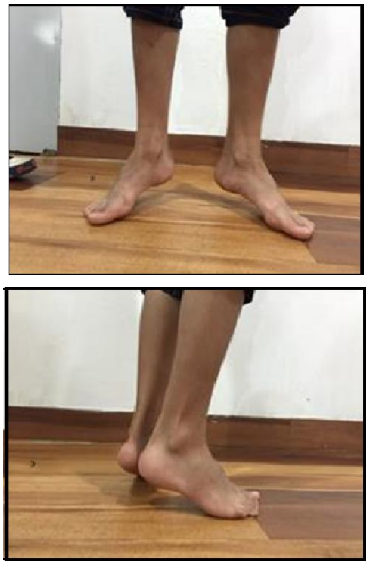
Table 2. Comparison of values of the patient with average 10 year old Asian boys

No	Distance	Average values of 10 year old Asian boy (mm)	Patient's values (mm)
1.	Inner canthal distance	29.16±3.31	30
2.	Outer canthal distance	78.86±7.7	96
3.	Inter pupillary distance	51.03±2.69	55
4.	Inter mammary distance	130±3	140

Table 3. Differential diagnosis for NS

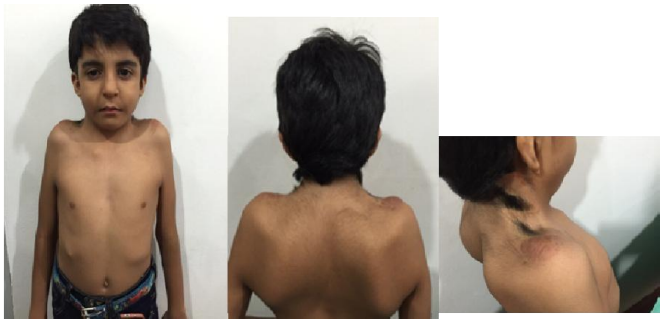
S. No	foetal alcohol syndrome	turner syndrome,	cardio-facio cutaneous syndrome,	costello syndrome,	leopard syndrome
	•Characteristic facial anomalies, growth retardation (intrauterine growth restriction and failure to have catch-up growth) •CNS involvement (cognitive impairment, learning disabilities, or behavioural abnormalities)	•Dysmorphicfacies, short stature and widely-spaced nipples but differs in that patients have an abnormal karyotype (45XO). •Only females are affected, patients have left-sided heart abnormalities, renal pathology and developmental delay	•Hypertelorism, down-slanting palpebral fissures. •Micrognathia, low-set ears, pulmonic valve stenosis, and keratosis pilaris	•Cardiac abnormalities, ECG anomalies, decreased growth velocity in the post-natal period caused by low growth hormone levels. •Feeding difficulties, misalignment of the teeth, and issues with vision. •Associated with Chiari I malformation, macrosomia	•Also referred to as Noonan Syndrome with Multiple Lentigines (NSML). •Patients classically have lentiginosis, ECG abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, •Retardation of growth, and sensorineural- deafness

On General physical examination, child had difficulty in sustaining attention, hyperactivity, and impulsive behavior which is suggestive of attention deficit/hyperactivity disorder. Gait abnormality characterized by an absence of normal heel-to-floor contact (heel strike) by both feet i.e. toe walking was found (Fig.1).



Picture 1. Characteristic toe walk

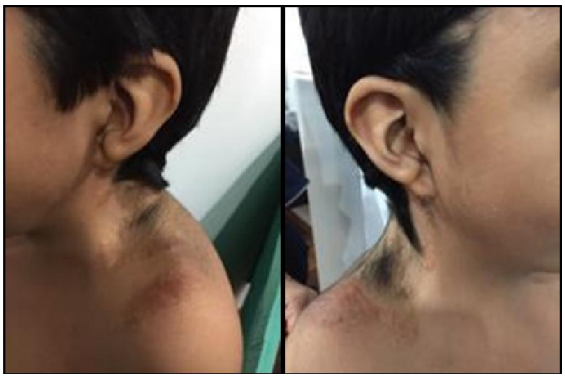
Other characteristic findings are short stature, short and scared neck with low hairline at the back of the neck, prominent right clavicular head, depressed sternum, and prominent floating rib on right side, small soft clavicles bilaterally. (Fig.2) Right testicle was absent.



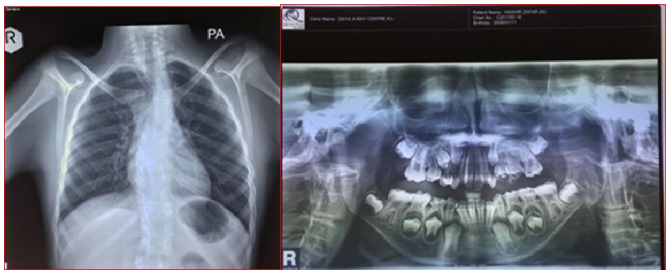
Picture 2. Front back lateral view

Child mental age was 4-5 yrs lesser compare to his age. Other like child's inner and outer canthal distance and inter pupillary and mammillary distance were measured (Table 2). Extra-oral examination revealed facial asymmetry due to facial hemi-atrophy on left side, hyper telorism with downward slanting of palpebral fissures and strabismus, eye brow were arched and diamond shaped, nasal tip is bulbous with deviated nasal septum, broad philtrum, ears are asymmetrical in length and are low set, posteriorly located with thick bilobed helixes.

(Fig-3) Lips are incompetent with proclined permanent maxillary central incisor. Lymph nodes were not palpable and for TMJ, no abnormality was detected. Hypo plastic jaws on left side were seen. Intra-oral examination shows mixed dentition with narrow, high arched palate, irregularly placed upper anterior teeth, and anterior deep bite, with heavy calculus deposits. Dental caries in retained primary and permanent teeth (16, 54,64,65, 75,74,84,46) were seen. Unerupted maxillary lateral incisor, retroclined maxillary left permanent incisor and midline shift of teeth towards left side of jaw were seen.



Picture 3. Thick bilobed helixes



Picture 4. PA chest OPG

Patient also had hyper-sensitive palate causing gag reflex. As the syndrome has a wide spectrum of disorders, child had undergone the following investigations like hematological, bio-chemical, radiographic analysis, ultra sound of abdomen, MRI pelvis, audiometry, cytogenic studies, ECG, HCG stimulation test. The complete treatment plan for full mouth rehabilitation that includes oral prophylaxis, extractions, and restorations of decayed teeth was discussed with the parents. As the child was not able to follow verbal commands, treating the child under nitrous oxide conscious sedation was discussed. Paediatrician's consent was obtained prior to procedure and all necessary treatments were done in two visits. The patient was periodically followed up during the subsequent follow-ups. Opinion was obtained from department of orthodontics regarding malocclusion which will be treated in later stages.

DISCUSSION

NS could be considered as brachial arch development syndrome with characteristic ocular, facial, cardiac and dental anomalies.

NS is also called as webbed neck syndrome. An obvious and evident webbing of the neck is generally present in only one fourth of the cases, while an apparent neck shortening with redundant skin on the neck and low posterior hairline are more commonly noted. The classic features of NS changes with age. In the new born, typical features include tall forehead. During infancy the head is relatively large with tall and prominent forehead. During childhood, the face may appear coarse or myopathic. Facial contour becomes more triangular with age, as the face lengthens. During adolescence and young adulthood neck is longer with accentuated webbing or prominent trapezius. In older individuals, the nasolabial folds are prominent and the skin appears thin and transparent. Growth retardation (Mendez and Opitz, 1985; Sharland *et al*., 1992; Ranke *et al*., 1988) is an important feature of Noonan syndrome, and short stature is found in 50-70% of cases in previously reported series. Short stature may be due to partial skeletal dysplasia as they are found to have disproportionably large trunk than legs, similar to what is seen with Turner syndrome. Early delay in motor milestones could probably be explained by the presence of hypotonia and hyper extensibility in the younger child. The characteristic bilateral toe walking shows prominent foetal pads on toes, which may be due to muscle spasticity and muscle dystrophy. Both the inner and outer canthal distance and inter-pupillary distance was increased which can also see in other syndromes like LEOPARD, apert syndrome. Inter-mammillary distance is also increased which shows wide chest with large distance between the nipples. These features may be more obvious in early childhood, but tend to become much less noticeable in adulthood.

The variety of clinical manifestations of this syndrome indicates that a multidisciplinary approach is necessary for diagnosis, treatment, and follow-up of these patients. In the present case, the child's haematological and bio-chemical investigations showed no abnormality. Cytogenetic studies shows male karyotype (46, XY) without numerical or structural chromosomal abnormality and was important in distinguishing between Turner and NS. Chest X-ray shows both the lung fields are clear, normal heart size and rib cage except right clavicle joint is more bulbous. (Fig. 4) 2D echocardiography shows structurally and functionally normal heart. Cervical spine and thoracic lumbar spine shows vertebral anomalies like scoliosis at thoraco-lumbar junction concave to right, block vertebrae, disc spaces are narrowed without paraspinal mass and blocked vertebrae. Ultrasonography of abdomen shows no abnormality, except right testes could not be localized.HCG stimulation test shows normal hormonal response. In MRI pelvis right testis is not visualized in the inguinal region or in the line of descent of testis. Audiometry values are normal. Orthopantomograph (OPG) shows mixed dentition stages of tooth development. Taurodontism, with mandibular first molars andopen apices was noted. Other findings are nasal polyp in right nostril with deviated nasal septum towards left and reduced ramus height with antigonial notch on left side of the mandible. (Fig. 4) There are several disorders that resemble NS phenotypically like LEOPARD, Foetal alcohol syndrome, Turner syndrome, Cardio-facial cutaneous syndrome, Costello syndrome (Judith Allanson, 2010). (Table3)

Majority of children with NS will grow up and function normally in the adult world. However, they may require special care and counseling. New medical problems may not be expected in adulthood. However, males who were born with undescended testes may have fertility problem. There is no evidence for gynecological or child bearing complications in females with NS. Adults with NS do not require special medical care.

Conclusion

Noonan syndrome is a genetic condition with characteristic phenotypic anomalies, but a wide range of clinical expression. Multidisciplinary treatment is the key to success in managing children with NS and the paediatric dentists play an important role to lead the health team. The children with NS usually have a wide array of health problems making it important for all specialties to be aware of the child's special care needs.

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