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RESEARCH ARTICLE

NOONAN SYNDROME - A CASE REPORT

Dr. Jaishri Pagare, Dr. Ankita Chormale, Dr. Vikrant Kasat, Dr. Rohini R. and Dr. Rashida Akolawala

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Abstract

Noonan syndrome (NS) is an autosomal dominant inherited disorder. 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 gene mutation will not exclude the diagnosis, as there are more undiscovered genes that cause NS. A well-known oral manifestation of Noonan syndrome is multiple unerupted teeth. Thus, the diagnosis of NS is still based on clinical features. We report a case of 16 year old female with the distinct clinical features of Noonan syndrome who has similar family history.

Introduction:-

Noonan's syndrome (NS) is a relatively common congenital autosomal dominant type of dwarfism that affects both males and females equally. It is used to be referred as a male version of a Turner's syndrome. Noonan syndrome is one of the most common genetic diseases associated with congenital heart defect, being second for frequency only to Down Syndrome.[1] The overall incidence of Noonan syndrome is believed to be between 1/1000 and 1/2000 livebirths. The syndrome was first recognized as a clinical entity in the 1963 by Noonan and Ehmke, when they described several patients with pulmonary stenosis associated with characteristic facial anomalies, webbed neck, short stature, chest deformity and undescended testes.[2] NS is the second most frequent cause of congenital syndromic heart disease, namely valvular pulmonary stenosis and hypertrophic cardiomyopathy[3].The characteristic findings of this syndrome include short stature, distinctive facial features, chest deformity, and congenital heart disease[4]

Noonan syndrome frequently presents with an autosomal dominant pattern of inheritance.[5] The pathophysiology of Noonan syndrome is not fully understood. PTPN11, SOS1, R1T1, RAF1 genes have been identified which are responsible for Noonan syndrome.[6] 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.

Case Report-

A 16 year old female patient born of non-consanguineous marriage reported to the department of Oral Medicine and Radiology with chief complaint of missing teeth since birth. Patient gave history of epilepsy in past, currently she complained about delayed puberty and excessive sweating.

Her maternal aunt and uncle had similar history of impacted teeth. Her mother has keloids over chest, back and upper limb (3 in number).

Patients physical examination revealed high hairline at the front of the head, antimongloid eyes, ptosis, hypertelorism, depressed nasal bridge, midface hypoplasia, excessive vertical height of face, short neck, (Fig 1a),

Corresponding Author:- Dr. Ankita Chormale

low set ears, low hair line at the nape of the neck (Fig 1 b) widely spaced nipples, underdeveloped breast, increasedcarrying angle and multiple naevi over face, chest and extremities. Her height was 122cm (Fig 2. showing height
<1st percentile) and weight was 23.5 kg (< 1st percentile).

Fig 1 a:- Photograph showing high hair line, hypertelorism, ptosis, depressed nasal bridge, excessive vertical facial height and short neck.

Fig 1 b:- Photograph showing low set of ears and low hair line at the neck.

Fig 2:- Photograph showing short height (<1st percentile).

Intraoral examination showed over retained 53, 63 and fully erupted 11,14,31,41 with multiple missing permanent teeth.

Her CBCT findings revealed multiple impacted permanent and supernumerary teeth, dilacerated roots of 16,26,36,37,46,47 (fig 3a), short neck of the condyle and flat condylar head (Fig 3b), underdeveloped maxillary and sphenoidal sinuses (Fig 3 c and d), hypoplastic bilateral pterygoid plates (Fig 3 e), and agenesis of frontal sinus and persistent metopic suture.(Fig 3 f)

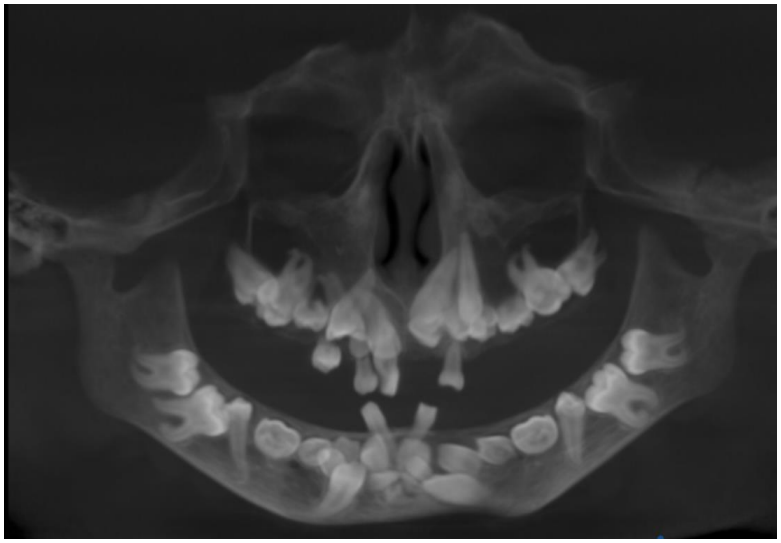

Fig 3 a:- Multiple impacted permanent and supernumerary teeth. Dilacerated roots of 16,26,36,37,46,47.

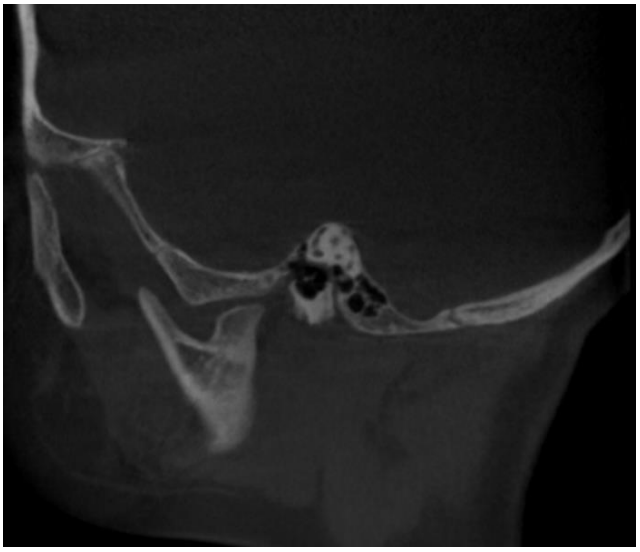

Fig 3 b:- Short neck of the condyle and flat condylar head.

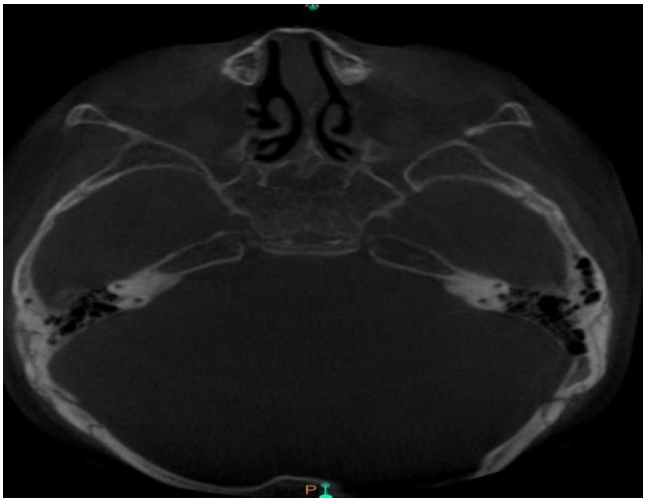

Fig 3 c:- Underdeveloped sphenoidal sinus.

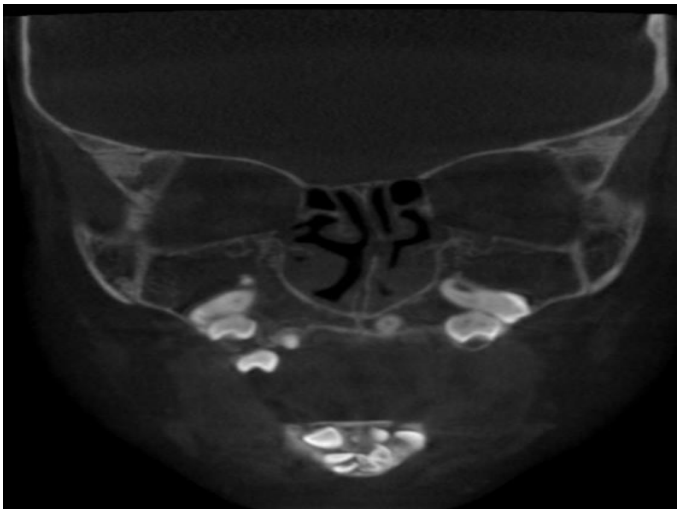

Fig 3 d:- Under developed bilateral maxillary sinuses.

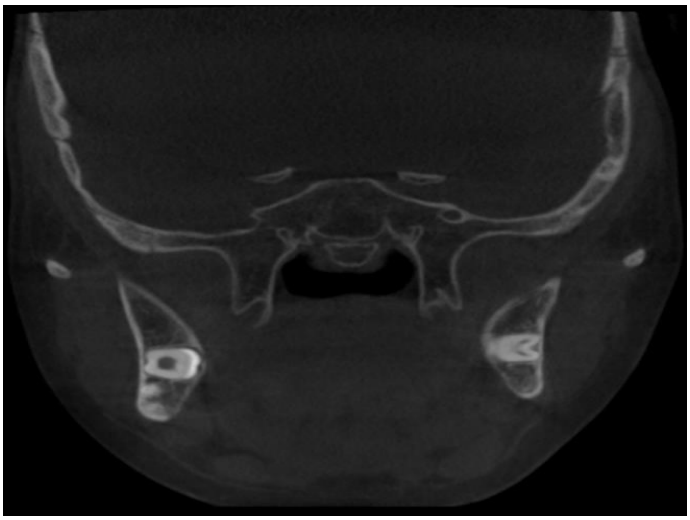

Fig 3 e:- Hypoplasia of bilateral pterygoid plates.

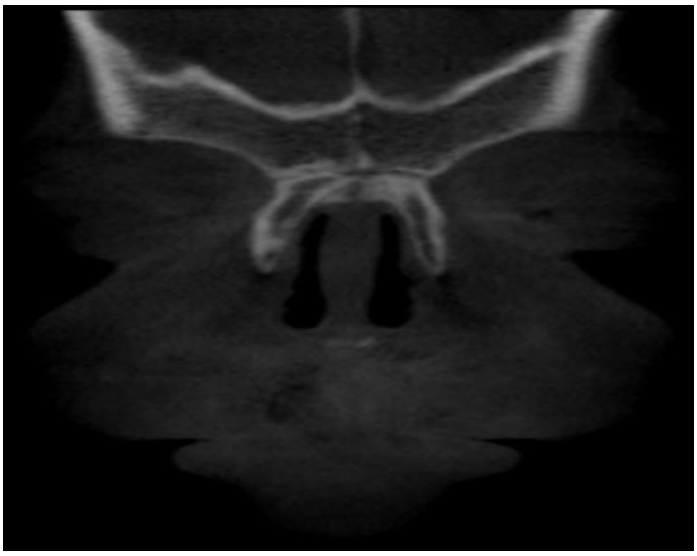

Fig 3 f:- Agenesis of frontal sinuses and persistent metopic suture.

Echocardiographic assessment showed mild tricuspid regurgitation and pulmonary hypertension.
Laboratory investigations were carried out which revealed vitamin D 8.49 ng/ml. (severe deficiency <10 ng/ml) and alkaline phosphatase 135 IU/L (42-132 IU/L).

From overall findings we gave a provisional diagnosis as Noonan syndrome

Discussion:-

Noonan syndrome is an autosomal dominant inherited disorder. Thus, parents with Noonan syndrome have a 50% chance of passing the mutation to the children. Noonan and Ehmke also noticed the high incidence of partial expression of this syndrome in one or both parents. The most commonly mutation in Noonan syndrome occurs in the PTPN11 gene (50%). Mutations seen in PTPN11 can be inherited, autosomal dominant or occur de novo through sporadic mutation. A smaller portion of mutations occurs in SOS1 (10-15%), RAF1 (5%), and RIT1 (5%) genes. Establishing the diagnosis of Noonan syndrome can be very difficult; especially in adulthood.[8] Associated abnormalities include ocular hypertelorism, ptosis, webbed neck, hydrothorax, short femur, short stature, skeletal malformations, cryptorchidism, cardiac anomalies (particularly pulmonary stenosis and hypertrophic obstructive cardiomyopathy) renal anomalies and varying degrees of mental retardation. Bleeding diatheses and platelet abnormalities also occur[9]

The diagnosis of NS can be made clinically, based on the diagnostic criteria given by van der Burgt et al[10] in 1994.

Feature	A= major	B = minor
1.Facial	Typical face	Suggestive face
2.Cardiac	Pulmonary valve stenosis and/ or typical ECG	Other cardiac defects
3.Height	<3rd percentile	<10th percentile
4.Chest wall	Pectus excavatum / pectus Carinatum	Broad thorax
5.Family history	First degree relative with definite NS	First degree relative with NS
6.Others	All 3 (males) Mental retardation, cryptorchidism, lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

According to this system, there should be 1A + one of 2A-6A or two of 2B-6B, 1B +two of 2A-6A or three of 2B-6B in order to make a definitive diagnosis of NS. This patient has **1A+3A+2B+5B** which is a definitive of Noonan syndrome according to the scoring system.

Noonan syndrome is the second most common syndromic cause of congenital heart disease, only after trisomy 21.The most common congenital heart defects are pulmonary stenosis (often with dysplastic valves; 50–60%) followed by hypertrophic cardiomyopathy (20%) and secundum atrial septal defect (6–10%). but other cardiovascular diseases such as ventricular septal defect, peripheral pulmonary stenosis, atrioventricular canal, aortic stenosis, valves abnormalities, aortic coarctation, and coronary artery anomalies have also been noted.[11] Echocardiogram of our patient showed patient mild tricuspid regurgitation and pulmonary hypertension**.**

Mean age of onset of puberty is delayed in patients of Noonan syndrome compared with the general population; 35% of boys enter puberty after age 13.5 years and 44% of girls enter puberty after age 13 years.[11]Our patient attained menarche at the age of 16 years.

Cryptorchidism at birth is common in male patients (77%). Urinary tract malformations such as pyelo-ureteric stenosis and/or hydronephrosis are present in 10% of cases. Increased bruising or bleeding is frequent, especially in childhood. Up to 55% of cases have a mild-to-moderate bleeding tendency.[12]

Abnormalities of pigmentation in NS include pigmented naevi (25%), cafe-au-lait spot (10%) and lentigines (3%). In our patient multiple naevi over face, chest and extremities are seen. Acute leukaemia and myeloproliferative disorders (MPD) have seen in some patients. Lymphatic vessel dysplasia, hypoplasia, or aplasia are common findings in NS (20%). Hearing loss is a frequent complication (15%–40%). Hepatosplenomegaly unrelated to cardiac failure is often present in infancy (26%–51%).[9]

There are a number of conditions which shows striking similarity with NS. The first to mention is Turner syndrome (45, X0), a well known chromosomal abnormality in girls. Thus, there are a group of syndromes with partially overlapping phenotypes in which causative mutations are found in genes of the RAS-MAPK pathway. It includes Cardio-Facio-Cutaneous syndrome, Costello syndrome and LEOPARD syndrome.Cardio-Facio-Cutaneous syndrome shows normal dental development. The predominant features of Costello syndrome are gingival hypertrophy and occlusal attrition while LEOPARD syndrome is associated with mandibular prognathism.

Treatment focuses on the problems that occur and is usually multidisciplinary as in most other syndromes. The presence ofcongenital cardiovascular diseases and hematological abnormalities may limit child's activity. No specific pharmacologic therapy is necessary. Patients with bleeding disorders must be advised against the use of aspirin and aspirin containing products or other medications which interfere with coagulation or platelet function. Growth hormone and vitamin D has been used to accelerate growth in some patients with this syndrome. After 3 months of vitamin D supplements and 1 month of follow up period our patient's serum vitamin D has increased to 22ng/ml with increase in height of 130 cm, weight 32 kg and onset of menarche. Dental treatment like replacement of missing teeth with overdenture with or without extraction of impacted teeth is desirable. All patients require continuous developmental, audiological and ophthalmological follow-up.[13]

There is no cure for Noonan syndrome as it is genetically inherited disorder. Prognosis in those with Noonan Syndrome is dependent on the expression of their phenotype. The severity of the heart defect is linked to the mortality and morbidity of patients. In our case patient has fair prognosis as the congenital heart defects are mild in nature.

Conclusion:-

Patients with Noonan syndrome usually report to oral physician with a chief complaint of missing teeth/delayed eruption/ unerupted teeth. Several etiological factors and syndromes are associated with missing teeth, in search of etiological factors we landed up in the diagnosis of Noonan syndrome. This article will help the oral physician to have indepth knowledge about clinical, oral manifestations and radiological findings of Noonan syndrome.

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