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A CASE OF NOONAN SYNDROME

General Medicine

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ABSTRACT

Noonan syndrome is a type of genetic disorder with wide variety of clinical features. Sometimes diagnosis may be difficult at early stage. We describe a case of 32 year old male with anaemia associated facial dysmorphism, short stature and hypertrophic cardiomyopathy. Genetic screening of this patient also has been tried. At present patient is being managed symptomatically.

KEYWORDS

Noonan syndrome, HOCM, short stature, anaemia, facial dysmorphology, genetic defect

INTRODUCTION:

Noonan syndrome is a syndrome with autosomal dominant type of inheritance caused by various genetic defects. Patient may present with wide variety of clinical features ranging from facial dysmorph ism, mental retardation to different types of cardiac anomalies. Usually identified at birth or later in childhood, but sometimes may be missed. Diagnosis is mainly clinical and supported by genetic studies. Role of growth hormone and IGF-1 with respect to short stature also have been discussed in various studies.

CASE REPORT:

32 year old male presented with progressive exertional dyspnea of 8 years and recurrent bleeding per rectum of 3 year duration. He had been receiving treatment for hypertrophic obstructive cardiomyopathy for 8 years .He also underwent evaluation for bleeding per rectum. Both upper G I endoscopy and sigmoidoscopy was done on September 2016. He had also received multiple blood transfusions for correction of post haemorrhagic anaemia. He had generalized seizures from childhood. His father died of cirrhosis of liver with heart failure at the age of 60 years. His father also had seizure. He was also short in stature. His father's brother had similar cardiac illness. His elder brother had no cardiac disorder, but he had facial dysmorphology and short stature(Fig.6). It was non consanguineous marriage.

Examination revealed short stature (150 c.m) (Fig.1) with severe pallor of mucous membrane and facial dysmorphism (Fig.2). He had ocular hypertelorism, micrognathia, lentigenes over cheek and malar region (Fig.2 &3). His occipito-frontal circumference was 25 cm and head circumference was 51 c.m. Hands showed incurved little finger on both sides (clinodactyly) (Fig.4) and had no transverse palmar crease. He had melanocytic neavus over the back of chest, near the spine of scapula. He had no chest wall or spine deformity. His forehead was broad with downward slanting palpebral fissures. High anterior hair line was present. (Fig2)

Fig.1: Patient with short stature

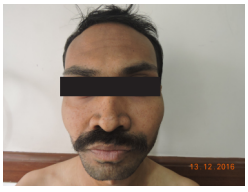

Fig.2: Ocular hypertelorism, broad forehead with downward slanting palpebral fissures, lentigenes over cheek and malar region

Fig .3: Image showing micrognathia

Fig. 4: Image showing clinodactyly

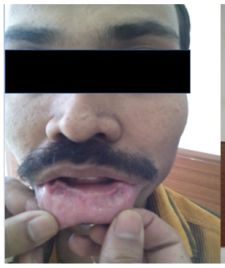

Fig. 5: Image showing bite marks in lower lip due micrognathia

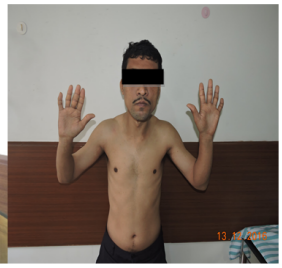

Fig. 6: Image of patient's elder brother with similar morphology

Vitals: Pulse: 74/min, regular, normal in volume, character, no radio-femoral delay.

BP: 140/90 mmHg in supine position.

Systemic examination revealed no cardiomegaly. There was grade 3/6

systolic murmur at the left sternal border, best heard during expiration which was not conducted to axilla. Heart sounds were normal. He had no signs of heart failure.

Abdominal examination did not reveal any visceral enlargement. No cryptorchidism and size of testes were normal in size. He was alert, co-operative and fully conscious. His IQ was normal. But scholastic performance was poor during his school days. Rest of systems were normal. Optic fundi were normal and vision was 6/6 bilaterally.

Investigations: Peripheral blood smear revealed evidence of microcytic hypochromic anaemia with Hb level of 7.6 gm/dl and PCV 24.4%. His total WBC count was 6100/mm3 and platelet count was 273000/mm3.His iron study revealed serum iron 23 mcg/ dl (Normal: 35-180mcg/dl) and ferritin level 6.7 ng/ml. (Normal= 20-250ng/ml). Total iron binding capacity 380 mcg/dl. (Normal= 250-425 mcg/dl).Transferrin saturation 6.05%. (Normal= 20- 50%).

OGD revealed large hiatus hernia, antral erosion and CLO test for H. pylori was negative. Colonoscopy revealed large rectal ulcer and grade III haemorrhoids. His stool occult blood was positive.

His serum creatinine was 0.92 mg/dl and thyroid function was normal. (T3- 135.65 ng/ dl, T4- 7.21ng/ dl and TSH- 2.79 UiU/ml). His bleeding time was 2 min and 30 sec and clotting time 4 min. a PTT & PT were normal. INR was 1.04. His serum testosterone was 5.06 ng/ml (Normal= 2.06-10.00 ng/ml)

Pure tone audiometry revealed mild sensorineural deafness. X- Ray skull AP showed small lesser wing of sphenoid. X- ray of both hands showed incurving of phalanx of both little fingers.

ECG: Left ventricular strain pattern

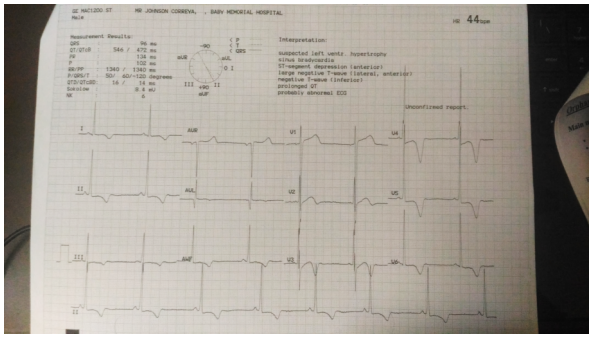

Fig .7

ECHO revealed hypertrophic obstructive cardiomyopathy, with mild to moderate LVOT obstruction. No regional wall motion abnormality. Normal left ventricular systolic function.

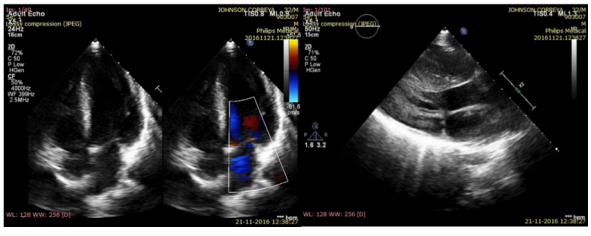

Fig. 8

USG abdomen was with in normal limits
Rectal biopsy showed ulceration with granulation tissue and glands showed normal architecture. The lamina propria showed oedema. No cytokeratin positive cells are seen in the ulcer. Biopsy was consistent with solitary rectal ulcer syndrome.

Genetic testing for PTPN 11 mutation was negative.

Discussion: Our patient had short stature, typical facial dysmorphology and congenital heart defect (HOCM) suggestive of Noonan syndrome.

Incidence of Noonan syndrome is estimated to be between 1:1000 to 1: 2500 live births[1]. The main facial features are ocular hypertelorism with downward slanting palpebral fissures; ptosis and low set posteriorly rotated ears with thickened helix[2].

This patient had short stature, ocular hypertelorism, characterized by interpupillary distance 59 mm, innercanthal distance is 32 mm and outer canthal distance is 84 mm.

In an evaluation of hypertelorism in genetic syndromes, compared to normal Egyptian children following data have been obtained; In this study about 17 children at 13 years of age had IPD of 58.41 with standard deviation of 3.59 and ICD of 30.12 with SD of 2.32 and OCD of 88.76 with SD of 3.38[3].

Orbital hypertelorism signifies increased distance between both medial side and lateral side of orbits. Inter orbital hypertelorism denotes increased distance between inner orbital walls. In our patient inner canthal distance and interpupillary distance were increased suggestive of interorbital hypertelorism[4].

Syndromic hypertelorism has many causes as chromosomal abnormalities, single gene disorder, developmental abnormalities of skull and brain and rare syndromes of unknown causes. Both dominant and recessive inheritances were reported. Noonan's syndrome is transmitted as autosomal dominant trait[5].

Characteristic chest deformities in Noonan's syndrome consist of pectus carinatum superiorly and pectus excavatum inferiorly can occur in 70-90 % of cases. 15% of cases have thoracic kyphosis, Cubitus valgus (50%), radio ulnar synostosis (20%), clinobrachydactyly (30%), joint hyper extensibility (50%) and talipes equinovarus (12%). This patient had clinodactyly characterized by incurved little finger in both hands, without any transverse palmar crease. Abnormal pigmentation can occur including multiple pigmented naevi (25%), café au lait spots (10%) and lentigenes(3%). Keratosis pilaris atrophicans faciei of face is present in 14% of cases and may lead to lack of eye brow. Our patient had multiple lentigens over the face and pigmented naevus over the back. Ophthalmic check-up showed normal vision and optic fundi[6].

He had micrognathia and high arched palate with prominent eyes with thick lips and prominent nasolabial folds. He had no webbing of neck.

Noonan syndrome is the second most common cause of congenital heart disease exceeded in prevalence only by Trisomy 21. Several cardio vascular phenotypes occur in Noonan's syndrome. Most common were pulmonary stenosis(often with dysplastic valves (50-60%)), hypertrophic cardiomyopathy (20%)secondary atrial septal defect (6- 10 %) but VSD, peripheral pulmonary stenosis, atrioventricular canal defect, aortic stenosis, mitral valve abnormalities, aortic coarctation, coronary artery anomalies have also been reported[7].

HOCM can be mild to severe and can be present from prenatal to late childhood. Almost of 25% of patients die because of heart failure with in first year, although rate of sudden death was lower than that for Familial HOCM[8,9].

This patient had mild to moderate LV outflow tract obstruction with mild mitral regurgitation with normal left ventricular systolic function without regional wall motion abnormality .He was diagnosed to have HOCM from the age of 24 years. His ECG showed evidence of LVH with strain pattern.

Birth weight and body length are initially normal in Noonan syndrome. Short stature is common manifestation of Noonan's syndrome. Pubertal growth spurt is often attenuated or delayed. Bone aging is also delayed[10]. Similarly our patient also had short stature. Growth hormone deficiency, neurosecretory dysfunction and growth hormone resistance can occur in Noonan's syndrome. Patients with PTPN 11 mutation associated Noonan's syndrome often have normal or slightly increased concentration of growth hormone and low concentration of IGF-I. PTPN 11 mutation is seen only in around 50% of patients with Noonan syndrome [11]. In this patient PTPN 11 mutation study was negative. Growth hormone and IGF-I levels were not estimated.

Up to 80% boys diagnosed as Noonan's syndrome have unilateral or bilateral cryptorchidism. Male gonadal dysfunction due to primary sertoli cell dysfunction is also reported[12].Our patient had no

cryptorchidism. Serum testosterone level was normal.

Haematological evaluation for anaemia in our patient showed evidence of microcytic hypochromic anaemia with adequate platelets and predominant neutrophils. His coagulation profile was normal. BT, CT, aPTT & Prothrombin time were normal. Our patient had bleeding rectal ulcer on colonoscopic evaluation and biopsy was consistent with solitary rectal ulcer syndrome. This may be confused with inflammatory bowel disease, but the biopsy of ulcer is confirmatory. Solitary rectal ulcer occurs in persons of all age and may be caused by impaired evacuation or and failure of relaxation of puborectalis muscle. Single or multiple ulcerations may arise due to sphincter over activity, higher intra rectal pressure during defecation and digital removal of stool[13].

Though haematological abnormalities like transient monocytosis, thrombocytopenia and myeloproliferative disorder, acute leukaemia and coagulation abnormalities are reported in Noonan's syndrome[14], none of them were present in our patient.

Our patient had normal intelligence and speech, but scholastic performance was poor. IQ was 71, which indicated borderline level of intelligence. Studies of cognitive ability in clinically diagnosed Noonan's syndrome suggested that the prevalence of intelligence impairment was about 20 %.(IQ < 70)[15] of patients and high frequency range in 25 % of patients[16]. Our patient had mild B/L sensory neural deafness.

Most recent scoring system for Noonan syndrome was developed in 1994[17].

• SCORING SYSTEM FOR NOONAN SYNDROME:

Features	A-Major	B-Minor
1-Facial	Typical facial Dysmorphology	Suggestive face dysmorphology
2-Cardiac	Pulmonary valve stenosis, HOCM and / or ECG typical of NS.	Other defects
3-Height	Less than 3rd Percentile	Less than 10th percentile
4-Chest wall	Pectus carinatum/ excavatum	Broad thorax
5-Family history	First degree relative with definitive NS	First degree relative with suggestive of NS
6-Other	Mental retardation, Cryptorchidism and lymphatic dysplasia	One of- mental retardation,cryptorchidism, lymphatic dysplasia

Definitive NS: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs

Out of 6 major criteria our patient has 3 major criteria (Typical facial dysmorphology, HOCM, Short stature(150 cm)) and one minor criteria(1st degree relative suggestive of Noonan's syndrome)[17].

In the family his brother had typical facial features and short stature without any cardiac manifestations.

His father had short stature and expired at the age of 60 years following chronic parenchymal disease of liver with portal hypertension and left ventricular dysfunction due minor coronary artery disease.

DIFFERENTIAL DIAGNOSIS:

Syndrome that were characterized by facial dysmorphology, short stature and cardiac defects may sometimes be difficult to differentiate from Noonan's syndrome notably Williams syndrome, Aarskog-Scott syndrome.

Sometimes cardio facio cutaneous syndrome, Costello syndrome, NF-1 and leopard syndrome may also come in differential diagnosis. Genetic analysis with characteristic clinical features may help to differentiate Noonan's syndrome from other conditions.

CONCLUSION:

A typical case of Noonan's syndrome detected at the age of 32 years was described here. He was referred to medicine department for evaluation of anaemia. Detailed evaluation showed typical features of Noonan's syndrome and haematological evaluation revealed microcytic hypochromic anaemia due to bleeding rectal ulcer and grade III haemorrhoids.

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