A Case of Noonan Syndrome Associated with Nephrotic Syndrome, Pituitary Mass and Pes Varus

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ABSTRACT

We report a case of a Filipino male diagnosed with Noonan syndrome on the basis of facial dysmorphism, chest deformity, short stature, mental and skeletal retardation, pulmonic stenosis and hypogonadism. In addition, he has three clinical features which are not known to be associated with the syndrome and are perhaps being reported for the first time: structurally normal kidneys with nephrotic syndrome, pituitary macroadenoma and pes varus.

Key Words: Noonan syndrome, congenital anomalies, genetics, nephrotic syndrome, pituitary mass, pes varus

Introduction

The Noonan syndrome was first recognized in 1963 when Noonan and Ehmke described nine patients with pulmonic stenosis associated with short stature, hypertelorism, mild mental retardation, ptosis, skeletal anomalies, and undescended testes among the males.[1] Although Noonan's patients shared several common clinical features with Turner's syndrome, these two clinical entities were easily distinguished by certain phenotypic peculiarities.[2] The major difference was the absence of chromosomal anomaly among Noonan's patients. Incidence is estimated at one case in 1,000 to 2,500.[3] In the Philippines, there are already three published cases of Noonan Syndrome—one diagnosed as a child and two as adults.[4, 5, 6.]

We report here a case of Noonan syndrome with multiple clinical features (Table 1), three of which were not previously known to be associated with the syndrome.

Case Presentation

The patient is a 15-year-old male, born full term by spontaneous vaginal delivery from a non-consanguineous marriage, the second child of a 26-year-old mother who allegedly did not have any illness or drug intake during her pregnancy. At birth, the boy was noted to have a protuberant chest and varus deformity of the left foot. There was webbing of the neck, depressed nasal bridge with broad apex nasi, anti-mongoloid slant of the eyes, low set ears and micrognathia. His phallus remained small and his testes undescended. He was developmentally delayed as he first crawled at five months of age, sat at one and a half years and was unable to arise from a sitting position until two and a half years of age. Despite these, he pursued schooling but had to repeat three grade levels because of poor academic performance. He was in grade 6 when he was seen in the hospital at age 15 years.

He was first seen at age 15 for dyspnea and generalized edema. Six months prior to initial consult, he developed bipedal edema rapidly progressing to anasarca. There was a slight decrease in urine output. There was tea-colored urine, but there was no dysuria. He eventually developed dyspnea, for which he had to be confined in a local hospital. He was diagnosed to have a "kidney disease with cardiac and hepatic complications." Management included digitalis, furosemide and cotrimoxazole and the patient was discharged much improved. However, in a week's time, there was recurrence of all the symptoms. He also developed moderate grade fever associated with cough. To further complicate things, four days prior to admission, he slipped in the bathroom floor, hit his right thigh, resulting in swelling and tenderness of the injured area. Subsequently, vesicles developed, and later ruptured exuding purulent material.

On admission, he was noted to be poorly nourished and was in moderate cardiorespiratory distress. He was awake but irritable, with a normal blood pressure, pulse rate of 112/minute and a respiratory rate of 34/minute. His actual body weight was 26 kg (<5th percentile for age) and height was 141 cm (<5th percentile for age). His head circumference was small for age at 50 cm as the mean for a 15-year-old male is 56.28 ±1.49 cm.[7] His chest circumference was likewise small for his age at 70 cm, with the mean value being 81.9±1.70 cm for 15-year-old boys.[8]

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Table 1. Clinical features of Noonan syndrome present in the patient

Clinical Features of Noonan Syndrome		
Known in published literature[13, 14]	**Present in the patient**	**Present in the patient but not previously reported to be associated with Noonan syndrome**
FACIAL		
Prominent epicanthal folds		
Ptosis		
Down-slanting (anti-mongoloid) palpebral fissures	☑	
Hypertelorism		
Short and broad nose, with depressed root and full tip	☑	
Ears that are low-set, posteriorly-rotated and have an oval shape and thickening of the helix	☑	
Upperlip has a deeply grooved philtrum		
Short neck with excess skin (webbed neck)	☑	
Low posterior hairline	☑	
Eyes much lighter in color than expected for family background		
SKELETAL AND EXTREMITIES		
Pectus deformity (pectus carinatum superiorly and pectus excavatum inferiorly)	☑	Pes varus deformity
Spinal deformities (scoliosis, kyphosis, spina bifida, cervical spine fusion)		
Upper extremity deformities (cubitus valgus, radio-ulnary synostosis)		
Lower extremity deformities (genu valgum, talipes equinovarus)		
Single transverse palmar (simian) crease	☑	
CARDIOVASCULAR		
Pulmonic valve stenosis	☑	
Atrial septal defect		
Partial atrioventricular defects		
Hypertrophic cardiomyopathy		
GROWTH AND ENDOCRINE		
Short stature	☑	Pituitary macroadenoma
Delayed bone age	☑	
Growth hormone deficiency and low IGF-1		
Delayed puberty	☑ Absent pubic and axillary hair	
Underdeveloped primary sex organs	☑ Micropenis	
RENAL AND GENITOURINARY		
Solitary kidney		Nephrotic syndrome
Renal pelvis dilatation		
Duplicated collecting system		
Cryptorchidism	☑	
NEUROLOGIC, COGNITIVE AND BEHAVIORAL		
Recurrent seizures		
Hearing loss		
Peripheral neuropathy		
Delay in motor milestones	☑	
Structural malformation and deformations of the central nervous system (Arnold-Chiari malformation, microcephaly, macrocephaly)	☑ Microcephaly – small head circumference at birth	
Lower level of intelligence	☑ Mental retardation; IQ of 74	
ORAL AND DENTAL		
High arched palate	☑	
Dental malocclusion		
Micrognathia	☑ + micro-maxilla	
Mandibular cyst		
LYMPHATIC		
Posterior cervical hygroma (webbed neck)	☑	

He had slightly pale conjunctivas, facial edema, an anti-mongoloid slant of the eyes, high arched palate (Figure 1), low set ears, low posterior hairline, webbed neck (Figure 2), and small mandible and maxilla. Funduscopy revealed normal findings with no visual field cuts on perimetry. His intercanthal distance was 3.5 cm while interpupillary distance was 6.5 cm. Dental evaluation showed chronic apical periodontitis with moderate gingivitis. He had pectus carinatum. His lungs had bronchial breath sounds with rales over mid-lung fields and bases. The point of maximal impulse and apex beat were at the 5th intercostal space, left midclavicular line. There was a thrill at the base with a 4/6 systolic murmur heard best over the 2nd to the 3rd intercostals spaces, left parasternal border; P2 was not

increased. His abdomen was globular and a fluid wave was noted. Liver span was 10 cm and the Traube's space was not obliterated.

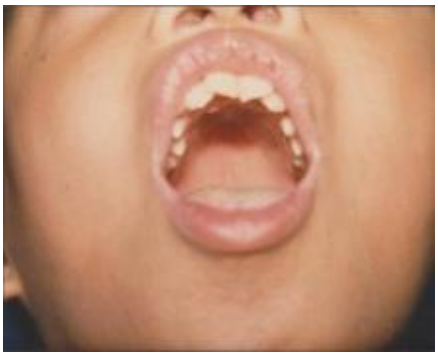

Figure 1. High-arched palate

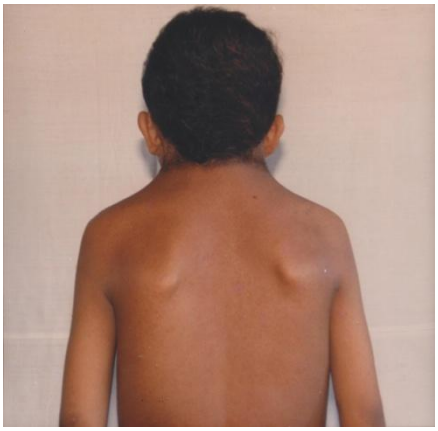

Figure 2. Low posterior hairline, low set ears and webbed neck

Pubic and axillary hair were absent, and penile length was short for age, at only 3.5 cm (Figure 3). The testes were palpable in the inguinal area.

He had a varus deformity of the left foot and a simian crease in the left palm. In addition, cellulitis was noted over his right thigh.

The initial impression was congestive heart failure secondary to a possible rheumatic heart disease, with cellulitis of the right thigh, community acquired pneumonia and a probable nephrotic syndrome. Noonan syndrome was still not recognized at the onset.

Laboratory Investigations

Further investigation then revealed other problems.

Cardiac. Electrocardiography revealed sinus tachycardia with extreme right axis deviation and right ventricular hypertrophy. An echocardiogram demonstrated right atrial and right ventricular dilatation and hypertrophy, adequate left ventricular function, pulmonary valve stenosis, and mild pericardial effusion.

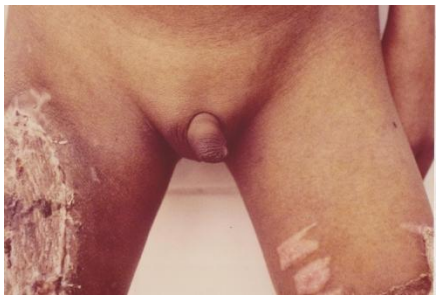

Figure 3. Micropenis, cryptorchidism and absence of pubic hair

Renal. The presence of nephrotic syndrome was documented: +3 to +4 albuminuria; elevated 24-hour urinary protein spillage of 4.13 to 8.13 g; low total serum protein of 32 g/L and low serum albumin of 19 g/L; and high serum cholesterol level of 7.22 mmol/L. Intravenous pyelography and renal ultrasound demonstrated no structural abnormality. Renal biopsy specimen under light and immunofluorescence microscopy revealed focal global sclerosis (Figure 4) and trace to +1 irregular mesangial and arteriolar deposits of IgM and C3, compatible with kidney findings in congenital heart disease and reflux nephropathy. The patient was started on Prednisone at a dose of 1 mg/kg/day.

Endocrine. The patient had cryptorchidism (testes were localized at the inguinal region as documented by abdominal CT scan) and micropenis. Serum testosterone was low at 145 ng/dL (normal: 360–990). Serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) were both low at 1.0 IU/L (normal: 1.2–5.0) and 1.3 IU/L (normal: 2.5–9.8), respectively, indicating secondary or tertiary hypogonadism. Pituitary CT scan demonstrated an intrasellar nodule, measuring 1.2 x 1.0 x 0.8 cm, consistent with a pituitary macroadenoma. The other anterior pituitary hormone assays were within normal: thyroid stimulating hormone (TSH) 2.8 mU/L (normal:0–3); prolactin 335 mU/L (normal: 110–510); growth hormone, baseline at 2.0 ng/mL; after 20 mins of exercise at 19 ng/mL; and after 20 mins of rest at 2.3 ng/mL (normal: 0-5); serum cortisol (in place of ACTH) 350 mmol/L (normal: 140–555).

Multiple physical anomalies. As was noted, these include short stature, anti-mongoloid slant of the eyes, low set ears, high arched palate, micro-maxilla and micrognathia, webbed neck, low posterior hairline, pectus carinatum, simian crease of left hand, varus deformity of left foot, and skeletal retardation (bone aging revealed an age of 10 years by Greulich and Pyle method) (Figure 5).

Dermatoglyphic analysis of our patient demonstrated intermediate triradii, simian crease, left hand, with a predominance of whorls at the second to fifth digits of both hands. Ulnar loops were noted on both thumbs. Total ridge count could not be determined due to damaged ridges.

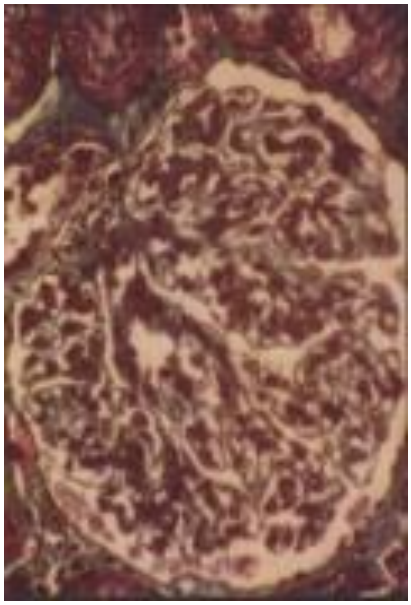

Figure 4. Renal biopsy specimen examined under light microscopy demonstrated focal global sclerosis

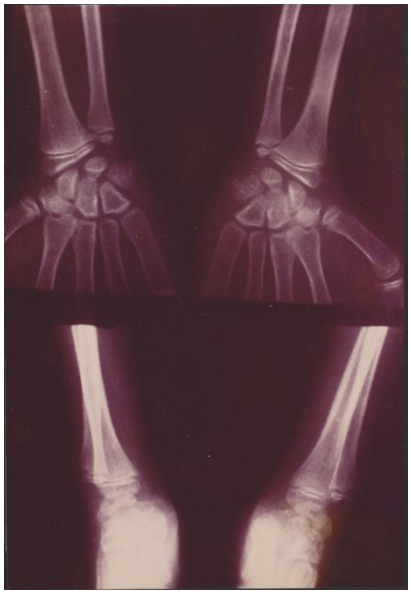

Figure 5. X-rays of the hand performed for bone aging revealed an age of 10 years by Greulic and Pyle method

Mental/Intellectual. Intelligence quotient tests using the Wechsler Adult Intelligence Scale revealed that his intellectual function was borderline with an IQ score of 74. His difficulties lie in analytical and synthetic skills and concentration ability.

The constellation of these clinical features and anomalies in a male led us to the consideration of Noonan syndrome. Because of the known genetic nature of this syndrome, an extensive family study and pedigree analysis (Figure 6) were performed on all available relatives. These revealed the presence of high arched palate, simian crease and chest prominence (occurring either singly or in combination). Of the 2nd generation consisting of 14 members, three were found to have at least one of the character traits considered. Of the 3rd generation consisting of 42 members (excluding the proband), nine were again noted to have the character traits; of these, seven exhibited high arched palate, three had simian crease of the hand, and another two had chest prominence. No abnormalities were apparent in both parents and an available grandparent. It is worth emphasizing that the finding of high arched palate, simian crease and prominent chest in some of the patient's relatives does not mean that these other relatives also have Noonan syndrome but since this can be inherited in an autosomal dominant manner, a more extensive dysmorphologic evaluation should be done to check if they fit the syndrome or not.

Cytogenetic. Analysis of G-banded metaphase chromosomes prepared from cultured lymphocytes of the proband revealed a normal male karyotype, 46,XY (Figure 7). In addition, interphase nuclei were stained with quinacrine, a fluorescent dye specific for the heterochromatin regions of chromosomes. Each interphase nucleus of the proband showed this intensely stained dot representing the distal portion of the Y chromosome.[9]

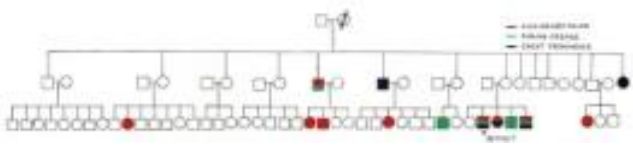

Figure 6. Pedigree analysis showing various following anatomic findings in the proband and his relatives

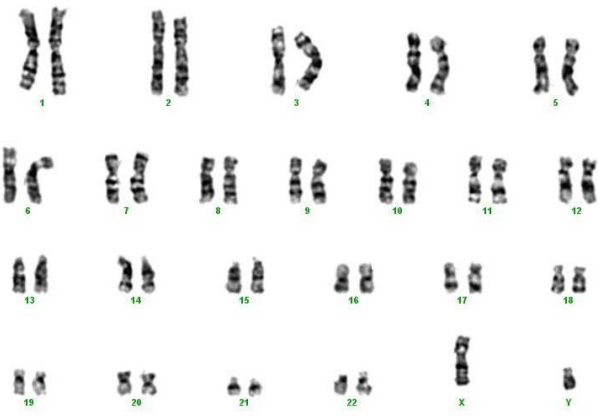

Figure 7. The normal male karyogram of the proband with Noonan syndrome

Discussion

Majority of the features that our patient manifested with are commonly seen in other cases of Noonan syndrome, such as the facial features, chest deformity, short stature, mental and skeletal retardation, pulmonic stenosis and hypogonadism. However, structurally normal kidneys with nephrotic syndrome, pituitary mass and varus deformity of the foot are not known to be associated with Noonan syndrome.

Renal anomalies have been described infrequently and usually consist of anatomical defects such as rotational errors, duplication, and hydronephrosis with pyeloureteral obstruction. Nephrotic syndrome was also recently documented in a case of Noonan syndrome.[10] The case reported by Gupta et al., however, had crossed fused ectopic kidneys grossly and focal segmental glomerulosclerosis histologically. In contrast, the case we report here had structurally normal kidneys by IVP and ultrasound and had focal global glomerulosclerosis histologically.

Known anomalies of the extremities include cubitus valgus, gracile fingers, short and stubby fingers, lymphedema, dystrophic nails, shortened fourth metacarpal, clinodactyly of the fifth finger, palmar simian crease and camptodactyly.[11] We have not seen a case manifesting with varus deformity based on our literature search.

There has been no reported case of Noonan syndrome with a pituitary mass similar to our patient. However, one patient from Greece was found to have a posterior pituitary tumor which turned out to be a low-grade pilocytic astrocytoma.[12] Our patient is suspected to have a pituitary macroadenoma based on the CT scan findings but it has not been excised and not subjected to histopathologic confirmation.

Summary

We reported a 15-year-old Filipino male who presented with 17 clinical features of Noonan syndrome. Because of these findings, the establishment of the diagnosis was not a difficult task. In addition, some of the features he manifested with are not known to be associated with the syndrome and are perhaps being reported for the first time: structurally normal kidneys with nephrotic syndrome, pituitary mass and significant varus deformity of the left foot.

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