CARDIOPATHY AND OCULAR ABNORMALITIES IN NOONAN SYNDROME

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ABSTRACT

We describe three children with Noonan syndrome with cardiopathy. One female child had cardiopathy and ocular abnormalities. The other two male children had congenital heart disease of which one had uncommon association of tricuspid valve dysplasia with regurgitation associated with endocardial cushion defect. Karyotypes of the female and one of the male children were normal. The growth hormone and thyroid hormone studies in the first and second male children were normal. All the three children were managed conservatively and followed-up.

Keywords: *Noonan syndrome, short stature, pulmonary stenosis, ocular abnormalities.*

SINGAPORE MED J 1994; Vol 35: 397-399

INTRODUCTION

Kobilinsky in 1883 described some of the features of Noonan syndrome (NS)[1]. But, it was Noonan[2] in 1963 and Pernot[3] in 1989 who comprehensively described this multiple malformation syndrome. The incidence is 1 in 1,000 to 1 in 2,500 live births[4].

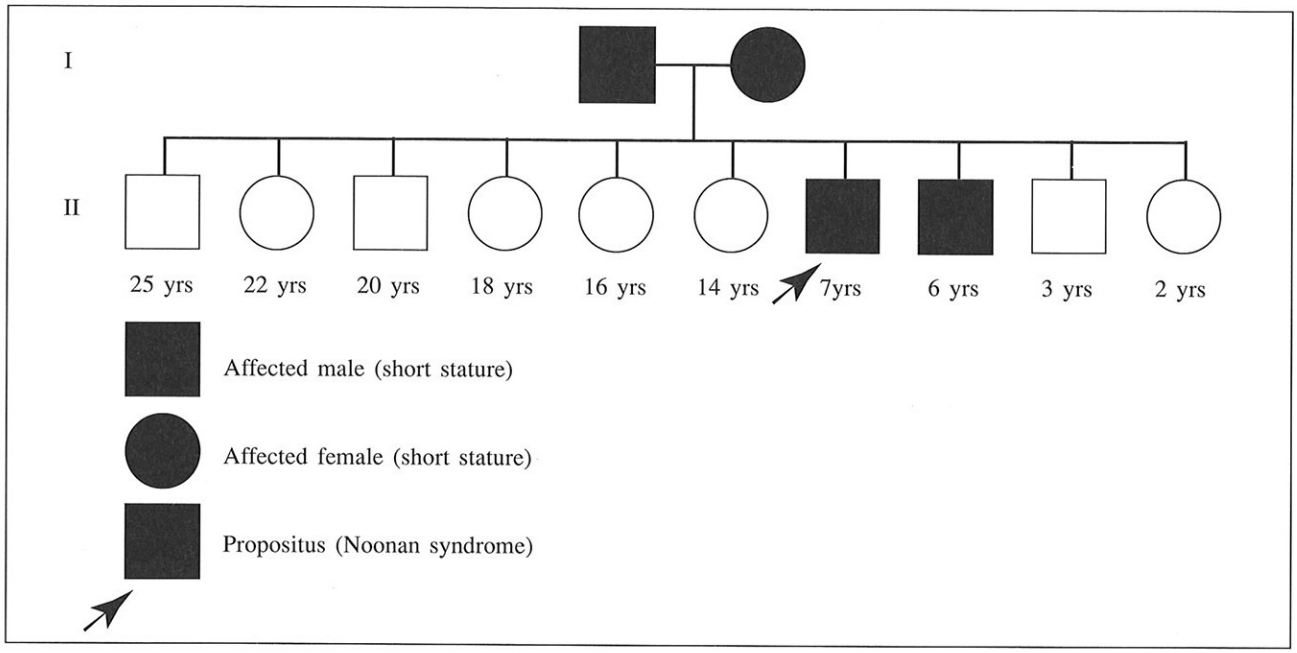
NS is characterised by facial anomalies, short stature, congenital heart disease, delayed puberty, skeletal, genital abnormalities, mild mental retardation[5] and blue green irides[4]. We describe three children with NS and associated cardiopathy, one of whom, a female child, had ocular abnormalities.

CASE REPORT

Case 1

A 7-year-old male child was referred for evaluation of short stature. He was born at term and was not asphyxiated. He gave a history of intermittent blue spells during crying below one year of age. He is the seventh of ten siblings. The height of his father, mother and younger brother were 154 cm, 148 cm and 103 cm (<3rd centile, height age of 4 years) respectively (Fig 1). Physical examination revealed the following: weight 16 kg (3rd to 10th centile), height 105 cm (<3rd centile, height age of 4.5 years), head circumference 48 cm (25 to 50th centile), pulse 96/min and respiratory rate 24/min. He was dull looking, acyanotic but not anaemic or jaundiced. His dysmorphic features included short stature, bilateral ptosis, downslanting palpebral fissures, hypertelorism, bilateral low set fleshy ears, depressed nasal bridge, webbing of the neck, pectus carinatum of the upper chest and excavatum of the lower chest, widely spaced nipples

Fig 1 - Pedigree Chart of Case 1 (Familial Short Stature)



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and underdeveloped external genitalia (Fig 2). The cardiovascular system examination revealed normal first and second heart sounds and a systolic thrill with grade 4/6 ejection systolic murmur over the second left intercostal space. The liver was palpable 1 cm below the right costal margin. Investigations done were as shown in Table I.

Table I - Summary of Investigations

Investigations	Case 1 The first male	Case 2 Female child	Case 3 The second male
Chest X-ray	mild post stenotic dilatation of pul. artery	cardiomegaly	cardiomegaly
ECG	RAD	RAD	LAD
ECHO	PVS	PVS PAG 78mmHg	Tricuspid valve dysplasia and regurgitation, Ostium primum type of ASD, moderate VSD.
Karyotyping	XY	XX	Not done
Hormone Levels: TSH T4 T3 Growth hormone	 7.6U/L 14.5nmol/L 2.8nmol/L 4.0ng/ml		 3.9ng/ml

TSH - thyroxine stimulating hormone
T4 - thyroxine
T3 - tri-iodothyroxine
ASD - atrial septal defect
VSD - ventricular septal defect
Pul. artery - pulmonary artery
PVS - pulmonary valve stenosis
PAG - pulmonary artery gradient
RAD - right axis deviation
LAD - left axis deviation

Case 2

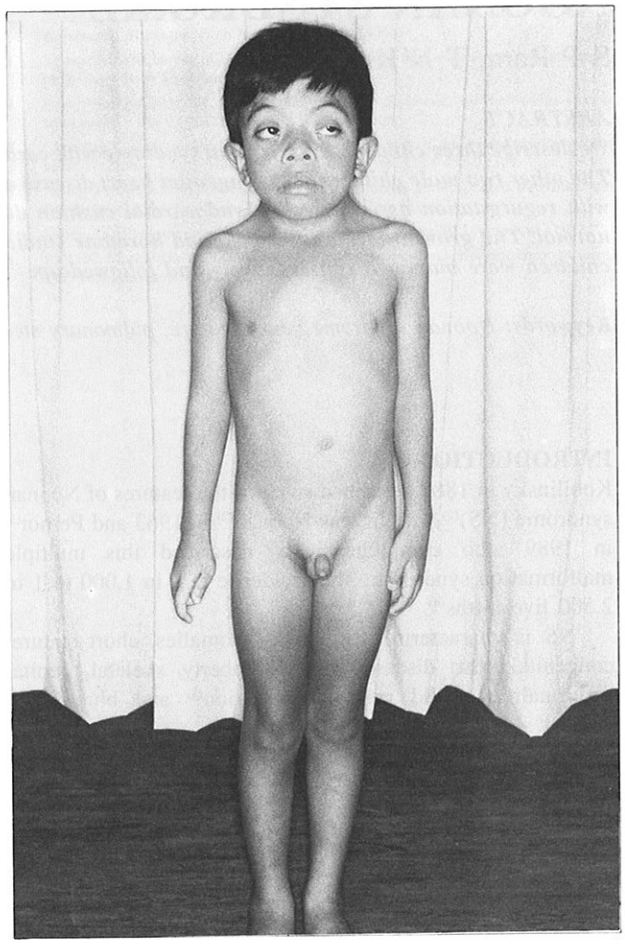
An 8-year-old Malay female child was referred for evaluation of heart murmur. The baby was delivered spontaneously by vertex delivery at a district hospital and cried at birth. The antenatal period of the mother was normal. Her weight at birth was 3400 gm. At one week of life, she was treated for breathlessness and became cyanosed during feeding and crying. Her motor and mental milestones were normal.

On examination, she was short for her age, not cyanosed or anaemic or clubbed. She weighed 18 kg (30 to 50th centile), her height was 104 cm (<3rd centile, height age of 4.5 years), head circumference 48.5 cm (25 to 50th centile) and interpupillary distance 7 cm (>97th centile). Her dysmorphic features included webbing of the neck, hypertelorism, low set ears, depressed nasal bridge, widely spaced nipples and shield like chest. Her ocular abnormalities included microphthalmus with rudimentary cornea, conjunctivalisation of corneal epithelium, blepharoptosis, a palpebral fissure length of 14mm, persistent pupillary membrane and coloboma of the iris and choroid. The fundus and lens were normal (Fig 3). Investigations were as shown in Table I.

Case 3

A 9-year-old male child (second male child) was evaluated for heart murmur. He was born to a 32-year-old mother and his father's age was 36 years. He weighed 18.6 kg (10 to 25th centile). His height and head circumference were 110 cm (<3rd centile, height age of 5 years and 3 months) and 49 cm (25 to 50th centile) respectively. He was the fourth of five siblings. The other siblings were normal. His milestones were normal. On examination, he had hypertelorism, webbing of the neck, widely spaced nipples and a broad chest. His pulse was 86/minute and respiratory rate 24/minute. The heart sounds were normal with a grade 3/6 systolic murmur. The liver was palpable 1 cm below the costal margin. Investigations were as shown in Table I. All three children were treated conservatively and followed up after discharge.

Fig 2 - showing Case 1, the male child with facial features of Noonan syndrome.

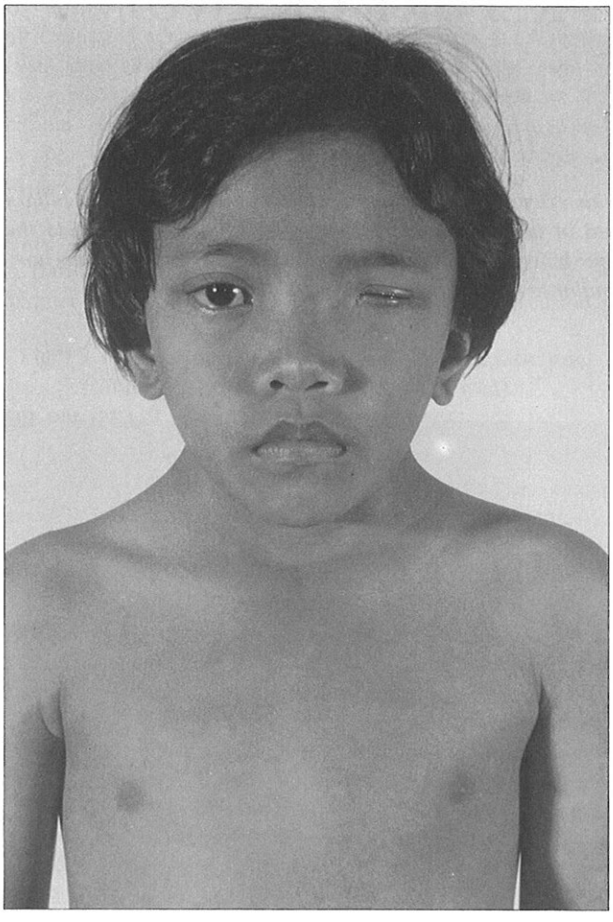


DISCUSSION

The mode of inheritance in NS has not been established. However, an autosomal dominant mode of inheritance with variable expressivity, and familial and sporadic cases have been reported. Two of the three children reported here, like most of the other reported cases, appear to be sporadic. Only Case 1 had a history of familial short stature. Karyotyping in two of our children was normal. The exact aetiopathogenesis of NS is obscure. Abnormal cell migration possibly due to lymphoedema, leads to the following clinical manifestations: wide neck, cryptorchidism, laterally placed nipples, low set posteriorly angulated ears, hypertelorism and downslanting palpebral fissures.[4]

Craniofacial abnormalities in children with NS consist of hypertelorism, epicanthic folds, ptosis of the eyelids, downslanting palpebral fissures [4], strabismus, saddle nose, low set ears and webbed short neck with low hair line. The

Fig 3 - showing the female child with Noonan syndrome with microphthalmus.



features in all the three children like facial anomalies, short stature, chest deformities and webbing of the neck were consistent with the diagnosis of NS.

Cardiac anomalies in children with NS include pulmonary valve stenosis (50% to 80%)[4,5], interatrial septal defect (20%), patent ductus arteriosus, obstructive and non-obstructive hypertrophic cardiomyopathy (17%). The less frequent cardiac lesions are aortic or other valvular dysplasia[3,4], septal defects and great vessel anomalies. In a case report by Amann et al, dysplastic atrioventricular valves with partial downward displacement of the septal leaflet of the tricuspid valve was described in a neonate with Noonan's phenotype[6]. Case 1, the first male child was asymptomatic and had mild to moderate pulmonary valvular stenosis. In Case 2, the pulmonary valve and artery size were normal but she had severe infundibular stenosis with gradient of 78 mmHg. Case 3 had endocardial cushion defect with moderate to severe tricuspid regurgitation associated with tricuspid valve dysplasia which is a less frequent feature in NS.

The ocular abnormalities in children with NS include antimongoloid slant of the palpebral fissures, hypertelorism, epicanthal folds, blepharoptosis and exophthalmos. The less frequent ocular anomalies are high myopia, keratoconus with acute hydrops, posterior embryotoxin and strabismus[7]. In the series of 151 of patients with NS by Sharland et al, the commonest ocular abnormalities observed were refractive error (67%)[8] and strabismus (63%) with amblyopia. In addition to the cardiopathy, Case 2 had left-sided microphthalmus and other abnormalities which are less frequently observed in NS.

The endocrine changes observed in children with NS consist of autoimmune thyroiditis, hypoparathyroidism and gonadotrophin deficiency[9]. The level of growth hormone and thyroid hormones were normal in Cases 1 and 3. The fertility rate varies depending on the gonodal status. Treatment consists of growth hormones replacement for short stature and corrective surgery for cardiac abnormalities and cryptorchidism. Functioning ovaries are present in affected females[2,9].

The common skeletal abnormalities in NS consist of micro or macrocephaly, dolicocephaly, micrognathia, delayed skeletal maturation, bitemporal bulging, proximal pectus carinatum, distal pectus excavatum, cubitus valgus and clinodactyly. The less frequent abnormalities are kyphoscoliosis, polydactyly, lordosis, Klippel Feil anomaly and dislocation of the head of the radius.

Other occasional abnormalities are high arched palate, bifid uvula, dental malocculsion, hypoplastic nails, pigmented nevi, keloids, hirsutism, haemangiomas, sensorineural deafness, lymph vessel dysplasia, hydrocephalus, inguinal and umbilical hernia and various other anomalies. Of the three children, only Case 1 had the classical chest abnormality of Noonan like proximal pectus carinatum and distal excavatum[10]. The head circumference in these three children was normal, similar to the observation by Sharland et al[8]. However, the height in all the three children was consistently below the third centile when compared to weight which varied from 3rd to 10th centile.

Prognosis depends on the severity of underlying cardiac disease. Thirty-three percent of children with NS are mildly mentally retarded (Intelligent Quotient ranges between 64-127, mean 102). Case 1, in this case report, highlights the need to do thorough clinical and echocardiographic evaluation of children with NS particularly in asymptomatic individuals.

ACKNOWLEDGEMENTS

We are thankful to Prof (Dr) Donald Hillman, Prof of Paediatrics, Department of Paediatrics, Hospital Universiti Sains Malaysia for his help in preparing this manuscript and Dr Lim, Paediatric cardiologist, Institut Jantung Negara, Kuala Lumpur for assessing the pulmonary artery gradient in one of our children with pulmonary stenosis and Dr Sivagnanum, Ophthalmologist, GHKB, Kelantan for his help in furnishing the literature regarding ocular abnormalities.

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