# *Syndrome of the month*

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# Noonan syndrome

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Noonan syndrome was first described over 20 years ago by Noonan and Ehmke[1]; they defined a specific group of nine patients with valvular pulmonary stenosis who, in addition, had short stature, mild mental retardation, hypertelorism, and unusual facies. In retrospect, the first case was probably described by Kobylinski in 1883.[2] Since that time, over 300 cases have been reported in medical publications. The incidence of Noonan syndrome has been estimated to be between 1 in 1000 and 1 in 2500 live births.[3] The cardinal features of Noonan syndrome are short stature, congenital heart defect, broad or webbed neck, a peculiar chest deformity with pectus carinatum superiorly and pectus excavatum inferiorly, and characteristic facies, which alter predictably with age to produce a discrete but changing phenotype which is described and illustrated below. Good reviews of Noonan syndrome are to be found by Mendez and Opitz,[4] Nora *et al*,[5] Char *et al*,[6] and Pearl.[7]

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## Clinical features*

### GROWTH

At birth the average length is 47 cm. Birth weight is generally normal (40%) but can be high, secondary to subcutaneous oedema. Prepubertal growth tends to parallel the 3rd centile (60%) with a relatively normal growth velocity. The pubertal growth spurt is often reduced or absent.[9] Delayed bone age has been reported in up to 20% of cases. Normal growth hormone levels with slightly raised somatomedin levels have been found in some patients.[10] Detailed growth curves for males and females with Noonan syndrome are now available.[11]

### CRANIOFACIAL

In the newborn period the main features are hypertelorism with downward slanting palpebral fissures (95%), low set, posteriorly rotated ears with a thick helix (90%), deeply grooved philtrum with

*Incidence figures are derived from reviews by Mendez and Opitz,[4] Pearl,[7] and Allanson[8] unless specifically referenced.

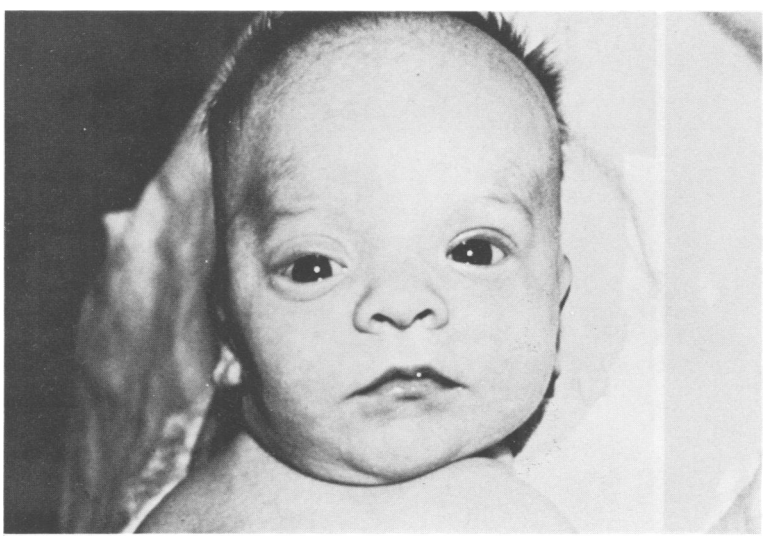

FIG 1 *Facial appearance in newborn period.*

high, wide peaks of the vermilion border of the upper lip (95%), high arched palate (45%), micrognathia (25%), and excess nuchal skin with low posterior hairline (55%) (fig 1). Facial appearance changes with age. In infancy the head appears relatively large with turricephaly, prominent eyes with level palpebral fissures, hypertelorism, and thick hooded eyelids. The nose has a depressed root, wide base, and bulbous tip (fig 2). In childhood the face often appears coarse or myopathic (fig 3). The contour of the face becomes more triangular with age. In the adolescent and young adult the eyes are less prominent and the nose has a pinched root, a thinner, higher bridge, and a wide base (fig 4). The neck lengthens, accentuating the webbing or prominent trapezius (90%). In the older adult (fig 5) there are prominent nasolabial folds, a high anterior hairline, and transparent, wrinkled skin. Hair may be wispy in the toddler, whereas it is often curly or woolly in the older child and adolescent. Features that are often present regardless of age are strikingly blue or blue-green irides, diamond shaped, arched eyebrows, and low set, posteriorly rotated ears with a thick helix (fig 2). The change in facial features is illustrated in the paper by Allanson *et al.*[12]

CARDIAC

Congenital heart defects are seen in two-thirds of patients. Common anomalies include pulmonary valvular stenosis (50%), atrial septal defect (10%), asymmetrical septal hypertrophy (10%), ventricular septal defect (5%), and persistent ductus arteriosus (3%). Pulmonary artery branch stenosis, mitral valve prolapse, Ebstein's anomaly, and single ventricles have also been described. The electrocardiograph characteristically shows a wide QRS complex, left axis deviation, giant Q waves, and a negative pattern in the left praecordial leads.[13]

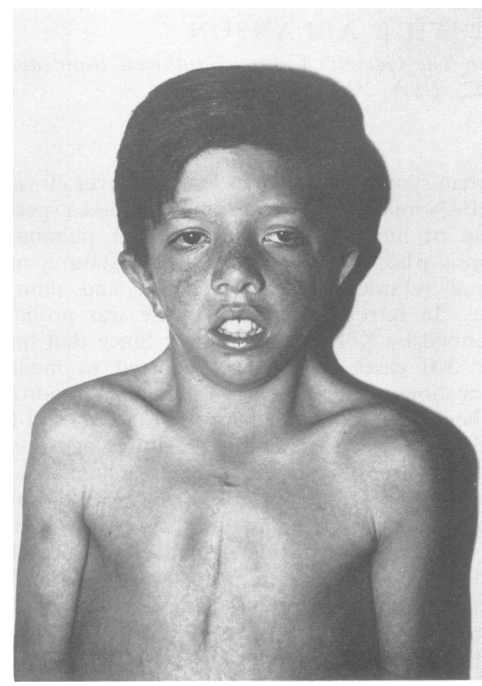

FIG 3 *The face in childhood.*

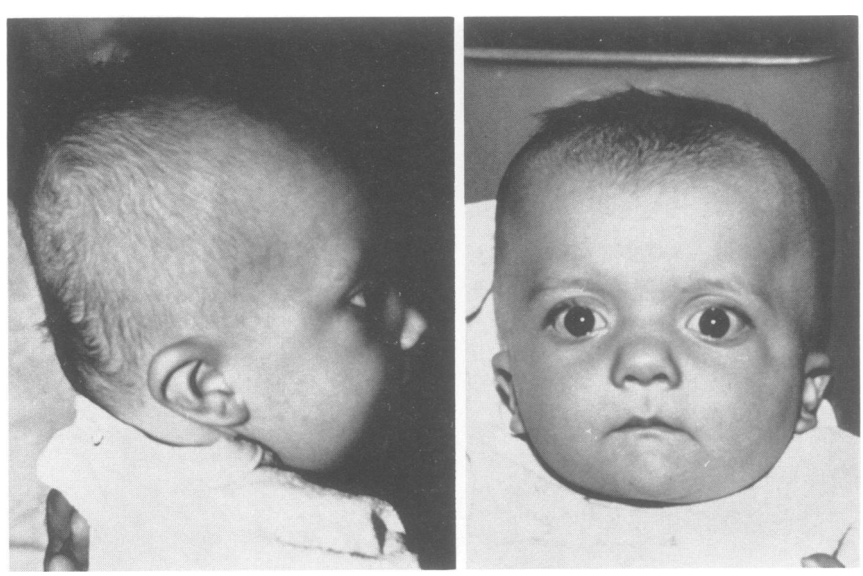

FIG 2 *An infant with Noonan syndrome.*

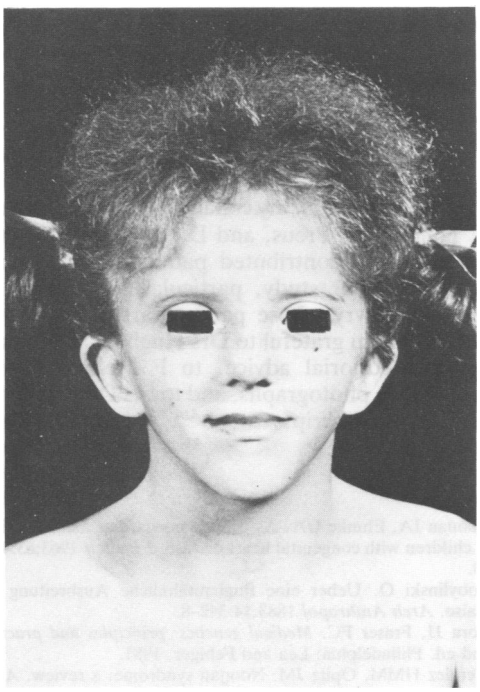

FIG 4 *An adolescent with Noonan syndrome.*

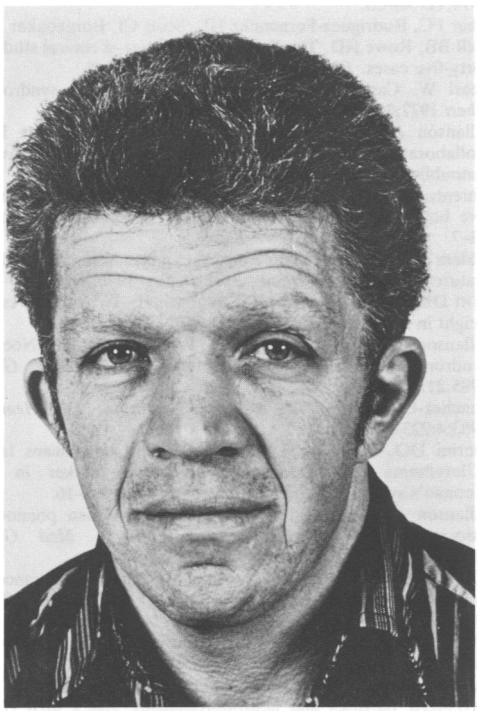

FIG 5 *An adult with Noonan syndrome.*

GENITOURINARY

In males, the pattern of pubertal development varies from normal virilisation and subsequent fertility to delayed but normal puberty or to inadequate secondary sexual development associated with deficient spermatogenesis secondary to earlier cryptorchidism (60%). The latter cases have raised gonadotrophin levels. The majority of females are fertile. Puberty may be normal or delayed. In general, gonadotrophin levels are normal.

SKELETAL

A characteristic pectus deformity is seen (fig 3) with pectus carinatum superiorly and pectus excavatum inferiorly (70%). The thorax is broad, taking on an inverted pyramid shape. In childhood, the upper chest appears to lengthen, with the appearance of relatively low set nipples and axillary webbing, which persist to adulthood. The shoulders are often rounded. Common features include cubitus valgus (50%), hand anomalies including clinobrachydactyly and blunt fingertips (30%), vertebral/sternal anomalies (25%), and dental malocclusion (35%).

ECTODERM

Various skin manifestations include café-au-lait patches (10%), pigmented naevi (25%), lentigines (2%), and keratosis pilaris atrophicans faciei (five cases).[14] Several patients with neurofibromatosis and the Noonan phenotype are documented,[15–17] including one with hyperplasia of the intestinal myenteric plexus.[18]

HAEMATOLOGY

Bleeding anomalies (20%) include factor XI deficiency,[19] von Willebrand's disease, and platelet dysfunction which may be associated with trimethylaminuria.[20 21]

LYMPHATICS

Congenital dysplasia, hypoplasia, or aplasia of lymphatic channels (20%), produces general lymphoedema (10 cases), peripheral lymphoedema (six cases), pulmonary lymphangiectasia (four cases), intestinal lymphangiectasia (three cases), hydrops fetalis (three cases), and cystic hygroma (two cases). These anomalies are well reviewed by Witt *et al.*[22]

OTHER FEATURES

Rarely associated features include autoimmune thyroiditis (five cases[23 24]), phaeochromocytoma (one case[25]), ganglioneuroma (one case[26]), malignant schwannoma (one case[27]), congenital contractures (four cases[28]), Chiari malformation with syringomyelia (one case[29]), skin and oral xanthomas (one case[30]), odontogenic keratosis (one case[31]),

malignant hyperthermia (eight cases[32–35]), polydactyly (one case[36]), congenital bone marrow hypoplasia (one case[37]), congenital hypoplastic anaemia (one case[38]), and vasculitis (two cases[39]).

### Behaviour/development

Prominent features are failure to thrive in infancy (40%), motor developmental delay (26%), learning disability with specific visual-constructional problems, and verbal performance discrepancy (15%). Language delay (20%) may be secondary to perceptual motor disabilities, mild hearing loss (12%), or articulation abnormalities (72%). IQ ranges between 64 and 127 with a median of 102.[40] Nora *et al*[5] found the IQ to be 10 points below that of unaffected family members. Mild mental retardation is seen in up to 35% of cases.[4 7 8]

### Differential diagnosis

The differential diagnosis includes Williams syndrome,[41] intrauterine exposure to primidone,[42 43] fetal alcohol syndrome,[44] and Aarskog syndrome.[45] Other cardiocutaneous syndromes such as LEOPARD syndrome, neurofibromatosis, and Watson syndrome have a markedly overlapping phenotype.

### Inheritance

Although the frequency of sporadic cases appeared to be high in early reports, more recent surveys show direct transmission from parent to child in between 30%[4 8] and 75%[3] of cases. Improved recognition of the adult phenotype and subclinical cardiac disease may further reduce the number of sporadic cases. Maternal transmission of the gene is far more common than paternal transmission (3:1). This is likely to be due to associated cryptorchidism and male infertility.

### Developmental basis

Sanchez-Cascos[13] has speculated that Noonan syndrome could be considered to be a branchial arch syndrome since the abnormalities of the head, neck, and heart seen in Noonan syndrome could be produced by abnormal transformation of the branchial apparatus into adult structures. An alternative hypothesis implicates lymphoedema in the production of the Noonan phenotype. Pterygium colli may follow intrauterine development of a cystic hygroma. Disruption of normal tissue migration or organ placement by lymphoedema may explain cryptorchidism, widely spaced nipples, low set, posteriorly rotated ears, hypertelorism, antimongoloid slant of the eyes, prominent trapezius, and abnormal dermatoglyphs. Clark[46] proposed that lymphatic obstruction could reduce right sided cardiac blood flow and cause pulmonary stenosis. This mechanism was demonstrated in the left heart of a canine model.[47]

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