Noonan syndrome: a brief overview

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Noonan syndrome is a relatively common dysmorphic syndrome. The typical features include short stature, cardiovascular abnormalities and a characteristic facies. Children with Noonan syndrome have a considerable number of potential health problems, which are highlighted in this article. However, most individuals with this condition live a normal life.

The incidence of Noonan syndrome is about 1 in 1000 to 1 in 2500 live births. Jacqueline Noonan first described this syndrome in 1963 (Noonan and Ehmke, 1963). Noonan syndrome is one of the most commonly encountered syndromes in paediatric cardiology (Pernot et al, 1989). It is prevalent worldwide in both sexes with no noted racial difference (Noonan, 1994).

INHERITANCE AND GENETICS

Many cases are sporadic but autosomal dominant inheritance has been reported in 30–75% of cases. Maternal transmission of the gene is more common than paternal transmission (3:1) (Allanson, 1987). The phenotype of Noonan syndrome may change between birth and adulthood, so past photographs of parents and family members should be carefully studied before labelling a case as sporadic (Noonan, 1994). A gene underlying this condition has been located on chromosome 12q24.1 and is found in about 50% of cases (Tartaglia et al, 2001).

CLINICAL FEATURES

Craniofacial

The facial features of Noonan syndrome change with age. The characteristic ocular features include hypertelorism with downslanting palpebral fissures and ptosis (Bertola et al, 1999). In a study of 58 consecutive patients with Noonan syndrome only three had absolutely normal eye examination; hypertelorism was present in 74%, ptosis in 48%, epicanthic fold in 39% and an anti-mongoloid slant in 38%. Refractive errors were present in 61%, strabismus in 48% and amblyopia in 33%. Twenty per cent of subjects had fundal change. Optic disc coloboma has been reported in Noonan syndrome. Light blue and light green irides are quite common (Lee et al, 1992).

The ears are generally low set and posteriorly rotated with a prominent thick helix. The palate is high arched and there may be a degree of micrognathia with moderate dental malocclusion. The patient's neck appears to be short and broad and there is a low posterior hairline (Bernier and Su, 1990).

Skeletal

Over 90% of patients have chest deformity, either pectus carinatum or pectus excavatum. The thorax is broad (taking an inverted pyramid shape) with relatively low set nipples and axillary webbing (Allanson, 1987).

Skin and lymphatics

Prominent fetal pads on the fingers and toes are common in patients with Noonan syndrome (Neild et al, 1984). Lymphatic dysplasia is a common occurrence in this syndrome. Pulmonary as well as intestinal lymphangiectasia with protein-losing enteropathy has been described (Keberle et al, 2000).

Cardiovascular

Cardiovascular anomalies are found in over 80% of patients with Noonan syndrome. The most common congenital heart diseases are pulmonary valvular stenosis, interatrial septal defect, and obstructive or non-obstructive hypertrophic cardiomyopathy (Pernot et al, 1989). A dysplastic, often stenotic pulmonary valve is the lesion most characteristic of Noonan syndrome. The cardiomyopathy, either obstructive or non-obstructive, may involve both ventricles whereas in non-syndromic cases it tends to involve only one ventricle. Ventricular septal defect, patent ductus arteriosus, pulmonary artery branch stenosis, mitral valve prolapse, Ebstein's anomaly and single ventricle have been reported in patients with Noonan syndrome (Noonan, 1994).

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Haematological

In a study of 72 individuals 65% had a history of abnormal bleeding or bruising and 40% had a prolonged activated partical thromboplastin time. Specific abnormalities in the intrinsic pathway of coagulation (partial factor XI:C, XII:C and VIII:C deficiencies) were found in 50% of patients. The pattern of inherited coagulation abnormalities seen in Noonan syndrome points to an autosomal regulation of the intrinsic coagulation pathway (Sharland et al, 1992a).

Gastrointestinal symptoms

Noonan syndrome is frequently associated with feeding difficulties and failure to thrive. The widespread intestinal dysmotility along with gastro-oesophageal reflux is likely to be the result of delayed development of the enteric nervous system. The severe gut motility problems generally improve after 3–4 years of age. There are case reports of pseudo-obstructive syndrome with malrotation of the midgut requiring surgery. They tend to have sporadic episodes of constipation without mechanical obstruction (Shah et al, 1999).

Endocrine features

Children with Noonan syndrome show a distinctive growth pattern. They are of normal size at birth, grow slowly during puberty and have a slightly delayed and decreased pubertal growth spurt. The bone age lags behind the chronological age. A defect of the growth hormone and insulin-like growth factor-1 axis may be present in some children (Ahmed et al, 1991). Bilateral cryptorchidism is a common feature with an abnormality of the hypothalamo–pituitary–gonadal axis. Testicular histology in these cryptorchid patients showed reduction of tubular diameter, and a reduction in the numbers of Leydig cells and spermatogonia (Nistal et al, 1983).

Neurology

The commonest neurological problem in Noonan syndrome is ptosis. Intellectual impairment, which is rarely present, is usually mild. Cerebrovascular pathology leading to thromboembolic events has been reported (Schon et al, 1992).

Behavioural and developmental problems

Developmental and behavioural difficulties have been noted in children with Noonan syndrome. Motor milestone delay is usual. In a study of 151 individuals the mean age of sitting unsupported was 10 months and walking was 21 months. In the same study abnormal vision (94%) and hearing (40%) were frequent findings, but 89% of the group were attending normal primary or secondary school (Sharland et al, 1992b).

PRENATAL FEATURES

Diagnosis can be quite difficult prenatally. The features that point to the diagnosis include maternal polyhydramnios, increased nuchal translucency, cystic hygroma, pleural effusions, non-immune hydrops fetalis, hydrocephalus, short femur, and cardiac and renal anomalies in a fetus with a normal karyotype (Achiron et al, 2000).

DIAGNOSIS

No definitive diagnostic test is available for Noonan syndrome. Although the syndrome manifests at birth it is usually diagnosed during childhood. The mean age of diagnosis was 9 years in one study (van der Burgt et al, 1999). Diagnosis relies solely on clinical features. In 1981 Duncan et al developed a scoring system to evaluate Noonan syndrome based on the most characteristic findings. There are several syndromes to be excluded while diagnosing this condition which include cardio-facial-cutaneous syndrome, neurofibromatosis, Noonan syndrome, LEOPARD syndrome (lentigenes, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis and subaortic valvular stenosis, abnormal genitalia, retardation of growth and deafness) and Costello syndrome (Fukushima, 1996).

MANAGEMENT

Noonan syndrome is quite heterogeneous, with some patients very mildly affected and others significantly disabled. The benefit of growth hormone treatment in Noonan syndrome is not uniformly recognized. It will improve height velocity in the short term. Longer-term therapy results in a waning of effect; initial indications are that final height is not improved substantially in most patients (Kirk et al, 2001). Owing to the high incidence and diversity of cardiac abnormalities, echocardiogram and Doppler study are important, as they will help in genetic counselling and in assessment of the natural history of the condition. These individuals should have regular ophthalmological and hearing assessment.

Each child with Noonan syndrome should also have a formal developmental assessment to identify the strengths and weaknesses of the particu-

lar child. Males with Noonan syndrome are capable of reproduction if cryptorchidism is treated early (Elsawi et al, 1994), and females are fertile (Noonan, 1994). Therefore in view of the multisystem involvement thorough assessment of the cardiovascular, skeletal, haematological and central nervous system should be done to successfully manage childbirth in these patients. They should be encouraged to join the various Noonan syndrome support groups available (see *Useful addresses*).

CONCLUSION

Most children with Noonan syndrome grow up and lead a normal life as adults. The prognosis mainly depends on the severity of the clinical features. The future lies in the hands of the geneticists for a better understanding of this syndrome. HM

Conflict of interest: none.

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KEY POINTS

- Noonan syndrome is a relatively common dysmorphic syndrome.
- Children with Noonan syndrome have multiple potential health problems.
- A thorough multisystem assessment is essential at diagnosis.
- Most children with Noonan syndrome lead normal lives as adults.

Useful addresses

The Noonan Syndrome Support group
PO Box 145
Upperco, MD 21155
USA
info@noonansyndrome.org
http://www.noonansyndrome.org

Birth Defects Foundation
BDF Centre
Hemlock Business Park
Hemlock Way
Cannock
Staffordshire WS11 2GF
www.birthdefects.co.uk
Tel: 01543 468888 (Monday–Friday 9.30 am–6.00 pm)