NOONAN AND TURNER SYNDROMES

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NOONAN SYNDROME

Noonan syndrome is one of the commonest syndromes associated with congenital heart disease. The inheritance is autosomal dominant. Major clinical features include short stature, congenital heart defects and a characteristic facies. Other systems are also involved and one of the intriguing associations id the presence of coagulation abnormalities.

Introduction

The association of a characteristic facial appearance with pulmonary valvular stenosis and short stature was first reported by Jacqueline Noonan in 1963[1]. The incidence of Noonan syndrome in the UK is unknown estimates of its frequency have suggested as incidence ranging between one in 1,000 to one in 2,000 live births[2].

It may be the second commonest syndrome associated with the congenital with congenital heart disease after down syndrome It is inherited in an autosomal dominant fashion with a high spontaneous mutation rate. It is a multisystem syndrome with growth, development, eye and cardiovascular system being the most frequently affected.

Clinical Features

craniofacial

The facial features include hypertelorism with a down-slanting palpebral fissures, ptosis and a depressed nasal bridge. The ears are low set and posteriorly rotated with a thick helix. Neck webbing (with a low posterior hair line) may be present in 30 percent of cases (figures 1) .

Facial appearance changes with age and the earlier coarse features which may suggest a diagnosis of a metabolic storage disorder in the first few years, become less pronounced in adulthood (figure 2).

Cardiovascular

this is one of the major features of the syndrome as 88 percent of patients will have some form of congenital heart defect. The majority will have pulmonary stenosis or cardiomyopathy. Hypertrophic cardiomyopathy could be present as an isolated lesion and can lead to severe heart failure in infancy. Other forms of congenital heart disease have been described[3] . Electrocardiographic abnormalities have been described, such as superior axis.

Growth and development

Short stature is a major feature of this syndrome. In the majority of patients the height is reduced and about half will be below the third centile. The head circumference is less affected and may be appropriate for the patient's age. Growth charts are available from retrospective studies[4] . Puberty is noted to be delayed in both sexes, but more significantly so in males. Undescended testes occurs in 77 percent of males.

Developmental delay is a frequent event in Noonan children. Speech and motor milestones are usually achieved later than average. Hearing problems due to conductive loss secondary to otitis media are common. Some infants may be hypotonic and may have problems with coordination during childhood. This could interfere with school performance and will warrant remedial help. It is worth noting that only a minority of these children will go to special schools. (nine-11 percent)

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[1] Noonan syndrome may be the second commonest syndrome to cause congenital heart disease after Down syndrome.

[2] Feeding difficulties are common and can cause severe failure to thrive, but will resolve with time.

[3] Squint and errors of refraction occur in over a third of patients and should be sought and treated.

[4] Serious bleeding may occur and a full coagulation screen is indicated.

Feeding difficulties

Seventy-six percent of children will present with feeding problems. This may range from slow feeding to poor sucking through to the need for tube feeding in a term baby. This is due to delay in maturation of the sucking and swallowing reflexes. Management represents a great challenge to both parents and professionals. These difficulties seem to improve after the first few years of life in most cases, and will mean that even a tube-fed baby will be able to feed independently given time.

Skeletal

The characteristic sternal changes are a prominent sternum (pectus carinatum) superiorly and a recessed sternum (pectus excavatum) inferiorly. Other features include cubitus valgus, broad thorax with wide spaced nipples and scoliosis. Hand abnormalities include clinodactyly, camptodactyly and prominent pads on the finger tips.

Ophthamological

Strabismus and significant refractive errors are commonly present including myopia and hypermetropia. Other eye abnormalities may be present and these children require careful ophthalmological assessment.

Coagulation

Most patients with Noonan syndrome have a history of abnormal bleeding. Abnormalities of the intrinsic pathway were recently documented in a large cohort of patients[5] . They include a prolonged partial thromboplasin time, and deficiencies of factors VIII, XI and XII. The abnormal bleeding history does not always correlate with these coagulation deficiencies raising the possibility of an unidentified platelet factor.

Dermatological

Dry skin is frequent and slow hair growth and curly hair have been reported. Increased pigmentary lesions such as caf'e-au-lait patches and lentigines have been reported. There is a small group of patients with an overlap between neurofibromatosis and Noonan syndrome, in which molecular rearrangements of the NF1 gene have been found.

Differential diagnosis

It is important in all cases to exclude Turner syndrome and other chromosomal abnormalities that present with a similar phenotype to Noonan syndrome. A karyotype should be performed in all the cases to exclude all these chromosomal alterations.
Williams syndromes is another syndrome with short stature, developmental delay and congenital heart disease. It may however be distinguished by the raised serum calcium in infancy and the presence of supravalvular aortic stenosis.
Aarskog syndrome also overlaps with the phenotype of Noonan syndrome. Interdigital webbing and "shawl scrotum" and the absence of congenital heart disease are important features for differentiation.

Genetics

Noonan syndrome is inherited as an autosomal dominant disorder with about half the cases having an affected parent. Cases with no family history are likely to represent new mutations. There is no specific prenatal diagnosis, but ultrasound scans during the second trimester of pregnancy have shown evidence of congenital heart disease or generalized lymphoedema.
The gene for Noonan syndrome has not yet been localized. Its localization and subsequent cloning will aid not only towards counseling of families, but will also help us to understand the possible aetiological

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[5] Chromosomes should be checked in all cases to exclude Turner syndrome and other chromosomal alterations.

mechanisms of this syndrome. It has been proposed that the gene may cause fetal oedema similar to that seen in Turner syndrome and hence produces many similar clinical features.

Table 1
Clinical features of Noonan syndrome

Cardiac:	
Pulmonary stenosis	62%
Cardiomyopathy	20%
Feeding difficulties	76%
Short stature	50%
Skeletal:	
Sternal abnormalities	95%
Scoliosis	12%
Ophthamological	94%
Undescended testes	77%
Hepatosplenomegaly	50%
Coagulation deficiencies	54%
Special Educational needs	10%

Practical Points

1. Noonan syndrome may be the second commonest syndrome to cause congenital heart disease after Down syndrome.
2. Feeding difficulties are common and can cause severe failure to thrive, but will resolve with time.
3. Squint and errors of refraction occur in over a third of patients and should be sought and treated.
4. Serious bleeding may occur and a full coagulation screen is indicated.
5. Chromosomes should be checked in all cases to exclude Turner syndrome and other chromosomal alterations.

Useful address: The Noonan Syndrome Society, 12D low street, Cheslyn Hay, Staffs WS6 7DS 90922) 415500 The society aims to provide support to both families and health professionals.