Noonan Syndrome

Noonan syndrome (NS) is a common genetic disorder with multiple congenital abnormalities. It is characterised by congenital heart disease, short stature, a broad and webbed neck, sternum deformity, variable degree of developmental delay, cryptorchidism, increased bleeding tendency and characteristic facial features that evolve with age.\[1\]

The term 'male Turner syndrome' is sometimes used as a synonym. This is incorrect and misleading and should not be used.

Epidemiology

- It is inherited in an autosomal dominant manner. The incidence of NS is estimated to be between 1 in 1,000 to 1 in 2,500 children.\[2\]
- NS is caused by mutations in the RAS/mitogen-activated protein kinase (MAPK) pathway which is essential for cell cycle differentiation, growth and senescence. A number of mutations have been identified with the four most common being PTPN11 (50% of cases), KRAS, SOS1 and RAF1 genes.\[3\]
- It is characterised by marked variable expressivity, making it difficult to identify mild cases. About 60% of cases are because of new spontaneous mutations.\[4\]

Clinical features\[3\]

Prenatal period\[5\]

- Antenatal ultrasound findings which suggest the possibility of NS are polyhydramnios, increased nuchal translucency and cystic hygroma. Other recognised features include scalp oedema, ascites and hydrops.
- All these features are nonspecific and do not assist in making a prenatal diagnosis unless there is a family history.

Facial appearance

- Facial appearance is the key to diagnosis but may be difficult to recognise in the neonatal period, especially when complicated by neonatal oedema.\[6\] The newborn has a tall forehead, hypertelorism and downslanting palpebral fissures. There may be ptosis, epicantthic folds and low-set ears.
- Facial features are easiest to recognise in the infant or young child. There is a relatively large head with a high forehead, low posterior hairline and a short uptilted nose. The nasal root is flat, the nasal tip is broad and the ears are low-set and posteriorly rotated.
- The facial features change with age and by adolescence the face has a triangular shape, being wide at the forehead and tapering to a pointed chin. In adults the features are often subtle and diagnosis can be difficult.

Musculoskeletal

- The neck is short, often with redundant skin in infancy, which manifests as webbing of the neck in older children.
- The chest is broad with widely spaced nipples and a specific chest shape which consists of pectus carinatum superiorly and pectus excavatum inferiorly.
- The hands show brachydactyly and persistence of fetal fingertip pads. Boys may have undescended testes. Many children have strikingly blue/green irides and curly or woolly hair.
- The arms may be held at an unusual angle - cubitus valgus.

Growth and feeding

- Birth weight and length are usually normal but problems with feeding and growth are common. Faltering growth may occur, prompting paediatric referral.
- Childhood growth follows normal pattern but most children are short with height around the third centile. Pubertal growth spurt is often delayed.
- Final adult height is reduced and short stature is present in up to 80%. Average height in males is 161 cm and in females between 150-152 cm.

Cardiac\[7\]

- Most children with NS have congenital heart disease with the frequency estimated to be between 50% and 90% in various studies.
- The classic lesion is a dysplastic or stenotic pulmonary valve, occurring in up to half of children with NS. This can be isolated or associated with other heart defects. Pulmonary stenoses may require balloon dilatation and there may be a need for repeat procedures.
- Other heart defects include atrial and ventricular septal defects, Fallot's tetralogy and coarctation of the aorta.
- Hypertrophic cardiomyopathy is present in up to 30% and may be present at birth, in infancy or in childhood. Hypertrophy can regress in a number of cases.
- The ECG is abnormal in 90%, with left axis deviation (superior axis) being most common and serving as a diagnostic pointer.\[8\]
Development and learning
- Learning disability occurs in 15-35% but is usually mild and most children function well in mainstream schools. Verbal performance is more often affected and speech therapy is frequently required.
- Early milestones are often delayed, with hypotonia and joint laxity contributing to some of the motor delay.
- No behaviour or psychiatric phenotype has been linked to children with NS. However, the incidence of attention deficit hyperactivity disorder (ADHD) is reported to be higher compared to unaffected siblings. [8]
- There is wide variation in the intellectual ability in adults with NS, with IQ scores ranging from 65 to 121. Most individuals are friendly, cooperative and willing to please but may have a moderate level of impairment of social cognition.

Eye and skin [3]
- Eyes are frequently affected, with more than 70% having a refractive error, usually myopia.
- Follicular keratoses over the extensor surfaces and face are recognised as markers for NS. Cafe-au-lait spots, pigmented naevi and lentigines are more frequent than in the general population.
- LEOPARD syndrome (Lentigines (multiple), Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Restriction of growth, Deafness). A diagnosis of LEOPARD syndrome should be considered in a child with Noonan phenotype with deafness and extensive lentigines.

Bleeding disorders [10]
- Nearly 40% of children with NS have a bleeding disorder with a history of easy bruising or bleeding. Clotting factor deficiencies, low platelet count and platelet dysfunction have all been described.

Genetic counselling [1]
- The risk of NS developing in the sibling of an affected person is 50% if the parent is affected; however, it is less than 1% if the parent is unaffected.
- Risk of transmission to the offspring of an affected individual is 50%. Pre-implantation genetic diagnosis can be offered in familial cases with known mutations.

- Fetal alcohol syndrome.
- Aarskog syndrome.
- LEOPARD syndrome.
- Cardio-facial-cutaneous (CFC) syndrome.
- Costello syndrome.
- Mosaic trisomy 22.
- Baraitser-Winter syndrome.
- Neurofibromatosis type 1.
- Turner syndrome.
- Jacobsen's syndrome. [12]

Diagnosis
- NS should be considered in any child who presents with a combination of two or more of the following features: [3]
  - A learning disability.
  - A cardiac defect (especially pulmonary stenosis).
  - A typical chest deformity.
  - Short stature.
  - Cryptorchidism
  - A family history of any of the above or a family history of NS
- These features should trigger a thorough clinical assessment focusing on specific clinical features recognised to be part of NS.
- Molecular genetic testing is widely available and can provide diagnostic confirmation in most cases, being especially valuable in mild cases. This can be achieved promptly and accurately using target next-generation sequencing. [13]
- Prenatal diagnosis can be offered where there is an affected parent and the mutation is known. Presence of polyhydramnios, increased nuchal translucency and cystic hygroma on prenatal ultrasound may provide important clues to the diagnosis.

Management

Intellectual and physical abilities are normal in most individuals with NS but some may need multidisciplinary evaluation and regular follow-up care. [14]

Management guidelines for paediatricians have been developed by an international guideline development group under the auspices of Noonan Syndrome Support Group (NSSG), and advise age-specific screening and testing for common health problems. [11]

Key recommendations of these guidelines cover all organ systems which can be affected and are as follows:
1. Genotype-phenotype issues - genetics consultation and follow-up. Positive gene testing can confirm diagnosis but negative gene test results do not rule out diagnosis.

2. Cardiovascular issues - all individuals should undergo a cardiac evaluation by a cardiologist at the time of diagnosis, including ECG and echocardiogram. Those found to have cardiac problems should remain under regular cardiac follow-up.

3. Growth and endocrine issues - children should be weighed and measured by the primary care provider and data should be plotted on appropriate growth charts.
   - Children with evidence of growth failure should have baseline investigations and nutrition optimised.
   - TFTs and antibodies should be done in those with symptoms of hypothyroidism or a goitre.
   - Children with delayed puberty should be referred to an endocrinologist.
   - Therapeutic interventions as indicated - growth hormone for growth failure, thyroxine for hypothyroidism, oestrogen or testosterone for pubertal delay.
   - Growth hormone has been successfully used in treatment of short stature associated with NS.[15]

4. Renal and genitourinary issues - all individuals should have renal ultrasound at the time of diagnosis. A repeat scan may be needed depending on the initial findings. Orchidopexy should be performed by 1 year of age if the testes remain undescended at that time.

5. Gastrointestinal issues - paediatric gastroenterology/nutrition consultation for feeding difficulties or recurrent vomiting.

6. Haematology issues - a screening FBC and coagulation screen at the time of diagnosis, repeated at 6-12 months if the screen is done in infancy.

7. Neurological, cognitive and behavioural issues - developmental screening annually with complete neuropsychological testing if the screening result is abnormal.

8. Eye and ear issues - detailed eye examination in infancy and/or at time of diagnosis and a hearing test in infancy or at the time of diagnosis, with an annual hearing test throughout early childhood.

9. Orthopaedic and dental issues - annual examination of the chest and back and careful oral examination at each visit.

10. Lymphatic issues - those with peripheral lymphoedema should be referred to specialty lymphoedema clinics.

11. Anaesthesia risk - individuals with NS should be considered at risk of malignant hyperthermia when receiving general anaesthesia, and certain anaesthetic agents need to be avoided.

Prognosis
The outcome is assessed on the extent and severity of the problems in the individual patient. Most individuals with NS are able to lead normal lives. Mortality is higher in those with hypertrophic cardiomyopathy, with an annual cardiac specific mortality of 1.2% in this group.[4]

Further reading & references
6. Noonan Syndrome 1, NS1; Online Mendelian Inheritance in Man (OMIM)

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