Review Article

The other side of Turner's: Noonan's syndrome

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ABSTRACT

Noonan Syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. NS is a clinical diagnosis. Establishing the diagnosis can be very difficult, especially in adulthood. There is a great variability in expression, and the phenotype becomes less pronounced with increasing age.

Key words: Turner's syndrome, Noonan's syndrome, short stature

Introduction

Noonan syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. NS is a clinical diagnosis. Establishing the diagnosis can be very difficult, especially in adulthood. There is a great variability in expression, and the phenotype becomes less pronounced with increasing age.

The incidence of NS is reported to be between 1 in 1000 and 1 in 2500 live births.[1]

Genes Related to Noonan Syndrome

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.117197

Mutations in the PTPN11, SOS1, RAF1, KRAS, NRAS, and BRAF genes cause Noonan syndrome.

Most cases of Noonan syndrome result from mutations in 1 of 3 genes, PTPN11, SOS1, or RAF1. PTPN11 gene mutations account for approximately 50% of all cases of Noonan syndrome. SOS1 gene mutations account for 10 to 15% and RAF1 gene mutations account for 5 to 10% of Noonan syndrome cases. About 2% of people with Noonan syndrome have mutations in the KRAS gene and usually have a more severe or atypical form of the disorder. It is not known how many cases are caused by mutations in the BRAF or NRAS genes, but it is likely a very small proportion. The cause of Noonan syndrome in the remaining 20% of people with this disorder is unknown.

The PTPN11, SOS1, RAF1, KRAS, NRAS, and BRAF genes all provide instructions for making proteins that are important in signaling pathways needed for the proper formation of several types of tissue during development. These proteins also play roles in cell division, cell movement, and cell differentiation (the process, by which cells mature to carry out specific functions). Mutations in any of the genes listed above cause the resulting protein to be continuously active, rather than switching on and off in response to cell signals. This constant activation disrupts the regulation of systems that control cell growth and division, leading to the characteristic features of Noonan syndrome.[2]

Clinical Features

Characteristic facial features that change with age

In the postnatal period, the forehead is broad and high; there is hypertelorism, epicanthic folds and downward

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slanting palpebral fissures, low-set posteriorly rotated ears with a thick helix, high arched palate, micrognathia, and a short neck with excess nuchal skin and a low posterior hairline. The contour of the face becomes more triangular with age, and in childhood, the face often appears coarse or myopathic, with prominent eyes and (unilateral or bilateral) ptosis and thick lips with prominent nasolabial folds. In the adolescent and young adult, the eyes are less prominent and the neck appears less short. Sometimes, there is marked webbing or prominent trapezius. Typically, older adults have prominent nasolabial folds, a high anterior hair line, thick hooded eyelids, and wrinkled skin.[3,4] The facial features can be subtle, especially at old age.

The most common congenital heart defect is pulmonary valve stenosis with dysplastic leaflets (50-62%).[5,6] Hypertrophic obstructive cardiomyopathy (HOCM) with asymmetrical septum hypertrophy is present in 20% of patients. Atrial septal defects occur in 6-10% of cases, ventricular septal defects occur in 5% of cases, and persistent ductus arteriosus occurs in 3% of cases.[4] Other congenital heart defects more often seen in NS are atrioventricular canal defect associated with subaortic obstruction and structural anomalies of the mitral valve.[7]

Electrocardiograms (ECG) from NS patients display wide QRS complexes with a predominantly negative pattern in the left precordial leads (62%). They also display left axis deviation and giant Q waves

Weight and length are usually normal at birth. Birth weight can be high due to subcutaneous edema. In such cases, marked weight loss occurs in the first week of life. Neonatal feeding difficulties and failure to thrive may be seen. Onset of puberty is delayed by approximately 2 years, and the pubertal growth spurt is often reduced or absent. The average bone age is also delayed by 2 years. Mean adult height is 162.5 cm in males and 152.7 cm in females. Both values are below the 3rd centile.[8]

Growth hormone (GH) levels are in the normal range. Somatomedin levels are elevated in some cases. GH treatment in pharmacological doses can be used to accelerate growth during the first years of life. Initial reports on the long-term effects of this treatment show a beneficial effect.

NS patients with a mutation in the PTPN11 gene respond less efficiently to GH than NS patients without a mutation in PTPN11.[9]

Characteristic chest deformities consist of pectus carinatum superiorly and pectus excavatum inferiorly. These sternal abnormalities are present in 70-95% of cases. The thorax is broad, and the internipple distance is large.

Other common orthopedic features include cubitus valgus (50%), radioulnar synostosis (2%), clinobrachydactyly (30%), joint hyperextensibility (50%), and talipes equinovarus (12%). Giant cell lesions of the jaw, similar to those seen in cherubism, have been reported in several patients.[3,4]

Undescended testicles at birth are common in male patients (77%). Increased luteinizing hormone and follicle stimulating hormone (FSH) levels are present in prepubertal boys.[10] High FSH levels and poor quality semen have been found in adults, suggesting a failure of spermatogenesis in patients with testicular maldescent.

In both sexes, pubertal development is delayed. Fertility is not impaired in female patients.

Urinary tract malformations are present in 10% of cases, mostly pyelo-ureteric stenosis and/or hydronephrosis.[8]

Acute leukemia and myeloproliferative disorders have been described in some patients.

Lymphatic vessel dysplasia, hypoplasia, or aplasia are common findings in NS (20%).[11,12] They lead to generalized lymphedema, peripheral lymphedema, pulmonary lymphangiectasia, or intestinal lymphangiectasia. The most common manifestation is dorsal limb lymphedema, which usually disappears during childhood. Ultrasound examination may reveal a cystic hygroma in early pregnancy. Spontaneous chylothorax may occur in childhood, and chylous effusion is a known complication of cardiac surgery and surgery for thoracic deformity.

Abnormalities of pigmentation in NS include pigmented nevi (25%), cafe-au-lait spots (10%), and lentigines (3%).[13]

Frequent ophthalmic abnormalities are strabismus (48-63%), refractive errors (61%), and amblyopia (33%). Anterior segment changes (63%) and fundal abnormalities (20%) may be present, nystagmus is seen in 10% of NS patients.[14]

Hearing loss due to otitis media is a frequent complication.

Hepatosplenomegaly unrelated to cardiac failure is often present in infancy.

In general, children with NS demonstrate mild motor delay, which may be partly attributed to the muscular hypotony that is often present in early childhood.

It is characterized by specific visual-constructional problems and verbal performance discrepancy. Mean full scale intelligence quotient (IQ) is 85, but there is a wide range in the level of intelligence.[15,16]

Prominent behavioral problems are clumsiness, eating problems, fidgety or stubborn spells, echolalia, and irritability.

The most recent scoring system was developed in 1994: Table 1.

Diagnosis

Diagnosis is based on clinical features

In other words, it is made when a physician feels that a patient has enough of the features to warrant the label indicating association. The patient can be screened for mutations in the PTPN11, SOS1, or KRAS genes; however, absence of a mutation will not exclude the diagnosis as there are more as yet undiscovered genes that cause NS.

Differential Diagnosis

There are a number of conditions with phenotypes strikingly similar to NS. The first to mention is Turner syndrome (45, X0), a well-known chromosomal abnormality in girls. Then, there are groups of distinct syndromes with partially overlapping phenotypes, in which causative mutations are found in genes of the RAS-MAPK pathway. These include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1), and LEOPARD syndrome (multiple lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness). Individuals with LEOPARD syndrome may have distinct mutations in PTPN11, which lead to a diminished catalytic activity of these SHP-2 mutants. Costello syndrome is caused by mutations in HRAS, NF1 by mutations in Neurofibromin and CFC syndrome by mutations in BRAF, KRAS, and MEK1/2.[17,18]

Table 1: Scoring system for Noonan's Syndrome (NS)

Scoring system for noonan syndrome (NS)#		
Feature	**A=Major**	**B=Minor**
Facial	Typical face dysmorphology	Suggestive face dysmorphology
Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defect
Height	<*P*3*	<*P*10*
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First degree relative with definite NS	First degree relative with suggestive NS
Other	Mental retardation, cryptorchidism, and lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

HOCM: Hypertrophic obstructive cardiomyopathy, **P*3 and *P*10 refer to percentile lines for height according to age, with the normal range of variation defined as *P*3-*P*97 inclusive, Definitive NS: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs, *adapted from[2], NS: Noonan syndrome, ECG: Electrocardiograms

Syndromes that are characterized by facial dysmorphology, short stature, and cardiac defects may sometimes be difficult to differentiate from NS, notably William's syndrome and Aarskog syndrome.[19]

Genetic Counseling

Before the child is born, consultations with parents may address the following, as appropriate:

- Explain the mechanisms for occurrence or recurrence of NS in the fetus and the recurrence risk in the family.
- Review the natural history and manifestations of NS, including variability.
- Discuss further studies that should be done, particularly those in the newborn period that will confirm the diagnosis. If miscarriage, stillbirth, or termination occurs, confirmation of the clinical diagnosis by autopsy is also important.
- Review the currently available treatments and interventions.
- Explore the options available to the family for the management and rearing of the child.

NS should be considered in all fetuses with polyhydramnion, pleural effusions, edema, and increased nuchal fluid with a normal karyotype.[20] If there is clinical evidence of NS in the fetus or a first-degree relative has NS, obstetric ultrasound is indicated at 12-14 and 20 weeks' gestation and again in the third trimester. Fetal echocardiography is indicated at 18-20 weeks' gestation. If NS is suspected in the unborn child, physical examination of the parents for features of the syndrome is indicated.

A DNA test for mutation analysis can be carried out on blood, chorionic villi, and amniotic fluid samples. Herewith also, pre-implantation genetic diagnosis becomes a possibility.

Management

The majority of children with NS will grow up and function normally in the adult world. However, they need special care and counseling. Below is a set of guidelines designed to assist physicians caring for NS patients and their families. Familiarity with the characteristic features of

NS is clearly important for clinical geneticists, cardiologists, surgeons, anesthetists, gynecologists, pediatricians, and dermatologists. Issues that need to be addressed at a given age are discussed.

Issues that need to be addressed.
From birth to 1 month – newborns.
- Confirm diagnosis.
- Extensive cardiological examination including echocardiography.
- Appropriate laboratory studies, including chromosome analysis and DNA analysis (PTPN11, KRAS), if possible.
- Document measurements.
- Hepatosplenomegaly?
- Undescended testes in male patients? Initiate treatment, if present.
- Weight loss in the first week.
- Hypotonia, poor feeding, and failure to thrive.
- Offer extensive genetic counseling to the parents.

From 1 month to 1 year – infancy.
- Growth and development.
- Serous otitis media.
- Cardiologic evaluation.
- Feeding and feeding difficulties.
- Support available to the family.
- Motor development (expect mild motor delay in most, but significant psychomotor delay in only a minority of patients).

From 1 to 5 years – early childhood.
- Growth and development.
- Cardiologic evaluation.
- Speech.
- Easy bruising/coagulation.
- Cutaneous findings.
- Partial growth hormone deficiency?
- Possibility of growth hormone therapy in very small NS children with partial growth hormone deficiency.
- Behavior and possible behavioral problems.

From 5 to 13 years – late childhood.
- Social adaptation.
- Skeletal age.
- Growth hormone therapy, if indicated.
- Cardiologic evaluation.
- School readiness/intellectual capabilities.
- Vision and hearing.
- Delay in puberty (on average about 2 years).
- Contact with other patients (especially valuable at this age)
- School performance.

From 13 to 21 years or older – adolescence to early adulthood.
- Auxological parameters.
- Cardiologic evaluation.
- Coagulation (bleeding abnormalities present in childhood often resolve with age).
- Growth hormone therapy (if indicated) until adult height is reached.
- School performance and choice of profession.
- Genetic counseling at adolescent or young adult age.

Prognosis

New medical problems are not expected to appear in adulthood. However, males who were born with undescended testes may have fertility problems. There is no evidence for gynecological or childbearing complications in females with NS.

It is clear that there is wide variability in the phenotypic expression of NS and that there are many unresolved questions. The phenotype varies from adults with mild facial features and a minimal pulmonary valve stenosis to severe dysmorphisms plus life-threatening heart disease in neonates. Furthermore, there is a wide variability in the intellectual and adaptive behavior.

The etiology of NS in individuals without mutations in PTPN11 or KRAS (almost 50% of cases) is still unknown. Research aimed at identifying the other gene (s) responsible for NS is ongoing.

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Cite this article as: Agarwal P, Philip R, Gutch M, Gupta KK. The other side of Turner's: Noonan's syndrome. Indian J Endocr Metab 2013;17:794-8.

Source of Support: Nil, **Conflict of Interest:** None declared.