NOONAN SYNDROME

A frequent autosomal dominant developmental disorder primarily characterized by short stature, typical facial features and heart defects.

Diagnosis

Related Diagnoses:

Erectile dysfunction | Hypogonadism

About Noonan syndrome

Noonan Syndrome (NS) is characterised by short stature (Pic. 1), typical facial dysmorphology and congenital heart defects. The incidence of NS is estimated to be between 1:1000 and 1:2500 live births.

The main facial features of NS are hypertelorism (an abnormally increased distance between two organs or bodily parts, usually referring to an increased distance between the eyes), ptosis (a drooping or falling of the upper eyelid) and low-set rotated ears (Pic. 2) situated behind with a thickened helix (the prominent rim of the auricle). The cardiovascular defects most commonly associated with this condition are pulmonary stenosis (stricture) and hypertrophic cardiomyopathy (a portion of the heart muscle is enlarged without any obvious cause). Other associated features are webbed neck (Pic. 3), chest deformity, mild intellectual deficit, cryptorchidism (undescended testes), poor feeding in infancy, bleeding tendency and lymphatic dysplasias (an abnormality of development).

A DNA test for mutation analysis can be carried out on blood, chorionic villi and amniotic fluid samples. NS should be considered in all foetuses with polyhydramnion (an excess of amniotic fluid in the amniotic sac), pleural effusions (excess fluid that accumulates in the pleural cavity), oedema and increased nuchal fluid with a normal karyotype.
A person with NS has up to a 50% chance of transmitting it to their offspring. The fact that an affected parent is not always identified for children with NS suggests several possibilities:

1. Manifestations could be so subtle as to go unrecognized (variable expressivity).
2. NS is heterogeneous, comprising more than one similar condition of differing causes, and some of these may not be inherited.
3. A high proportion of cases may represent new, sporadic mutations.

With special care and counselling, the majority of children with NS will grow up and function normally in the adult world. Management should address feeding problems in early childhood, evaluation of cardiac function and assessment of growth and motor development. Physiotherapy and/or speech therapy should be offered if indicated. A complete eye examination and hearing evaluation should be performed during the first few years of schooling. Preoperative coagulation studies are indicated. Signs and symptoms lessen with age and most adults with NS do not require special medical care.

**Associated disease**

- pulmonary stenosis (a dynamic or fixed obstruction of flow from the right ventricle of the heart to the pulmonary artery)
- hypertrophic cardiomyopathy (a portion of the myocardium (heart muscle) is enlarged without any obvious cause, creating functional impairment of the heart)
- mental retardation
- cryptorchidism
- lymphatic dysplasia
- acute leukaemia

**Complications**

Spontaneous chylothorax (a type of pleural effusion, results from lymph formed in the digestive system called chyle accumulating in the pleural cavity due to either disruption or obstruction of the thoracic duct) may occur in childhood and chylous effusion is a known complication of cardiac surgery and surgery for thoracic deformity.

Hearing loss due to otitis media is also a frequent complication.

**Risk factors**

- genetic predisposition
New medical problems are not expected to appear in adulthood. However, males who were born with undescended testes may have fertility problems due to azoospermia (a man not having any measurable level of sperm in his semen).

In the past, men with azoospermia were classified as infertile, and a sperm donor was initially considered one of the best options for conceiving. Currently, the knowledge that many causes of azoospermia can be reversed is widespread in the medical literature and practice. Thus, any trusted specialized assisted reproductive center will request a urologist/andrologist to provide sperm for an ART procedure.

There is no evidence for gynaecological or childbearing complications in females with NS.

**Prevention**

Preimplantation genetic diagnosis (PGD) allows genetic diagnosis of embryos in very early stages, with the purpose of avoiding the transmission of genetic diseases to offspring. PGD represents an alternative to prenatal diagnosis and termination of pregnancy, in couples at risk of transmitting these disorders.

**Symptoms**

Symptoms of Noonan syndrome may include the following:

**Heart**

Up to ~85% of people with NS have one of the following heart defects:

- pulmonary valvular stenosis (50–60%)
- septal defects: atrial (10–25%) or ventricular (5–20%)
- hypertrophic cardiomyopathy (12–35%)

**Lungs**

- restrictive lung function has been reported in some patients

**Genito-urinary system**

- cryptorchidism (undescended testicles)

**Stature**
- short stature

**Lymphatic system**
- posterior cervical hygroma (webbed neck)
- lymphedema

**Musculoskeletal**
- joint pain or muscle pain especially in adults, which can vary in severity
- undifferentiated connective tissue disorders
- scoliosis
- prominence of breast bone (pectus carinatum)

**Neurological**
- arnold-chiari malformation (type 1), which can lead to hydrocephalus, has been noted in some patients
- seizures

**Eyes**
- hypertelorism (widely set eyes) (95%)
- epicanthal folds (extra fold of skin at the inner corner of the eye)
- ptosis (drooping of the eyelids)
- proptosis (bulging eyes)

**Ears and hearing**
- low-set ears (in over 90%)
- backward-rotated ears (over 90%)
- thick helix (outer rim) of ear (over 90%)
- incomplete folding of ears

**Therapies**

**Self therapy**

There is no self therapy for Noonan syndrome.

**Conventional medicine**

The majority of children with NS will grow up and function normally in the adult world. However, they need special care and counselling. Familiarity with the characteristic features of NS is clearly important for clinical geneticists, cardiologists, surgeons, anaesthetists, gynaecologists, paediatricians and dermatologists.
Pharmacotherapy

Growth hormone (GH)

Short stature is a frequent feature of Noonan syndrome (NS), a disease caused by mutations of genes encoding components of the protein-signalling pathway. To date, numerous patients have been treated with growth hormone (GH) in various countries. However, this treatment is still controversial, as its efficacy is a matter of debate. The final height gain of GH therapy represents 5 to 10 cm, at best, which is disappointing considering the length and burden of the treatment.

Surgical therapy

There is no surgical therapy for this condition.

Assisted reproduction

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy. Some forms of ART are also used with regard to fertile couples for genetic reasons (preimplantation genetic diagnosis).

Among women with older reproductive age, with history of repetitive abortions or genetic disorders, genetic analysis is highly recommended. The PGS/PGD allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.

Men with cryptorchidism had a good chance of sperm retrieval when undergoing micro-TESE (testicular sper extraction). The concept of micro-TESE is to identify the areas of probable sperm production within the testes based on the size and appearance of the seminiferous tubules, with the aid of optical magnification. Micro-TESE is advocated to be more efficient than other methods of sperm acquisition, such as TESE and Testicular Sperm Aspiration (TESA). The reasons are the greater success in obtaining sperm and lower tissue removal that facilitates sperm processing and lessens testicular damage.

In fact, cryptorchid men tended to have slightly higher sperm retrieval rates relative to all other men with nonobstructive azoospermia, although the difference in pregnancy rates was not statistically significant. In men
with cryptorchidism, there is a correlation with both testicular volume and age at orchiopexy (a surgery to move an undescended testicle into the scrotum and permanently fix it there).

If all efforts to extract vital sperm cells fails, then donated ones may be recommended.

Find more about related issues

Diagnoses

Erectile dysfunction
The inability (that lasts more than 6 months) to develop or maintain an erection of the penis during sexual activity.
Learn more at: www.fertilitypedia.org/therapy/diag/erectile-dysfunction

Hypogonadism
A medical term which describes a diminished functional activity of the gonads – the testes and ovaries.
Learn more at: www.fertilitypedia.org/therapy/diag/hypogonadism

Symptoms

Low facial and body hair growth
Decrease of facial and body hair in males.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-facial-and-body-hair-growth

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi
Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment. Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used. Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

**Gallery**

**Pic**
*Short stature and lean weight of the patient.*

**Pic**
*Low set posterior ears.*

**Pic**
*A 12-year-old female with Noonan syndrome. Typical webbed neck. Double structural curve with rib deformity.*
Sources

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