NOONAN SYNDROME

1. What is Noonan Syndrome?

Noonan syndrome is a genetic condition that can cause a wide range of distinct features and health problems. The condition is present from birth, although milder cases may not be diagnosed until a child gets older. It is a relatively common syndrome as it is estimated that around 1 in 1,000 to1 in 2,500 children are born with it. It equally affects both sexes and all ethnic groups.

2. What causes Noonan syndrome?

Noonan syndrome is caused by a defect/mutation in one of several genes such as PTPN11, SOS1, RAF1, RIT1 and KRAS.

3. How is Noonan Syndrome inherited?

In some cases, the responsible gene that is associated with Noonan syndrome is inherited from one of the child's parents. The parent with the faulty gene may or may not have obvious features of the condition themselves. Only one parent needs to carry the faulty gene to pass it on and each child of the family has a 50% chance of being born with the condition. In other cases, the condition is caused by a new genetic fault that isn't inherited from either parent. In these cases, the chance of the parents having another child with Noonan syndrome is very small.

4. Which are the most common characteristics of Noonan syndrome?

The 3 most common characteristics of Noonan syndrome are:

- unusual facial features
- short stature (restricted growth)
- heart defects present at birth (congenital heart disease)

5. Which are the main facial features of Noonan Syndrome?

Children with Noonan syndrome have distinctive facial features such astriangular face, tall forehead, widely spaced eyes (hypertelorism), that are usually pale blue or blue-green in color and down slanting palpebral fissures. There may be ptosis, epicanthic folds and low-set ears that are rotated backward. Many children with Noonan syndrome have a deep groove in the area between the nose and mouth (philtrum)and a low hairline at the back of the neck.

6. Do other organs or systems get affected?

Children with Noonan syndrome also have abnormalities that affect other organs and systems as well such as:

- high-arched palate: the palate is unusually high and narrow, that can lead to difficulties with feeding and speech
- feeding problem: babies with Noonan syndrome may have problems sucking and chewing, and may vomit soon after eating

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- lymphoedema: a build-up of fluid in the lymphatic system (a network of vessels and glands distributed throughout the body), mainly present in hands and feet.
- webbed neck: short neck with excess skin folds
- skeletal problems: The chest is broad with widely spaced nipples and a specific chest shape which consists of pectus carinatum superiorly and pectus excavatum inferiorly. The arms may be held at an unusual angle. Some affected people may also have spine abnormalities such as scoliosis or kyphosis.
- increased bruising or bleeding: sometimes the blood doesn't clot properly, which can make children with Noonan syndrome more vulnerable to bruising and heavy bleeding from cuts or medical procedures
- behavioral problems: some children with Noonan syndrome may be fussy eaters, behave immaturely compared to children of a similar age, have problems with attention and have difficulty recognizing or describing their or other people's emotions
- eye conditions: including a squint (where the eyes point in different directions), a lazy eye (where one eye is less able to focus) and/or astigmatism (slightly blurred vision caused by the front of the eye having an irregular shape)
- hearing problems: Hearing loss secondary to otitis media is a frequent complication. Sensorineural hearing loss, which is a type of hearing loss related to damage to the inner ear is less frequent.
- hypotonia: decreased muscle tone, which can mean it takes your child a bit longer to reach early developmental milestones.
- renal problems: renal ectopia (one kidney in a different location than expected) or anatomical abnormalities
- undescended testes: in boys with Noonan syndrome, one or both testes may fail to drop into the scrotum (sac of skin that holds the testes)
- dental problems: abnormalities related with the number and the morphology of teeth
- craniosynostosis: the bones in the skull fuse together too early

7. Which are the most common congenital heart diseases affecting children with Noonan syndrome?

Most children with Noonan syndrome will have some form of congenital heart disease. This is usually one of the following:

- pulmonary valve stenosis: 50-60%
- hypertrophic cardiomyopathy (the muscles of the heart are much larger than they should be): 20%
- septal defects (a hole between 2 of the chambers of the heart): 6-10%

8. Are there problems related with growth, puberty, and fertility?

Short stature: Children with Noonan syndrome usually have normal length at birth but their growth declines over time.

Delay of puberty: Puberty typically occurs a few years later than normal for both boys and girls.

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Infertility: male infertility is more common even when cryptorchidism is not present. Fertility does not seem to be affected in women

9. Do children with Noonan syndrome have neurodevelopmental problems?

Affected children may have neurodevelopmental delay and fail to catch their developmental milestones at the appropriate age. Most people with Noonan Syndrome have normal intelligence, but 10% to 40% require special education or have an IQ slightly lower than the general population. Children with Noonan Syndrome have a higher rate of clumsiness, poor coordination, stubbornness, and irritability.

10. Do affected children have a predisposition to cancer?

People with Noonan syndrome may develop some types of cancer, particularly those involving the blood-forming cells (leukemia). It has been estimated that children with Noonan syndrome have an eightfold increased risk of developing leukemia or other cancers over age-matched peers

11. Is there a predisposition for autoimmune diseases?

Most studies have found a higher incidence of autoimmune thyroiditis compared to the general population. It also seems that there is a correlation with other autoimmune diseases such as lupus erythematosus

12. How is Noonan syndrome diagnosed?

Noonan syndrome may be suspected if a child has some of the signs and symptoms associated with the condition. It is possible that routine ultrasound scans during pregnancy may detect possible signs of the condition in the baby. These signs are increased nuchal translucency, polyhydramnios (an excessive amount of amniotic fluid) and cardiac abnormalities. In most cases, Noonan syndrome can be confirmed by a blood test for the various genetic mutations.

13. What is the prognosis for Noonan Syndrome?

Long-term outcome depends largely on the presence and severity of congenital heart defects. Studies have indicated that people with Noonan syndrome have a 3-fold higher mortality rate than those in the general population. However, with special care and counseling, most children with Noonan syndrome grow up and function normally as adults. Signs and symptoms tend to lessen with age, and new medical problems associated with the condition are generally not expected to appear in adulthood.

14. What is the long term follow up for Noonan patients?

There is no single treatment for Noonan syndrome, but it is possible to treat many aspects of the condition.

Children should be followed up and treated appropriately for the following:

1. Cardiac function/surgery if needed
2. Treating feeding problems especially during the first months of life

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3. ENT follow up
4. Ophthalmological follow up
5. Thyroid function tests
6. Neurodevelopmental assessment
7. Help may be needed for school and learning difficulties
8. Clotting screen should be done before all kinds of surgery
9. Treatment with human growth hormone may be suggested to help with final height. Although treatment with growth hormone is generally safe and well tolerated, patients with Noonan syndrome should be carefully monitored as they may have hypertrophic cardiomyopathy and they are more susceptible to malignancies compared to non-affected children.

15. Useful links for parents:

1. Noonan Syndrome Foundation. https://www.teamnoonan.org/
2. Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines. Pediatrics 2010;126:746–759
3. https://www.orpha.net/data/patho/Pro/en/NoonanGuidelines2011.pdf