FACTSHEET #11
LYMPHATIC DISORDERS

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Lymphatic disorders are a well-recognised complication of Noonan syndrome. They can lead to swelling (oedema), due to the accumulation of fluid in the body.

The lymphatic system is a network of channels and glands throughout the body that helps fight infection and remove excess fluid. It drains extra fluid – lymph – that has passed out of the blood and into tissues and returns it back to the blood. Issues with the lymphatic system can lead to oedema – an excess of watery fluid collecting in the body's tissues or cavities.

Before birth (prenatal)

Abnormalities in development of the lymphatic system can become apparent during pregnancy.

The prenatal issues for Noonan Syndrome are:

- **Increased neck thickness (nuchal translucency):** Between 11 and 14 weeks of pregnancy, ultrasound is used to measure the size of the translucent space behind the neck of the fetus – the nuchal translucency. The size reflects the amount of fluid that has accumulated under the skin of the fetus. Nuchal translucency tends to be increased in Noonan syndrome, as well as in other chromosome disorders such as Down syndrome and Turner syndrome.

- **Hydrothoraces:** Accumulation of fluid in the pleural cavity (the space between the lungs and the walls of the chest) of the fetus.

- **Fetal Hydrops:** Abnormal fluid collections in the fetus, such as around the heart or lungs, in the abdomen, or in the skin and soft tissues.)

Children and adults

Swelling of the feet at birth is often described in Noonan syndrome, and some of the characteristics of this condition – webbed neck, low-set ears, low hairline and drooping of the upper eyelid (ptosis) – may be related to oedema in the womb.

Persistent lymphatic disorders are rare, however. When they do occur, they can affect:

- **Legs:** Lymphoedema is a long-term (chronic) condition that causes swelling in the body's tissues. In Noonan syndrome it usually affects the legs, so is termed **bilateral lower limb lymphoedema**.

- **Genitals:** Swollen genitals can be caused by the backflow of **chyle** (a milky fluid containing fat droplets which drains from the small intestine into the lymphatic system during digestion). If the central lymphatic channels do not control the flow correctly, chyle can mix with lymph and be routed into the genitals and legs. This is called **chylous reflux**.

- **Small intestine:** Abnormalities of the lymph vessels supplying the lining of the small intestine can lead to intestinal lymphangiectasia which is associated with a range of problems, including:

  - abdominal discomfort
  - diarrhoea
  - leaking of albumin and other protein-rich materials into the intestine (called

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protein-losing enteropathy)
- ◊ too little albumin in the blood, causing swelling in the peripheries
- ◊ reduced levels of antibodies and therefore immunodeficiency.

- **Chest:** Lymphatic fluid can leak into the space between the lung and chest wall. When this fluid builds up in the lungs, it can cause a severe cough, chest pain and difficulty breathing. The condition is termed **chylothorax**.

The age of onset of these problems varies – for some, swelling begins at birth, in childhood, or even adulthood.

The causes of these lymphatic-related problems in people with Noonan Syndrome are not fully understood. It appears that there is an abnormality of the central lymphatic channels (a central conducting lymphatic anomaly, CCLA) caused by both too many but leaky lymphatics and obstruction of the lymphatics.

It is also not clear why this may present later in life – the triggers are not known.

Specialist Tests

Lymphoscintigraphy: A technique called lymphoscintigraphy is used to investigate lymphoedema. A radiolabelled tracer is injected, which then allows an image of the lymph drainage pathways to be created using a gamma camera.

Lymphangiography: Intranodal lymphangiography with a contrast (lipiodol) or Magnetic Resonance Lymphangiography (MRL) can be used to image the central lymphatic system and identify any abnormalities and leaks.

Management and treatment

It is important to treat any swelling or leakage to reduce the size and discomfort of the swelling and to reduce the risk of infection (cellulitis).

Peripheral swelling can be controlled with made-to-measure compression garments and possibly bandaging.

Good skin care is essential to prevent the introduction of infection (cellulitis). People with oedema are very prone to cellulitis and can become very unwell with this infection. Recurrent cellulitis can cause progressive damage to the lymphatics.

Sometimes, it may present with leakage from the genital region, particularly in males. It is probably better if this is investigated and treated sooner rather than later. Leakage from the scrotal area is more difficult to treat - compression shorts may help.

A low fat, high protein diet may reduce the amount of swelling. Cryotherapy or surgery may be an option. Further investigations (lymphangiography) can be performed to detect the leaky lymphatics and glue them.

In 2020, US doctors reported that a Noonan syndrome patient with severe lymphatic issues had been treated successfully with trametinib (an inhibitor of mitogen-activated protein kinase, a component of the Ras/MAPK pathway).

What do do if you suspect a lymphatic problem?

Lymphatic problems in Noonan Syndrome usually presents with swelling in the legs and/or genital region.

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If there is fluid elsewhere in the body, this should be treated and investigated in a specialist centre.

It is recommended that all affected individuals are referred initially to one of the two main specialist centres for investigation and diagnosis in the UK:

St George's NHS Foundation Trust (www.stgeorges.nhs.uk)

University Hospitals of Derby and Burton NHS Trust (www.uhdb.nhs.uk)

But there are also lymphoedema therapists throughout the UK who can help with the compression garments. The map of these centres can be found on the **British Lymphology Society** website (www.thebls.com).

Care of the Child with Lymphoedema guidelines are available from **The International Lymphoedema Framework** (www.lympho.org).

Support can also be found from **The BLS Children with Lymphoedema Special Interest**

REFERENCES/FURTHER READING

Joyce S, Gordon K, Brice G, et al. The lymphatic phenotype in Noonan and Cardiofaciocutaneous syndrome. Eur J Hum Genet. 2016;24(5):690-696.

Dori Y, Smith C, Pinto E, Snyder K, March ME, Hakonarson H, Belasco J. Severe Lymphatic Disorder Resolved With MEK Inhibition in a Patient With Noonan Syndrome and SOS1 Mutation. Pediatrics. 2020 Dec;146(6)

Gordon K, Moore M, Van Zanten M, Pearce J, Itkin M, Madden B, Ratnam L, Mortimer PS, Nagaraja R, Mansour S. Case Report: Progressive central conducting lymphatic abnormalities in the RASopathies. Two case reports, including successful treatment by MEK inhibition. Front Genet. 2022 Sep 27;13:1001105

Rachel Torok, Brian Feingold, Matthew Bochkoris, Andrew McCormick, MEK inhibition in Noonan syndrome patient with severe cardiovascular and lymphatic disease, Progress in Pediatric Cardiology, Volume 72, 2024, 101704

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