Improving the understanding of the anatomy and lymph flow in the central lymphatic system in patients with Noonan Syndrome Spectrum Disorder

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To get a better insight into the central conducting lymphatic system in adult volunteers with Noonan Syndrome (NS) without clinical symptoms or signs of lymphatic disease compared to NS and CardioFacioCutaan syndrome patients with severe lymphatic...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spleen, lymphatic and reticuloendothelial system disorders
Study type	Observational invasive

Summary

ID

NL-OMON53172

Source
ToetsingOnline

Brief title
The lymphatic phenotype in Noonan Syndrome Spectrum Disorder

Condition

- Spleen, lymphatic and reticuloendothelial system disorders
- Congenital and hereditary disorders NEC

Synonym
Central conducting lymphatic anomalies in patients with Noonan Syndrome Spectrum Disorder; Abnormal central lymphatic system in patients with Noonan Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Million Dollar Bike ride en For Wishdom

Intervention

Keyword: Central lymphatic system, MRI Lymphangiography, Noonan Syndrome Spectrum Disorder, Ras/MAPK pathway

Outcome measures

Primary outcome

Anatomical categorizing and measurements of both the thoracic duct and the cisterna chyli (conducted in the coronal plane on whichever MR sequence offers the best visualization of these structures). Measurements consist of the maximal diameter of the thoracic duct and the diameter at the level of the diaphragm, and the width and length of the cisterna chyli.

Lymph flow velocity will be determined on the dynamic MR lymphangiography by measuring the distance of contrast movement covered over time in cm/min.

Secondary outcome

Patient characteristics such as: age, gender, body height and weight, clinical history and genetic background.

Study description

Background summary

Noonan Syndrome Spectrum Disorders (NSSDs) are attributed to pathogenic variants in genes associated with the Ras/MAPK signaling pathway and are categorized as RASopathies. Lymphatic diseases manifest in approximately 36% of individuals with NS over their lifetime, displaying varying symptoms, severity,

and onset. However, the precise prevalence of lymph flow disorders among RASopathy patients remains unknown, primarily due to the presence of unrecognized symptoms and the subsequent lack of diagnosis.

Presently, there is no established protocol for diagnosing lymph flow disorders. In many instances, the diagnosis is primarily based on symptomatic presentation rather than an assessment of the underlying abnormal lymph anatomy or flow. Tests such as lymph scintigraphy exist to evaluate lymph flow, but they suffer from limited spatial and temporal resolution. Some medical institutions employ MR T2 imaging, which visualizes fluid (lymph) but not its flow. A more recent advancement in diagnosis is the implementation of dynamic MR lymphangiography (DMRL) with intranodal contrast injection, initially developed in Philadelphia and subsequently introduced at Radboudumc. This DMRL scan enables visualization of lymph flow within the central lymph vessels, facilitating the diagnosis of anatomical and flow irregularities.

By relying solely on symptom-based diagnoses without addressing the underlying cause, therapeutic interventions tend to focus on alleviating symptoms rather than addressing the pathological factors. For instance, patients diagnosed with primary lymphedema (which implies an unknown etiological cause) may possess anatomical or functional abnormalities within the central conducting lymphatic system that are not identified as the causative factors of lymph flow issues. Enhancing the diagnostic process requires a comprehensive understanding of the pathophysiology, which can be achieved by studying the central conducting lymphatic system in NS patients with and without lymphatic diseases. This research endeavor aims to ultimately refine therapeutic interventions tailored to the specific pathological causes underlying these conditions.

Study objective

To get a better insight into the central conducting lymphatic system in adult volunteers with Noonan Syndrome (NS) without clinical symptoms or signs of lymphatic disease compared to NS and CardioFacioCutaan syndrome patients with severe lymphatic disease and healthy volunteers. (ongoing study: (Lymphomics; improving the understanding the anatomy of the lymphatic system and the direction and velocity of lymph flow; approved by the Medical Ethics Committee at Radboud University Medical Center Nijmegen file number 2021-7514).

- The anatomy of the central lymph vessels will be studied in NSSD patients without (a history of) lymphatic symptoms. This will be done using dynamic MR lymphangiography (DMRL) with intranodal contrast injection. End point is an overview of the anatomy of the central lymph vessels in lymph-healthy NS patients. This will be compared with the anatomy of the central lymph vessels in healthy volunteers without NS and without lymphatic symptoms, and patients with NSSD and a history of lymphatic symptoms.

- The velocity and direction of the contrast in the central lymphatics will be

studied in NSSD patients without (a history of) lymphatic symptoms. This will be done using the same DMRL. End point will be an overview of normal values of contrast velocity and direction This will be compared with the velocity and direction of flow in healthy non-NS volunteers as reference.

Study design

This is a single center, prospective collection of data of MR lymphangiography in our center.
The anatomy of the central lymph vessels will be studied. The MR lymphangiography scans
will also be reviewed for measurements such as the width of the thoracic duct and the
location of inflow into the subclavian vein. In addition, the velocity of the contrast will be
measured on the post-contrast MR images.

Study burden and risks

Participation in this study places subjects at minimal risk. Subjects will undergo placement of a small needle in an inguinal lymph node on both sides, with very little risk of bleeding and/or infection, as with other minimal invasive procedures. The dynamic MR lymphangiography will take approximately two hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Noonan Syndrome confirmed by genetic test with a class 4 or 5 pathogenic variant according to ClinVar
- 18 years and older (no restriction for sex)
- Willing and able to have MR lymphangiography scanning in the Radboudumc
- Oral and written informed consent
- None of the exclusion criteria

Exclusion criteria

- unsuitable for MRI (e.g. metallic objects in the body, severe claustrophobia)
- A history of symptoms related to lymphatic disease
- pregnancy
- renal insufficiency
- liver cirrhosis
- History of surgery related to cardiovascular disease with hemodynamic consequence
- Other genetic diseases

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-03-2024
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	Gadolinium-Based Contrast agent + Emla Lidocain;prilocaine créme
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	29-11-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84520.091.23