Lymphatic Phenotype of Noonan Syndrome

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Contributor: Lotte Kleimeier , , Jos M. T. Draaisma

Noonan Syndrome (NS) is a multisystem disorder, caused by dysregulation of the Ras/MAPK signaling pathway. Pathogenic gene variants in the Ras/MAPK pathway can therefore lead to various lymphatic diseases such as lymphedema, chylothorax and protein losing enteropathy.

Noonan Syndrome | lymphatic disease | dynamic contrast-enhanced MR lymphangiography | central conducting lymphatic anomaly

1. Introduction

Noonan Syndrome (NS) is a multisystem disorder, caused by dysregulation of the Ras/MAPK signaling pathway [1][2][3] and 19 Pathogenic variants in genes encoding for components of this pathway have been identified and linked to NS, of which PTPN11, SOS1, RAF1 and RIT1 are the most prevalent [4][5][6]. Other, less prevalent, mutated genes include BRAF, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, RRAS and SOS2 [4]. Pathogenic variants in these genes lead to an over-activation of the Ras/MAPK pathway, resulting in an over-activation of Extracellular Signal-regulated kinase (ERK)-1 and ERK-2. These kinases are suggested to play a pivotal role in the development of the lymphatic system [7][8]. Therefore, excessive ERK activation is thought to be the cause of lymphatic disease in patients with NS leading to as chylo-thorax, lymphedema and protein losing enteropathy [9]. On prenatal imaging, abnormal lymphatic development may present as increased nuchal translucency, hydrops fetalis, hydrothorax and ascites [10].

A recently conducted retrospective cohort study and systematic review shows that the lifetime prevalence of lymphatic disease in patients with NS is 36%. [10]. Genotype-phenotype studies in patients with NS found that lymphatic disease is more prevalent in patients with NS due to pathogenic variants in SOS2 and RIT1 [10][11][12].

Diagnosis and treatment of lymphatic diseases in patients with NS remain difficult due to its variable presentation, severity and, probably, underlying unknown pathophysiologic mechanism. Some authors suggest that lymphatic disease in patients with NS may be the sequalae of Central Conducting Lymphatic Anomalies (CCLA) [1][13][14][15][16][17]. CCLA is a disease that affects large lymphatic vessels in the middle of the torso, resulting in blockage and subsequent leakage of normal drainage of lymph fluid [14][18][19]. CCLA have traditionally been unsuitable for traditional medical and surgical interventions.

The definitive diagnosis for CCLA requires physical examination and medical history as well as visualization of the central lymphatic system. The central lymphatic system can be visualized using heavily T2-weighted MR imaging

(T2 imaging) due to its high water content. However, this technique does not provide information about the lymphatic flow and is not specific to the lymphatic tissue. Dynamic contrast enhanced lymphangiography (DCMRL) is a new imaging technique that is performed by introducing the gadolinium contrast agent into inguinal lymph nodes. DCMRL allows the evaluation of anatomy as well as the flow in the lymphatic system with excellent temporal and spatial resolution [20].

2. Imaging the Lymphatic System

Visualization and imaging of nearly translucent, lymphatic vessels has always been very challenging. Few scientists have risen to the challenge of studying the lymphatic system by introducing contrast into the lymphatic vessels. In the 17th century, Frederik Ruysch injected air into the lymphatic vessels, and visualized the semilunar valves that allow the unidirectional flow in the lymph vessels.[21] The anatomist Mascagni visualized the lymphatic vessels by filling them with mercury (1787) [21]. During recent decades several radiological and nuclear methods have been developed to image the lymphatic vessels.

Lymphoscintigraphy has traditionally been the modality of choice for peripheral lymphedema. It is performed by injecting colloidal imaging agents subcutaneously between the toes or fingers. The image acquisition in lymphoscintigraphy is performed repeatedly over time thus allowing direction and quantification of the lymphatic flow. One of the main drawbacks in lymphoscintigraphy is low spatial resolution. Coupling it with single photon emission computed tomography (SPECT) provides much better spatial information [22].

Visualization of the central lymphatics can be performed using T2 imaging that is designed to image all water containing structures, including the lymphatic vessels. However, T2-imaging is static and does not provide any information about flow direction or velocity. DCMRL is performed by injecting gadolinium-based contrast agent into inguinal lymph nodes and following the propagation of the contrast through the para-iliac lymphatic vessels into the thoracic duct using a series of short T1 weighted MR sequences, which can be reconstructed into a time lapse movie visualizing the dynamics [23]. DCMRL has demonstrated its usefulness in central lymphatic flow disorders, such as chylothorax, protein losing enteropathy, chylous ascites, lymphedema or scrotal/vaginal chyle leakage, often present in NS [20].

3. Clinical Manifestation Compared to Radiological Findings in Patients with NS

DCMRL and T2 imaging were performed in seven patients with NS and lymphatic diseases. Informed consent for publication was acquired from all parents and, when appropriate, patients aged 12 years or older. This research has been approved by the Medical Ethics Committee at Radboud University Medical Center Nijmegen (file number 2020-6852).

Patient 1: 11-year-old female was diagnosed with NS and a de novo pathogenic variant in SOS2 (c.800T>A p.(Met267Lys)). Prenatal ultrasounds showed polyhydramnios. She had no signs of the lymphatic disorders until six

years of age, when she presented with lower extremity lymphedema. The T2 imaging showed a partially developed thoracic duct, pulmonary (interstitial) and periportal edema and lymphangiectasia in the retroperitoneal space and mesentery. DCMRL demonstrated retrograde lymphatic flow in the lung interstitium, mesenteric and periportal lymphatic vessels, findings that are consistent with CCLA.

Patient 2: 17-year-old female who was diagnosed with NS, with a pathogenic variant in SOS2 (c.800T>A p.(Met267Lys)). Prenatal ultrasounds showed an increased nuchal translucency (>3 mm) without polyhydramnios. She had no signs of the lymphatic disorders until the age of nine years, when she developed lymphedema of the lower extremities and abdominal wall. In addition, she had neuropathic pain in both feet. The T2 images suggested a partial aplasia of the thoracic duct, an enlarged cisterna chyli, peritoneal lymphatic cysts, lymphangiectasia in the retroperitoneal space, and subcutaneous body wall as well as signs of pulmonary interstitial edema were also noted. DCMRL showed no contrast opacification of the thoracic duct, and retrograde flow in the peribronchial, mesenteric and periportal lymphatic vessels, as well as dermal backflow in the abdominal wall, findings that are consistent with CCLA.

Patient 3: 32-year-old female was diagnosed with NS, and a de novo pathogenic variant in SOS2 (c.800T>C p.(Met267Thr)). Prenatal ultrasounds showed polyhydramnios. She presented with lymphedema in the extremities during infancy, which improved within the first few years of her life. At 16 years she again developed severe lymphedema of the upper and lower extremities. DCMRL showed a dilated, and in intermittently duplicated, thoracic duct, without cisterna chyli. However there was no failure to empty into the thoracic duct or the subclavian vein. In addition, there was no abnormal retrograde lymphatic flow or extravasation of contrast. Therefore, these findings were not consistent with CCLA, according to the definition of Ricci, K.W. et al. (2021)

Patient 4: 20-year-old male was diagnosed with NS and a pathogenic variant in RIT1 (c.280G>A (p.(Ala77Thr)). At the age of 6 years, he developed chylous ascites, followed by chylothorax, lymphedema of the lower extremities and scrotal area, and scrotal chylous leakage. The T2 imaging showed left-sided pleural fluids and mesenteric edema. DCMRL images showed partial aplasia of the thoracic duct, retrograde contrast flow into the scrotum as well as dermal backflow and lymphangiectasia behind the cecum and throughout the retroperitoneum, findings that are consistent with CCLA **Figure 1**.

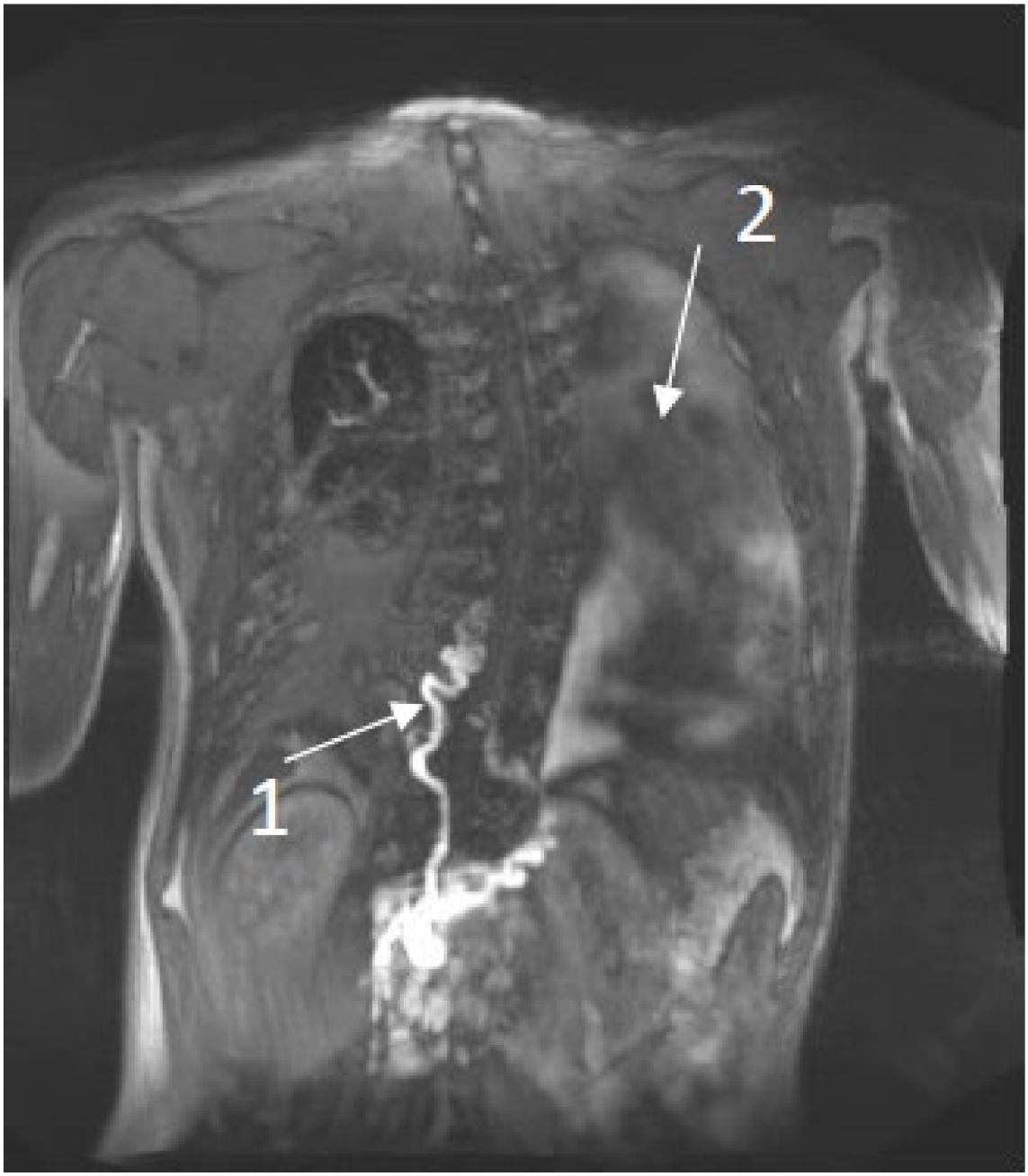

Figure 1. DCMRL results of a 20-year-old male with NS. 1. Abnormal tortuous thoracic duct and partial aplasia. 2. Left-sided pleural fluid.

Patient 5: 31-year-old female was diagnosed with NS and pathogenic variant in PTPN11 (c.181G>A p.(Asp61Asn)). Prenatal ultrasound information was not available. At the age of one year she developed chylothorax after cardiac surgery for repair pulmonary valve stenosis. At the age of ten years she developed lymphedema of the lower extremities as well as vulvar and labial lymphangiectasia, and genital lymphorrhea. At the age of 26 years, she underwent surgical resection of the vulvar lymphangiectasia, which has been reported by Winters et al. [24] T2 imaging shows a dilation of the thoracic duct and lymphangiectasia behind the cecum and throughout the

retroperitoneum. DCMRL showed dermal backflow towards the labia, lower extremities, and the abdominal wall, findings that are consistent with CCLA.

Patient 6: 27-year-old male was diagnosed with NS and a pathogenic variant in SOS1 (c.1277A>C p.(Gln426Pro)). During adulthood, he was diagnosed with protein losing enteropathy. T2 images showed a normally developed thoracic duct. DCMRL demonstrated normal antegrade flow in the thoracic duct however retrograde flow into the mesentery; which can potentially explain the protein losing enteropathy, findings that are consistent with CCLA.

Patient 7: 34-year-old male was diagnosed with NS and pathogenic variant in PTPN11 (c.182A>G (p.Asp61Gly)). He was diagnosed with pericardial effusion at the age of 18 years, and chylothorax at the age of 32. T2 imaging visualized bilateral pleural and pericardial fluid as well as ascites, mesenterial and subcutaneous edema and pelvic cysts. DCMRL showed a tortuous, dilated and partially duplicated thoracic duct, without cisterna chyli, as well as retrograde flow into the periportal lymphatic vessels and dermal backflow in the abdominal wall, findings that are consistent with CCLA.

The clinical lymphatic diseases of CCLA seen in these patients include lymphedema, chylothorax, genital lymph leakage and protein losing enteropathy. In all patients the thoracic duct was abnormal. In six patients the retrograde flow in the peribronchial, periportal or mesenteric lymphatic vessels, or dermal backflow was demonstrated.

There are several case reports, and one case-series, reporting on the clinical lymphatic diseases and radiological findings of CCLA in patients with NS. Combined, they reported ten patients with chylo-thorax, three patients with protein losing enteropathy, two patients with ascites, two patients with lymphedema, and two patients with additional lymphangiectasia, either mesenteric and retroperitoneal or pulmonary [1][13][15][16][17]. **Table 1** summarizes the results of clinical manifestation of the radiological findings. In 12 out of 14 patients the anatomy of the thoracic duct was evaluated, all of them reporting on an abnormal development of the thoracic duct, which varies in nature. In addition, all articles report on lymphatic flow abnormalities, indicating CCLA.

Table 1. Summary of the clinical manifestation of lymphatic disease and radiological findings of 14 previously published case reports.

Nr.	Age (y) (m/f)	Clinical Manifestation of Lymphatic Disease	Radiological Findings			Reference
			TD	Flow abnormalities	Other findings	

Nr.	Age (y) (m/f)	Clinical Manifestation of Lymphatic Disease	Radiological Findings			Reference
1	14 (f)	CT, PLE, MLA, RLA	ND	Retrograde mesenteric and pulmonary flow	Leak of contrast into duodenal lumen, abnormal CLS	Dori, Y [13]
2	13 (m)	LE, PLE, HT	ND	Pleural fluids ascites	oedematous intestine	Keberle, M [17]
3	17 (f)	PLE	absent	ND	abdominal collateral lymphatics and bilateral iliac lymphangiectasia	Matsumoto, T [16]
4	61 (m)	LE, SLE	Occlusion at the neck	Increased pelvic and retroperitoneal flow	PLA, abdominal ascites	Othman, S [15]
5	0.9 (f)	CT	Dilated	Bilateral perfusion	-	Biko [1]
6	0.6 (m)	CT	Double duct, central TD not present	Bilateral perfusion	Body wall edema	Biko [1]
7	0.1 (m)	CT	ND	Bilateral pleural effusions	Body wall edema, ascites	Biko [1]
8	0.8 (m)	CT, ascites	absent	Bilateral perfusion	Body wall edema, ascites	Biko [1]

Nr.	Age (y) (m/f)	Clinical Manifestation of Lymphatic Disease	Radiological Findings			Reference
9	7 (f)	CT	absent	Bilateral perfusion	Pericardial effusion, ascites	Biko [1]
10	0.2 (m)	CT	absent	Bilateral perfusion	Body wall edema	Biko [1]
11	0.1 (f)	CT	rudimentary	Bilateral perfusion	ascites	Biko [1]
12	0.1 (f)	CT	Double duct	Perfusion right lung	-	Biko [1]
13	0.1 (m)	CT, anasarca	Dilated	Bilateral perfusion	Network of lymphatic collaterals in left neck, body wall edema, ascites	Biko [1]
14	5 (m)	ascites	absent	Peritoneum perfusion	Ascites	Biko [1]

CLS: central lymphatic system, CT: chylo-thorax, f: female, HT: hydrocele testis, LE: lymphedema, m: male, MLA: mesenteric lymphangiectasia, ND: no data, PLA: pulmonary lymphangiectasia, PLE: protein losing enteropathy, RLA: retroperitoneal lymphangiectasia, SLE: scrotal lymphedema.

4. Possible Implications for Therapeutic Options

Traditionally, the treatment approaches for the symptoms of lymphatic conditions are tailored to the clinical presentation. Physiotherapy, including compression therapy, exercise and manual lymphatic drainage, are often used in the treatment of lymphedema [25].

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Pleural and abdominal cavity drainage is used as a symptomatic treatment of chylothorax and chylous ascites. This is often combined with diet modification to reduce chyle production. Similar diet modifications are used successfully in patients with protein losing enteropathy [26][27].

Pharmacological treatments include octreotide or propranolol. Octreotide is used to reduce the chyle production in chylous effusions, especially for the congenital form, and also in children with NS [28]. Propranolol therapy for chylous effusions was recently reported, but there is little experience with propranolol in NS patients [29]. The exact mechanism of propranolol is still unknown. Perhaps the inhibitor of the β2-adrenergic receptor leads to decreased expression of lymphangiogenic factors, such as vascular endothelial growth factor (VEGF) [29].

In case of failure of conservative treatment, surgical interventions can be considered when the local lymphatic anatomy and flow pattern is known. Surgical lympho-venous anastomosis has been performed to treat lymphedema. Surgical ligation or percutaneous embolization of thoracic duct may be performed in patients with chylous effusions. Otman et al. [30]. described a 61-year-old man with NS with severe pulmonary insufficiency due to thoracic duct obstruction, which improved following surgical TD-venous anastomosis [31]. Waters et al. reported a patient with NS and recurrent lymphangiectasia that was successfully treated with a 2-stage approach using lympho-venous anastomosis followed by excision of the vulvar lesion and reconstruction [24].

All these therapeutic strategies target the specific clinical presentation, and not the general underlying mechanism. However, as shown before, in NS there may be an underlying CCLA. New insights into lymphangio-genesis and lymphatic vasculature remodelling show that pathogenic variants in genes in the Ras/MAPK signalling pathway may be the cause of persistent lymphatic dysfunction and abnormalities [14][33][34].

Knowledge of and experience with therapeutic interventions of the Ras/MAPK pathway is emerging across a spectrum of both adult and Pediatric cancers with somatic mutations in the Ras/MAPK pathway [13][14]. A drug therapy that is still in its experimental phase in patients with germline mutations is targeting the increased activity of the Ras/MAPK pathway that is stimulated by most NS genotypes [31]. This has led to the hypothesis that a MEK inhibitor, as used in oncologic patients, could be beneficial in patients with NS and severe lymphatic disease due to CCLA [13][14]. MEK inhibition could lead to resolution of symptoms and remodelling of the central lymphatic system.

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