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Systematic Literature Review of Lymphatic Imaging-Guided Procedural Management of Noonan Syndrome

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Abstract

OBJECTIVE(S): To assess through literature case analysis how advances in lymphatic imaging, interventional radiology, and lymphatic vascular microsurgery illuminate and improve the lymphatic-flow status in select patients with Noonan Syndrome (NS) who have undergone surgical intervention as a part of their comprehensive and individualized treatment plan. Also, to illustrate the spectrum of lymphatic complications that can occur in this patient population when lymphatic flow through abnormal vasculature is surgically disrupted.

METHODS: A literature review was performed by searching “Noonan AND Lymphatic AND Imaging” in the PubMed database. Inclusion criteria for this study were 1) diagnosis and clinical description of at least one original patient with Noonan syndrome, 2) imaging figures depicting lymphatic structure/function OR description of lymphatic imaging findings when a figure is not present, and 3) documentation of either lymphatic surgical intervention or lymphatic complications resulting from other procedures. Patient cases were first grouped by documented surgical intervention type, then clinical outcomes and lymphatic imaging results were compared.

RESULTS: A total of 18 patient cases from 10 eligible publications were included in our review. Lymphatic imaging findings across all patients included lymphatic vessel dysplasia along with flow disruption (n=16), thoracic duct malformations (n=12), dermal lymphatic reflux (n=7), and dilated lymphatic vessels (n=4). Lympho-venous anastomosis (n=4) resulted in rapid improvement of patient symptoms and signs. New onset-lymphatic manifestations noted over 10–20 years for 2 of these patients were chylothorax (n=1), erysipelas (n=1), and gradual-onset non-chylous scrotal

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lymphorrhea (n=1). Targeted endovascular lymphatic disruption via sclerosis, embolization, or ablation (n=8) results were mixed depending upon the degree of central lymphatic involvement and included resolution of symptoms (n=1), post-operative abdominal hemorrhage (n=1), stable condition or minor improvement (n=5), and death (n=2). Large lymphatic-vessel ligation or accidental incision (n=6) occurred during thoracotomy (n=4), scrotoplasty (n=1) and inguinal lymph node biopsy (n=1). These resulted in post-operative onset of new onset-regional lymphatic reflux (n=5), chylothorax (n=4), death (n=3), or persistent/unchanged symptoms (n=1).

CONCLUSIONS: Imaging of the central lymphatics enabled characterization of lymphatic developmental features and guided operative management of lymphatic vascular defects in patients with Noonan syndrome. This review of the literature suggests that surgical preservation or enhancement of central lymphatic return in patients with Noonan syndrome may improve interventional outcomes, while disruption of central lymph flow has significant potential to cause severe post-operative complications and worsening of the patient's clinical condition.

TABLE OF CONTENTS SUMMARY

A literature review of 18 Noonan syndrome patients who underwent either lympho-venous anastomosis or targeted disruption of abnormal peripheral lymphatics showed significant post-operative improvement when lymphatic imaging could demonstrate enhanced lympho-venous return. Preserving central lymphatic flow is essential for favorable interventional outcomes in Noonan syndrome patients with lymphatic manifestations.

Keywords

Noonan Syndrome; Lymphatic Imaging; Lympho-Venous Anastomosis; Congenital Lymphatic Dysplasia; Thoracic Duct Decompression

Introduction:

Noonan Syndrome (NS) is an autosomal dominant congenital genetic disease resulting from mutations in genes of the RAS/RAF/ERK signaling pathway[1]. This disease occurs with an estimated frequency of 1:1000–2500 live births across all ethnicities in both males and females[2]. Clinically, NS patients present with a phenotype similar to Turner Syndrome with classic features such as webbed neck, low palpebral fissures, low set ears, pectus sternal deformity, widely spaced nipples, barrel-shaped chest, and scoliosis[2].

Complications associated with NS include (but are not limited to) congenital heart disease, pulmonary lymphangiectasia renal/urological structural abnormalities, bleeding disorders, increased risk of juvenile myelomonocytic leukemia, hearing/visual abnormalities, lymphatic vascular malformations, and fistulous chylous reflux complications such as chylothorax and protein-losing enteropathy[1,2,3].

Although NS treatment appears to be an area of increasing interest across the literature, only a limited number of publications address lymphatic-specific etiologies of many NS syndromic sequelae, and there is infrequent discussion about the fundamental role of lymphatic imaging findings during treatment planning and follow-up[4]. Even fewer publications specifically address how these imaging findings relate to the surgical

management of the unique lymphatic vascular complications observed in this patient population. There is also a deficit in the literature regarding post-operative lymphatic sequelae due to imaging-confirmed disruptions in congenitally abnormal lymphatic vasculature.

In this review of the literature, we address these deficits by evaluating all known published reports of NS patients who underwent lymphatic imaging and lymphatic surgery as part of their comprehensive management plan, as well as the cases of NS patients who experienced iatrogenic lymphatic sequelae from other procedures. We correlate the lymphatic outcomes of documented surgical interventions with the available pre- and post- operative lymphatic imaging findings. Comparison between planned lympho-vascular intervention and iatrogenic disruption groups helps to further illustrate the relationship between lymphatic flow status and the spectrum of possible NS surgical outcomes. This also expands the relevance of our findings to include providers who participate in non-lymphovascular surgical management of NS patients.

Methods:

We first used the PubMed database to find all the studies included in this literature review. We searched “Noonan AND Lymphatic AND Imaging,” which yielded 40 results. This database search term was the only one used, search parameters covered all time periods and included all publication types, last accessed September 22, 2021. Inclusion criteria for this study were 1) Diagnosis and clinical description of at least one original patient with NS, 2) Imaging figures depicting lymphatic structure/function OR description of imaging findings when a figure is not present, and 3) Documentation of either lymphatic surgical intervention or lymphatic complications resulting from other surgeries. Eligibility for inclusion in this publication was determined by manually reading/reviewing each article resulting from our database search. The “references” section of each article was also manually reviewed to identify other eligible articles that may not have resulted from our PubMed search. Of the 40 original PubMed papers that appeared on our search, 12 met our inclusion criteria as described above.

We then excluded publications featuring ultrasound (US) diagnosis of NS *in utero* since available research suggests fetal US findings do not correlate with post-natal patient outcomes or potential disease severity[5]. To our knowledge, novel US modalities for lymphatic visualization such as high-frequency ultrasound have not been used as an evaluation method for NS patients at the time of this publication. We did not exclude studies based on patient age, gender, or genotype as long as there were no karyotype abnormalities as would be expected in patients with Turner syndrome. Of the 12 papers that met our inclusion criteria, 2 were excluded based on the discussed exclusion criteria.

Using the criteria mentioned above, 10 publications from our PubMed search were eligible for inclusion in our review, reporting 18 individual patient cases. These patients were grouped into one of three lymphatic surgical categories: Ligation/Incision, Targeted Intravascular Disruption, and Lympho-Venous Anastomosis. Lymphatic imaging results,

patterns of clinical findings, and available interventional outcomes were then compared among the 18 NS patients as Table 1 and with greater detail as Supplemental Table 1.

Review of the Literature and Surgical Outcomes:

A total of 18 NS patients underwent both lymphatic imaging and surgical management relevant to the patient's lymphatic status. Imaging modality utilization included chest X-ray (n=4), conventional oil contrast lymphangiography (n=11), lymphoscintigraphy (n=4), CT lymphangiography (n=2), Indocyanin Green Lymphography (n=1), MRL (n=8), and dc-MRL (n=7). Twelve patients underwent lymphatic imaging with more than one modality (67%) while six patients were imaged using only one modality (33%). Imaging findings across all patients included lymphatic vessel dysplasia along with flow disruption (n=16), thoracic duct malformations (n=12), dermal lymphatic reflux (n=7), and dilated lymphatic vessels (n=4). As an aside, gene mutations were identified for eight patients. Mutations in PTPN11 (n=7) were most commonly noted, and KRAS (n=1) was also identified, while ten patients were unspecified. Examples of lymphatic anomalies seen either pre- or post-op included lymphedema (n=9), chylothorax (n=12), genital lymphorrhea (n=6), chylous ascites (n=6), and lymphocutaneous fistula (n=3). A comprehensive list of our findings is included as Supplemental Table I.

Six patients had surgical incision or ligation of lymphatic vessels during surgical procedures such as thoracotomy (n=4), scrotoplasty (n=1) and inguinal node biopsy (n=1). These resulted in post-operative onset of new lymphatic reflux issues (n=5), chylothorax (n=4), death (n=3), and persistent or unchanged symptoms (n=1). Authors frequently attributed these post-operative complications to iatrogenic disruptions in lymphatic flow.

Eight patients underwent targeted lymphatic endovascular ablation, embolization, or sclerosis planned with lymphatic imaging. Post-operative results noted were resolution of symptoms (n=1), post-operative abdominal hemorrhage (n=1), stable condition or minor improvement (n=5), and death (n=2). Procedures targeting peripheral lymphatic vessels which did not obstruct central lymphatic flow were not associated with significant complications, while the sequelae of central lymphatic occlusion were severe. To elaborate on our prior publication, the patient who experienced post-operative hemorrhage was patient 1 (P1)[6]. Initial imaging and LVA procedure for P1 were published by Howarth and Glovicski in 1998[7]. Due to gradual recurrence of genital swelling and leakage over 12 years, P1 was evaluated with LAS, MRL, and CT imaging leading us to pursue interventional lymphatic sclerosis using doxycycline if communication could be demonstrated intra-operatively between left lower pelvic lymphatics and the scrotum. No communication with the scrotum was demonstrable, and the procedure was discontinued. Several hours after the procedure was discontinued, P1 was returned to the angiography suite for abdominal and pelvic hemorrhage requiring two packed red blood cell transfusions. A left superior gluteal artery embolization was performed using micro coils, after which no further bleeding occurred. The patient's condition stabilized, and he was discharged home after three days in the hospital.

Four patients underwent LVA to address lymphatic dysfunction. Resolution of acute symptoms was evident in all four patients. Long-term improvement was documented for three of these, while the fourth (published by Biko et al.)[8] was presumably lost to follow-up, as they were transferred in stable condition to a local community hospital for continuation of medical and dietary management[8]. One-year follow-up for the recently published case by Othman et al.[9] indicated return to baseline, increased exercise tolerance, and resolution of pulmonary lymphangiectasia and chylothorax without recurrence[9]. Follow-up between 10–20 years for our Patients 1 and 3 as previously published[6] observed new or recurring lymphatic reflux manifestations including chylothorax (n=1) and erysipelas (n=1) for Patient 3, and gradual-onset non-chylous scrotal lymphorrhea (n=1) for Patient 1. These findings support a continued need for regular clinical follow-up and possible follow-up surgery in NS patients who undergo LVA.

Discussion/Conclusions:

Lymphatic involvement in NS pathogenesis first began to receive attention in 1974 after the publication of a case series by Minkin et. al.[10], which characterized and analyzed the congenital lymphedema observed in many NS patients[10]. Clinical lymphedema severity is graded by most experts on a scale of 0-III, with grade-III representing the most severe cases (elephantiasis) and grade-0 being asymptomatic or very early stage[11]. NS patients in the literature frequently exhibit primary and secondary lymphedema and undergo multiple combinations of both conservative and invasive treatments. Since the time of Minkin et al.'s publication, numerous imaging genetic and clinical studies have pointed toward congenitally acquired lymphatic dysfunction/dysplasia as the etiological root for many of the symptoms and signs observed in patients with NS[1,4,8,12].

Imaging of the lymphatic system has evolved rapidly over the past several decades. Widely available imaging methods include conventional oil-contrast lymphography (LAG), CT lymphography (CTL), nuclear imaging methods such as lymphoscintigraphy (LAS) and single-proton emission computerized tomography (SPECT), and various magnetic resonance lymphography (MRL) modalities. We have previously suggested that early evaluation with lymphatic imaging should be performed for NS patients as a guide to individualized treatment regardless of a patient's initial clinical manifestation[6]. Conservative management strategies for NS-associated lymphatic dysfunction include medium/light-chain triglyceride diets, compression garments, and manual lymph drainage massage therapy. Published lymphatic surgical methods for NS include lymphatic vessel ligation, targeted endovascular disruption (embolization, sclerosis, ablation, etc.) and lympho-venous anastomosis (LVA). Good patient outcomes have previously been associated with achievement of improved lymphatic flow, and imaging of the lymphatic system has been shown in many cases to be fundamental to therapeutic planning and success[4,6,8].

Early imaging of the lymphatic system remains an imperative tool to guide individualized NS patient management through operative as well as non-operative methods. As noted by Biko et al.[8] and demonstrated by Othman et al.[9], we propose that surgical intervention in this population is most likely to achieve clinical success when lymphatic flow and central circulatory reentry of lymph into the venous system are preserved[8,9]. We observe that when

NS lymphatic manifestations are more peripheral such as with abnormal fistulas, targeted lymphatic disruption may be of benefit as long as central lymphatic flow is preserved. Significant post-operative improvement was noted for all four patients who underwent LVA, although we still recommend that patients be followed closely by their physicians for signs of new or recurrent lymphatic problems. Additionally, surgeons and interventionalists who perform otherwise routine procedures on a patient with NS should take into account the prevalence of lymphatic vascular anomalies that put the patient at risk of lymphatic disruption or dysfunction. This awareness may help increase the utilization of pre-operative lymphatic imaging in these patients and decrease the chance of complications secondary to iatrogenic central lymphatic flow disruptions.

It is important to note that lymphatic surgery in NS patients has not been widely researched, and the generalizability of these conclusions is limited by the small number of published studies in this area. Future studies should continue to be oriented toward characterization of NS clinical manifestations, lymphatic imaging results, and long-term post-operative outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ARTICLE HIGHLIGHTS

Type of research:

Systematic review of the literature

Key Findings:

Lymphatic imaging and surgical management was utilized for 18 Noonan Syndrome patients with lymphatic manifestations. Lympho-venous anastomosis (n=4) improved symptoms in 100% of cases, targeted lymphatic intravascular disruption (n=8) improved or maintained symptoms in 75%, and central lymphatic disruption via ligation/incision (n=6) resulted in iatrogenic complications in 100% of cases.

Take home Message:

Preservation or enhancement of central lymphatic return via lymphatic imaging-guided intervention such as lympho-venous anastomosis results in improved clinical outcomes for patients with Noonan Syndrome.

Table 1:

Literature review case findings

Patient Study Set (year of publication) Ref	No. Operatively Managed Patients	Case Profiles			
		Clinical Manifestations	***Lymphatic Imaging/ Diagnostics***	***Surgical/ Interventional Management***	***Documented Outcomes***
Study 1 (1978)[13]	**1**	Chylothorax, failure to thrive	CXR, Autopsy	Ligation of thoracic lymph vessels	Death
Study 2 (1980)[14]	**1**	Perineal/genital lymphedema	C-LAG	Inguinal lymph node biopsy	New onset lymphatic symptoms
Study 3 (1980)[15]	**2**	Cardiac defects (n=2)	CXR	Cardiac surgery	New onset lymphatic symptoms (n=2)
***Study 4 (1998)** [7]	**1***	Chylous ascites; lymphedema; genital lymphorrhea	MRL, LAS, C-LAG	Abdominal LVA	Marked improvement
Study 5 (2016)[4]	**2**	Lymphedema (n=2); genital lymphorrhea (n=1)	LAS	Thoracic duct ligation (n=1), Scrotoplasty (n=1)	Death (n=1); Improvement with some persistent symptoms (n=1)
Study 6 (2019)[16]	**1**	Lymphedema, lymphocutaneous fistulae, chylocolporrhea	C-LAG, CT, LAS	Lymphatic lipidiol embolization	Resolution without recurrence at 12 months (n=1)
Study 7 (2019)[8]	**7**	Chylothorax (n=6); ascites (n=3)	C-LAG (n=7), MRL (n=6), dc-MRL (n=5)	Lymphatic embolization (n=6), LVA (n=1)	Death (n=2), Stable or Improved (n=4), Resolution (LVA, n=1)
Study 8 (2020)[17]	**1**	Cardiac defects; chylothorax	ICG, dc-MRL	Thoracic duct ligation, two cardiac surgeries	Death
***Study 9 (2021)** [6]	**2***	Lymphedema, ascites, genital lymphorrhea, lymphocutaneous fistula	CT, MRL, LAS, CXR	Inguinal LVA (n=1), lymphatic doxycycline sclerosis (n=1)	Improvement 20-yr post op (LVA, n=1), Stable (n=1)
Study 10 (2021) [9]	**1**	Acute Chylothorax and Pulmonary Insufficiency	C-LAG, dc-MRL	LVA (thoracic duct)	Fluid overload (immediate), Resolution (1-year)

CXR= Chest X-Ray; C-LAG = Conventional Oil-Contrast Lymphangiography; CT = Computerized Tomography; MRL = T2-Weighted Magnetic Resonance Lymphography; dc-MRL = Dynamic-Contrast (T1-Weighted) Magnetic Resonance Lymphography; LAS = Lymphoscintigraphy; ICG = Indocyanin Green Lymphography; LVA = Lympho-Venous Anastomosis