Lymphatic anomalies during lifetime with Noonan syndrome or Noonan-like syndromes:

Clinical presentation, prevalence, and genotype-phenotype correlations

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Introduction

- Noonan syndrome and Noonan like syndromes, are genetic-multivariant disorders
- Caused by pathogenic variants in the Ras/MAPK pathway
- Pathogenic variants in the Ras/MAPK pathway are associated with an abnormal development of the lymphatic system
- The clinical presentation varies between patients.
- The prevalence of lymphatic anomalies is **20%**
- Lymphatic anomalies most often presented as increased NT, Chylothorax and Lymphedema
- Lymphatic anomalies seem to occur more often in RIT1 and SOS2

Objective

To provide an overview of the clinical presentation, prevalence and genotype-phenotype relations concerning lymphatic anomalies during life in patients with NS or Noonan-like syndromes.

Material and Methods

Data analysis

- Retrospective cohort study with **267** participants (136 males, 131 females)
- Median age of **18 (IQR 9-34)**
- Data on prenatal and postnatal lymphatic anomalies were collected
- **Prevalence** of lymphatic anomalies were investigated according to the stage of life, stratified by pathogenic variants
- **Genotype-phenotype correlations** were investigated using Fisher's exact test.

Results

Table 1| Prevalence of lymphatic anomalies during life in different pathogenic variants

Variant	Prenatal	Postnatal	Lifetime
All*	26/148 (18)	42/267 (16)	56/267 (21)
PTPN11	14/82 (17)	24/156 (15)	32/156 (21)
LZTR1	3/9 (33)	**6/14 (43)**	6/14 (43)
SOS2	1/2 (50)	**3/3 (100)**	**3/3 (100)**
SHOC2 *NS-LAH*	3/6 (50)	1/6 (17)	**4/6 (67)**

*pathogenic *A2ML1*, *BRAF*, *CBL*, *KRAS*, *LZTR1*, *MAP2K1*, *NF1*, *PPP1CB*, *PTPN11*, *RAF1*, *RIT1*, *RRAS*, *SOS1*, *SOS2*, and *SHOC2* variants
Orange color indicates a statistically significance

- Genotype-phenotype correlation analyses also showed a high postnatal prevalence during childhood in patients with **RAF1**

Table 2| Associations between prenatal lymphatic anomalies and postnatal lymphatic anomalies during infancy in patients with Noonan syndrome and Noonan-like syndromes (n=148)

	Postnatal lymphatic anomalies during Infancy		
Prenatal lymphatic problems	**N**	**n(%)**	**Odds ratio (95% CI)**
No	122	8 (7)	
Yes	26	11 (42)	**10.5 (3.6-30.1)**

CI: confidence interval; N: number n(%) number of patients with postnatal lymphatic anomalies

- 2/14 (14%) patients with only an increased NT prenatally, suffered from lymphedema as infant
- 6/7 patients with chylothorax prenatally, had chylothorax during infancy
- 4/5 (80%) patients with hydrops fetalis prenatally, had lymphatic problems during infancy.

Discussion

- **The main strength**: overview of the clinical presentation according to stage of life
- **Limitation**: low number of patients within certain pathogenic variants and inevitable selection bias

Conclusion

NS patients with prenatal lymphatic anomalies have an increased risk of lymphatic anomalies during infancy. With a total lifetime prevalence of **21%**
Genotype-phenotype correlations were found in pathogenic ***SOS2, LZTR1, RAF1*** **and** ***SHOC2*** variants.

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ITHACA European Reference Network for rare or low prevalence complex diseases — Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

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