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

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

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

Data analysis

• 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)

<table>
<thead>
<tr>
<th>Prenatal lymphatic problems</th>
<th>Postnatal lymphatic anomalies during Infancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>No</td>
<td>122</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
</tr>
</tbody>
</table>

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.