A Deleterious EPHB4 Mutation Suppresses PROX1 Expression and Disrupts Lymphatic Development in Neonatal Non-immune Hydrops

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A Deleterious EPHB4 Mutation Suppresses PROX1 Expression and Disrupts Lymphatic Development in Neonatal Non-Immune Hydrops

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Background

- Hydrops Fetalis, a fatal condition, mostly non-immune in origin (85%)
- Etiology in unknown in 20% cases
- 15% associated with lymphatic malformation
- Ephrin type B receptor 4 (EPHB4) plays important role in lymphatic development
- Prospero Homeobox 1 (PROX1), a transcription factor, is responsible for terminal lymphatic fate specification

Objective

- To test the hypothesis that EPHB4 mutations can cause hydrops fetalis and to explore the role of PROX1

Design/Methods

- 35-week infant with non-immune hydrops infant required thoracentesis due to pleural effusions
- Infant died of septic shock on DOL 145
- Whole exome sequencing (WES)
- MRI lymphangiogram
- Immunohistochemistry (IHC) on autopsy specimens
- In-vitro functional studies—human embryonic kidney cells (HEK293) and immortalized human pulmonary microvascular endothelial cells (HPMEC-IM)

Results

- WES - EPHB4 c.2098G>A (p.Ala700Thr) variant
- MRI lymphangiogram—Complete absence of any visible central lymphatic ducts
- Autopsy revealed anasarca, absent thoracic duct, depletion of lymphoid tissue of the reticuloendothelial system, lungs with pulmonary lymphangiectasia
- IHC studies—loss of PROX1 staining in the endothelial cells of the large lymphatic channels in the lung and small intestinal villi with preservation of podoplanin expression in the same channels.

- In-vitro functional studies—EPHB4 (p.Ala700Thr) variant disrupts phosphorylation of EPHB4 in HEK293 and HPMEC-Im cells and results in decreased ERK (extracellular signal related kinase) phosphorylation (Thr980) and PROX-1 expression in HPMEC-Im

Conclusion

- Genetic mutation in the EPHB4 led to hydrops in our proband by disrupting PROX-1 mediated lymphatic development.