"SNARE"-ing the reason for post-cardiac surgery critical illness-related corticosteroid insufficiency through genetic evaluation

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Background

- Neonates undergoing congenital heart disease (CHD) surgery with post-cardiac surgery critical illness-related corticosteroid insufficiency (CIRCI) or adrenal insufficiency can manifest through pulmonary hypertension and hemodynamic instability.
- Morbidity and ICU care is high in these patients requiring significant treatment with inotropic support and IV steroids.
- Mortality in this population ranges from 2-17%, the cause of the differences amongst patient populations is still unknown.
- As human biomarker evaluations are increasingly able to be completed, we sought to identify possible gene differences seen in neonates with post-cardiac surgery critical illness-related corticosteroid insufficiency (CIRCI).

Methods

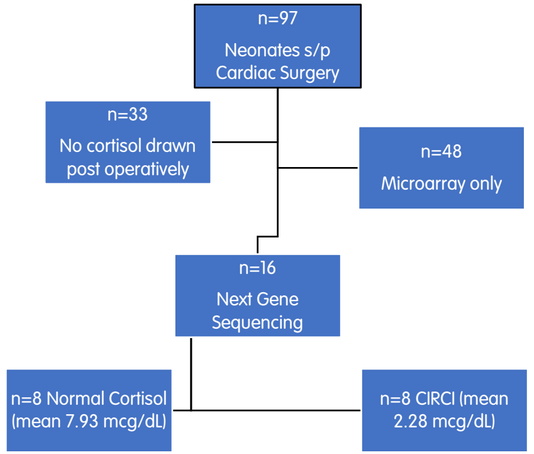
- Single-site, de-identified, retrospective study, of neonates who underwent CHD surgery from August 2018 - July 2020 and who had DNA Next Generation Sequencing (NGS) performed per standard care through the institution's Genome Center
- Neonates with NGS testing done and had a cortisol level drawn as standard of care with hemodynamic instability were grouped by CIRCI (cortisol $\leq$4.5mcg/dL) and Normal Cortisol
- DNA sequence analysis was performed using Partek® Flow® software, using Bowtie 2 to align reads to hg38 and Partek Genotype likelihood algorithm to identify a list of aberrations within patient genomes
- Expression of pulmonary hypertension, hypotension, and hemodynamic instability were used as filters.

https://voca.ro/156pRUHELqUD

	CIRCI (n=8)	Normal (n=8)	Total (n=16)
Male	87.5% (7/8)	75% (6/8)	81.3% (13/16)
White	87.5% (7/8)	87.5% (7/8)	87.5% (14/16)
Single Ventricle CHD	87.5% (7/8)	75% (6/8)	81.3% (13/16)
Central/ BT shunt	37.5% (3/8)	62.5% (5/8)	50% (8/16)
Norwood / Hybrid	50% (4/8)	12.5% (1/8)	31.3% (5/16)
Reintubation	75% (6/8)	37.5% (3/8)	56.3% (9/16)
Mean Length of Stay (days)	59.5	53.5	59.5 $\pm$ 112.6 (mean + SD)
Median Length of Stay (days)	109.5	115.8	112.6
Transplant Free Survival	75% (6/8)	87.5% (7/8)	81.3% (13/16)

Results

- STX1A gene mutation was found in 100% of the neonates with CIRCI and none of the neonates with a normal cortisol and hemodynamic instability
- No differences in gestational age, age in days and weight at surgery, bypass times, rate of ECMO or vasoactive use
- Median length of stay with CIRCI versus normal was 59.5 and 53.5 days, respectively
- Variable time for post-operative cortisol lab draw between groups
  - CIRCI group: median 2.71 and mean 2.88 days
  - Normal Cortisol group: Median 1.1 to mean 8.15 days



Discussion

- STX1A is in the SNARE family coding for protein Syntaxin- responsible for fusion of synaptic vesicles with the presynaptic plasma membrane
- Animal models - STX1A has cardiac implications related to post-operative cardiac dysfunction and excitation-contraction with calcium channel kinetics (Virdi, 2019)
- Critical deletion region of Williams-Beuren Syndrome

Conclusions

- Potentially novel genetic abnormalities were seen in neonates with CIRCI within the STX1A gene; ongoing genetic associations to CIRCI with pulmonary hypertension and hemodynamic instability are being evaluated
- Future studies may include investigations for genetic abnormalities involving larger and multi-site cohorts.
- Longer-term potential aligns with the clinical development of a genetic biomarker panel to be performed prior to neonatal cardiac surgery to evaluate gene levels and potential predisposition to the development of CIRCI and associated mortality and morbidity risk.

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