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Identification of critical illness-related corticosteroid insufficiency after congenital heart surgery with next generation sequencing

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Background

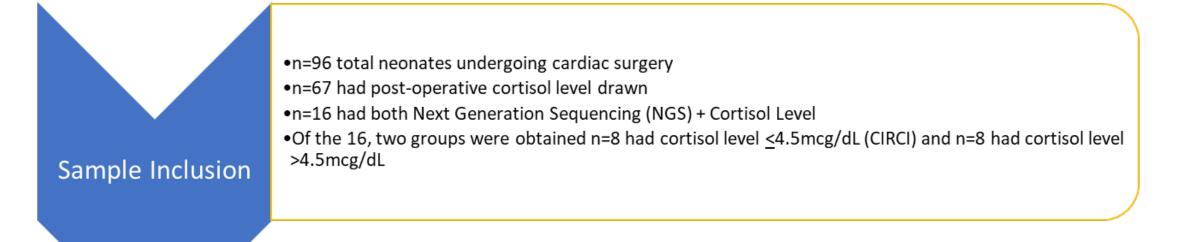
 Critical illness-related corticosteroid insufficiency (CIRCI) is common after cardiac surgery and is a cause of hemodynamic instability.

Objectives

- Identify genetic abnormalities
 related to CIRCI in pediatric patients
 after congenital heart surgery.
- Describe differences in clinical outcomes between CIRCI and non-CIRCI groups.

Methods

- Single-center retrospective study of neonates who underwent cardiac surgery between August 2018 to July 2020.
- Patients who had obtained postoperative cortisol levels and next gen DNA-sequencing (NGS).



•DNA sequencing analysis grouped by CIRCI and Non-CIRCI using Partek FLOW Software
•Filtered for confidence of mutations 20 and above, exluciding common variants detectable in more than 1% of the general population
•Bowtie2 used to align reads to hg38
•Partke Genotype liklihood algorithm used to identify aberrations for each neonate
•Finally, Clinical Insight sofwtare (Qiagen) applied for variant interpretation of biologic filters for pulmonary hypertention and hemodynamic instability

Demographic and Descriptive Analysis

•100% of n=8 neonates with CIRCI had a heterozygous STX1A mutation, 0% of n=8 neonates had that same mutation. Genetic results were deidentified to the neonate level.

Gender, race, ethnicity, gestational age, cardiac diagnosis, surgery type, STAT category,
 Lowest cortisol level, hydrocortisone given, open chest, ECMO, bypass time, discharge weight, Preoperative intubation, extubation, reintubation post-operatively, post-operative creatinine and BUN, Transplant free survival, ventilator days, length of stay, length of ICU stay, VIS scores, NIRS values, lactic acid, mixed venous values all for 0-7 days post-operatively

•Demographic and descriptive variables analysis using SPSS using medians due to sample size

Results

- Seven gene mutations were present in 75-100% of patients with CIRCI.
- The CIRCI group had 100% incidence of heterozygous gene mutation on STX1A with splicing and loss of function compared to 0% incidence in the non-CIRCI group.

Table 1. Patient demographics and postoperative outcomes

	CIRCI	Non-CIRCI	P-value
Patients (n)	8	8	
Age at surgery (days)	10 (9 - 27)	9.5 (6 - 20)	0.62
Gestational age (weeks)	39 (38 - 41)	39 (38 - 40)	0.65
Weight at surgery (kg)	3.25 (2.73 - 4.8)	3.41 (2.6 - 4)	0.69
CPB time (minutes)	118.5 (81 - 177)	127 (107 -181)	0.80
STAT Category			
1	0	1	
2	0	0	
3	0	0	
4	4	4	
5	4	3	
Cortisol (mcg/dL)	2.15 (0 - 4.5)	5.95 (4.6 - 17.8)	< 0.001
CICU Length of stay	33 (5 - 125)	19.5 (8 - 45)	0.02
(days)	, , ,		
Total length of stay	59.5 (49 - 307)	53.5 (21 - 343)	0.28
(days)		, , , , , ,	
Minimum SvO2 POD 0	44.25 (14.7 - 77.4)	60.75 (23.7 - 80.3)	0.49
(%)			
Maximum VIS POD 0	13 (0 - 22.5)	8 (5 - 45)	0.12
Total mechanical	13 (3 - 22)	9.5 (3 - 18)	0.30
ventilation (days)	, ,	` ′	

Data is represented in median (range).

CPB, cardiopulmonary bypass; CICU, cardiac intensive care unit; STAT, The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery score, SvO2, mixed venous oxygen saturation; POD, postoperative day; VIS, vasoinotropic score.

Conclusion

- Rapid testing for gene mutations
 has the potential to detect patients
 at risk for critical illness-related
 corticosteroid insufficiency with
 hemodynamic instability.
- Further research in larger patient cohorts is required to determine the statistical and clinical significance of these genetic abnormalities.







