Pediatric Case Report: Oxygenator Change Out Due to Hypercholesterolemia

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Objectives

- Pathophysiology of Alagille Syndrome and Hypercholesterolemia in children
- Case presentation and outline of our experience in conducting cardiopulmonary bypass in a patient with Alagille Syndrome and Hypercholesterolemia
- Describing CPB events, oxygenator failure and successful oxygenator changeout and eventual failure of the second oxygenator

Alagille Syndrome
ALGS
What is Alagille Syndrome?

- Etiology:
  - Alagille syndrome is an autosomal dominant mutation with variable expression localized to the JAG1 gene (20p12).
  - The JAG1 gene product functions as a ligand for the NOTCH-1 receptor
    - Interactions between JAG1 ligand and notch-1 receptor play an important role in the determination of ultimate cell fate

Alagille Syndrome – Cardiac

- Cardiovascular: The most common cardiac lesions:
  - Structural cardiac disease and hyperlipidemia or atherosclerosis contribute to morbidity and mortality of Alagille syndrome.
  - Stenosis within the pulmonary tree (peripheral pulmonic stenosis) with or without other structural lesions
  - Hemodynamically significant lesions include ASD, VSD, TOF, PDA and Pulmonary Atresia (PA).

Alagille Syndrome - Symptoms

- Prolonged neonatal Jaundice
- Liver biopsy findings reveal paucity of intrahepatic bile ducts
- Right sided heart disease
- Most often ALGS is hereditary

ALGS - Hepatic

- Bile Duct:
  - Moving the fluid (bile) from Liver and Gallbladder to small intestine where it helps to digest fat from food
Alagille Syndrome – Hepatic

- Hepatic disease is a key feature of Alagille syndrome.
- Most infants present with Cholestatic Jaundice.
- Hepatosplenomegaly is common
- Xanthomas (Hypercholesterolemia)
- Fat-soluble vitamin deficiencies and coagulopathies

Alagille Syndrome – Hepatic

- Cholestatic Jaundice:
  - Obstructed bile flow in the liver. Jaundice results from an excessive accumulation of bilirubin in the body
- Hepatosplenomegaly:
  - Infectious – enlargement of both liver and spleen
- Xanthomas (Hypercholesterolemia)
  - Fatty growths develop underneath the skin

Alagille Syndrome

Additional Abnormalities

- Skeletal:
  - Abnormalities of the vertebrae, ribs, and hands
- Neurologic:
  - Mild developmental delay and mental retardation

Alagille Syndrome

Additional Abnormalities...cont.

- Renal:
  - Renal dysplasia being the most common anomaly
  - Mutations in NOTCH2 and JAG1 contributes to the renal dysplasia and proteinuria
How is Alagille Syndrome Treated?

• Frequent consultations with Ophthalmologist, Hematologist, Cardiologist, Neurologist and Nephrologist are essential
• Medium Chain Triglycerides (MCT Oil) as nutritional supplement
• MCT: Aiding in weight loss, protecting the skin, optimizing digestion, boosting energy, strengthening the immune system, regulating hormones and increasing cognitive function

How is Alagille Syndrome Treated?

• Diet: Supplementation of fat-soluble vitamins is necessary
• Vitamin supplements for vitamin deficiencies
  • Problems with fat digestion and absorption may lead to a deficiency of fat-soluble vitamins (A, D, E and K).
  • ADEK Multivitamin and Calcium supplement

Incidence and Prevalence of ALGS

• Current estimate of incidence:
  • 1:30,000 - 1:45,000
• Current estimate of prevalence:
  • 1 in every 100,000 live births
• Prognosis:
  • Cardiac and liver disease alters life expectancy
Low density lipoprotein apheresis during cardiopulmonary bypass of hypercholesterolemic patients.

Miyawaki F1, Suma K, Shiroma K, Kaneko H, Doi T, Hayashi K, Azuhata K, Higashida R, Amano T, Satoh T.

Abstract

Treatment of children with homozygous familial hypercholesterolemia: Safety

for each procedure was to treat approximately two blood volumes as determined by the following equation: weight (kg) × 80 ml/kg × 2. The duration of each procedure was about 2 hours.

From the Department of Pediatrics and The General Clinical Research Center, The University of Texas Southwestern Medical Center at Dallas.

J Pediatr 1992; Volume 120, Number 6-892-898

Effect of Cardiopulmonary Bypass on Plasma Levels of Lipoprotein (a) in Hypercholesterolemic Patients

Murat GÜVENER,1 MD, Ibrahim UCAR,1 MD, Murat OZKAN,1 MD, Omer F DOGAN,1 MD, Fatih T SERİT,1 MD, and İlhan PASAOĞLU,1 MD

JPN Heart Jounal; Vol 42 (563-574), No 5; September 2001

Conclusion: An increased passage of Lp (a) to the subendothelium as a result of increased endothelial permeability during ischemic and reperfusion period is speculated. Also, the thrombotic effect of Lp (a) may be important for early graft occlusion and restenosis. Therefore pre or intraoperative treatment modalities such as LDL apheresis may be of considerable value in hypercholesterolemic patients to prevent excessive Lp (a) formation. Further investigations are necessary and studies with different designs should be conducted.
Pediatricians should identify children at highest risk for the development of accelerated atherosclerosis by screening cholesterol levels in children who

Dermatological manifestations: (a) Eruptive xanthoma, (b) tendon xanthoma, (c) tuberous xanthoma in a 12-year-old girl with homozygous familial hypercholesterolemia (FH). (d) Her father who was diagnosed with heterozygous FH with coronary artery disease after a coronary angiography.

Hypercholesterolemia after Tx

Hypercholesterolemia is common after pediatric heart transplantation: initial experience with pravastatin

Conclusions:

- Hypercholesterolemia is prevalent in pediatric cardiac transplant recipients.
- Pravastatin therapy is effective in decreasing TC and LDL levels, without side effects.
- Further studies are necessary to determine whether pravastatin treatment is beneficial in decreasing CAV.
Recommendations from Lit Reviews

• Summary: Plasmapheresis with preoperative exchange transfusion would benefit to conduct a safe CPB in this subgroup of patient population

Patient Presentation

History and Present Illness

• Alagille syndrome
  • Including bilateral peripheral pulmonary stenosis and functional bicuspid aortic valve
• Jaundice, cholestasis, elevated transaminases
• JAG1 mutation.
• Brain: hypoplasia or absence of the left transverse sinus
• On Respective Medications (Allergies: Milk)

Patient – Relevant Info

Preoperative Lab Values:
Total Cholesterol: 1347mg/dl
LDL: 687mg/dl
Triglycerides: 782mg/dl
Surgery Plan

• Scheduled surgery: PA augmentation and Coarctation Repair with cardiopulmonary bypass (CPB).
• Conventional normothermic CPB plan was discussed and established
• Per surgeon no XC and/or CPG

CPB Events

Pre CPB Concerns – HCT and ATIII

• Severe Hypercholesterolemia
• Baseline HCT: 21%
• Preoperative Antithrombin-III: >199%
• ATIII: Repeated in the OR: 196%

Pre CPB Concerns-Slope and HDR

• Baseline ACT was 127 seconds. There were no issues to maintain ACT above 480 seconds during bypass
• Heparin Dose Response (HDR) slope: 185sec/units/ml
• Projected heparin concentration was 1.7units/ml
• Heparin:
  • Loading dose: (4.1units/ml) - 4800U
  • During CPB: 4.1units/ml
CPB

- CAPIOX FX05 Oxygenator was used
- The CPB prime: Plasmalyte-A, packed red blood cell, heparin, mannitol, calcium chloride, sodium bicarbonate, 25% albumin
- After preBUF: Total priming volume: 390mL
- Prime – ABG: Post dilutional HCT ~30% and near normal variables

Bypass Events

- Loading dose Heparin – Routine Cannulation - ACT - CPB
- On bypass ACT, arterial and venous blood gases were done and it was good
- Blood from LA vent was VERY DARK
- CPB @20 min: Blood return from vent and the venous blood were very dark.

Bypass Events-cont.

- (SvO₂) was around 75% and lactate level was below 2mmol/L.
- The surgeon was notified about the extreme darkness of the blood.
- Methemoglobin - 0.33%

Bypass Events-cont.

- CPB @40 min:
  - Venous blood became very dark, lactate and pCO₂ level started elevating, SVO₂ dropped drastically (<50%)
  - pO₂ levels started dropping below 100mmHg with adequate art-flow, sweep and FiO₂ at 100%
Bypass Events-cont.

- Surgeon and the entire team were notified about the failing oxygenator
- Repeated blood gases (both arterial and venous) and all parameters were evaluated to justify the failing/failed oxygenator

Bypass Events-cont.

- CPB @45 min:
- Oxygenator - poor gas diffusing capability and compromising patient’s hemodynamics
- The surgical team: Discussed and concluded that the pathophysiological high fat content (hypercholesteremic) may deposits on the membrane and prevents gas exchange

Bypass Events-cont.

- After periodic evaluation of the functional integrity of the oxygenator, it has been decided to change the oxygenator
- CPB was terminated for 133 seconds and the defective oxygenator was replaced by a pre-primed oxygenator

Post Oxygenator Changeout

- Till 20 min everything was fine
- Within 20-25 minutes on second pump run with the new oxygenator, the 2nd oxygenator was giving early signs of failure
- The proximity to coming off bypass averted another change out
- Sighing Effect of the failing oxygenator helped temporarily
Post Oxygenator Changeout-cont.

- Patient was not cross-clamped or cardioplegic arrest was not achieved. The entire procedure was carried out on normothermic (34°C) CPB.

How to Define a Failing Oxygenator

- A-FLOW
- ALP
- MAP
- FiO2 and GasQ
- NIRS-R
- FLANK
- pCO2, pO2, SAO2, SVO2 and HCT

Failing Oxygenator

Arterial Flow vs. Gas Flow
**Follow-up: Failed Oxygenator**

- We sent the defective oxygenator to TERUMO for further evaluation to know the exact cause for the oxygenator failure.
- Alagille syndrome with hypercholesterolemia which may have resulted in the failure due to a lipid layer being covered oxygenator membrane and prevent gas exchange.

**Summary**

- Lessons Learned: CPB considerations in Alagille Syndrome:
  - CPB in Hypercholesterolemia: It’s risky and challenging.
  - Preop Plasmapheresis (exchange transfusion with 1-2 times CBV) could be a safe option to reduce the fat (high cholesterol) content.
  - Option of keeping another oxygenator in the circuit was suggested but we felt that was not safe since the fat content may cause the oxygenator to fail repeatedly.

**Summary cont.**

- Simulation drill of OXY change out much helpful.
- Be cautious with hypercholesterolemia in patients scheduled for redo-transplants and simultaneous multiple organ (LIVER) transplants.
- Plasmapheresis is the only safe option in Hypercholesteremic patients requiring CPB.
- 2 to 2.5 times more than normal ranges of fat content (cholesterol, LDL and Triglycerides is abnormal) is not safe.

**Thanks**