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Peri-Operative Stress-Related Cardiomyopathy Following Pediatric Liver Transplant– A Case Series

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Abstract

Perioperative stress related cardiomyopathy has been extensively described in adults undergoing liver transplantation to be associated with adverse outcomes. Reports of stress related cardiomyopathy among children is scarce and is usually associated with better clinical outcomes compared to adults. We describe 3 instances of pediatric liver transplantation who developed stress related cardiomyopathy during the perioperative period and had adverse clinical outcomes.

Keywords: Pediatric Liver Transplantation; Stress related cardiomyopathy; Heart failure.

Introduction

Stress cardiomyopathy is a syndrome characterized by transient regional systolic dysfunction of the left ventricle (LV), mimicking myocardial infarction, but in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture [1]. This was first described in Japan and was called Takatsubo Cardiomyopathy [2]. There are multiple synonyms for this condition like apical cardiomyopathy/stress-related cardiomyopathy/broken heart syndrome [2]. Ever since the first description from Japan, the condition has been described all over the world and is known to occur in the setting of any acute medical illness and surgery.

The majority of the cases of stress-related cardiomyopathy have been reported in adults [3]. Multiple factors precipitate this entity like emotional/physical stress, sepsis, surgical stress [4,5] owing to hemodynamic instability, prolonged surgical time, and massive blood loss [6]. Patients undergoing liver transplant can have all these factors in addition to the systolic and diastolic dysfunction [7] associated with chronic liver disease which makes them prone to develop stress-related cardiomyopathy during any period of their clinical course. This entity has been described well in adults undergoing liver transplantation [6]. However, its occurrence in the pediatric population is under-reported and poorly understood. We would like to present our experience with 3 children who developed stress-related cardiomyopathy during the post-operative period. The clinical details, course, and outcomes of each case are described in table 1.

Case Report

All 3 cases received standardized anesthesia management. After attaching non-invasive monitoring anesthesia was induced using fentanyl, propofol, and atracurium. The trachea was intubated using an appropriately sized cuffed endotracheal tube. This was followed by the placement of invasive lines under ultrasound guidance in the form of a right internal jugular vein and bilateral radial arterial lines. Maintenance of anesthesia was done using sevoflurane along with fentanyl and atracurium infusions. Intravascular volume replacement was done using balanced salt solutions and 5% human albumin. Packed red cells are transfused to keep the hemoglobin levels around 8 gm/dl. The administration of blood components was directed by the amount of clinical oozing present as well as the thromboelastogram trace.

Case 1

A 15-year-old male patient was admitted to our hospital with cryptogenic chronic liver disease and was evaluated for transplantation. The patient had PELD score of 20. No abnormality was detected in the pre-operative ECG whereas the ECHO revealed a mildly dilated left atrium with no evidence of systolic or diastolic dysfunction. The dissection phase was associated with massive bleeding from the large collaterals which required administration of large amounts of blood products (22 units of packed cells, 10 FFPs, 5 platelets, and 4 cryoprecipitates) along with an excessive requirement of inotropes by the end of surgery.

The patient was shifted to the post-transplant ICU for further management. Hypotension and sinus tachycardia with mild ST segment elevation was observed in the immediate post-operative period which was unresponsive to fluid challenge. He was started on methylene blue infusion suspecting refractory vasoplegia. A transthoracic ECHO was done at this point which revealed diminished left ventricular ejection fraction of 35% with apical ballooning, basal hyper contractility, SVR of 1400 with PA systolic pressures of 40 mm HG with right ventricular dysfunction. A Chest roentgenogram was suggestive of pulmonary

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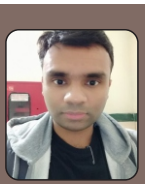
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edema associated with high oxygen requirements. His Trop T level was 0.154 ng/ml and NT pro-BNP was found to be elevated at 1543 ng/l.

Based on these findings we decided to postpone extubating the patient until clinical parameters improved. Pharmacological interventions in the form of nitroglycerine & milrinone infusions were started to reduce the afterload. Diuretic infusion was started to reduce the preload as well as to decongest the lungs. Low perfusion pressures (mean arterial pressures of 50 mm HG) were accepted. SVR was maintained between 800-900 dynes sec cm-5. The child was put on low tidal volume and moderate PEEP ventilation strategy. Urine output was maintained at 1 ml/kg/hour.

By the third day, there was a considerable improvement in hemodynamics, oxygenation indices, and chest x-ray findings. ECHO done at this stage showed an EF of 45 % and PA pressures of 30 mm Hg. He was gradually weaned and extubated by the end of the third day. On the 5th postoperative day he developed atrial fibrillation which was controlled by pharmacological cardioversion. Because of persistent hypokalemia furosemide was stopped and he was initiated on spironolactone.

His recovery was delayed owing to delayed graft function, wound sepsis, and critical illness myopathy. He was discharged on the 50th postoperative day with good graft function and muscle strength

Case 2

A 15-year-old boy who had undergone Kasai operation presented with decompensation for liver transplantation. Preoperative evaluation including ECG and ECHO was unremarkable. His intraoperative course was complicated with excessive bleeding and inotropic requirements. At the end of the surgery, he was shifted to the ICU with 3 inotropes (noradrenaline, vasopressin, and dopamine). ECHO was done which revealed an EF of 27% with apical ballooning of the left ventricle. He further went on to develop Atrial fibrillation which was controlled by amiodarone.

On the 3rd postoperative day, an ECHO was repeated, the findings of which were similar to the previous ECHO. He was febrile the entire day along with multiple episodes of ventricular tachycardia for which he underwent DC cardioversion. Cultures were sent and antibiotics were upgraded. Over the next few days, he seemed to respond to the therapy with a reduction in inotropic requirements and improvement in arterial blood gases which lead to extubation on the 5th post-operative day. However, he developed gram-negative sepsis during the further clinical course with deteriorating hemodynamics and liver functions and was reintubated on the 10th post-operative day. This time he went into multi-organ failure and ultimately expired on the 12th post-operative day.

Case 3

An 8-year-old male child presented to our hospital with Hepatitis A induced Fulminant liver failure. He was intubated and initiated on CRRT immediately on admission to our ICU given poor sensorium and elevated ammonia levels. His king's college criteria were suggestive of a poor outcome hence transplant workup was expedited. His preoperative cardiac evaluation was unremarkable.

His intraoperative period was uneventful and he was shifted to the intensive care unit for post-operative management. Initial signs showed favorable recovery of liver functions with correcting lactates, acidosis, INR, and ammonia. Sedation was switched off on the 2nd postoperative day and an attempt was made to wean him off mechanical ventilation.

At this point, it was noted that he had developed pulmonary edema following which an ECHO was done which showed global left ventricular hypokinesia with an ejection fraction of 27%. ECG at this showed flattening of t waves which persisted even after electrolyte abnormalities were corrected. Keeping in mind the pulmonary edema we continued CRRT with titrated ultrafiltrate in spite of normal ammonia levels. By POD5 his ejection fraction had improved to 45 % and we had stopped CRRT as there were no signs of fluid overload. He was taken off mechanical ventilation.

On the 9th postoperative day, he started developing recurrent episodes of vomiting, fever, and abdominal distention. A CT abdomen was done which were suggestive of dilated bowel loops. He was taken up for a re-look laparotomy which revealed an ileal perforation and gangrenous patches all over the small bowel and much of the large bowel. After primary repair of the perforation and a biopsy, he was shifted back to the ICU. Liposomal Amphotericin B was started based on clinical suspicion of invasive mucormycosis. However, he developed a cardiac arrest on the 10th postoperative day following which he could not be resuscitated. Biopsy report from the small intestine revealed mucormycosis posthumously.

Table 1: Summary of the Cases

Sl No	Demographics	Etiology	Presentation	ECG	TropI/Nt BNP	Echo	Outcomes
1	15 year, male	Cyrptogenic	Refractory hypotension & tachycardia	ST elevation	0.154ng/ml ; 1542 ng/l	EF 40 %	Delayed graft recovery
						Apical ballooning	Wound infection
						Basal hypercontractility	Critical illness myopathy
						Mild RV dysfunction	
2	15 year,male	EHBA	Hypotension, atrial fibrillation	VF+AF	3ng/ml;	27% EF with apical ballooning	Gram negative sepsis
					900ng/l	Mild RV dysfunction	MODS
							Death
3	8 year, male	Hepatitis A, ALF	Pulmonary oedema	T wave flattening	1.2ng/ml;	27 % EF, global LV hypokinesia	Invasive Mucormycosis
					1754ng/l		MODS
							Death

Abbreviations: EHBA – Extrahepatic Biliary Atresia, ALF – Acute Liver Failure, EF – Ejection Fraction, RV – Right Ventricle, LV – Left Ventricle, MODS – Multi Organ Dysfunction Syndrome

Discussion

Stress cardiomyopathy has been well described and extensively reported in adults. Early-onset HF after surgery directly reflects surgery-related stress to the myocardium or hemodynamic changes. Stress-related cardiomyopathy, therefore, cannot be missed as a cause of systolic heart failure in the perioperative period of non-cardiac surgery[8]. However, this condition has been under-reported in children, probably because most of the reported cases of stress-related cardiomyopathy in children were associated with a favourable clinical outcome[9].

We were able to identify 2 retrospective reviews of stress-related cardiomyopathy in the paediatric population[9,10]. Emotional stress was the most common precipitant of cardiomyopathy in both the reviews as opposed to physical stress in adults. The ECG changes, ECHO findings, and rise in serum biomarkers were similar in both the population groups[9,10]. However overall outcomes seemed to be better in the pediatric population as opposed to the adults which probably explains the relative lack of

awareness of this condition among children. According to the Mayo Clinical Criteria, the absence of an obstructive coronary lesion or evidence of acute plaque rupture is one of the hallmarks of the diagnosis of takotsubo cardiomyopathy[3]. We couldn't find any case reports of coronary angiogram done in children to confirm the diagnosis of stress-induced cardiomyopathy[9].

Management of this syndrome remains supportive and empirical. Initial management is similar to acute heart failure with therapy aimed at decreasing preload and afterload. Most of the studies in adults recommend the use of assist devices like IABP and VAD early in the clinical course keeping in mind the deleterious effects of intravenous inotropes and vasopressors in the setting of catecholamine excess[11]. In pediatrics however intravenous pressor agents are relatively safer as opposed to adults[9]. In addition to these decongestive measures like diuretics, anti arrhythmics and ACE inhibitors have been helpful[9].

An extensive literature review did not yield any reports of this condition among the pediatric population undergoing liver transplantation. We believe children undergoing liver transplantation are also susceptible to develop stress-induced cardiomyopathy owing to a variety of factors. Preoperative & post-operative emotional stress, substantial blood loss, massive transfusion, overall hemodynamic instability, high doses of vasoactive agents, pain, and agitation in the post-operative period are some of the factors that can precipitate stress-related cardiomyopathy. In addition to this, it has to be kept in mind that cirrhotic cardiomyopathy which is characterized by impaired systolic & diastolic response to stress and electrophysiological abnormalities[7] is often underappreciated in pediatric transplant population which may be a major precipitating factor for perioperative cardiac failure.

All of our cases had no apparent pre-existing cardiac abnormalities. The intraoperative period in 2 of the cases was stormy owing to excessive blood loss, hemodynamic instabilities, massive blood transfusion, and use of a high dose of vasoactive agents. It is safe to assume that these factors contributed to the development of stress-related cardiomyopathy in these patients. None of our patients required mechanical circulatory support and seemed to respond to conventional supportive measures. However, It is important to note that 2 cases had impaired and sluggish graft function post-operatively as well as progression into multi-organ failure. Even though one of our patients survived, his post-operative course was complicated with delayed graft function, wound infections and critical illness myopathy.

The differential diagnosis of acute heart failure in the pediatric population involves viral and autoimmune myocarditis[10]. We tried to rule out both these entities on all the 3 patients by sending autoimmune markers and viral markers which were negative in all the cases. Endomyocardial biopsy was not done in any of the cases.

Similar to adults it is interesting to note that echocardiographic findings in our cases were also on a spectrum ranging from classical apical ballooning to global hypokinesis[11]. It is important finding to note that 2 of our cases were associated with right ventricular dysfunction. Reports of Right ventricular involvement associated with stress-related cardiomyopathy has been rare. One retrospective review of 47 adult patients with stress-related cardiomyopathy found out RV dysfunction among 9 patients[12]. RV dysfunction had significantly reduced LVEF and graver outcomes[12]. The presence of a biventricular failure further complicates hemodynamic management. We refrained from introducing a PA catheter in both of our patients owing to the presence of frequent arrhythmias coagulopathy. The presence of RV dysfunction might be even more deleterious in LT patients since it might lead to graft dysfunction.

Conclusion

Even though it is a syndrome predominantly seen in adults, stress-related cardiomyopathy is not uncommon among the pediatric population. Perioperative stress-related cardiomyopathy in pediatrics presents the same way as in adults with similar clinical features. The outcomes of this condition seem to be good in a general pediatric population, but there is an under-appreciation of this condition in pediatric liver transplant recipients. Our limited experience with this condition in the pediatric liver transplant population suggests significant adverse outcomes. In light of this it is imperative that surgeons, anesthesiologists, and intensivists managing children undergoing liver transplant be aware of this entity, management, and implications.

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