45 Heterotaxy Syndrome

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Heterotaxy syndrome (HS) constitutes a constellation of defects based on issues with laterality in the body's organs. Several gene loci have been identified and initial genetic screening should be offered in every child diagnosed with HS. HS affects many organs but the most clinically relevant in infancy are cardiac defects, which can be severe.

In general, HS can be classified into right-atrial isomerism (RAI; asplenia) or left-atrial isomerism (LAI; polysplenia), depending on whether there's predominance of right-sided or left-sided structures, respectively. Patients with RAI have 2 morphologic RAs and lungs, and usually no spleen. On the contrary, patients with LAI have 2 morphologic LAs and lungs, in addition to polysplenia. This classification, although not 100% specific, can help categorize cardiac defects as the rhythm and venous anomalies follow the "duplicated" and "missing" atria. Patients with RAI have a higher likelihood of pulmonary venous issues and tachyarrhythmias. Those with LAI are more likely to lack sinus and AV nodes and are at a higher risk for bradyarrhythmias. They are also more likely to have an interrupted IVC with separate hepatic vein insertion.

Cardiac Involvement

Initial management of patients with HS focuses on palliating their cardiac defects. Very frequently, these patients have single ventricle cardiac lesions – most commonly, unbalanced atrioventricular septal defects (AVSD) with double-outlet right ventricle and malposed great vessels. Initial surgical/interventional management is based on whether the pulmonary valve is normal, stenotic, or atretic, and whether the patient needs a PA band or an additional source of pulmonary blood flow. Care must be taken to evaluate the pulmonary veins, as anomalous veins are frequently present and can require urgent repair if obstructed. It is important in the face of obstructed pulmonary veins not to over- or underestimate the amount of obstruction across the pulmonary valve. Patients will be more cyanotic due to elevated PVR and thus it is more helpful to evaluate the pulmonary valve anatomically than by the gradient obtained by echocardiography. Due to many of these patients having a single RV and AVSD-type atrioventricular valve, they are less able to handle pulmonary overcirculation, leading to ventricular dilation and increased AV valve regurgitation. For this same reason, care should be taken to assure adequate afterload reduction and diuresis.

Repair of total anomalous pulmonary venous return (TAPVR) on patients with HS can pose significant challenges for future single-ventricle palliation. In particular, the site of anastomosis of the pulmonary veins to the atria may be on the way of future Fontan completion. Patients with dextrocardia and a right-sided IVC (or hepatic veins) may require creation of an extracardiac Fontan conduit behind the mass of the heart (usually with a reinforced ringed Gore-Tex® graft).

Patients with HS are particularly prone to having arrhythmias (Niu et al. 2018). Those with RAI often have dual sinus and AV nodes that can set them up for reentrant supraventricular tachycardia and atrial tachycardia. Many patients will also have atrial

suturelines (after TAPVR repair) that can also put them at risk for atrial tachycardia. Those with LAI may present with complete heart block that will need to be paced early due to their associated anatomic cardiac abnormalities.

Extracardiac Involvement

Patients with HS tend to have extracardiac organ-system involvement. All patients with HS should be assumed to be functionally, if not anatomically, asplenic. Even those with polysplenia should be treated with prophylactic antibiotics as the splenules are generally hypofunctional. Patients are especially susceptible to infections with encapsulated organisms. The literature supports prophylactic treatment at least through 5 years of age. Patients should also receive the pneumococcal vaccine. At TCH, the standard of care is to treat with amoxicillin during this period. The absence of Howell-Jolly bodies (especially in infancy) can be misleading and nuclear medicine scanning can be helpful to assess splenic function beyond infancy, but it is not reliable before this time.

Inversion of abdominal organs should be evaluated and can affect appropriate placement of a nasogastric/orogastric tube. Care should be taken to look for location of the hepatic mass and stomach bubble on initial radiography. Malrotation is frequently diagnosed and all patients should have an upper GI series to confirm this diagnosis. Initially at TCH, all patients with malrotation underwent an elective Ladd's procedure after they had stabilized from their Glenn palliation or any surgeries required in infancy. The approach has recently changed after reviewing all patients and concluding that postoperative complications after Ladd's procedure (mainly bowel obstruction) exceeded the risk of developing a volvulus (Abbas et al. 2016). Patients are now not offered surgical intervention prophylactically. All parents are now instructed that children with HS should be evaluated with any abdominal pain, obstructive symptomatology, and/or vomiting to rule out volvulus as the cause. It is also important in these children to remember that their appendix is infrequently in the "normal" position and appendicitis can present without the classic right-lower-quadrant pain. Any abdominal pain associated with fever should be thoroughly worked up. If patients have any intra-abdominal surgery, they should have an incidental appendectomy at that time for this same reason.

Bronchial anatomy follows whether patients have RAI or LAI. Patients with RAI have bilateral trilobed lungs and eparterial bronchi, while patients with LAI have bilateral bilobed lungs and hyparterial bronchi. Generally, these anatomic changes in the lungs are of no clinical consequence though should be kept in mind in those with RAI as they can have bilateral upper lobe collapse. Patients with HS can also have problems with ciliary dyskinesia and should be evaluated for this, especially if they are having recurrent pulmonary infections or obstruction.

Long-Term Follow-Up

Long-term follow-up of patients with HS needs to take into account the systemic nature of the syndrome and that multiple organ systems may be involved. In patients with pulmonary vein repairs, special attention should focus on evaluating for reobstruction and

if present, proceeding with early intervention. Afterload reduction is important as the AV valves are more likely to become regurgitant than normal mitral or tricuspid valves.

It is important to control rhythm disturbances in these patients. Frequent Holter monitoring should be performed to evaluate for occult arrhythmias, as they are more frequent than in other cardiac lesions. Timing of the bidirectional Glenn procedure should be based on oxygen saturation and whether or not the patients have ventricular dysfunction and/or AV valve regurgitation, as these can improve with ventricular offloading. Some of these patients may undergo creation of a "pulsatile" Glenn (leaving some degree of prograde flow across the RVOT) due to the higher likelihood that systemic venous anatomy or PVR may preclude them from further single-ventricle palliation.

Evaluation prior to a Fontan procedure is focused at assessing hemodynamics, but also at evaluating anatomic variations that may make Fontan completion challenging, in particular systemic and pulmonary venous abnormalities. It is our preference to delay Fontan completion in these patients until symptomatically required rather than at a certain age, as baffling of anomalous venous structures is usually required and can be less challenging in larger patients. Preoperative assessment should also include evaluation for arteriovenous malformations and portosystemic shunts that can lead to cyanosis after the Fontan procedure. Portosystemic shunts should be occluded.

Transplantation is not automatically precluded in these patients as some patients can have reasonable outcomes. However, anomalies in systemic and pulmonary venous anatomy may preclude heart transplantation from a technical standpoint.

In general, the management of patients with HS involves early anatomic delineation and staged surgical palliations. Appropriate surveillance for the development of rhythm disturbances, ventricular dysfunction, significant AV valve regurgitation, or pulmonary venous obstruction is imperative. In addition, the clinician should be aware of the associated organ system abnormalities that can impact the lives of these children.

Suggested Readings

Abbas PI, Dickerson HA, Wesson DE. Evaluating a management strategy for malrotation in heterotaxy patients. J Pediatr Surg 2016;51:859-862.

Broda CR, Salciccioli KB, Lopez KN, et al. Outcomes in adults wiht congenital heart disease and heterotaxy syndrome: a single-center experience. Congenit Heart Dis 2019;doi: 10.1111/chd.12856.

Niu MC, Dickerson HA, Moore JA, et al. Heterotaxy syndrome and associated arrhythmias in pediatric patients. Heart Rhythm 2018;15:548-554.