Cardiac Corner: Heterotaxy and the Multi-organ System Failures Due to Disorders of "Sidedness"

Gil Wernovsky, MD; Benjamin Hopkins, OMSIV (Discussant)

The X-ray and clinical history described at the beginning of this journal (see page 18) are pathognomonic for patients with heterotaxy syndrome, sometimes called isomerism. I like to consider heterotaxy as a "multi-organ system failure" from an anatomic rather than a physiologic perspective. Heterotaxy usually presents to the cardiologist and neonatologist because of abnormal oxygen delivery, clinical findings, or both. It usually involves two or more organ systems at the time of presentation. Heterotaxy represents the downstream manifestations of a single abnormality during organogenesis.

"I like to consider heterotaxy as a "multi-organ system failure" from an anatomic rather than a physiologic perspective. Heterotaxy usually presents to the cardiologist and neonatologist because of abnormal oxygen delivery, clinical findings, or both. It usually involves two or more organ systems at the time of presentation. Heterotaxy represents the downstream manifestations of a single abnormality during organogenesis."

In the structurally normal heart (and patient), ciliary motion in the early phases of embryogenesis determines left-right differentiation. When ciliary motion is disordered, there is a loss of left-sided and right-sidedness of organ development, causing asymmetry or duplication of many organ systems. Disorders of "sidedness" frequently result in students and clinicians reciting a long or exhaustive list of potential abnormalities in this patient population. Please see Thiel and colleagues' position paper from the Pediatric Cardiac Intensive Care Society for an in-depth discussion from an expert review of the anatomic considerations, surgical considerations, noncardiac issues, and long-term outcomes in this challenging group of patients (1) (link).

Let us think about anatomic disorders of sidedness resulting in multi-organ system abnormalities. We can start at the head, moving through the ears, sinuses, lungs, heart, liver, spleen, abdomen, and genitourinary tract.

Nervous:

In the brain, it has been shown that there is increased extra-axial cerebrospinal fluid volume, delayed brain maturation, subtle dysplasia, including the hippocampus and olfactory bulb, and, in many patients, a higher composite dysplasia score (2).

Some delayed maturation may be due to ciliary dysfunction and abnormal circulatory flow from the structurally abnormal fetal heart. One relatively interesting relationship that's just been shown is an increased incidence of dyslexia in patients with ciliary disorders (3). In addition, there has not yet been conclusive research that traditional "left brain and right brain" findings differ in patients with heterotaxy.

Cardiac:

The heart is the organ that generally presents as the hallmark of heterotaxy. When one thinks about all of the things that could go wrong in the sidedness of the heart, many things come to mind. There may be one or two superior vena cava or one or two inferior vena cava; if there is one of either cava, it could be on either side. The anatomy of the atrium could look like a right atrium, anatomically, or a left atrium, anatomically. Usually, there are two atrioventricular valves. However, one of the more common abnormalities in heterotaxy is a common atrioventricular valve. Additionally, the two ventricles may be reversed, or there may be only one or two ventricles, with one being hypoplastic.

"The heart is the organ that generally presents as the hallmark of heterotaxy. When one thinks about all of the things that could go wrong in the sidedness of the heart, many things come to mind. "

Further, the pulmonary artery may be absent or severely stenotic, and the aortic arch may be on the right side. The pulmonary veins may be abnormally located on the right atrium or drain in an ipsilateral fashion. Finally, the conduction system may be abnormal. Typically, when there are two superior vena cava, there are two sinus nodes. There may be no sinus node when there is only a left superior vena cava, and AV node conduction, not surprisingly, can also be abnormal.

Although these abnormalities have been lumped under the terms asplenia/Right Atrial Isomerism and "poly"-splenia/Left Atrial Isomerism in the past, those terms are somewhat obsolete at this time, and it is best to describe the findings in detail, as there are many more exceptions to the rule.

"The next area that becomes clinically significant, particularly as the children age, is the respiratory tract's ciliary dysfunction. These patients struggle with frequent ear infections, sinusitis as children, bronchitis, and deeper respiratory infections."

Pulmonic:

The next area that becomes clinically significant, particularly as the children age, is the respiratory tract's ciliary dysfunction.

These patients struggle with frequent ear infections, sinusitis as children, bronchitis, and deeper respiratory infections. In addition to the functional abnormality of ciliary dysfunction, there are increased postoperative respiratory complications in heterotaxy patients with respiratory ciliary dysfunction (4). In the short term, primary ciliary dyskinesia affects postoperative recovery and has been associated with the increased need for tracheostomy (4).

In addition to functional abnormalities, the lungs may be abnormally structured. The right lung is normally a three-lobed structure, and the left is a two-lobed structure. There can be two anatomically right lungs, two anatomically left lungs, or a reversed nature of the normal lung lobar arrangement. In addition, the right pulmonary artery and left pulmonary artery take a typical course where, in structurally normal condition, the right pulmonary artery passes in front of the right main stem bronchus, and the left pulmonary artery traverses over the left main stem bronchus. These anatomic relationships are frequently abnormal in children with heterotaxy. Finally, the venous anomalies of the IVC and portal venous system can complicate cardiac reconstruction and may contribute either to pulmonary hypertension or pulmonary arteriovenous malformations.

"Some patients with anatomically two left atriums, "poly"-splenia, may develop signs of biliary atresia at the typical time frame long after a surgical intervention has been considered and undertaken (5)."

Gastrointestinal:

The liver is frequently involved in patients with heterotaxy, and there is often a propensity for gallstones. Some patients with anatomically two left atriums, "poly"-splenia, may develop signs of biliary atresia at the typical time frame long after a surgical intervention has been considered and undertaken (5). In addition, in the abdomen, at least 70% of patients have malrotation and will require a LADS procedure (5). They may present with volvulus and a small bowel obstruction.

There is a propensity for pancreatitis and an annular pancreas and, curiously, a higher incidence of diabetes mellitus (5). Duodenal and anal atresia affects approximately 10% to 15% of these children. Both duodenal and anal atresia are more common with bilateral right-sidedness. All patients have functional asplenia, even in the presence of "poly"-splenia. There is an increased risk of infection with encapsulated organisms, and lifelong antibiotic prophylaxis, similar to sickle cell disease, is recommended (5).

"The American Academy of Pediatrics recommends that pneumococcus and H. flu vaccines be given, in addition to seasonal vaccinations that should be considered, including influenza, salmonella, and meningococcus."

The American Academy of Pediatrics recommends that pneumococcus and H. flu vaccines be given, in addition to seasonal vaccinations that should be considered, including influenza, salmonella, and meningococcus.

"A single horseshoe kidney and a hypoplastic, dysplastic, or even solitary kidney are common. Due to ureteral abnormalities, patients with heterotaxy are predisposed to urinary tract infections, pelvic-ureteral obstruction, and nephrolithiasis."

Genitourinary:

Finally, there are genitourinary and reproductive abnormalities. A single horseshoe kidney and a hypoplastic, dysplastic, or even solitary kidney are common. Due to ureteral abnormalities, patients with heterotaxy are predisposed to urinary tract infections, pelvic-ureteral obstruction, and nephrolithiasis. In boys, there can be bilateral cryptorchism and infertility in many of the men. This has been described in the past as Kartagener's syndrome, with a risk of testicular cancer in young adults. The impact of the genitourinary system abnormalities might become more apparent with longer patient survival.

Survival:

Finally, it is essential to talk about counseling babies with a fetal diagnosis of heterotaxy. Frequently, the heart is the primary focus of our counseling, mainly as a result of the birth of a baby. As it relates to many of these babies, having a functionally univentricular heart and requiring staged reconstruction toward a Fontan operation (6).

"In heterotaxy, the five-year survival is only about 40% to 50% if there is one functioning ventricle (7). However uncommon, it is also essential to mention the abnormalities mentioned above, including the potential for respiratory infections, the potential for developmental disabilities, the potential need for abdominal surgery, and, in men, infertility issues."

In heterotaxy, the five-year survival is only about 40% to 50% if there is one functioning ventricle (7). However uncommon, it is also essential to mention the abnormalities mentioned above, including the potential for respiratory infections, the potential for developmental disabilities, the potential need for abdominal surgery, and, in men, infertility issues. Full body evaluation, prenatal or

System	Multi-organ System Failure	Specific in Left Atrial Isomerism	Specific in Right Atrial Isomerism
Nervous	CNS dysfunction		
Cardiac	Cardiac complexity generally determines the outcome. TAPVR particularly troublesome association	Two left atrial appendages, cardiac defects, congenital heart block, interruption of the IVC with azygous vein continuation.	Two right atrial appendages, severe cardiac defects, malposition of IVC with IVC and aorta parallel on the same side of the spine
Pulmonic	Pulmonary Hypertension	Bilateral bilobed lungs	Bilateral trilobed lungs
Gastrointestinal	Volvulus, biliary atresia	Polysplesia	Asplenia
Genitourinary	Horseshoe kidney, hypoplastic, dysplastic, or solitary kidney. Cryptorchidism, infertility in men		

Table 1. Disorders of "Sidedness"

antenatal, is necessary for the workup of patients found to have heterotaxy. Prenatal counseling for parents is challenging due to the ever-evolving nature of a multi-organ system dysfunction.

Suggested Reading:

1. https://pubmed.ncbi.nlm.nih.gov/36085154/
2. https://pubmed.ncbi.nlm.nih.gov/33731242/
3. https://pubmed.ncbi.nlm.nih.gov/32000924/
4. https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.202202-116OC

Answers for abnormal findings:

1. Dextrocardia.
2. Midline liver.
3. Right-sided UA line, indicative of right-sided aortic arch
4. Left-sided UV line, indicative of a left-sided IVC
5. As marked by the endotracheal tube, the trachea is deviated to the patient's left, another sign of a right-sided aortic arch.

References:

1. Teele SA, Jacobs JP, Border WL, Chanani NK. Heterotaxy Syndrome: Proceedings From the 10th International PCICS Meeting. World J Pediatr Congenit Heart Surg. 2015 Oct;6(4):616-29. doi: 10.1177/2150135115604470. PMID: 26467876.
2. Panigrahy A, Lee V, Ceschin R, Zuccoli G, Beluk N, Khalifa O, Votava-Smith JK, DeBrunner M, Munoz R, Domnina Y, Morell V, Wearden P, Sanchez De Toledo J, Devine W, Zahid M, Lo CW. Brain Dysplasia Associated with Ciliary Dysfunction in Infants with Congenital Heart Disease. J Pediatr. 2016 Nov;178:141-148.e1. doi: 10.1016/j.jpeds.2016.07.041. Epub 2016 Aug 26. PMID: 27574995; PMCID: PMC5085835.
3. Brandler WM, Paracchini S. The genetic relationship between handedness and neurodevelopmental disorders. Trends Mol Med. 2014 Feb;20(2):83-90. doi: 10.1016/j.molmed.2013.10.008. Epub 2013 Nov 23. PMID: 24275328; PMCID: PMC3969300.
4. Harden B, Tian X, Giese R, Nakhleh N, Kureshi S, Francis R, Hanumanthaiah S, Li Y, Swisher M, Kuehl K, Sami I, Olivier K, Jonas R, Lo CW, Leatherbury L. Increased postoperative respiratory complications in heterotaxy congenital heart disease patients with respiratory ciliary dysfunction. J Thorac Cardiovasc Surg. 2014 Apr;147(4):1291-1298.e2. doi: 10.1016/j.jtcvs.2013.06.018. Epub 2013 Jul 22. PMID: 23886032.
5. Loomba RS, Geddes GC, Basel D, Benson DW, Leuthner SR, Hehir DA, Ghanayem N, Shillingford AJ. Bacteremia in Patients with Heterotaxy: A Review and Implications for Management. Congenit Heart Dis. 2016 Dec;11(6):537-547. doi: 10.1111/chd.12395. Epub 2016 Jul 18. PMID: 27425254.
6. Escobar-Diaz MC, Friedman K, Salem Y, Marx GR, Kalish BT, Lafranchi T, Rathod RH, Emani S, Geva T, Tworetzky W. Perinatal and infant outcomes of prenatal diagnosis of heterotaxy syndrome (asplenia and polysplenia). Am J Cardiol. 2014 Aug 15;114(4):612-7. doi: 10.1016/j.amjcard.2014.05.042. Epub 2014 Jun 6. PMID: 24996551; PMCID: PMC4307386.
7. Alsoufi B, McCracken C, Schlosser B, Sachdeva R, Well A, Kogon B, Border W, Kanter K. Outcomes of multistage palliation of infants with functional single ventricle and heterotaxy syndrome. J Thorac Cardiovasc Surg. 2016 May;151(5):1369-77.e2. doi: 10.1016/j.jtcvs.2016.01.054. Epub 2016 Feb 26. PMID: 27085618.

Disclosure: *The authors have no conflicts of interests to disclose.*

NT

Corresponding Author



Gil Wernovsky, MD, FAAP, FACC
Senior Consultant in Pediatric Cardiology and Cardiac Critical Care
Children's National Hospital
Professor of Pediatrics
George Washington School of Medicine and Health Sciences
Washington DC, USA
Email: gwernovsky@childrensnational.org

Corresponding Author



Benjamin Hopkins, OMS IV
Western University of Health Sciences
College of Osteopathic Medicine of the Pacific
Email: Benjamin.Hopkins@westernu.edu