Heterotaxy Syndrome and Intestinal Rotation Abnormalities

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abstract

BACKGROUND: Infants with heterotaxy syndrome (HS) have abnormal lateralization of organs along the right-left body axis. Intestinal rotation abnormalities (IRAs) are a potential source of morbidity and mortality. For this study, our objective was to prospectively observe a cohort of infants with HS and determine the incidence and natural history of IRA.

METHODS: Infants ≤6 months of age with HS were enrolled in this prospective observational study. Exclusion criteria were other congenital abnormalities that necessitated abdominal surgery. HS was defined as any arrangement of organs that was not situs solitus or situs inversus along with associated congenital heart disease. The investigation for IRA was at the discretion of each participating center.

RESULTS: Infants were recruited from January 2012 to December 2016. Thirty-eight infants from 7 institutions were included; 22 infants had right isomerism and 16 infants had left isomerism. Twenty-nine infants (76%) were evaluated for IRAs; 21 of 29 evaluations (72%) were abnormal. Eight infants were investigated because of symptoms, and 21 infants were evaluated routinely. The median age at symptom presentation was 46 days (range: 5–171 days). Seven infants had a Ladd procedure; 4 were prophylactic, with 3 as part of a combined procedure, and 3 were emergent. No child suffered acute midgut volvulus over a median follow-up of 1.6 years (range: 0.06–4.93 years).

CONCLUSIONS: IRAs are common in infants with HS. Infants with symptoms presented by 6 months of age. There was no failure of expectant management resulting in midgut volvulus during a median follow-up of 1.6 years.

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WHAT'S KNOWN ON THIS SUBJECT: Intestinal rotation abnormalities (IRAs) are commonly associated with heterotaxy syndrome (HS) and may be an important source of morbidity. There is disagreement as to whether an asymptomatic infant with HS and IRA should have a prophylactic Ladd procedure.

WHAT THIS STUDY ADDS: This was the first multi-institutional study in which a cohort of infants with HS was prospectively observed. Children with symptomatic IRAs presented by 6 months of age, but not all children required a Ladd procedure. No child developed midgut volvulus or complications from the Ladd procedure.

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Children with heterotaxy syndrome (HS) have an abnormal lateralization of the abdominal and thoracic organs as well as isomerism of their atrial appendages.[1] They often also have complex congenital heart disease.[1] Children with HS may have intestinal rotation abnormalities (IRAs), which put them at risk for midgut volvulus.[2] IRAs are defined as any deviation from normal midgut rotation.[3] Advances in cardiac surgery have improved survival in children with HS such that there is increasing attention to IRAs and their management.

Historically, a diagnosis of IRA was followed by a Ladd procedure irrespective of the child's symptoms. There is agreement that any symptomatic child with IRA needs immediate surgical evaluation. The role of a prophylactic Ladd procedure in an asymptomatic child is unresolved. Recently, there has been a paradigm shift away from prophylactic Ladd procedures in infants with HS given the anesthetic risk associated with shunted single ventricle physiology, the low prevalence of volvulus in this group, and the higher prevalence of post–Ladd procedure complications, including small-bowel obstruction.[4–7] There is no published literature detailing the natural history of IRA in older patients with HS. IRAs in the non-HS population may present beyond infancy but tend to have an atypical presentation with chronic symptoms.[8,9]

The morbidity of an elective Ladd procedure in all asymptomatic infants needs to be balanced against the morbidity in the occasional infant who develops midgut volvulus and requires an emergency laparotomy. As this population continues to increase as a result of continuing advances in cardiovascular care, it is vital to devise an evidence-based treatment model. For this multi-institutional study, our objective was to prospectively observe a cohort of infants with HS and determine the incidence, spectrum of disease, and natural history of IRA and secondary midgut volvulus. We hypothesized that asymptomatic infants with HS and IRA would not benefit from a prophylactic Ladd procedure because the risks of a prophylactic intervention outweighed its potential benefit.

METHODS

This study was approved by the local ethics research board of each participating institution. Infants were recruited from 7 institutions across North America: Stollery Children's Hospital in Edmonton, Alberta; Alberta Children's Hospital in Calgary, Alberta; Royal University Hospital in Saskatoon, Saskatchewan; Health Sciences Center in Winnipeg, Manitoba; Children's Medical Center in Dallas, Texas; Advocate Children's Hospital in Oak Lawn, Illinois; and Children's Hospital and Medical Center in Omaha, Nebraska. Stollery Children's Hospital is the cardiac surgical referral center for 3 smaller children's hospitals staffed by fully trained pediatric cardiologists. The other 3 enrolling institutions are all congenital cardiac surgical centers.

HS was defined as any arrangement of internal thoracoabdominal organs that was not situs solitus or situs inversus with associated congenital heart disease.[10–12] HS was separated into isomerism of the right atrial appendages, typically associated with asplenia, which we term right isomerism (RI), and isomerism of the left atrial appendages, usually associated with polysplenia, which we term left isomerism (LI). Study inclusion criteria included a diagnosis of HS, an age of ≤6 months, and written informed consent from a parent or legal guardian. Families of infants with a prenatal diagnosis of HS were consented and enrolled into the study at their first presentation to hospital; for the vast majority of infants, this was immediately after birth. No infant was enrolled after symptomatic presentation. Exclusion criteria were other congenital abnormalities that necessitated abdominal surgery. Data were collected from each institution and entered into a secure Web application (research electronic data capture) that was designed and managed in Canada (University of Alberta, Edmonton, Canada).

Data were collected from local hospital medical records, including operative, radiologic, and echocardiographic records. Data collection included demographic data, cardiac and medical diagnoses, diagnostic imaging results, cardiac catheterization procedures, and cardiac and gastrointestinal surgeries. Infants were evaluated for IRA at the discretion of their treating medical team. IRAs were defined as any deviation from normal midgut rotation. Data revealed an indication for IRA evaluation, methods of evaluation, and evaluation results. Results were classified as positive (malrotation); negative (normal intestinal rotation); nonrotation (the small intestine is located primarily on the right side of the abdomen, and the large intestine is located primarily on the left side of the abdomen); or indeterminate (unable to determine intestinal rotation). IRA investigations were interpreted by local pediatric radiologists. Data in which the clinical course of the children was detailed were collected, including the performance of a Ladd procedure or other gastrointestinal surgeries, indications for a Ladd procedure (prophylactic, including those that were part of a combined procedure or an emergent procedure), complications after a Ladd procedure, and the development of a symptomatic intestinal obstruction in those children with IRA who did not have a Ladd procedure.

Continuous variables are presented as mean (SD) and median (interquartile range or range) as appropriate, and categorical variables are presented as counts (percentages). Fisher's exact test and unpaired *t* tests were used to calculate *P* values when applicable. *P* values of ≤.05 were considered statistically significant. Analyses were conducted by using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

Infants were enrolled from January 2012 to December 2016. Thirty-eight infants (53% boys) were included; 22 infants had RI, and 16 infants had LI (Table 1). Two infants with LI who also had duodenal atresia were excluded because they had open abdominal surgery in which a Ladd procedure was performed incidentally. Thirty-four infants (90%) had an antenatal diagnosis of HS; of the 30 infants (79%) with single ventricle physiology, 24 infants had an unbalanced atrioventricular septal defect with either the hypoplastic left or right ventricle, and 4 infants had atresia of an atrioventricular valve. Two infants (both with RI) had a balanced atrioventricular septal defect and were initially palliated with a systemic-to-pulmonary artery shunt for pulmonary atresia or severe pulmonary stenosis. The median (range) length of follow-up was 1.6 years (0.06–4.93 years).

Twenty-nine infants (76%) were evaluated for IRA; 8 were symptomatic, and 21 were asymptomatic. All infants were investigated by using upper gastrointestinal imaging (UGI); 94% had a UGI with a small bowel follow through. Twenty-one of the 29 infants who were evaluated (72%) had IRA; 14 infants had malrotation, and 7 had nonrotation. Eight infants were investigated because of concerning symptoms, which included not tolerating feeds (*n* = 3), vomiting (*n* = 2), bilious vomiting (*n* = 1), hematochezia (*n* = 1), and abdominal distention and tenderness (*n* = 1) (Table 2). The median (range) age at symptom presentation was 46 days (5–171 days). The oldest symptomatic infant presented at 171 days of age with nonbilious vomiting; the UGI demonstrated malrotation. A Ladd procedure was not performed, and the infant was managed expectantly with no further gastrointestinal symptoms (follow-up of 483 days).

TABLE 1 Cardiac Anatomy and IRAs of 38 Children With HS

Variable	RI (*n* = 22), *n* (%)	LI (*n* = 16), *n* (%)	*P*
Single ventricle physiology	21 (96)	9 (56)	.01
Symptoms of IRA	5 (23)	3 (19)	0.99
Investigated for IRA	15 (68)	14 (88)	.25
IRA	12 (80)[a]	9 (64)[b]	.43
Ladd performed	4 (18)	3 (19)	0.99
Deceased	7 (31)	2 (13)	.25

[a] *n* = 15.
[b] *n* = 14.

Of the 8 infants who were investigated because of symptoms, 7 had IRA (malrotation [*n* = 3] and nonrotation [*n* = 4]; Table 2). One infant had discrepant findings between the UGI and the operative findings. Three infants had a Ladd procedure: 2 infants had an emergent Ladd procedure at 5 days and 2 months of age, respectively, and 1 infant had a prophylactic Ladd procedure as part of a combined procedure with a peritoneal dialysis catheter insertion 45 days after the initial symptom presentation. No infant had findings of volvulus at their Ladd procedure. Of the 4 symptomatic infants with IRA who did not have a Ladd procedure (2 had symptoms of vomiting, and 2 were not tolerating their feeds), none presented with symptoms of intestinal obstruction. These children were managed for a median (range) of 1.6 years (1.32–3.1 years).

Twenty-one asymptomatic infants were routinely evaluated by using UGI; 14 (67%) had IRA (11 with malrotation and 3 with nonrotation). One infant with malrotation had an immediate prophylactic Ladd procedure. One infant with nonrotation by UGI had a prophylactic Ladd procedure as part of a combined procedure with a gastrostomy tube at 966 days of age. One infant with a UGI diagnosis of malrotation developed possible symptoms of intestinal obstruction, including irritability and episodic increases in his lactate, at 18 days of age after initial cardiac palliation. He had an emergent laparotomy and Ladd procedure that revealed incomplete rotation without bowel wall congestion, suggesting acute or intermittent volvulus.

Nine infants were not evaluated for IRA; 5 were too hemodynamically unstable to investigate, including 2 infants who died before the IRA investigation and 1 infant who presented with abdominal distention and a radiograph of free intraperitoneal air at 20 days of age. At the time of the emergent laparotomy and incidental Ladd procedure, she had nonrotation without volvulus or Ladd's bands. The remaining infants were not evaluated at the discretion of their referral institution. No families refused an investigation for IRA.

In total, 7 children had a Ladd procedure (4 had a prophylactic Ladd procedure, and 3 had an emergent Ladd procedure; Table 3). Five had single ventricle physiology at the time of their Ladd procedure; the Ladd procedure

TABLE 2 Description of 8 Symptomatic Infants With HS

Patient No.	Heterotaxy Type	Primary Cardiac Diagnosis	Symptoms Suggesting IRA	Age at Symptoms, d	UGI Results	Ladd Procedure Performed	Age at Ladd Procedure, d	Findings at Ladd Procedure
A4	RI	UAVSD, DORV, PS, TAPVR	Not tolerating feeds	121	Positive	No	—	—
C1	RI	Dextrocardia, UAVSD, DORV, PS, TAPVR	Vomiting	61	Positive	No	—	—
D1	LI	UAVSD, hypoplastic arch, interrupted IVC	Vomiting	171	Positive	No	—	—
D2	LI	Dextrocardia, UAVSD, PA, interrupted IVC	Hematochezia	38	Negative	No	—	—
E2	RI	UAVSD, PS, TAPVR	Abdominal distention and tenderness	5	Nonrotation	Yes	5	Nonrotation with wide mesentery and no volvulus; chylous ascites
E7	RI	AVSD, DORV, aorta anterior and to the right of pulmonary artery, PS, TAPVR	Not tolerating feeds	46	Nonrotation	Yes with PDC	95	Incomplete rotation without volvulus, inflammation, multiple jejunal perforations
E8	RI	Dextrocardia, L-looped ventricles, UAVSD, DORV, PS	Not tolerating feeds	46	Nonrotation	No	—	—
S3	LI	DORV, LAVV atresia, interrupted IVC	Bilious vomiting	23	Nonrotation	Yes	64	Nonrotation with Ladd's bands adhering duodenum to cecum and right colon

AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; IVC, inferior vena cava; LAVV, left atrioventricular valve; PA, pulmonary atresia; PDC, peritoneal dialysis catheter; PS, pulmonary stenosis; TAPVR, total anomalous pulmonary venous return; UAVSD, unbalanced atrioventricular septal defect; —, not applicable.

was performed before or after their initial palliative cardiac procedure (none were delayed until after a bidirectional superior cavopulmonary anastomosis). There were no findings of volvulus at the time of the Ladd procedure. There were no complications after the Ladd procedure. There was no statistical difference in the incidence of IRA between infants with RI and infants with LI (80% vs 64%; $P = .43$). There was no failure of expectant management of an abdominal catastrophe in those children with IRA who did not have a Ladd procedure.

Nine children died (7 had single ventricle physiology) at a median (range) age of 3.5 months (0.6–29 months). Survival in this series was higher in the cohort with LI (87%) compared with the cohort with RI (68%) although this did not reach statistical significance ($P = .25$). The cause of death was known in 8 children; 3 children died after a cardiac arrest because of previous limitations on their care, 2 children died of respiratory failure, 1 child died of chronic renal failure, 1 child died of a severe bleeding complication while on extracorporeal life support, and 1 child died after cardiac arrest with severe hypoxic-ischemic injury to the central nervous system.

DISCUSSION

IRAs are not a distinct entity but a continuum of abnormalities of the position and peritoneal attachment of the large and small bowel, which reflects a failure that occurs at any time in midgut development. In this study, we aimed to determine the incidence, spectrum of disease, and natural history of IRA in infants with HS as well as the incidence of secondary midgut volvulus in a multi-institutional prospective cohort of infants with HS. The main findings of this study include (1) a 72% incidence of IRA, which is consistent with previous literature[5,6,13,14]; (2) no failure of expectant management in asymptomatic infants (specifically, no infant developed volvulus); and (3) no difference in symptomatic presentation nor incidence of IRA between infants with RI and infants with LI.

The authors of a recent single-center series report an incidence of IRA of 60% to 83% in screened patients with HS.[5,6,13,14] The authors of two recent systematic reviews report similar results.[15,16] The first included 11 heterogeneous retrospective studies of 649 patients with HS.[15] Of the 44% of patients who were screened, 47% had IRA. Of the entire cohort, there was a 1.2% prevalence of volvulus, with no studies describing failure of observation. The second meta-analysis (24 studies, including 1433 patients with HS) suffers from similar limitations as Landisch et al[15] with heterogeneity in reporting overall incidence of IRA, detection rate of IRA after screening asymptomatic cases, prevalence of volvulus, and surgical

TABLE 3 7 Children Who Had a Ladd Procedure

Patient No.	Heterotaxy Type	Primary Cardiac Diagnosis	Screened for IRA	Reason for UGI	Symptoms	Age at Symptoms, d	UGI Results	Age at Ladd Procedure, d	Reason for Ladd Procedure	Degree of Malrotation	Presence of Volvulus	Complications After Ladd Procedure
A1	LI	UAVSD, d-TGA, PA, interrupted IVC	Yes	Routine screening	—	—	Positive	22	Prophylactic	Incomplete rotation	No	None
E2	RI	UAVSD, PS, TAPVR	Yes	Symptoms	Abdominal distention	5	Nonrotation	5	Emergent	Nonrotation	No	None
E4	RI	UAVSD, DORV, PA	Yes	Routine screening	—	—	Nonrotation	966	Prophylactic, combined procedure with GT	Nonrotation	No	None
E7	RI	AVSD, DORV, aorta anterior and to the right of pulmonary artery, PS, TAPVR	Yes	Symptoms	Not tolerating feeds	46	Nonrotation	95	Prophylactic, combined procedure with PDC	Incomplete rotation	No	None
S3	LI	DORV, LAVV atresia, interrupted IVC	Yes	Symptoms	Bilious vomiting	23	Nonrotation	64	Emergent	Nonrotation	No	None
S5	LI	Dextrocardia, AVSD, hypoplastic arch, interrupted IVC	No	—	AXR suggested free intraperitoneal air	20	—	20	Prophylactic, combined procedure with emergent laparotomy for query NEC	Nonrotation	No	None
S6	RI	UAVSD, DORV, PA, obstructed TAPVR	Yes	Routine screening	—	18	Positive	18	Emergent	Incomplete rotation	No	None

AVSD, atrioventricular septal defect; AXR, abdominal x-ray; DORV, double outlet right ventricle; d-TGA, dextro-transposition of the great arteries; GT, gastrostomy tube; IVC, inferior vena cava; LAVV, left atrioventricular valve; NEC, necrotizing enterocolitis; PA, pulmonary atresia; PDC, peritoneal dialysis catheter; PS, pulmonary stenosis; TAPVR, total anomalous pulmonary venous return; UAVSD, unbalanced atrioventricular septal defect; —, not applicable.

complications.[16] It reports a 58% incidence of IRA in screened patients. Both reviews report higher risks of perioperative complications than that of volvulus.[15,16] The reported risk of small bowel obstruction after a Ladd procedure is as high as 27%.[5,17,18] The incidence of postoperative complications after the Ladd procedure may be as high as 61%.[5,17,19]

There is controversy in the literature on whether every asymptomatic infant with HS needs to be investigated for IRA and, if present, whether an elective Ladd procedure should be offered. There is agreement that any symptomatic infant needs an immediate surgical evaluation. We believe that evaluating for IRA gives both the care team and the family additional information about patient risks, particularly if they live far from tertiary care. Heightened awareness to the complexity of this patient population is crucial to its management. The absence of IRA is useful information for the medical team, especially in those patients with single ventricle physiology who may have an atypical presentation of volvulus.[20] Families and primary care physicians need to be educated about the potential implications of abdominal or nonspecific symptoms and the risk of a possible abdominal catastrophe. Patients with single ventricle physiology may remain in the hospital beyond their first month of life. The natural history of IRA in the general population suggests that 80% of symptomatic patients present in the first month, and 90% present in the first year.[21,22] If they remain asymptomatic and have a close follow-up at discharge, they can be discharged from the hospital without receiving a prophylactic Ladd procedure. Similarly, if they remain asymptomatic at the time of their bidirectional cavopulmonary anastomosis (typically at 4–6 months of age), they are unlikely to require a Ladd procedure because the natural

history of IRA suggests a low risk of subsequent volvulus.

It is important to avoid overtreating those infants with HS who do not have a narrow mesentery given their increased perioperative risk of complications.[23,24] These risks continue into adulthood when presentation of IRA may occur with vague gastrointestinal symptoms.[8,9] Little is known about the natural history of IRA in patients with HS after infancy. This may be because patients die either of their cardiac disease or other morbidity secondary to HS (including IRA), they remain asymptomatic, or they are subject to publication bias. In a recent study, authors who used statistical analysis to assess the need for surgery in asymptomatic children and adults with IRA (but without HS) found that an observation without a prophylactic Ladd procedure was preferred among older patients.[25] Any increased surgical risk, as would be expected for any child with cardiac disease, further lowered the age threshold at which an observation was preferred over a prophylactic surgery. Another retrospective review of 170 patients with IRA described that 48% of patients presented as adults.[8] Of that group, the incidence of volvulus at the time of diagnosis was 12% (operative findings confirming volvulus that required an intestinal resection were not reported). This suggests that the natural history of IRA progressing to acute midgut volvulus is low. Although it is uncertain if we can extrapolate the non-HS experience to the population that has HS, health care providers should be suspicious of chronic abdominal symptoms that may be related to an undiagnosed IRA in older children and adults.

Papillon et al[26] suggest that the rotation variant predicts the width of the mesentery and the risk of volvulus. The intent to characterize the severity of malrotation has yielded inconsistent findings.[26] They and others have[26,27] separated IRA into distinct anatomic categories: (1) true malrotation with a narrow mesenteric stalk, (2) nonrotation with a broad mesentery, and (3) atypical rotation defined as malposition of the ligament of Treitz or duodenal malposition. Unfortunately, there is often discordance between the imaging and operative findings,[28] which is also noted in this study. In this study, the cohort was divided into categories of malrotation and nonrotation on the assumption that the nonrotated bowel would have a wide mesenteric base. That assumption is likely incorrect because our cohort includes infants with nonrotated intestines who developed symptoms suggestive of volvulus. Unfortunately, we have subsequently discovered infants with nonrotation both by UGI and direct inspection at the laparotomy who had a narrow mesentery. Even in the absence of a narrow mesenteric stalk, infants with IRA remain at risk for volvulus secondary to Ladd's bands. There are no specific tests that will accurately predict the width of the vascular pedicle. The addition of a contrast enema that reveals a mobile cecum and right colon may identify infants at a higher risk of volvulus secondary to a narrow vascular pedicle. Attempting to characterize IRA on the basis of the position of the duodenal-jejunal junction relative to the pylorus is less compelling than the duodenal-jejunal flexure that fails to cross vertebral pedicles and may signify a narrow vascular pedicle. UGI has been shown to be a sensitive imaging modality for the presence of IRA[29]; the presence or absence of symptoms should guide surgical decision-making.

It has been suggested that infants with LI have a lower incidence of IRA compared with infants with RI.[30] However, malrotation was defined on the basis of operative findings describing the presence of Ladd's bands and a narrow mesentery. This narrow operative definition misses the wide spectrum of IRA. There was no difference in IRA between infants with RI and infants with LI in the current study, which is similar to others.[14] Children with LI have a better cardiac prognosis with typically less severe congenital heart disease.[31,32] These data do not support differing expectant management in asymptomatic infants with HS on the basis of their variety of isomerism.

Although a multi-institutional study, the study size was small, reflecting the rarity of HS, which is estimated at a 1:10 000 ratio.[33] Symptomatic infants consistently presented before 6 months of age although eligibility for the study included an age <6 months; it is possible that older children with HS not included in this study may develop midgut volvulus beyond 6 months of age. Because the majority of enrolling institutions were tertiary congenital cardiac surgical centers, there is the possibility of referral bias in this study. Seventy-nine percent of infants had complex single ventricle physiology and needed neonatal palliation. In this study, we may have missed children with HS who had a less severe congenital heart disease that did not require cardiac surgery in infancy, or alternatively, we may have missed neonates who died of either volvulus or severe congenital heart disease before a surgical referral. Unfortunately, we were not able to evaluate 100% of infants, the majority because they were too unstable. Eighty percent of infants were cared for at a single cardiac surgical institute (Stollery Children's Hospital), where we have an ongoing dialogue with an engaged general surgical team, and as such, even symptomatic infants were carefully observed, and not all had a Ladd procedure. We cannot extrapolate

our experience of careful observation to other institutions.

CONCLUSIONS

IRAs are present in the majority of screened infants with HS. Infants with symptomatic IRA presented by 6 months of age. UGI is useful in diagnosing the presence of IRA and informing the family and medical team. The presence or absence of symptoms should guide surgical decision-making. Expectant management for the asymptomatic infant is reasonable because no infant managed as such developed midgut volvulus.

ABBREVIATIONS

HS: heterotaxy syndrome
IRA: intestinal rotation abnormality
LI: left isomerism
RI: right isomerism
UGI: upper gastrointestinal imaging

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