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Impact of gastrointestinal comorbidities in patients with right and left atrial isomerism

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Abstract

Background and aim: Heterotaxy syndrome, being right atrial isomerism (RAI) or left atrial isomerism (LAI), often presents with Congenital Heart Disease (CHD). Intestinal abnormalities, including malrotation are common. We assessed the spectrum of gut abnormalities and their impact on medium-term outcome in a cohort of patients with fetal and postnatal diagnoses of heterotaxy syndrome. *Methods:* We reviewed the cardiology records of heterotaxy syndrome patients from two centres, regarding the presence of CHD, time for cardiac intervention, presence of gastrointestinal abnormalities, and type/time of surgery. A questionnaire about gastrointestinal status was sent to patients <18 years old. Kaplan–Meier curves were derived for survival data and freedom from intervention. *Results:* Data were included for 182 patients (49 RAI and 133 LAI) of 247 identified. Questionnaires were sent to 77 families and 47 replied. CHD was present in all RAI and 61.7% of LAI cases. Thirty-eight patients had abdominal surgery (20.9%), similar for RAI and LAI (20.4% versus 21%, p> 0.99): Ladd procedure in 17 (44.7%), non-Ladd in 12 (31.5%), and both procedures in 9 (23.7%). Ten-year freedom from Ladd procedure for all was 86% for the whole cohort (RAI = 87%; LAI = 85%, p = 0.98). Freedom from any gastrointestinal surgery at 10 years was 79% for the whole cohort (RAI = 77%; LAI = 80%, p = 0.54). Ten-year freedom from cardiac surgery was 31% for the whole cohort (RAI = 6%; LAI = 43%, p < 0.0001). *Conclusions:* In our cohort, one in five patients required abdominal surgery, mostly in their first year of life, similar for RAI and LAI. Between 1 and 10 years of follow-up, the impact of gastrointestinal abnormalities on outcome was minimal. Medium term survival was related to CHD.

Heterotaxy syndrome refers to the abnormal arrangement of organs along the left–right axis that is neither situs solitus nor inversus.[1,2] Birth incidence is reported as 1:10,000.[3,4] Heterotaxy syndrome can be further divided in two diagnostic categories: right atrial isomerism (RAI) and left atrial isomerism (LAI). In LAI, there is dominance of left-sided structures, typically associated with multiple spleens (polysplenia), bilateral bilobed lungs, bilateral hyparterial bronchi, and two morphological left atria. The inferior vena cava is interrupted with azygos continuation to the superior vena cava. In RAI, there is dominance of right-sided structures with bilateral trilobed lungs, bilateral eparterial bronchi, and two morphological right atria. Asplenia is common and often there are bilateral superior vena cavas.[5] The cardiac development in heterotaxy is often abnormal and leads to a wide spectrum of cardiac defects. CHD is common in both LAI and RAI and often more complex in RAI.[6]

Heterotaxy syndrome is often associated with abnormal rotation and fixation of the intestine, termed malrotation. Gut malrotation is thought to occur in 40–90% of patients with heterotaxy syndrome.[7–12] Any disruption to the processes of rotation or fixation results in intestinal rotational abnormality of the small bowel. This is not a single distinct entity but rather a spectrum of disease that depends on the stage of intestinal rotation or fixation that was interrupted.[13,14] In its severe form, intestinal rotational abnormality results in a narrow mesenteric pedicle and predisposes to mid-gut volvulus, thus leading to small bowel ischaemia and infarction. Little is known regarding the diversity of intestinal disease in heterotaxy syndrome.[15]

The primary aim of this research project was to investigate the impact of gastrointestinal abnormalities on patients with heterotaxy syndrome, to inform prenatal counselling of heterotaxy syndrome cases with less severe form of CHD.

Methods

This is a retrospective study of patients with known RAI or LAI, identified from paediatric and fetal cardiac databases in our tertiary institutions, Royal Brompton Hospital and St George's University Hospital. The diagnosis of heterotaxy syndrome was determined by previous criteria reported in the literature.[16,17] We included patients born after 1971, the year when the paediatric cardiology service was established at the Royal Brompton Hospital. For those patients, we expected to have fully updated medical records from birth onwards. All available medical records were reviewed regarding abdominal symptoms, investigations, diagnosis, surgical interventions, and documentation of any related major complications. Definition of abdominal symptomatology was challenging as it often overlaps with cardiac symptomatology in neonatal life. Therefore, we only included cases where medical notes explicitly described symptoms of malrotation, namely vomiting, bilious vomiting, abdominal distention, and reported in the context of suspected malrotation. Information regarding presence of CHD, cardiac diagnosis, need, and time for cardiac surgery was also recorded.

Outcome (alive or dead) at the time of data review was noted and all live patients under the age of 18 years living in the United Kingdom were identified. A letter was posted to parents inviting them to complete a questionnaire (Supplementary materials 1 and 2) regarding their child's abdominal symptoms, date and time of any screening test for abdominal problems, date and type of any abdominal surgery, and known complications following surgery. Two different questionnaires were designed, which reflected if the child was known to have undergone previous abdominal surgery (Supplementary material 1) or not (Supplementary material 2), based on their medical records.

The study was approved by the National Research Ethics Committee (Reference: 15-SC-0504). The need for informed consent for retrospective review of data was waived, but consent was obtained from those contacted by post.

Statistical analysis

Categorical data are presented as number (n, %) and comparisons between groups are made using the chi-squared or Fisher's exact test. Numeric data are presented as median (interquartile range).

Kaplan–Meier survival curves were plotted to assess freedom from cardiac intervention, any gastrointestinal surgery, and Ladd surgery for the whole cohort and for RAI versus LAI patients. The Log-rank test was used to assess difference in freedom from intervention between these two groups. All tests were two-sided and significance was set at $p < 0.05$. The analysis was done using STATA version 14.1 and Prism 9 version 9.1.2 software.

Results

A total of 247 patients with the diagnosis of RAI or LAI were identified. Of these, 182 patients were included in this study and constituted our cohort. Sixty-five patients were excluded from the study due to insufficient information in medical notes (n = 45), patients being born before 1971 (n = 13), or the diagnosis of isomerism was unclear (n = 7). The oldest patient was born in 1971 and the youngest in 2015. A significant proportion of our cohort, 42.3% (77/182) presented due to abnormal findings in prenatal screening. The cardiac fetal scan diagnosis and non-cardiac comorbidities are presented in Table 1.

Letters and appropriate questionnaires were posted to patients that were alive and under 18 years old living in the United Kingdom (n = 77). A total of 45 (58%) families replied. Their answers were in agreement with the information obtained from the medical notes in all but one case, where the child had surgery for duodenal atresia and malrotation, which was not reported in the cardiac records.

Of the 182 cases, 133 patients had LAI (73.0%) and 49 had RAI (26.9%). CHD was present in all cases with RAI, compared to 61.7% of cases with LAI.

Gastrointestinal symptoms

Abdominal symptoms were not consistently documented in the records that go back to approximately a 50-year time span. Symptoms were recorded in 24.2% of patients (44/182). In the majority (29/44, 65.9%), symptoms developed during the first year of life. Four cases of duodenal atresia were suspected prenatally due to symptomatic polyhydramnios. The diagnosis was confirmed postnatally.

Gastrointestinal investigations

Abdominal investigations to rule out rotational abnormalities were carried out in 42 of 182 (23%) patients: 29 had an upper gastrointestinal contrast study and 13 underwent abdominal ultrasound. Twenty-two symptomatic patients were investigated: 12 had malrotation, but in 2 cases, surgery was not performed as patients died due to associated CHD. In eight patients, malrotation was excluded; however, two did have surgery due to persistent symptoms. Two additional patients had surgery, but the results of the investigations were not recorded. Of the 20 asymptomatic patients that were investigated, none was found to have malrotation.

Surgery (gastrointestinal)

From our total cohort, 38 patients (20.8%) had abdominal surgery, 28 of the 133 cases of LAI (21%) and 10 of the 49 patients with RAI (20.4%) (Tables 2 and 3). Thirteen presented with vomiting, which was bilious in two. Four cases presented antenatally with suspected diagnosis of duodenal atresia and were all postnatally confirmed and underwent successful surgery in the first few days of life. For the remaining surgical cases, no relevant symptomatology was reported in the cardiac notes. Of all surgical cases, 17 (44.7%) underwent the Ladd procedure only; nine (23.7%) had both Ladd and non-Ladd abdominal surgeries and 12 (31.5%) had non-Ladd surgery only (Table 2 and 3).

A total of 27 non-Ladd surgical procedures were performed in 21 patients. Nine had duodenal or intestinal atresia, six required gastrostomy insertion or gastropexy, six had Nissen's fundoplication, and four procedures were performed to treat biliary atresia and gall bladder pathology.

Follow up and outcome (Kaplan-Meier survival curves)

Of the initial cohort, 149 patients were alive. The median follow-up time was 8.9 years (interquartile range = 2.74–21.7). The median survival for patients without the need for cardiac intervention was 0.76 years, (interquartile range = 0.05–4.7). Figure 1a and b are Kaplan–Meier curves, showing freedom from cardiac intervention for the whole cohort and comparison between RAI and LAI, respectively. Ten-year freedom from cardiac surgery was 31%

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Table 1. Fetal cardiac scan findings and non-cardiac comorbidities

Number of patients	Prenatal cardiac diagnosis	Extracardiac findings
20	LAI, normal intracardiac anatomy	
3	LAI, AVSD	
2	LAI, partial anomalous pulmonary venous drainage	
2	LAI, normal intracardiac anatomy	Duodenal atresia
2	LAI, HLHS, bilateral SVCs	
2	RAI, AVSD, DORV	
1	LAI, normal intracardiac anatomy	Right-sided spleen
1	LAI, normal intracardiac anatomy	Right-sided stomach
1	LAI, normal intracardiac anatomy	Right-sided stomach, midline liver, asplenia
1	LAI, dextrocardia, RAA with aberrant left subclavian artery, fetal bradycardia	
1	LAI, normal intracardiac anatomy, fetal bradycardia	
1	LAI, dextrocardia, AVSD, coarctation of the aorta, bilateral SVCs, CHB	
1	LAI, AVSD, partial anomalous pulmonary venous drainage, CHB	Right-sided stomach
1	LAI, DIRV, DORV, RAA	
1	LAI, dextrocardia, morphological RV to the left, discordant VA connections, small perimembranous VSD, CHB	
1	LAI, normal intracardiac anatomy	Ventriculomegaly, partial agenesis of the vermis, enlarged cisterna magna
1	LAI, morphological RV to the left, pulmonary and hepatic venous return to left-sided LA, perimembranous VSD, RAA, bilateral SVCs	
1	LAI, dextrocardia, small perimembranous VSD	
1	LAI, aberrant right subclavian artery	Duodenal atresia, midline liver
1	RAI, dextrocardia, AVSD, DORV, morphological RV to the left, bilateral SVCs	
1	LAI, tetralogy of Fallot, bilateral SVCs	Right-sided stomach and spleen
1	LAI, bilateral SVCs	
1	LAI, AVSD, partial anomalous pulmonary venous drainage, dysplastic and regurgitant right AV valve, bilateral SVCs	
1	LAI, DORV with pulmonary atresia, duct supplying branch pulmonary arteries, bilateral SVCs	
1	LAI, aortic coarctation	Right-sided stomach
1	LAI, dextrocardia, left-sided RV, discordant VA connection	
1	LAI, DIRV, DORV, AVSD, PAPVD, bilateral SVCs	
1	LAI, discordant VA connections, perimembranous VSD, PAPVD,	
1	LAI, mitral stenosis, large perimembranous VSD, pulmonary atresia, RAA, bilateral SVCs	Right-sided stomach
1	LAI, tetralogy of Fallot, subaortic ridge	Right-sided stomach
1	LAI, common atrium, TAPVD, bilateral SVCs	
1	LAI, bilateral SVCs, VSD, pulmonary stenosis	IUGR
1	LAI, dextrocardia pulmonary veins to left-sided LA and systemic veins to right-sided LA, biventricular AV connection (right-sided LA to LV and left-sided LA to RV), pulmonary atresia, confluent branch pulmonary arteries supplied by large duct	
1	LAI, Tetralogy of Fallot	
1	LAI, dextrocardia, secundum ASD, bilateral SVCs	
1	RAI, AVSD, pulmonary atresia, TAPVD, bilateral SVCs	Polyhydramnios, right-sided stomach
1	RAI, AVSD, common AV valve to RV, pulmonary atresia, aorta arising from RV, aortopulmonary collatterals, supracardiac TAPVD, RAA	

(*Continued*)

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Table 1. (*Continued*)

Number of patients	Prenatal cardiac diagnosis	Extracardiac findings
1	RAI, mesocardia, absent left AV connection, single-outlet heart with aorta from RV	Right-sided stomach
1	RAI, AVSD, bilateral SVCs	
1	RAI, AVSD, pulmonary atresia, RAA, TAPVD	Central liver, ascites
1	RAI, dextrocardia, DIRV via common AV valve, hypoplastic LV, single outlet RV to aorta with pulmonary atresia, supracardiac TAPVD	
1	RAI, AVSD, DORV, TAPVD, bilateral SVCs	
1	RAI, AVSD with aorta from RV and pulmonary atresia, TAPVD, bilateral SVCs	Ascites Central liver
1	RAI, DIRV via common AV valve, DORV, TAPVD, single left SVC	
1	LAI, partial AVSD, bilateral SVCs	Duodenal atresia
1	LAI, coarctation of the aorta, muscular VSD	
1	RAI, AVSD	
1	RAI, partial AVSD, no VSD, left IVC to left-sided RA, bilateral hepatic venous connections, bilateral SVC drainage to atria	
1	RAI, supracardiac TAPVD, AVSD, double inlet and double outlet solitary indeterminate ventricle	
1	RAI, Biventricular AV connection with morphological RV to the left, DORV	
1	RAI, dextrocardia, systemic and pulmonary venous return to the left-sided RA, hypoplastic right-sided LV, DORV, RAA	
1	RAI, unbalanced AVSD with small LV, DORV, infracardiac TAPVD	

ASD = atrial septal defect; AV = atrioventricular; AVSD = Atrioventricular septal defect; CHB = complete heart block; CS = Coronary sinus; DIRV = Double inlet right ventricle; DORV = Double outlet right ventricle; HLHS = hypoplastic left heart syndrome; IUGR = Intrauterine growth restriction; IVC = Inferior vena cava; LA = left atrium; LAI = left atrial isomerism; LV = left ventricle; PAPVD = Partial anomalous pulmonary venous drainage; RA = right atrium; RAA = right aortic arch; RAI = right atrial isomerism; RV = right ventricle; SVC = Superior Vena Cava; TAPVD = total anomalous pulmonary venous drainage; VA = ventriculoarterial; VSD = ventricular septal defect.

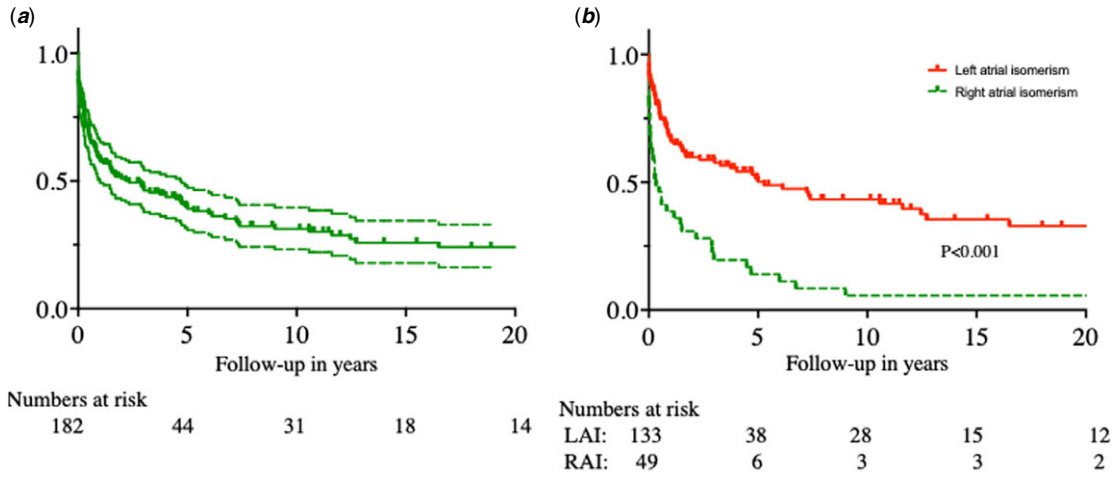

Figure 1. (a) Kaplan–Meier curve, showing freedom from cardiac intervention for the whole cohort. (b) Kaplan–Meier curve, comparing freedom from cardiac intervention for RAI versus LAI.

(95% CI = 23–39%) for the whole cohort, for RAI 6% (95% CI = 1–16%), and for LAI 43% (95% CI = 33–53%), $p < 0.0001$.

Figure 2a and b represent Kaplan–Meier curves for freedom from any gastrointestinal surgery for the whole cohort and comparison of RAI and LAI cohorts, respectively. Freedom from any gastrointestinal surgery for the whole cohort at 1 year was 87% (95% CI = 80–91%), for RAI 86% (95% CI = 76–96%) and for LAI 87% (95% CI = 81–92%), $p = 0.54$. Freedom at 10 years was 79% (95% CI = 72–85%) for all patients, and 77% (95% CI = 64–90%) and 80% (95% CI = 73–87%) for RAI and LAI respectively, $p = 0.54$. At 20 years, overall freedom from any gastrointestinal surgery was 77% (95% CI = 69–83%) for all patients, and 71% (95% CI = 54–89%) and 79% (95% CI = 71–87%) for RAI and LAI respectively, $p = 0.54$.

Figure 3a and b show freedom from Ladd procedure for the whole heterotaxy syndrome population and comparison of RAI

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Table 2. Demographic data and information related to heterotaxy, gastrointestinal symptoms, investigations, and surgery

Variable	Overall number of patients	RAI	LAI	p-Value
Number of patients	182	49	133	
Male, n (%)	79 (43.6%)	27 (55.1%)	52 (39.1%)	0.24
Patients diagnosed with CHD, n (%)	142 (78%)	49 (100%)	82 (61.7%)	0.04
Patients requiring cardiac intervention in neonatal period, n (%)	40 (21.9%)	18 (36.7%)	22 (16.5.%)	0.03
Patients requiring cardiac interventions in infancy (excluding neonatal period), n (%)	37 (20.3%)	9 (18.4%)	28 (21%)	0.84
GI symptoms, n (%)	44 (24%)	12 (24.5%)	32 (24%)	>0.999
Elective screening – not requiring surgery, n (%)	26/42 (61.9%)	3/9 (33.3%)	23/33 (69.7%)	
GI surgery, n (%)	38 (20.8%)	10 (20.4%)	28 (21.0%)	>0.999
Ladd surgery, n (%)	26 (14.2%)	6 (12.2%)	20 (15.0%)	0.84
Non-Ladd surgery, n (%)	12 (6.5%)	4 (8.2%)	8 (6.0%)	0.74

GI = gastrointestinal; LAI = left atrial isomerism; n = number; RAI = right atrial isomerism.

Table 3. Data regarding detailed description of the abdominal surgeries performed in right and left isomerism patients

Case – patient identification	Isomerism diagnosis	Ladd procedure	Non-Ladd GI surgery
1-(18)	LAI	+	–
2-(21)	LAI	+	–
3-(22)	LAI	–	Duodenal atresia
4-(23)	LAI	+	–
5-(26)	RAI	+	–
6-(32)	LAI	–	Cholecystectomy
7-(38)	LAI	+	1. Oesophageal atresia and tracheoesophageal fistula 2. Dilatation of oesophageal stricture 3. Ligation of tracheoesophageal fistula and primary anastomosis 4. Gastrostomy and Nissens fundoplication
8-(41)	LAI	+	Blood clot removal
9-(49)	LAI	+	–
10-(51)	RAI	+	1. Nissens fundoplication 2. Inguinal hernia
11-(52)	RAI	+	Gastrostomy insertion
12-(66)	LAI	+	Biliary atresia
13-(67)	LAI	–	Nissens fundoplication
14-(72)	RAI	–	1. Nissens fundoplication 2. Redo Nissens fundoplication and gastrostomy
15-(81)	LAI	–	PEG insertion
16-(88)	LAI	–	Gastrostomy
17-(90)	RAI	–	Nissens fundoplication and PEG insertion
18-(97)	LAI	+	–
19-(103)	LAI	+	–
20-(107)	LAI	+	–
21-(108)	LAI	+	–
22-(116)	LAI	+	–
23-(119)	LAI	–	Duodenal atresia
24-(120)	RAI	–	1. Duodenal atresia 2. Gastrostomy and jejunostomy

(*Continued*)

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Table 3. (*Continued*)

Case – patient identification	Isomerism diagnosis	Ladd procedure	Non-Ladd GI surgery
25-(122)	RAI	+	–
26-(128)	LAI	–	Intestinal atresia
27-(130)	LAI	+	Jejunostomy
28-(131)	RAI	+	–
29-(136)	RAI	+	Jejunostomy
30-(143)	RAI	–	Biliary atresia
31-(145)	LAI	+	–
32-(150)	LAI	+	–
33-(157)	LAI	+	Nissens fundoplication
34-(158)	LAI	+	–
35-(182)	LAI	+	–
36-(185)	LAI	+	–
37-(188)	LAI	+	Duodenal atresia and biliary atresia
38-(195)	LAI	–	Duodenal atresia

GI = gastrointestinal; LAI = left atrial isomerism; PEG = percutaneous endoscopic gastrostomy; RAI = right atrial isomerism; + = yes; – = no.

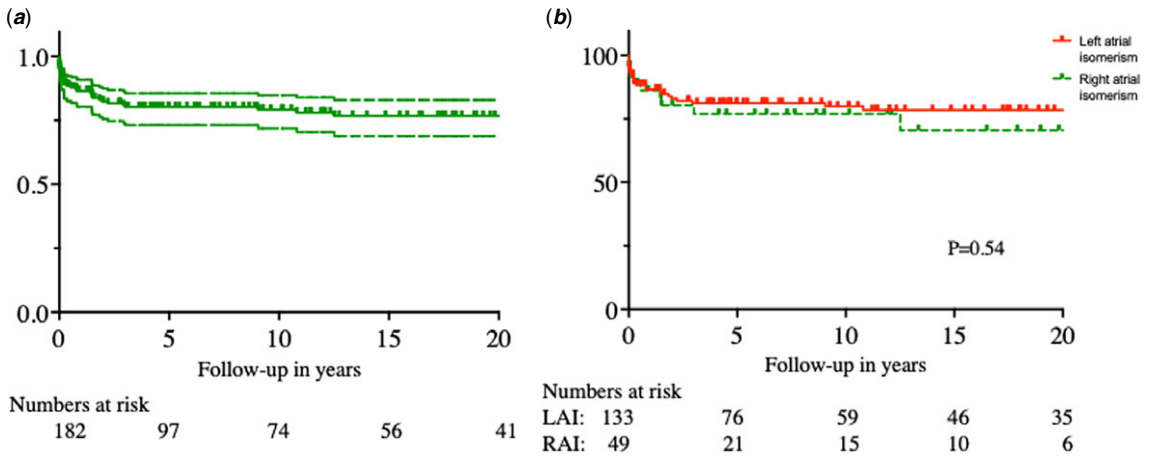

Figure 2. (***a***) Kaplan–Meier curve, showing freedom from any GI surgery for the whole cohort. (***b***) Kaplan–Meier curve, comparing freedom from any GI surgery for RAI versus LAI. GI: gastrointestinal.

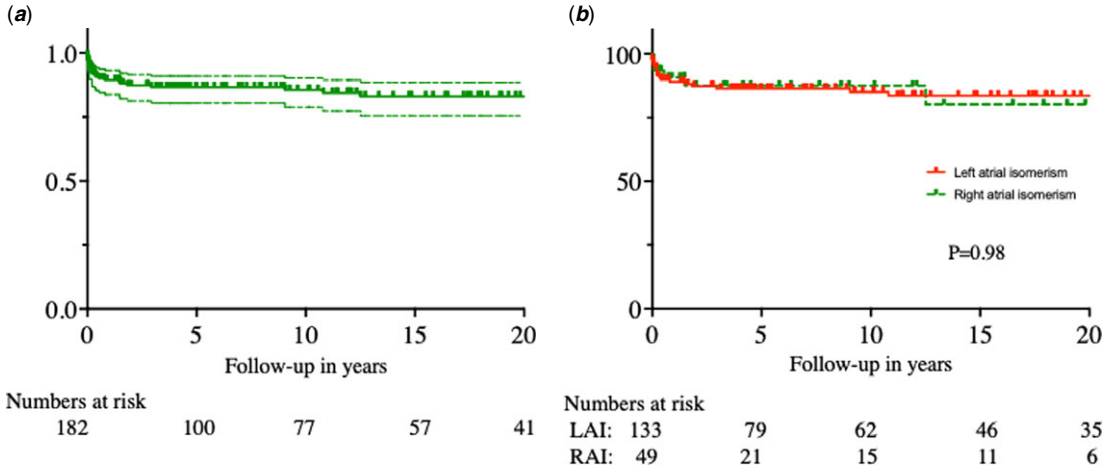

Figure 3. (***a***) Kaplan–Meier curve, showing freedom from Ladd surgery for the whole cohort. (***b***) Kaplan–Meier curve, comparing freedom from Ladd surgery for RAI versus LAI.

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and LAI cohorts, respectively. Freedom from Ladd procedure for the whole cohort at 1 year was 89% (95% CI = 84–93%), for RAI was 91% (95% CI = 77–96%), and for LAI was 89% (95% CI = 82–93%), p = 0.98. Overall freedom from Ladd procedure at 10 years was 86% (95% CI = 79–90%), for RAI 87% (95% CI = 72–94%), and for LAI 85% (95% CI = 77–90%). At 20 years freedom from Ladd procedure was overall 83% (95% CI = 78–91%) for the whole cohort, for RAI 80% (95% CI = 57–92%) and for LAI 83% (95% CI = 76–89%), p = 0.98.

Discussion

Our study comprises to date the largest series of heterotaxy syndrome patients from cardiology hospital databases, exploring combined cardiac and gastrointestinal outcomes. The medium-term gastrointestinal-related outcome for patients with heterotaxy syndrome is encouraging. In our series, approximately 20% required gastrointestinal surgery due to symptoms. Freedom from any gastrointestinal surgery at 10 years was almost 80% reflecting low impact on outcome. This information is useful to guide parental counselling following antenatal diagnosis of heterotaxy syndrome, especially because cases of LAI with no associated major CHD are increasingly identified prenatally.[18] Our results indicate the spectrum of gastrointestinal morbidity. We have shown that among operated cases, the Ladd procedure for classic malrotation was required in approximately 2/3 of cases, whereas non-Ladd interventions were performed in about half, including surgery for intestinal atresia in 43% of operated cases.

The mechanisms regulating abdominal lateralisation are complex and yet not fully understood. Rotation of the intestine in the embryo is a long process starting during the 5th week of gestation and continuing into infancy[14] and is defined by genetic and molecular factors.[19] The exact pathophysiological pathway that leads to the increased need for non-Ladd abdominal surgery and particularly for duodenal atresia in this patient group has not been elucidated yet, although there have been previous reports.[14] The continuum of the embryological intestinal rotation has been elaborately described and gives insight into the mechanical aspects of the spectrum of the intestinal rotational abnormality. It can be presented as movement of two leading loops, the duodenojejunal and the cecocolic loop, around the superior mesenteric artery through an arc of 270 degrees in a counterclockwvise direction.[20] The artery runs at right angles with the posterior wall and is to be considered the axis of rotation. The duodenojejunal loop starts superior to the superior mesenteric artery and comes to lie to the left of the artery. The cecocolic loop starts inferior to the artery, lying on the right of the artery. Any disruption in the process of rotation tends to prevent attachment of the mesentery (fixation) of the small and large bowel, resulting in mobile intestine and predisposing to volvulus.[20] Abnormalities due to the failure of rotation and/or fixation can occur at any phase of the above-described process and may involve only a part or all of the mid-gut. This leads to several variations of malrotation and/or malfixation and accounts for the spectrum of clinical presentations varying in severity from asymptomatic malrotation to complete non-rotation, namely atresia at multiple intestinal levels.

We found no significant difference in gastrointestinal comorbidity between cases of RAI and LAI. This is in agreement with Lim et al.[6] Nevertheless, Hill et al,[15] showed that malrotation was seen more often in RAI than LAI among patients who underwent abdominal exploration. The difference could be due to the smaller size cohort in their study (n = 38) or different characteristics of the populations studied.

The overall better cardiac outcome in LAI compared to RAI is well known.[6,21,22] In accordance with this, our 10-year freedom from cardiac surgery was 31%, with striking difference between RAI and LAI (6% versus 43%, p < 0.0001). This also highlights the need to better understand the risk faced by LAI patients related to potential gastrointestinal complications.[23]

Although the existing literature comprises several articles regarding the outcome of heterotaxy syndrome patients, there is controversial quantification of the impact of gastrointestinal abnormalities. Escobar-Diaz et al offers a comprehensive study on the outcome of patients diagnosed prenatally, and reports increased hazard ratio for postnatal death when extracardiac anomalies (gastrointestinal anomalies, genetic defects, Central Nervous System anomalies, and others) are present, with no subgroup analysis regarding gastrointestinal morbidity.[21] In a univariate analysis and in the multi-variate analysis model excluding the variable of the birth weight from Gilljam et al, biliary atresia and gastrointestinal abnormalities were associated with increased mortality.[24] This is not supported by other studies.[6,25]

Our study contributes to current literature. It comprised a larger patient cohort, with a longer follow-up time and included questionnaires to families along with the retrospective review of patients' records. We sought to elaborate on the impact of gastrointestinal disease on morbidity and mortality, offering an overview of the symptomatology and investigations recorded, the gastrointestinal procedures undertaken, and event-free survival from cardiac and gastrointestinal surgery during an average period of 10 years (a span of 2.74–21.7 years) in the LAI and RAI patient cohort.

Gastrointestinal management in heterotaxy syndrome has been controversial,[5,18,21] with no consensus concerning screening asymptomatic patients[5,12,15,25,26] or operating asymptomatic malrotation.[4,5,11,12,14,27,28] Concerns exist about higher morbidity associated with the Ladd procedure in asymptomatic patients including post-operative small bowel obstruction,[27] which needs to be balanced against the risk of mid-gut volvulus in the unoperated malrotation. In our study group, there were no major gastrointestinal surgical complications, but no patient was treated prophylactically. There was no patient presenting with acute mid-gut volvulus. This is in agreement with a review by Elder and colleagues.[29] However, in view of the design of this study, the optimal treatment strategy for gastrointestinal disease cannot be gauged from our series. A larger, prospective series is needed to determine an evidence-based treatment paradigm.[30]

Limitations of our study include the retrospective review of the paediatric cardiology notes, particularly due to occasional brief reports on abdominal symptomatology and complications after gastrointestinal procedures. This is likely due to changes over time in the understanding of the importance of the association between CHD and gastrointestinal abnormalities in the heterotaxy syndrome. Therefore, we only included cases where medical notes explicitly described symptoms of malrotation, namely vomiting, bilious vomiting, and abdominal symptoms, and were reported in the context of suspected malrotation. We tried to overcome this limitation, by including relevant questions on the symptomatology and on the surgical complications in the questionnaires we sent to parents. For patients who died from CHD in the neonatal period, autopsy findings to confirm or not the presence of malrotation are

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not available. Although death was mostly attributable to cardiac cause, it is impossible to completely exclude the stress of surgery as an impetus for abdominal decompensation.

Conclusions

In our cohort, one in five patients required abdominal surgery, the majority in their first year, similar to RAI and LAI. Between 1 and 20 years of follow-up, the impact of gastrointestinal abnormalities on outcome was minimal. Medium term survival was related to CHD.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation [UK Medicines for Human Use (Clinical Trials) Regulations] and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional National Research Ethics Committee (Reference: 15-SC-0504).

References

1. Raya A, Izpisua Belmonte JC. Insights into the establishment of left-right asymmetries in vertebrates. Birth Defects Res C Embryo Today 2008; 84: 81–94.
2. Raya A, Izpisua Belmonte JC. Sequential transfer of left-right information during vertebrate embryo development. Curr Opin Genet Dev 2004; 14: 575–581.
3. Lin AE, Ticho BS, Houde K, Westgate MN, Holmes LB. Heterotaxy: associated conditions and hospital-based prevalence in newborns. Genet Med 2000; 2: 157–172.
4. Salavitabar A, Anderson BR, Aspelund G, Starc TJ, Lai WW. Heterotaxy syndrome and intestinal rotational anomalies: impact of the ladd procedure. J Pediatr Surg 2015; 50: 1695–1700.
5. Yu DC, Thiagarajan RR, Laussen PC, Laussen JP, Jaksic T, Weldon CB. Outcomes after the Ladd procedure in patients with heterotaxy syndrome, congenital heart disease, and intestinal malrotation. JPediatrSurg 2009; 44: 1089–1095.
6. Lim J, McCrindle B, Smallhorn J, et al. Clinical features, management, and outcome of children with fetal and postnatal diagnoses of isomerism syndromes. Circulation 2005; 112: 2454–2461.
7. Nakada K, Kawaguchi F, Wakisaka M, Nakada M, Enami T, Yamate N. Digestive tract disorders associated with asplenia/polysplenia syndrome. J Pediatr Surg 1997; 32: 91–94.
8. Ditchfield MR, Hutson JM. Intestinal rotational abnormalities in polysplenia and asplenia syndromes. PediatrRadiol 1998; 28: 303–306.
9. Strouse PJ. Disorders of intestinal rotation and fixation ("malrotation"). Pediatr Radiol 2004; 34: 837–851.
10. Ferdman B, States L, Gaynor JW, Hedrick HL, Rychik J. Abnormalities of intestinal rotation in patients with congenital heart disease and the heterotaxy syndrome. Congenit Heart Dis 2007; 2: 12–18.
11. Tashjian DB, Weeks B, Brueckner M, Touloukian RJ. Outcomes after a Ladd procedure for intestinal malrotation with heterotaxia. J Pediatr Surg 2007; 42: 528–531.
12. Graziano K, Islam S, Dasgupta R, et al. Asymptomatic malrotation: diagnosis and surgical management: an american pediatric surgical association outcomes and evidence based practice committee systematic review. J Pediatr Surg 2015; 50: 1783–1790.
13. Pockett CR, Dicken B, Rebeyka IM, Ross DB, Ryerson LM. Heterotaxy syndrome: is a prophylactic ladd procedure necessary in asymptomatic patients? Pediatr Cardiol 2013; 34: 59–63.
14. McVay MR, Kokoska ER, Jackson RJ. Jack Barney Award. The changing spectrum of intestinal malrotation: diagnosis and management. Am J Surg 2007; 194: 712–717, discussion 718-9.
15. Hill SJ, Heiss KF, Mittal R, et al. Heterotaxy syndrome and malrotation: does isomerism influence risk and decision to treat. J Pediatr Surg 2014; 49: 934–937, discussion 937.
16. Cohen MS. Clarifying anatomical complexity: diagnosing heterotaxy syndrome in the fetus. Prog Pediatr Cardiol 2006; 22: 61–70.
17. Van Praagh S, Santini F, Sanders S. Cardiac malpositions with special emphasis on visceral heterotaxy (asplenia and polysplenia syndromes). In: Keany JF, Lock JE, Fyler DC (eds). Nadas's Pediatric Cardiology, 2nd edn. Saunders Elsevier, Philadelphia, 2006: 589–608.
18. D'Emidio L, Carvalho JS. Left isomerism in the fetus: is it always bad news? frequency andd outcome of cases in the 'normal heart'. Ultrasound Obst Gyn 2007; 30: 475–475.
19. Kloesel B, DiNardo JA, Body SC. Cardiac embryology and molecular mechanisms of congenital heart disease: a primer for anesthesiologists. Anesth Analg 2016; 123: 551–569.
20. Snyder WH, Chaffin L. Embryology and pathology of the intestinal tract: Presentation of 40 cases of malrotation, From the Surgical Service of Los Angeles Childrens Hospital and the University of Southern Califonal School of Medicine, 1954, 368–379.
21. Escobar-Diaz MC, Friedman K, Salem Y, et al. Perinatal and infant outcomes of prenatal diagnosis of heterotaxy syndrome (asplenia and polysplenia). Am J Cardiol 2014; 114: 612–617.
22. Serraf A, Bensari N, Houyel L, et al. Surgical management of congenital heart defects associated with heterotaxy syndrome☆. Eur J Cardio-THORAC 2010; 38: 721–727.
23. Pepes S, Zidere V, Allan LD. Prenatal diagnosis of left atrial isomerism. Heart (British Cardiac Society) 2009; 95: 1974–1977.
24. Gilljam T, Mccrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of left atrial isomerism over a 28-year period at a single institution. J Am Coll Cardiol 2000; 36: 908–916.
25. White SC, Dean PN, McGahren ED, Gangemi JJ, Vergales J. Malrotation is not associated with adverse outcomes after cardiac surgery in patients with heterotaxy syndrome. J Pediatr Surg 2018; 53: 1494–1498.
26. Papillon S, Goodhue CJ, Zmora O, et al. Congenital heart disease and heterotaxy: upper gastrointestinal fluoroscopy can be misleading and surgery in an asymptomatic patient is not beneficial. J Pediatr Surg 2013; 48: 164–169.
27. Pockett CR, Dicken BJ, Rebeyka IM, Ross DB, Ryerson LM. Heterotaxy syndrome and intestinal rotation abnormalities: a survey of institutional practice. J Pediatr Surg 2013; 48: 2078–2083.
28. Choi M, Borenstein SH, Hornberger L, Langer JC. Heterotaxia syndrome: the role of screening for intestinal rotation abnormalities. ArchDisChild 2005; 90: 813–815.
29. Elder CT, Metzger R, Arrington C, Rollins M, Scaife E. The role of screening and prophylactic surgery for malrotation in heterotaxy patients. J Pediatr Surg 2014; 49: 1746–1748.
30. Tan YW, Khalil A, Kakade M, et al. Screening and treatment of intestinal rotational abnormalities in heterotaxy: a systematic review and Meta-Analysis. J Pediatr 2016; 171: 153–62 e1-3.

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