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Original Article

Clinical characteristics of heterotaxy syndrome with congenital heart defects: A ten-year single-center experience

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Abstract

Aim: Congenital heart defects (CHDs) are a major component of heterotaxy syndrome (HS), contributing significantly to high morbidity and mortality. The anatomical variability, surgical complexity, and poor prognosis of HS-associated CHDs present major clinical challenges.
Material and Methods: We retrospectively reviewed 292 patients diagnosed with HS and CHDs at The First Hospital of Tsinghua University between January 2014 and December 2023. Demographic information and cardiac imaging data were collected to analyze the spectrum of cardiac malformations, spleen anatomy, sex distribution, and the frequency and distribution of major structural abnormalities.
Results: The cohort included 292 patients (mean age 6.8±8.7 years), with females accounting for 40.8%. Dextrocardia was present in 50%. The asplenia type was most common (42.8%), followed by unisplenia (41.8%) and polysplenia (15.4%). The most frequent cardiac malformations were single ventricle (61.9%), conotruncal anomalies (54.5%), and pulmonary stenosis (42.8%). The overall incidence of anomalous pulmonary venous connection was 7.8%, with total anomalous pulmonary venous connection (TAPVC) accounting for 6.8%. Gender analysis revealed a significantly higher proportion of males in the asplenia group (66.4% vs. 33.6%, $P<0.05$) and in the unisplenia group (59.0% vs. 41.0%, $P<0.05$). Although females were more frequent in the polysplenia group (57.8% vs. 42.2%), the difference was not statistically significant ($P>0.05$).
Conclusion: HS with CHDs presents with complex and diverse anatomical abnormalities and is associated with challenging management and poor prognosis. This ten-year single-center study provides a comprehensive overview of the clinical spectrum of HS-associated CHDs and reveals significant sex differences among patients with asplenia, unisplenia, and polysplenia. These findings may contribute to clinical classification, preoperative assessment, and individualized management strategies.

Keywords: Heterotaxy syndrome, congenital heart defect, splenic abnormality

INTRODUCTION

Heterotaxy syndrome (HS) is a rare congenital disorder characterized by abnormal arrangement of thoracoabdominal organs along the left–right body axis (1), with an estimated prevalence of approximately 1 in 10,000 live births (2). HS frequently involves cardiac anomalies, which account for 3%–6% of all congenital heart defects (CHDs) (3). These complex malformations are the leading cause of morbidity and mortality in HS patients (4).

HS is traditionally categorized into right atrial isomerism (RAI) and left atrial isomerism (LAI), based on atrial appendage morphology. RAI is typically associated with asplenia, midline liver, and bilateral trilobed lungs with eparterial bronchi, whereas LAI is characterized by polysplenia, midline liver, and bilateral bilobed lungs with hyparterial bronchi. However, increasing evidence suggests that atrial appendage morphology, bronchial pattern, and splenic anatomy often do not correlate perfectly (5), limiting their utility in guiding diagnosis and management. Therefore, we conducted a 10-year retrospective review to better

characterize the clinical features of HS and inform surgical strategies.

MATERIAL AND METHODS

The research was reviewed and received approval from the Ethics Committee of the First Hospital of Tsinghua University. The approval number is (R)2025-043-01, and the approval date is 22.07.2025.

Study Population

We retrospectively reviewed the medical records of 292 patients with HS and congenital heart defects treated at The First Hospital of Tsinghua University from January 2014 to December 2023. Diagnosis was based on published criteria (4).

Inclusion criteria: Patients with congenital heart defects and abnormal arrangement of thoracoabdominal organs, including midline liver, polysplenia or asplenia, any arrangement of liver and spleen combined with mesocardia, or situs solitus liver and spleen combined with dextrocardia, situs inversus liver and spleen combined with levocardia, and patients with situs inversus liver and spleen with dextrocardia accompanied by atrioventricular valve and/or great artery malpositions.

Exclusion criteria: Patients with situs solitus and simple CHDs; mirror-image dextrocardia with simple defects. We reviewed available medical records, including demographics, clinical findings, imaging results, and complications.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as counts (percentages). Comparisons between groups were made using chi-square tests. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 292 patients with HS and associated CHDs were included in this study. The mean age was 6.8±8.7 years, and 119 patients (40.8%) were female. Baseline characteristics are summarized in Table 1. Asplenia was present in 125 patients (42.8%), polysplenia in 45 (15.4%), and single-sided spleen in 122 (41.8%). Regarding cardiac position, 128 (43.8%) had levocardia, 146 (50.0%) had dextrocardia, and 18 (6.2%) had mesocardia.

In terms of cardiac anomalies, the most common defects were single ventricle (61.9%), conotruncal malformations (54.5%), pulmonary stenosis (PS) (42.8%), superior vena cava (SVC) anomalies (33.9%), pulmonary atresia (PA) (17.5%), and atrioventricular (AV) septal defect (16.4%). Anomalous pulmonary venous connection was relatively rare, identified in 7.9% of patients (total type 6.8%, partial type 1.0%). Abnormal aortic arch sidedness was also observed, with right-sided and midline arches accounting for 25.3% and 4.5% of cases, respectively (Table 2).

Gender distribution analysis is shown in Table 3. Among patients with asplenia, the proportion of males was significantly higher than that of females (66.4% vs. 33.6%, P<0.05). In the polysplenia group, females outnumbered males, although the difference was not statistically significant (57.8% vs. 42.2%, P>0.05). Among patients with unilateral spleen, males were also significantly more common than females (59.0% vs. 41.0%, P<0.05).

Table 1. Baseline characteristics and extracardiac findings in patients with HS

Clinical characteristics	n (%)
Female	119 (40.8)
Age (years)	6.8±8.7
Cardiac position	
Levocardia	128 (43.8)
Dextrocardia	146 (50)
Mesocardia	18 (6.2)
Spleen morphology	
Asplenia	125 (42.8)
Polysplenia	45 (15.4)
Unilateral spleen	122 (41.8)

Data given as mean±SD or n (%)

Table 2. Types of CHDs in patients with HS

CHDs	n (%)
Single ventricle	181 (61.9)
Conotruncal anomaly	159 (54.5)
Double outlet right ventricle	71 (24.3)
l-TGA	26 (8.9)
d-TGA	7 (2.4)
PA	51 (17.5)
Tetralogy of Fallot	2 (0.7)
Common arterial trunk	2 (0.7)
Atrioventricular canal defect	48 (16.4)
Aortic arch sidedness abnormality	87 (29.8)
Right aortic arch	74 (25.3)
Midline aortic arch	13 (4.5)
PS	125 (42.8)
SVC anomalies	99 (33.9)
Bilateral SVC	52 (17.8)
Left SVC	47 (16.1)
Anomalous pulmonary venous connection	23 (7.8)
TAPVC	20 (6.8)
PAPVC	3 (1.0)

Data given as n (%); l-TGA, congenitally corrected transposition of the great arteries; d-TGA, complete transposition of great arteries; PA: pulmonary atresia, PS: pulmonary stenosis, SVC: superior vena cava, TAPVC: total anomalous pulmonary venous connection, PAPVC: partial anomalous pulmonary venous connection

Table 3. Gender distribution by splenic type in HS patients

Splenic type	Female n (%)	Male n (%)	χ^2	P-value
Asplenia	42 (33.6)	83 (66.4)	13.448	<0.001
Polysplenia	26 (57.8)	19 (42.2)	1.089	0.30
Unilateral spleen	50 (41.0)	72 (59.0)	3.967	0.046

DISCUSSION

HS is a complex congenital disorder involving abnormal arrangement of thoracoabdominal organs along the left-right axis. Among its manifestations, CHDs are the most critical determinants of morbidity and mortality. CHDs in HS are often complex and involve multiple segments of the cardiovascular system, thus a segmental approach to structural assessment is essential for individualized diagnosis and treatment planning.

This study retrospectively reviewed 292 patients with HS and associated CHDs over a 10-year period at our institution. The results showed that asplenia was the most common splenic anomaly, followed by unilateral spleen. Gender analysis revealed that males accounted for approximately 2/3 of the patients with no spleen, while females were relatively more prevalent in patients with multiple spleens. The gender differences observed in this study are consistent with previous literature (2, 6-8), suggesting a potential sex-related distribution bias among HS subtypes, which warrants consideration in clinical assessment and perioperative management.

RAI is typically associated with severe cardiac malformations, making surgical management particularly challenging (2). RAI is considered one of the most severe forms of congenital heart disease (9), with a 5-year survival rate of 30–74% (2,10). Common structural anomalies include single atrium, single ventricle, AV septal defect, and common AV valve regurgitation (11). Bilateral SVCs and anomalous pulmonary venous connections are frequently observed (12,13), with studies showing that nearly half of RAI patients have total anomalous pulmonary venous connection (TAPVC) (11). In addition, the inferior vena cava often runs adjacent to the aorta, and hepatic veins may drain contralaterally (14). Absence of the coronary sinus is also common, with coronary veins draining directly into the atrium due to bilateral morphologic right atrial appendages (11). Great artery abnormalities, such as transposition of the great arteries, double-outlet right ventricle, and right ventricular outflow tract obstruction, are also prevalent in this group (15,16).

In contrast, LAI is generally associated with milder cardiac malformations, and about 13% of patients may have normal intracardiac anatomy (8). The 5-year survival rate ranges from 65–84% (2,17), which is better than RAI but still lower than other types of congenital heart disease (16). The most characteristic anatomical feature of LAI is interruption of the inferior vena cava (IVC) with azygos continuation to the SVC, with an incidence of approximately 60–90% (8,12). Bilateral SVCs are also relatively common; statistics show that over 50% of LAI patients have bilateral SVCs (8). However, unlike RAI, where SVCs drain directly into the atria, in LAI they typically drain via the coronary sinus (11). Most LAI patients have normal pulmonary venous return, although partial anomalous pulmonary venous connection (PAPVC) can be seen in some cases (11). The atrioventricular septum is usually more intact in LAI, though complete or partial AV septal defects can still be observed (18).

However, classification methods based on atrial appendage morphology are not entirely ideal. Firstly, accurate recognition of atrial appendage morphology in imaging studies presents technical challenges. Our study found that it is often difficult to clearly define atrial appendage features in clinical practice; in such cases, the type of spleen an associated cardiac malformations may be more practically valuable. Secondly, the morphology of the atrial appendage, bronchial anatomy, and splenic development do not always correspond consistently, with frequent occurrences of crossover or atypical presentations. As research has advanced, increasing evidence indicates that traditional classifications based on atrial appendage morphology often do not align with the actual patterns of cardiac and extracardiac malformations, and the guidance value for clinical diagnosis and treatment decisions is limited (5). Similarly, our study also observed inconsistencies in the arrangement of thoracoabdominal organs. Currently, there is a stronger emphasis on segmental structural analysis of the cardiovascular system to achieve individualized comprehensive diagnosis and therapeutic assessment. Therefore, establishing a detailed spectrum of cardiac malformations in patients with HS is of great significance for better understanding their anatomical structures and optimizing surgical strategies.

Numerous studies have demonstrated that TAPVC is strongly associated with poor postoperative outcomes and high mortality (16). Even after surgical repair, reinterventions are often required (19). Obstructed TAPVC has been identified as an independent risk factor for mortality in RAI patients (20). Eronen et al. reported that 29% of RAI patients with TAPVC were inoperable, and those who underwent surgery had a 75% mortality rate (21). In our study, the overall incidence of pulmonary venous anomalies was 7.8%, with 6.8% for TAPVC—much lower than the 30.9%reported by Sebastian et al. (22). This discrepancy may be related to the patient population characteristics at our center, a comprehensive tertiary medical institution. Therefore, early detection and timely intervention for TAPVC, particularly the obstructive type, are essential to improving the prognosis of HS patients.

Restricted pulmonary blood flow, such as PS and PA, is another important prognostic factor in HS, especially among patients requiring staged single-ventricle palliation (23). These conditions

are more prevalent in RAI. In our cohort, the incidence of PA was 17.5%, and 42.8% had PS—comparable to Bhaskar et al.'s findings of 26.4% and 36.3%, respectively (24). Pulmonary artery maldevelopment is highly clinically relevant in patients with HS and should be thoroughly evaluated preoperatively in terms of anatomical features and blood flow to guide the formulation of individualized surgical strategies.

In recent years, with the continuous improvement of cardiac surgical techniques and perioperative management, the surgical outcomes of HS patients have improved (25), but the overall treatment outcome is still unsatisfactory. A single-center study reported a postoperative mortality rate of 20.8% (16). This is closely related to the complex multisystem anomalies associated with HS, including pulmonary/systemic venous anomalies, single-ventricle physiology, outflow tract obstruction, significant arrhythmias, and immunodeficiency from splenic dysfunction (4). Currently, there is still debate over whether the presence of HS affects postoperative outcomes in cardiac surgery. The traditional view considers HS as an important factor leading to poorer prognosis after cardiac surgery (4). However, some recent studies have proposed a different view, suggesting that HS is not an independent risk factor for Fontan circulation failure (26).

This study has several limitations. First, as a retrospective review, some data were incomplete, introducing potential selection bias. Second, since the data were collected at a cardiac referral center, most patients had more severe malformations, potentially underestimating the prevalence of milder forms. Lastly, long-term follow-up data were lacking. Prospective, multicenter studies with larger samples are needed.

CONCLUSION

HS is associated with a wide spectrum of intracardiac and extracardiac malformations. It leads to difficult diagnosis, complex treatment, and poor prognosis, posing a great challenge to clinical management. This study presents a 10-year single-center experience summarizing the anatomical features of cardiac defects in HS and highlights significant gender differences among patients with asplenia, polysplenia, and single spleen. These findings may provide valuable reference for clinical classification, preoperative assessment, and development of individualized treatment strategies.

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