International Journal of Cardiology 268 (2018) 100–105

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Long-term survival and phenotypic spectrum in heterotaxy syndrome: A 25-year follow-up experience☆

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ARTICLE INFO

Article history:
Received 6 October 2017
Received in revised form 3 February 2018
Accepted 13 February 2018

Keywords:
Congenital heart defect surgery
Heterotaxy
Isomerism
Polysplenia
Asplenia
Spleen

ABSTRACT

Background: Heterotaxy syndrome (HS) is a group of congenital disorders characterized by abnormal arrangement of thoraco-abdominal organs across the left-right axis of the body, classified as right (RAI) and left atrial isomerism (LAI)·We investigated the long-term survival and phenotypic spectrum in our HS cohort. Results are compared to literature data.
Methods: This is a single centre, observational, both retro and prospective study. Cardiac features, surgical management and abdominal ultrasound (US) of all HS patients were reviewed or investigated if missing. We evaluated all anatomical data and their clinical impact on survival, arrhythmias, infections, and heart transplant (HT).
Results: 136 patients were classified as RAI (81) and LAI (55). Long-term survival and freedom from HT reached 69.8% and 87.8% at 40 years in RAI and LAI, respectively. Multivariate analysis showed that LAI is an independent predictor for pacemaker implantation ($p = 0.019$). Splenic status varied in both groups: in RAI, abdominal US showed asplenia, polysplenia and normal spleen in 48%, 4% and 32% of patients, respectively, whereas in LAI polysplenia, asplenia and normal spleen occurred in 64%, 4% and 16% of cases, respectively.
Conclusions: Mortality was significantly lower (9%) compared to literature (50%). Although patients with RAI experienced a higher mortality, no independent predictors were found. We demonstrated that the obsolete cardiac definition of "asplenia" and "polysplenia" instead of RAI and LAI is misleading, because of the high variability of the splenic phenotype among patients of both groups.

1. Introduction

Heterotaxy syndrome (HS) is a class of congenital disorders characterized by abnormal arrangement of thoraco-abdominal organs across the left-right axis of the body, secondary to failure of establishing the normal asymmetry during embryonic development [1–4]. Right atrial isomerism (RAI) and left atrial isomerism (LAI) are subtypes of HS, characterized by bilateral right or left-sidedness of the organs, respectively [1]. The disorder is typically associated with complex cardiovascular malformations (CVM), especially in RAI category [2,5–7], and is diagnosed in approximately 1 to 5000–7000 live births although it is difficult to give reliable recent epidemiologic data due to the rarity of the disease and the rapid development of prenatal diagnosis that will change remarkably the prevalence of this condition [8,9]. A spectrum of extracardiac anomalies is part of HS, involving lungs, liver, spleen, intestine, central nervous system and other midline defects [5,6,10–14]. One of the clinically and immunologically significant implications of HS is the frequent involvement of the spleen [1,15–17]. Although not all RAI are associated with absence of the spleen nor all LAI have polysplenia, it has become a "traditional" practice to stratify HS into the subsets of "asplenia" and "polysplenia" syndrome on the basis of the cardiovascular setting without a thorough search for splenic tissue by dedicated abdominal ultrasound scan (US) [2,5,7,18]. The association of several CVM, the complexity of surgery, predisposition to conduction defects, and susceptibility of asplenic patients to infections, all seem to contribute to high mortality and morbidity since early infancy [13].

☆ "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation."

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https://doi.org/10.1016/j.ijcard.2018.02.050
0167-5273/

Recently, outcomes improvement were reported; however, few studies demonstrated perspectives of survival beyond 5 years of age [18,19], and little is known regarding survival through adulthood in HS [20]. We reviewed our experience in HS in our tertiary centre Bambino Gesù Children Hospital and Research Institute to determine and classify the observed CVM, their correlation with the shape and distribution of abdominal organs and the impact on survival, infections, arrhythmias, and heart transplant (HT). Moreover, survival curve reports in HS were reviewed and compared to our results. Our findings were also graphically compared to literature reports.

2. Methods

We reviewed medical records of HS patients referred to our tertiary care centre from 1990 to 2015. This is a single-centre, observational, both retro and prospective analysis. All data, including the cardiac diagnosis and surgical reports, were extracted from our cardiac database, case notes, reports of echocardiography, catheterisation, and operative notes. HS patients were classified in RAI or LAI. In addition to the morphology of the atrial appendages, HS was subclassified as RAI on the basis of evidence of total anomalous pulmonary venous connection (TAPVC), complete atrioventricular septal defect (AVSD) -as constant features of RAI- and juxtaposed abdominal aorta and inferior vena cava (IVC), and LAI on the continuation of the IVC through the azygos venous system [21]. Furthermore, if surgery was done, diagnosis was confirmed by direct inspection of atrial appendages' morphology. Moreover, other indirect way to establish HS can be through the observation of the morphology of bronchi, lungs and upper abdominal organs through specific imaging of abdominal ultrasound and or angio MRI/CT scan whenever indicated. In this specific study we mainly focused on the primary level imaging investigations yield. Patients with situs inversus totalis were excluded from the current analysis.

All records were reviewed to assess the splenic status. Whenever missing, new abdominal US was performed by experienced paediatric radiologists using a Philips IU22 real-time sonographic system (Philips Healthcare, the Netherlands). The US always started with a systematic overview through 1 to 6 MHz curvilinear transducers followed by more detailed imaging using 5 to 12 MHz linear transducers. Each investigation aimed to identify the splenic tissue in order to verify the following points: the existence or absence, the number (single or multiple) and the site (i.e. left or right hypochondriac region). If there was a single spleen, the longest diameter was measured on a coronal image obtained through the splenic hilum. We diagnosed asplenia when US failed to trace any splenic tissue, while polysplenia was defined as US detection of two or more spleens. Whenever available, US data were compared to abdominal CT scan and MRI findings. These data were correlated with patients' characteristic sand associated cardiac malformations. Numbers were reported as absolute number and percentages. Patients with complex phenotypes and lost at follow-up were excluded from analysis.

2.1. Statistical analysis

All statistical analysis was performed by SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA). Continuous variables are presented as mean value, standard deviation (SD) and range or median value (interquartile range, IQR), as appropriate. Categorical variables are expressed as absolute numbers or percentages. Chi-squared test was used to compare categorical variables >5, while Fisher's exact test was used to compare those <5.Survival data and freedom from heart transplant were analyzed and graphically reported by the Kaplan-Meier method. Log rank test was used for comparison between groups. Patients who did not experience an event were censored at the time of the last follow-up. Univariate and multivariate analysis for risk factors was performed by logistic regression analysis. Variables with p values <0.2 in the univariate analysis were considered eligible for entering multivariable analysis. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI). p-Value was considered significant when ≤0.05. In addition we plotted on the same chart our and the previously described survival studies in HS.

3. Results

3.1. Study cohort

A total of 161patients with situs anomalous were referred to our tertiary Bambino Gesù Children Hospital and Research Institute: 136 were diagnosed with HS, 20 with situs inversus totalis and 5 were unclassified due to lack of sufficient imaging data. Two patients with complex phenotypes (CHARGE syndrome and VACTERL association) were excluded from the study. Of the 136 patients initially included in our cohort, 22 were lost at follow-up (9 LAI, 13 RAI) and consequently excluded from survival curves and analysis. The demographic characteristics of the population are described in Supplementary Table 1.

3.2. Cardiac findings

On the basis of sequential segmental analysis and cardiac features we divided the HS patients into two main groups: 81 RAI and 55 LAI. Similar to literature data, the most relevant cardiovascular lesions in LAI were: interruption of the IVC with azygos continuation ($p < 0.0001$), partial anomalous pulmonary venous connection (PAPVC) ($p = 0.023$), partial AVSD and common atrium ($p < 0.0001$), isolated atrial septal defect (ASD) ($p = 0.001$), isolated ventricular septal defect (VSD) ($p < 0.0001$) and complete atrioventricular block (AVB) ($p = 0.001$). On the other hand, the RAI group showed a statistically significant correlation with the following lesions: TAPVC ($p = 0.008$), balanced or unbalanced complete AVSD ($p = 0.009$ and $p < 0.0001$, respectively), double outlet right ventricle (DORV) ($p = 0.017$), transposition of great arteries (TGA) ($p = 0.006$) and pulmonary artery branches hypoplasia ($p = 0.027$).

We reported sequential segmental analysis including less common features in Supplementary Table 2.

3.3. Surgery

Surgical treatment was performed in 130. As expected, RAI patients were majorly subject to univentricular palliation 73/81 (90%). Half of these patients successfully reached the Fontan stage and they are mostly in active follow up. Univentricular option was less represented in LAI 19/55 (35%) and almost half underwent biventricular correction 31/55 (56%). Few LAI patients did not need surgery at all 5/55 (9%). Supplementary Table 3 summarizes the surgical options and outcomes in the studied cohort.

3.4. Conduction defect

Pacemaker (PM) implantation was necessary in 19/55 LAI patients (35%). The causes were congenital AVB (6patients), congenital severe sinus node dysfunction (2 patients), postoperative AVB (6 patients), and long term sinus node dysfunction (5 patients). PM insertion was a rare event in RAI group 2/81 (2%) both for long-term sinus node dysfunction. But RAI were prone to develop re-entrant tachycardia due to paired sinus and AV nodes. At multivariate analysis, LAI is an independent predictor for PM implantation (OR: 12; 95% CI: 1.2–110; $p = 0.031$). Permanent cardiac pacing procedure was epicardial in both RAI patients and in 13 LAI while it was endocardial for the remaining 6 LAI patients.

3.5. Spleen

Accurate analyses were also performed on spleen characteristics in terms of numbers and position, whenever was identified. In RAI patients, the review of abdominal US records showed high variability in splenic tissue distribution including asplenia, polysplenia and normal spleen in 39 (48%), 3 (4%) and 26 (32%) patients, respectively. In patients with single spleen the position was left-sided in11 and right-sided in 15 cases. In polysplenic RAI, the position was left-sided in2and right-sided in 1 patient. In LAI group we observed a similar variability in terms of existence, number and position of the splenic tissue: polysplenia was diagnosed in 35 (64%), asplenia in 2 (4%) and normal spleen in 9 (16%). In LAI patients with single spleen, the organ was left-sided in 5 cases and right-sided in 4. In the polysplenic group, splenic tissue was left-sided in 15, right-sided in 8 and with unspecified position in 11 cases. Specific records were missing for 13 RAI (17%) and 9 LAI (16%). Fig. 2 shows the flow chart of our method for classifying the splenic anomalies in our cohort. We also reviewed the literature and classified the reported series according to our method (Fig. 2 and Supplementary Table 4).

As asplenia is associated to an increased risk of severe bacterial infections, we treated all asplenic RAI and LAI patients with antibiotic