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Predictors of Mortality in Patients with Isomerism

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Abstract

Background: The so-called heterotaxy, or isomerism, is associated with increased morbidity and mortality. Previous studies have identified various risk factors associated with increased mortality in those with isomerism. The aim of this study was to identify such risk factors in our single center experience.

Methods: Retrospective review of patients cared for at the Children's Hospital of Wisconsin was carried out to identify patients with isomerism who received care between January 1998 and December 2014. Clinical and surgical data were collected for all these patients. Univariate analysis was conducted to compare characteristics between those who died during this period and those who remained alive. Logistic regression was then conducted to identify independent risk factors for mortality.

Results: We included a total of 83 patients in our analysis. Of these patients, 17 (20%) died during the period of follow-up. The only independent risk factor found to be associated with mortality after logistic regression was the need for extracorporeal membrane oxygenation. Univariate analysis had also identified increased duration of ventilatory support after initial cardiac palliation as associated with mortality, but we did not include this feature in the logistic regression due to the low number of patients.

Conclusion: The need for extracorporeal membrane oxygenation is associated with increased mortality in those with isomerism. No cardiac malformations were identified as independent risk factors of mortality. A larger multicenter effort is required to better identify risk factors associated with mortality in patients with isomerism.

Keywords: Mortality; Isomerism; Patients; Diagnosis; Pneumonia

Introduction

The so-called heterotaxy is characterized by isomerism of the thoracic organs and random arrangement of the abdominal organs [1-4]. For this reason, among others, it is better referred to simply as isomerism [1]. Isomerism can be further segregated into the subsets of left or right on the basis of the morphology of the atrial appendages, which is the most constant feature of isomerism, and the only example of isomerism found within the heart. Delineation between the subsets of left and right isomerism allows for inferences to be made regarding associated cardiac and extracardiac malformations, as well as organ dysfunction. Thus, these features can be appropriately screened, potentially permitting earlier detection and appropriate intervention.

Isomerism is associated with congenital malformations in nearly all organ systems, many of which can now be detected on fetal evaluation [5,6]. The number of organ systems affected in a single patient can be variable. The effects on the organs systems, furthermore, go beyond simply being anatomic, entailing additional functional abnormalities. For instance, any splenic anatomy, including a normal appearing, normally located, solitary spleen may be associated with splenic dysfunction [7]. This is associated with increased prevalence of thrombocytosis and bacteremia [8-11]. Abnormalities in the development of the cardiac conduction system predispose to arrhythmias [12-14]. Bronchopulmonary isomerism may also have functional implications.

These anatomic and functional abnormalities potentially decrease survival in those with isomerism, such that those with congenital malformations of the heart in the setting of isomerism have lower survival than those with the same congenital cardiac malformations but without isomerism. Although there has been improvement in survival associated with isomerism in the recent era, differences are still present. We set forth, therefore, to determine the risk factors for mortality in those with isomerism.

Methods

Patients with isomerism cared for at Children's Hospital of Wisconsin from January 1998 to January 2014 were retrospectively identified. Data regarding their cardiac and non-cardiac anatomy, cardiac surgical palliations, and other findings associated with isomerism were collected by chart review. Cardiac anatomy was analyzed by use of echocardiography, although findings were confirmed with catheterization studies, computed tomography, and magnetic resonance imaging when available, using the principle of sequential segmental analysis [15]. Bronchial morphology was determined using chest radiographs, computed tomography, and magnetic resonance imaging [16,17]. Intestinal malrotation was assessed by review of upper gastrointestinal studies. Splenic status was analyzed most often by abdominal ultrasonography, but some patients also had computed tomographic or magnetic resonance imaging from which splenic anatomy could also be noted. As it had not been a routine feature during our study period for the surgeons to document the morphology of the atrial appendages at the time of surgery, and because of the presumed difficulty associated with imaging the appendages, specific data relating to their morphology was not available. Instead, we used an aggregate of all the collected features to segregate the entire cohort into the subsets or right or left isomerism. Data regarding surgical palliation was obtained from the operative notes. This included the precise procedure, the times required for cardiopulmonary bypass and aortic cross-clamping, and any operative complications. We also noted whether or not patients were extubated in the operating room.

The total postoperative length of mechanical ventilation, as well as need for reintubation in the postoperative period, was also collected, along with total length of stay associated with surgical palliation. Continuous data is presented as mean or standard deviation, while descriptive data is presented as actual number and percentage. Continuous variables were analyzed using Student's t-test, the Mann-Whitney-U test, or analysis of variance where appropriate. Descriptive data were analyzed using chi-square analysis or Fisher's exact test. Chi-square analysis was used to compare features between those dying and those who were still alive. Variables with a p-value of less than 0.2 were then entered as independent variables into a logistic regression, with mortality as the dependent variable. Continuous variables were not entered into the regression, as the study was grossly underpowered for this purpose. Statistical analysis was done using SPSS version 20.0 (Chicago, IL). A p-value of less than 0.05 was considered statistically significant.

Results

We included a total of 83 patients retrospectively identified for inclusion in this analysis. Of these, 17 (20%) died during the period of follow-up. Median age of death was 3 months, with a range of 1 day to 23 years. Median follow-up was 5.3 years, with a range from 0.3 years to 33.6 years, in those who remained alive during the study period, and was a median of 0.5 years, with a range from 0.1 years to 22.6 years, in those who died during the study period. Characteristics were then compared between those who remained alive and those who had died during this period. In univariate analysis, those who died were more likely to have a common atrioventricular junction (odds ratio 3.658, 95% confidence interval 0.959 to 13.946), to have required extracorporeal membrane oxygenation (odds ratio 22.400, 95% confidence interval 4.064 to 123.472), and to have experienced an episode of bacteremia (odds ratio 5.630, 95% confidence interval 1.723 to 18.390).

Prenatal diagnosis, genetic mutation, pulmonary atresia, anomalous pulmonary venous connections requiring surgical intervention, left as opposed to right isomerism, intestinal malrotation, surgery for intestinal malrotation, abdominal arrangement, splenic anatomy, presence of arrhythmia, need for pacemaker placement, repair status at last follow-up, or sinupulmonary symptoms were not associated with mortality.

Surgical characteristics were not associated with mortality other than the number of days of mechanical ventilatory support after initial cardiac palliation, the number of days the chest remained open after initial cardiac palliation, and the length of hospitalization associated with the initial cardiac palliation. Those who died required a median of 21 days of postoperative mechanical ventilatory support after initial cardiac palliation, in comparison to 1.5 days in those who did not die (p=0.030). Those who died underwent delayed sternal closure at a median of 3 days after initial cardiac palliation, compared to zero days in those who did not die (p=0.023). Prolonged hospitalization duration was also associated with mortality, as those who died had a median duration of 125 days after initial cardiac palliation compared to 22 days in those who survived (p=0.006). In addition, length of hospitalization after the second cardiac palliatiative procedure was also prolonged in those who died, with a median of 70.5 days compared to 14 days in those who survived (p=0.024) is shown in **Tables 1 and 2**.

Table 1: Comparison of cardiac and clinical characteristics between those with isomerism who died and remained alive during follow-up.

	Alive (n=66)	Deceased (n=17)	P-value	Odds ratio and 95% confidence interval
Age at death	--	6.3 months (1 day to 22.6 years)	--	--

Prenatal diagnosis	43 (72)	10 (71)	0.986	0.988 (0.273 to 3.585)
Identified genetic mutation	10 (47)	3 (63)	0.472	1.852 (0.341 to 10.047)
Common atrioventricular junction	37 (56)	14 (82)	0.047	3.658 (0.959 to 13.946)
Double outlet right ventricle	23 (35)	7 (41)	0.628	1.309 (0.440 to 3.895)
Double inlet left ventricle	1 (2)	0 (0)	0.610	--
Bilateral superior caval veins	33 (50)	8 (47)	0.829	0.889 (0.306 to 2.585)
Interruption of the inferior caval vein	23 (35)	3 (18)	0.173	0.401 (0.104 to 1.539)
Discordant atrioventricular connections	10 (15)	4 (24)	0.411	1.723 (0.466 to 6.368)
Discordant ventriculoarterial connections	13 (20)	4 (24)	0.727	1.254 (0.351 to 4.486)
Pulmonary atresia	19 (29)	6 (35)	0.602	1.349 (0.437 to 4.170)
Pulmonary veins requiring intervention	21 (32)	8 (47)	0.240	1.905 (0.644 to 5.632)
Intestinal malrotation	26 (39)	8 (53)	0.313	1.731 (0.592 to 5.060)
Surgery for intestinal malrotation	24 (80)	8 (80)	1.000	1.000 (0.167 to 5.985)
Age at malrotation surgery (days)	7.0 (1.0 to 140.0)	21.0 (3.0 to 57.0)	0.754	--
Inferred isomerism sidedness Right Left	42 (64) 24 (36)	11 (65) 6 (35)	0.935	-- --
Bronchial morphology Right Left	12 (20) 48 (80)	1 (7) 13 (93)	0.255	-- --
Abdominal arrangement Left sided stomach, right sided liver Right sided stomach, left sided liver Midline liver	20 (31) 25 (38) 20 (31)	4 (31) 6 (46) 3 (23)	0.828	--
Splenic anatomy Absent Multiple Single	38 (59) 9 (14) 18 (27)	13 (81) 1 (6) 2 (13)	0.23	-- -- --
Arrhythmia	35 (53)	6 (35)	0.192	0.483 (0.160 to 1.460)
Need for pacemaker	10 (15)	2 (12)	0.723	0.747 (0.148 to 3.779)
Need for extracorporeal membrane oxygenation	2 (3)	7 (41)	<0.0001	22.400 (4.064 to 123.472)
Bacteremia	9 (14)	8 (47)	0.002	5.630 (1.723 to 18.390)
Underwent initial cardiac palliation	62 (94)	14 (82)	0.125	0.301 (0.060 to 1.499)
Age at initial cardiac palliation (days)	15.5 (0 to 871.0)	7.0 (0 to 518.0)	0.391	--
Number of ventilatory days after initial cardiac palliation	1.5 (0 to 44.0)	21.0 (2 to 114)	0.030	--
Number of days chest open after initial cardiac palliation	0 (0 to 13.0)	3 (0 to 28.0)	0.023	--
Length of hospitalization for initial cardiac palliation (days)	22.0 (3.0 to 225.0)	125.0 (13.0 to 235.0)	0.006	--
Underwent second cardiac palliation	48 (73)	13 (77)	0.755	1.219 (0.351 to 4.231)
Age at second cardiac palliation (months)	8.0 (0.5 to 123.0)	5.0 (0.5 to 138.8)	0.855	--
Number of ventilatory days after second cardiac palliation	0 (0 to 6.0)	3.0 (2.0 to 5.0)	0.262	--

Number of days chest open after second cardiac palliation	0 (0 to 4)	0 (0 to 4)	0.704	--
Length of hospitalization for second cardiac palliation	14 (4 to 225)	70.5 (0 to 235)	0.024	--
Underwent third cardiac palliation	23 (35)	4 (24)	0.427	--
Age at third cardiac palliation (years)	4.3 (0.5 to 10.0)	4.5 (0.5 to 9.5)	0.623	--
Number of ventilatory days after third cardiac palliation	0 (0 to 6.0)	3.0 (3.0 to 3.0)	0.348	--
Number of days chest open after third cardiac palliation	0 (0 to 3.0)	0 (0 to 0)	0.683	--
Length of hospitalization for third cardiac palliation	9.0 (o to 197.0)	34.0 (6 to 41)	0.755	--
Repair status at last follow-up Functionally univentricular Biventricular Transplant	43 (65) 21 (32) 2 (3)	14 (82) 2 (12) 1 (6)	0.241	-- -- --
Recurrent upper respiratory infections	11 (17)	2 (12)	0.620	0.667 (0.133 to 3.339)
Recurrent pneumonia	3 (5)	1 (6)	0.818	1.313 (0.128 to 13.473)
Chronic lung disease	6 (9)	3 (18)	0.312	2.143 (0.477 to 9.633)
Reactive airway disease	8 (12)	2 (12)	0.968	0.967 (0.186 to 5.035)
Need for home oxygen	15 (24)	4 (24)	0.955	--
Tracheostomy	2 (3)	0 (0)	0.468	--
Follow-up duration (years)	5.3 (0.3 to 33.6)	0.5 (0.1 to 22.6)	0.877	--

A logistic regression was then conducted to determine those factors independently associated with death. The dependent variable for this regression was death with the following being entered as independent variables: need for extracorporeal membrane oxygenation, history of bacteremia, chronic arrhythmia, presence of an interrupted inferior caval vein, and presence of a common atrioventricular junction. Need for extracorporeal membrane oxygenation (odds ratio 9.302, 95% confidence interval 1.401 to 61.764) was the only factor that remained significant after regression analysis, and thus was identified as an independent predictor of mortality in the setting of isomerism.

Table 2: Results of regression analysis.

	Coefficient	p-value	Odds ratio (95% Confidence interval)
Interrupted inferior caval vein	-0.658	0.445	0.518 (0.095 to 2.808)
Arrhythmia	-0.598	0.379	0.550 (0.145 to 2.084)
Need for extracorporeal membrane oxygenation	2.230	0.021	9.302 (1.401 to 61.764)
Bacteremia	1.430	0.076	4.178 (0.861 to 20.278)
Common atrioventricular junction	1.010	0.196	2.745 (0.595 to 12.665)

Discussion

Isomerism, also known as heterotaxy, has been associated with increased mortality, although the precise mechanisms have yet to be entirely elucidated. Congenital malformations of the heart do not account for all of this mortality, although those with isomerism and congenital malformations of the heart are known to have an increased mortality when compared to those with similar congenital malformations in the absence of isomerism [18,19]. As several organ systems can be impacted by isomerism, we sought to determine the risk factors associated with mortality in those with isomerism. After regression analysis, the need for extracorporeal membrane oxygenation was found to be the only independent risk factor for mortality. Specific congenital malformations of the heart, history of bacteremia, repair status, splenic anatomy, nor the type of isomerism sidedness were not associated with mortality.

Mortality, in the setting of isomerism, appears to be greatest in the first three years of life [20]. Particularly for those requiring functionally univentricular palliation, this period is characterized by hospitalization and hemodynamic instability as patients undergo the initial staged surgical procedures. During this period, isomerism mediates an increased need for delayed sternal closure, longer duration of mechanical

ventilation, and greater risk of bacteremia, all of which can increase the risk of mortality [10,11,21,22]. The increased duration of mechanical ventilation may be secondary to underlying ciliary dyskinesia, demonstrated to be found in slightly over half of patients with congenital malformations of the heart and isomerism [21]. Increased pulmonary vascular resistance, and pulmonary hypertension, may also lead to the more adverse pulmonary phenotype found in some patients with isomerism [23]. Patients with pulmonary atresia and obstructed anomalous pulmonary venous connections are known to be at particularly high risk [24]. The increased risk of bacteremia is likely due to splenic dysfunction and alterations in B-cell populations, further compounded by the presence of invasive monitoring lines and endotracheal tubes [25,26].

Extracardiac malformations of isomerism, such as those found in the central nervous system, genitourinary system, and gastrointestinal system may also require surgical intervention. These malformations themselves, or the interventions associated with these, may also increase morbidity and mortality in the setting of isomerism. These include hydrocephalus necessitating the need for a cerebral shunt or intestinal malrotation necessitating a Ladd's procedure [27].

Previous studies investigating mortality in isomerism have served to identify risk factors. These have included obstructed pulmonary venous connection, anomalous pulmonary venous connection, functionally univentricular circulation, congenital heart block, having noncardiac anomalies, mild or greater atrioventricular valvar regurgitation, having a common atrioventricular junction, aortic coarctation, need for neonatal surgery, and right ventricular outflow tract obstruction [19,28-39]. None of these features, however, proved to be associated with mortality in our analysis. Identification of factors associated with mortality in those with isomerism, nonetheless, will allow for increased vigilance in those shown to be at high risk. As more is understood about these risk factors, and what mediates them, interventions may be available to help reduce this risk. More thorough and accurate risk assessment will also allow for more appropriate counseling.

Our study is limited by a relatively small number of patients, which leaves it underpowered. The single center nature of the study has its strengths, but limits the study by reducing the numbers available for analysis. Differences in surgical management and intensive care strategies, however, can lead to different results amongst individual centers. Despite this shortcoming, there is a need for a large multicenter collaboration to identify risk factors for mortality in a larger cohort of patients with isomerism. This would also allow for identification of institution specific factors, which may also affect outcomes.

Conclusion

Patients with isomerism are at increased risk of mortality if they require extracorporeal membrane oxygenation. In contrast to previous reports, this study did not identify any specific cardiac malformations associated with increased mortality. There is a need for a large multicenter study to better identify risk factors for mortality in this patient population.

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