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Isomerism is not Associated with Thrombocytosis or Thromboembolic Events in Adulthood: Results from a National Database Study

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Abstract

Background: So-called heterotaxy, better called bodily isomerism, is associated with increased frequency of thrombocytosis and thromboembolic events in childhood. This is likely mediated by splenic dysfunction present with isomerism. Data for adults with isomerism is lacking with a paucity of data regarding thrombosis and isomerism. This study aimed to determine the risk of thrombocytosis and thromboembolic events in adults with isomerism.

Methods: The 2012 iteration of the Nationwide Inpatient Sample was used. International classification of disease codes were used to identify admissions associated with isomerism, thrombocytosis, and thromboembolic events. Chi-square analysis was conducted to determine factors associated with thrombocytosis and various thromboembolic events. Logistic regression was used to estimate the adjusted odds ratio of isomerism

Results: A total of 6,907,109 admissions were included, 861 of which had isomerism. Thrombocytosis was equally prevalent in those with and without isomerism with a frequency of 0.1%. Acute thromboembolic events were equally prevalent in both groups as well, with lower extremity thromboembolic events being most prevalent in both. Older age and male gender were both independent risk factors for thromboembolic events but not isomerism.

Conclusion: Thrombocytosis and acute thromboembolic events are not more common in those with isomerism. They do, however, occur at a younger in those with isomerism and are associated with increased length and cost of hospitalization.

Keywords: Isomerism; Heterotaxy; Laterality; Spleen; Polysplenia; Asplenia; Splenectomy; Platelet count; Thrombocytosis; Clots; Thromboembolism

Abbreviations: NIS: Nationwide Inpatient Sample; HCUP: Healthcare Cost Utilization Project; AHRQ: Agency for Healthcare Research and Quality.

Introduction

Bodily isomerism, also referred to as heterotaxy, consists of isomeric findings in various organ systems [1-3]. The central nervous, cardiovascular, bronchopulmonary, gastrointestinal, genitourinary, and immune system may demonstrate malformations in the setting of bodily isomerism (hereafter to be referred to simply as isomerism) [4-6]. In regards to the immune system, there may be absence of the spleen, presence of multiple spleens, or a solitary, normally located spleen. Regardless of the splenic anatomy, however, functional asplenia may be present, increasing the risk of bacteremia, particularly in younger children [7,8]. While splenic anatomy has often been used to segregate isomerism into the asplenia and polysplenia type, it is now understood that isomerism is better segregated on the basis of atrial appendage morphology into right or left [2]. Those with right or left isomerism demonstrate a different constellation of findings ranging from cardiac malformations, anomalies in the cardiac conduction system, cardiac arrhythmias, and extracardiac malformations [9-11].

The implications of functional asplenia also go beyond an increase in the risk of bacteremia. Previous studies of patients with functional asplenia have demonstrated increased platelet counts, with an increased frequency of thrombocytosis (platelet count greater than 450,000 per microliter) [12-14]. This increased risk of thrombocytosis has been demonstrated to be present for weeks to months after onset of asplenia [12,15-17]. Most of this data comes from patients requiring splenectomy. Studies of platelet counts and subsequent risk of thrombosis in patients with isomerism is scarce. Yamamura and colleagues demonstrated higher platelet counts in children with complex congenital malformations of the heart and what they referred to as the asplenia syndrome. They also demonstrated an increased risk of thrombosis in those with asplenia [16]. Such data regarding platelet counts and thromboembolic events in adults with isomerism is not available.

We used data from the Nationwide Inpatient Sample to conduct a cross-sectional study by which to compare the prevalence of thrombocytosis and thrombosis in patients with and without isomerism.

Methods

Institutional review board review approval was waived as this studied utilizes deidentified data from a national database. This was done by the institutional review board at our institution as the database utilized contains deidentified information and has thus been identified as a database that does not require institutional review board approval when utilized for manusripts. Consent was not obtained by the authors

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for this study as the data was derived from a national database. This cross-sectional study is in compliance with the Helsinki declaration.

Nationwide inpatient sample

The Nationwide Inpatient Sample (NIS), Healthcare Cost Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ) is a large database designed to capture data from approximately 20% of all community hospital admissions in the United States. All patients cared for at these selected hospitals are included in the NIS. Rehabilitation and long-term acute care hospitals are excluded from this database. Patients from all regions of the United States with a variety of payer types are captured in this database. Data from a total of 44 states is captured. A majority of admissions in this database involve adult patients. The NIS data otherwise used a self-weighting design to help reduce confidence intervals. Data variance from the NIS can be self-validated for specific iterations although this has not been formally published for the 2012 iteration.

Patient identification

Data regarding hospital admissions was obtained from the 2012 NIS which is the most recent iteration of the database. Patients with isomerism were identified using the International Classification of Diseases, Ninth Revision (ICD-9) code 746.87. Patients with situs inversus were not included in this group as not all situs inversus portends isomerism. Admissions associated with thrombocytosis were identified by an ICD-9 code of 289.9.

Acute inferior caval vein thrombosis was identified by: 453.2; acute renal vein thrombosis by: 453.3, acute neck vein thrombosis by: 453.85, 453.86, 453.87; acute leg vein thrombosis by 453.40, 453.41, 453.42; acute arm vein thrombosis by 453.81, 453.82, 453.83, and 453.84. An aggregate endpoint of any acute venous thrombosis was created using data from all the aforementioned thromboembolic events. Primary and secondary diagnosis fields were used to collect this data.

Arterial thrombosis was not investigated in this study as anecdotally it is venous thromboembolism that is appreciated in patients with isomerism [16]. This is based on clinical experience as studies have not formally investigated this as of yet.

No patients were excluded from this analysis. Unfortunately it is not possible from the NIS data to determine which admissions represented readmissions within the same year so this could not be accounted for.

Data identification and collection

Demographic information including, gender, and race were collected for each admission. Admission characteristics such as admission month, length of stay, and cost of stay were collected as well. Information regarding comorbid conditions was also collected. Hyperlipidemia was identified using 272.0, 272.1, 272.2, and 272.3 hypertension using 401.0, 401.1 and 401.9. Overweight or obese patients were identified using 278.00, 278.01, and 278.02 with smokers being identified by 305.1.

Data of interest in regards to isomerism included cardiac anatomy as well splenic anatomy. The following congenital cardiac malformations commonly associated with isomerism were collected:functionally univentricular hearts using 745.3, double outlet right ventricle using 745.11, atrioventricular septal defect using 745.60 and 745.69, partial anomalous pulmonary venous connection using 747.42, and total anomalous pulmonary venous connection using 747.41. Splenic abnormality, either absence of a spleen or presence of multiple spleens, was collected using 759.0. It was not possible to distinguish between those with absence of a spleen or multiple spleens due to the ICD-9 coding strategy.

Statistical analysis

A cross-sectional study was conducted. Continuous variables are reported using mean and standard deviation while categorical variables are reported using absolute frequency and percentages. Continuous variables were analyzed using a student t-test or Mann-Whitney-U test as appropriate with categorical variables being analyzed using chi-square analysis. Baseline characteristics such as age, gender, race, and comorbid conditions were compared between those with and without isomerism. A univariate cross tabulation analysis was conducted to determine the odds of having thrombocytosis and specific venous thromboembolic events in patients with and without isomerism. Logistic regression analysis was also conducted with acute venous thrombosis as the dependent variable and the following independent variables: isomerism, age, race, gender, smoking status, overweight or obese, hyperlipidemia, hypertension, diabetes mellitus, acute kidney injury, chronic kidney injury, myocardial infarction, functionally univentricular heart, thrombocytosis and prophylactic aspirin use.

All statistical analysis was done utilizing SPSS Version 20.0 (Chicago, IL).

Results

Overall characteristics

Data from a total of 6,907,109 admissions from 2012 were included in the analysis. Of these, 861 (0.01%) were associated with isomerism. This resulted in the prevalence of isomerism in this cohort being approximately 1 in 10,000. Overall characteristics of these admissions did differ between those with and without isomerism. The age at admission tended to be lower, length of hospital stay tended to be longer, and cost of hospital stay tended to be longer in those with isomerism versus those without. Admissions associated with isomerism tended to consist of more males, more Hispanics, and more Asian or Pacific Islanders. Smoking, hyperlipidemia, hypertension, diabetes mellitus, acute kidney injury, chronic kidney disease, overweight or obesity, obstructive sleep apnea were all less prevalent with isomerism. All congenital malformations of the heart were more common with isomerism as well. Inpatient mortality was higher in admission with isomerism (Table 1).

Thrombocytosis and thromboembolic events

Thrombocytosis was equally prevalent in both groups with a prevalence of 0.1% (crude odds ratio 3.69, 95% confidence interval 0.52 to 26.27). Acute venous thrombosis was present in 1.1% of the total cohort. There was no statistically significant difference in the prevalence of acute venous thrombosis between those with and without isomerism (crude odds ratio 0.75, 95% confidence interval 0.35 to 1.57). When the risk of acute venous thrombosis was compared between the two groups with respect to specific site of thrombosis there was no difference noted. Acute leg vein thrombosis was the most common in both with (0.3% prevalence) and without (0.8% prevalence) isomerism (crude odds ratio 0.44, 95% confidence interval 0.14 to 1.39). Acute renal vein thrombosis was the least common in both the group with (0%) and without (0.1%) isomerism. Acute inferior caval vein thrombosis (crude odds ratio 4.32, 95% confidence interval 0.61 to 30.71), acute

neck vein thrombosis (crude odds ratio 2.89, 95% confidence interval 0.90 to 8.98), and acute arm vein thrombosis (crude odds ratio 0.50, 95% confidence interval 0.08 to 3.53) also did not differ between the two groups (Table 2).

When looking at characteristics of only those admissions associated with acute venous thrombosis, in a univariate fashion, it is of note that those with isomerism tended to be associated with acute venous thrombosis at a younger age (34.14 ± 23.77 *vs.* 63.76 ± 17.99 years, p<0.0001), longer hospitalization (39.86 ± 27.41 *vs.* 9.93 ± 13.33 days, p<0.0001), and increased cost ($720,076.43 *vs.* $93,342.34, p<0.0001).

Isomerism was not an independent risk factor for any acute venous thrombosis. Age and gender were both significant risk factors for acute venous thrombosis.

Discussion

This analysis demonstrates no increased risk of thrombosis in adults with isomerism after multivariate analysis. Thrombocytosis was present in 0.1% of those with isomerism and 0.1% of those without isomerism, similar to findings of previous population based studies [18]. These findings are not particularly surprising. While studies have demonstrated a large percentage of thrombocytosis being secondary to functional asplenia, up to 19% of cases of extreme thrombocytosis, this thrombocytosis has been demonstrated to generally resolve within months [12,15,19]. Platelet counts may increase 30% to 100% in the immediate postoperative period after splenectomy, with up to 85% of patients having thrombocytosis in this period. Platelet counts generally peak between postoperative day 7 and 20 and then return to normal in weeks or months, rarely taking years to normalize [15].

If postsplenectomy data is applied to the congenital asplenia population then it would be reasonable to consider birth the equivalent of time of splenectomy. Thus, it would become apparent that thrombocytosis secondary to functional asplenia would then be present in a majority of these children and resolve within the first year of life. Thrombocytosis secondary to other causes such as infection, trauma, surgery, and anemia may still occur, although thrombocytosis due to the functional asplenia should be resolved [15].

Yamamura and colleagues were able to demonstrate this in a study of patients with complex congenital malformations of the heart requiring

	No isomerism (n=6,906,248)	Isomerism (n=861)	p-value
Age at admission (years)	51.28 ± 25.82	25.49 ± 30.21	<0.0001
Female	4,007,523 (58.0)	379 (44.0)	<0.0001
Current smoker	888,276 (12.9)	50 (5.8)	<0.0001
Hyperlipidemia	348,536 (5.0)	19 (2.2)	<0.0001
Hypertension	2,386,574 (34.6)	158 (18.4)	<0.0001
Diabetes mellitus	1,509,816 (21.9)	85 (9.9)	<0.0001
Acute kidney injury	629,878 (9.1)	56 (6.5)	0.008
Chronic kidney disease	812,138 (11.8)	63 (7.3)	<0.0001
Overweight or obese	724,704 (10.5)	55 (6.4)	<0.0001
Obstructive sleep apnea	302,485 (4.4)	28 (3.3)	0.106
Race White Black Hispanic Asian or Pacific Islander Native American Other	 4,360,026 (66.9) 967,372 (14.8) 742,364 (11.4) 168,044 (2.6) 47,063 (0.7) 236,681 (3.6)	 447 (56.2) 97 (12.2) 172 (21.6) 35 (4.4) 6 (0.8) 38 (4.8)	 <0.0001
Length of hospital stay	4.65 ± 6.73	11.39 ± 25.90	<0.0001
In-hospital mortality	133,994 (1.9)	45 (5.2)	<0.0001
Myocardial infarction	172,377 (2.5)	17 (2.0)	0.327
Functionally univentricular	347 (0.1)	67 (7.8)	<0.0001
Double outlet right ventricle	546 (0.1)	85 (9.9)	<0.0001
Atrioventricular septal defect	0 (0.0)	0 (0.0)	--
Partial anomalous venous connection	196 (0.1)	11 (1.3)	<0.0001
Total anomalous venous connection	236 (0.1)	15 (1.7)	<0.0001
Absence of a spleen or presence of multiple spleens	687 (0.1)	39 (4.5)	<0.0001
Tetralogy of fallot	1,414 (0.1)	12 (1.4)	<0.0001
Ventricular septal defect	7,525 (0.1)	79 (9.2)	<0.0001
Secundum atrial septal defect	29,410 (0.4)	126 (14.6)	<0.0001

Table 1: Characteristics of hospitalizations for those with and without isomerism. Crude odds ratios are presented.

	No isomerism (n=6,906,248)	Isomerism (n=861)	Crude odds ratio (Odds ratio and 95% confidence interval)	p-value
Thrombocytosis	2,173 (0.1)	1 (0.1)	3.694 (0.520 to 26.269)	0.161
Acute inferior caval vein thrombosis	1,859 (0.1)	1 (0.1)	4.319 (0.607 to 30.709)	0.111
Acute renal vein thrombosis	539 (0.1)	0 (0)	--	0.795
Acute neck vein thrombosis	8,349 (0.1)	3 (0.3)	2.889 (0.903 to 8.976)	0.055
Acute leg vein thrombosis	53,505 (0.8)	3 (0.3)	0.448 (0144 to 1.391)	0.154
Acute arm vein thrombosis	16,130 (0.2)	1 (0.1)	0.497 (0.080 to 3.530)	0.475
Any acute venous thrombosis	74,855 (1.1)	7 (0.8)	0.748 (0.356 to 1.574)	0.443

Table 2: Frequency of thromboembolic occurrences in those with and without isomerism.

univentricular palliation and with or without what they identified as asplenia syndrome. Average platelet count shortly after birth in those with asplenia was 557,000 per microliter. By the time of the Glenn procedure, done at a mean age of 11.9 months in the study, platelet counts were 313,000 per microliter in those with asplenia. Platelet counts increased after the Glenn and Fontan procedures, as expected, but late after Fontan mean platelet count was 336,000 per microliter [16]. Loomba et al. found similar results with increased thrombocytosis at time of the Norwood and Glenn palliations but not thereafter [20].

The major concern associated with thrombocytosis is the risk off thromboembolism. Studies have demonstrated a 5 to 10% risk of thromboembolism after splenectomy, with a majority of this being venous thromboembolism shortly after onset of functional asplenia [12]. Yamamura and colleagues studied the risk of thromboembolism in children with what they referred to as asplenia syndrome. Their study found a 28% risk of thromboembolism in those with asplenia versus 10% in those without. Risk of Blalock-Taussig shunt malfunction, brain infarction, Fontan thromboembolism, and venous thromboembolism was higher in those with asplenia. These events were all in childhood, primarily in the period before the Fontan [16].

Interestingly, in the current analysis, we found that acute venous thrombosis occurred at a significantly younger age in the setting of isomerism. Hospitalizations associated with acute venous thrombosis also tended to be longer and costlier, although the precise etiology of this is unclear. It should also be noted that this was noted with only univariate analysis.

Few case reports have described thromboembolism in adults with chronic thrombocytosis secondary to functional asplenia. This is due to the low frequency of chronic thrombocytosis in those with functional asplenia. Adults with chronic thrombocytosis secondary to functional asplenia have been documented to have had primarily venous thromboembolic events, although some did have arterial thromboembolic events including myocardial infarction. Those believed to have venous thromboembolic events secondary to thrombocytosis as a result of functional asplenia should be treated accordingly with antiplatelet therapy. Aspirin, hydroxyurea, anagrelide and ticlodipine are all options for antiplatelet therapy in adults, although data is most readily available for aspirin for children [12-14,17]. All adults with isomerism need not be on antiplatelet therapy, although those with functionally univentricular hearts and Fontan circulation may benefit from this to reduce the risk of venous thromboembolism [21].

Adults with isomerism do not have an increased risk of thrombocytosis or subsequent thromboembolism. Very few adults with isomerism will have persistent thrombocytosis that is secondary to functional asplenia. In the event that thrombocytosis is found in an adult, however, it is important to keep in mind that isomerism may always be an underlying factor for this finding.

This analysis benefits from a large sample size which allows for the analysis of a rare condition such as isomerism, believed to have an incidence of 1 in 10,000 [22,23]. The prevalence of isomerism in this cohort was also found to be 1 in 10,000. Additionally, the availability of a variety of clinical data, as coded by ICD-9 codes, allowed for multivariate analysis to be performed.

This study is not without its limitations, however. Firstly, we were unable to segregate isomerism into right or left. Additionally, coding for congenital cardiac malformations is not ideal to help extract precise information about the cardiac anatomy that would be needed for this. Other anatomic findings to help segregate into right and left isomerism, such as splenic anatomy, are also not precise as both absence of a spleen and presence of multiple spleens were coded with a single code. Properly capturing the arrangement of the abdominal organs was not possible for similar reasons. Also, not all ICD-9 codes have been validated over the years, particularly those used to code for congenital cardiac malformations. A large percentage of those with isomerism didn't have a congenital heart defect that was documented or was coded under a nonspecific ICD-9 code which did not allow identification of a specific lesion. Additionally, coding also becomes an issue when identifying patients with thrombocytosis. The ICD-9 code used to identify patients with thrombocytosis includes "unspecified disease of blood and blood-forming organs" which also entails thrombocytosis. Thus, we do overestimate the prevalence of thrombocytosis in our analysis. It must also be acknowledge that several ICD-9 codes have not been validated which is the case of the majority of the codes utilized in this study. Platelet counts were also unavailable for use and thus we were only able to look at presence of absence of thrombocytosis. Absolute platelet counts would allow for a linear regression to be carried out as well which may further delineate what platelet count is truly worrisome for thromboembolic events by means of sensitivity analysis. The results must also be interpreted with the understanding that this cohort represents patients who have survived into adulthood and thus these findings are not applicable to pediatric patients with isomerism. Although survival with isomerism has improved, overall survival at 20 years of age is still approximately 50% [24]. There are several codes for venous thromboembolism as well. While we attempted to capture all of these it is possible that some other codes used to code such events were missed.

Future investigations would include prospective studies of patients with isomerism from 18 years of age onward to characterize the development of thrombocytosis as well as thromboembolic events. The use of antiplatelet agents in prevention of thromboembolic events in subgroups of adult isomerism patients with higher risk of such events may also be of interest, particularly those with Fontan circulation. Due to the low number of patients this would best be done in a multicenter fashion.

Conclusion

Isomerism is not associated with increased prevalence of thrombocytosis or prevalence of acute venous thromboembolism. Acute venous thromboembolism does tend to occur at a younger age in association with isomerism and is associated with longer and costlier hospitalizations in the presence of isomerism.

Ethics Statement

As described in the methods, this study complies with the Helsinki Declaration. As this study utilized deidentified publicly available data, IRB approval was not required.

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