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Dextrocardia: When Right is Wrong!

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Abstract

Introduction/Background: Dextrocardia is a malposition of the heart in the thoracic cavity. Dextrocardia has been known to cause diagnostic dilemmas with atypical presentations in acute coronary syndrome, as well as technical challenges in patients who require interventions such as coronary catheterization, transcutaneous aortic valve replacement, ablation for arrhythmias, or pacemaker/defibrillator placement. Transcription factor Pitx2 has been shown to have a fundamental role during cardio-genesis, and its misexpression has been implicated in arrhythmogenesis and congenital heart diseases including visceral situs inversus. This association between congenital heart diseases and arrythmias is intriguing and need exploring. We aimed to quantify the likelihood of arrhythmias in patients with dextrocardia.

Materials and Methods: A descriptive, retrospective study was conducted on the National Inpatient Sample (NIS) databases for the year 2016. Patients with dextrocardia and arrhythmias were selected based on appropriate diagnostic codes. We used propensity score-matching to assemble a matched cohort in which adults with dextrocardia and controls balanced on measured baseline characteristics. This was done to reduce the confounding effect of between-group imbalances on outcomes. Complex survey design, weights, and clustering were accounted for during analysis. Multivariate regression analysis was performed to determine the relationship of arrhythmias and length of hospitalization with dextrocardia.

Results: The prevalence of arrhythmias in patients with dextrocardia was significantly higher than the control group. Overall, the odds of arrhythmia were higher for patients in the dextrocardia group when compared to a propensity matched control group [adjusted Odds ratio OR 2.60, Confidence Interval (CI) (1.67-4.06), p<0.001]. When looking at only principal/primary diagnosis on admission, the odds of an admitting diagnosis of arrhythmia were significantly higher in the dextrocardia group when compared to the matched cohort [adjusted OR 3.70, CI (1.26-10.89), p 0.02]. The increased odds of arrhythmia in dextrocardia patients were mostly accounted for by the increased odds of atrial fibrillation/atrial flutter [OR 3.06, CI (1.02-9.18), p 0.046] in these patients. No significant difference was found in the odds of other arrhythmias or the length of stay between the two groups.

Conclusion: In a large inpatient population, patients with dextrocardia were more likely to have arrhythmias especially atrial fibrillation/atrial flutter than patients without dextrocardia. Ours is the first study that investigates the clinical manifestations of molecular and embryologic associations between congenital heart disease and arrhythmias.

Introduction

Humans establish anatomical left-right asymmetry during embryogenesis. Variation from this normal arrangement—referred to as situs solitus results in heterotaxy. Heterotaxy may manifest as randomization (situs ambiguus) or complete reversal (situs inversus) of normal organ position. [1] Situs inversus may be associated with malposition of the heart in the thoracic cavity with or without malformations. Normally, the embryonic straight heart tube initially turns to the right, then grows to the left until the ventricular portion occupies a normal left thoracic position. Thus left thoracic heart (levocardia) with situs solitus is the normal arrangement in humans. Dextrocardia refers to positioning of the heart on the right side of the thoracic cavity and is commonly associated with situs inversus. Mesocardia refers to the heart lying in a central position in thorax. The four cardiac malpositions described are as below. [2]

1. Situs solitus with dextrocardia
2. Situs inversus with dextrocardia
3. Situs inversus with levocardia
4. Mesocardia associated with situs solitus, situs inversus or situs ambiguus

Transcription factor Pitx 2 has been shown to have a fundamental role during cardiogenesis, and its misexpression has been implicated in arrhythmogenesis as well as visceral situs and congenital heart diseases.[3] This association between congenital heart diseases and arrythmias is intriguing and need exploring. Previously, Momma et al is the

Key Words

Dextrocardia, Arrhythmias, Atrial fibrillation, Atrial flutter

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only study that attempted to describe arrhythmias in dextrocardia. That study was limited by a very small patient population of only 40 patients.[4] Our study is the first study to describe the incidence of arrhythmias in patients with dextrocardia using the National Inpatient Sample database.

Materials and Methods

A descriptive, retrospective study was conducted on the National Inpatient Sample (NIS) databases for year 2016.[5] NIS database is available from Healthcare Cost and Utilization Project, originally created by the Agency for Healthcare Research and Quality through a Federal-State-Industry partnership. It is the largest all-payer inpatient care public database in the United States which includes a 20% sample of patients from all hospitals in participating states. Discharges from all hospitals are sorted by hospital ownership, bed size, teaching status, urban/rural location, and four U.S census regions, and every fifth discharge is selected. Each observation in the sample represents a unique hospitalization with information about patient demographics (age, gender, race and ethnicity), hospital characteristics, diagnoses at discharge (one primary and up to 29 secondary), up to15 procedure codes, payer status information, length of stay, and discharge disposition. The diagnosis and procedures are available as International Classification of Diseases- Tenth Revision (ICD-10) codes. Weights are assigned to each discharge and are stored in each record in the data element discharge weight (DISCWT).[5] The study was exempted from institutional review board approval, and the requirement for informed consent was waived because the database uses previously collected de-identified data.

Admissions with Dextrocardia were selected based on the pertinent ICD-10 codes Q240 and ICD-10 code Q893 was used to identify situs inversus. Patients with concurrent arrhythmias as a primary or secondary diagnosis were selected based on appropriate ICD-10 codes. Additional comorbidities were identified as baseline characteristics and for matching using the appropriate ICD-10 codes (available via request from the corresponding author). Analyses were conducted on adults aged 18 or greater.

The primary outcome of interest was the occurrence of arrhythmias as a primary/principal diagnosis or any diagnosis (primary or secondary) in patients with dextrocardia. Secondary outcomes were the occurrence of atrial fibrillation/atrial flutter, cardiac conduction delay, cardiac arrest, supraventricular tachycardia and ventricular tachycardia in patients with dextrocardia. An additional secondary outcome was the difference in length of stay in patients with dextrocardia compared to those without.

We used propensity score-matching to assemble a cohort in which adults with dextrocardia versus without dextrocardia were balanced on measured baseline characteristics. This was done to reduce the confounding effect of between-group imbalances on outcomes. Covariates used in matching were: current or previous cardiovascular diseases, prior interventions for coronary artery disease, comorbidities (listed in Table 1), electrolyte imbalances, cardiogenic shock and respiratory failure. We used nearest-neighbor matching model without replacement to match our cohorts. Maximum propensity difference (caliper width) allowed was 0.01. Patients with dextrocardia without a matched observation were excluded. In the final analysis, 1255 patients with dextrocardia were compared to 1255 matched patients. We examined differences in each covariate using t-test/chi-squared test to assess the efficacy of the propensity score model.

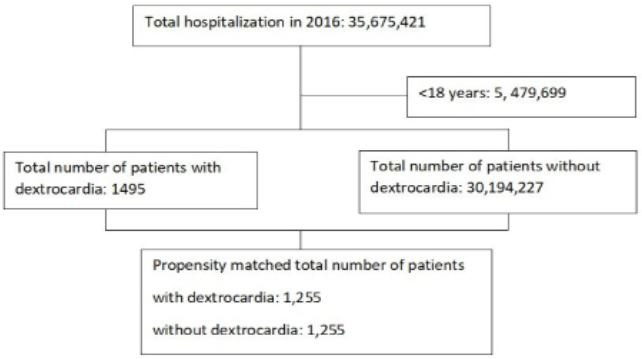

Figure 1: **Selection of the patient cohort.**

Statistical analysis was performed using STATA 13.1 (Stata Corp, College Station, TX). Complex survey design, weights, and clustering were taken into account during analysis. Weights were applied to the unweighted NIS data using "SURVEY" procedures in Stata, producing a nationwide discharge-level estimate for discharges from all hospitals in the USA. We computed mean, standard deviation, frequency, and percentages as our descriptive variables. Differences in mean and percentage were assessed using the t-test and chi-squared test respectively. Multivariate regression analysis was performed to find the relationship between Dextrocardia and length of stay and incidence of arrhythmias. A two-sided p-value of <0.05 was chosen as level of statistical significance.

Observational studies using administrative data, such as ours, require proper comorbidity adjustment between study and control group, to reduce bias. Two popular methods for comorbidity burden assessment are the Elixhauser comorbidity system, a set of 30 comorbidity indicators, and the Charlson co-morbidity index—a composite score summarized by a weighted combination of 17 comorbidities.[6,7] Several studies have demonstrated Elixhauser comorbidity system to be superior for predicting various outcomes.[8] We utilized Elixhauser score developed by van Walraven, a weighted composite score based on the Elixhauser system, as a measure of the comorbidity burden for adjustment between the patients with dextrocardia and the matched control group.[9]

In the multivariate regression analysis, the following variables were used: insurance type, age, gender, race, smoking status, hyperlipidemia, coronary artery disease, current or prior myocardial infarction, acute kidney injury, prior percutaneous coronary intervention, prior coronary artery bypass grafting, family history of coronary artery disease, personal history of cardiac arrest, cardiogenic shock, elixhauser score, respiratory failure requiring ventilation.

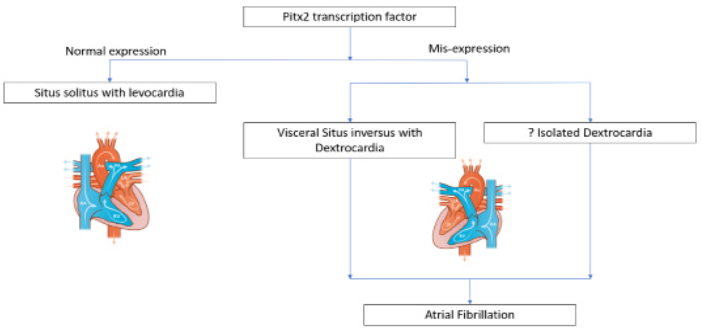

Figure 2: **Schematic representation of potential association between Dextrocardia and Atrial Fibrillation.**

Results

There were a total of 35,675,421 admissions in the year 2016. Out of these 1,495 patients were adults with a diagnosis of dextrocardia, of which 4.35% also had a diagnosis of situs inversus. After propensity-score based matching 1,255 adults with dextrocardia were matched with 1,255 adults without dextrocardia. (Figure 1)

The mean age of patients with dextrocardia was 54.95 + 21.4 years. Among all patients with dextrocardia, 50.5% were female, 62.23% were white and the mean Elixhauser comorbidity score was 3.99 + 2.25. There was no significant difference between the dextrocardia group and the propensity matched control group with respect to the baseline demographics and comorbidity variables listed in Table 1 except for exposure to smoking.

The prevalence of arrhythmia in patients with dextrocardia when compared to controls was significantly higher (44.62% vs 26.69%, p <0.001). (Table 1) Arrhythmia as the principal or primary admitting diagnosis was also assessed to be significantly higher in patients with dextrocardia when compared to controls (6.38% vs 2.39%, p=0,031).

Overall, the odds of arrhythmia as any diagnosis (primary or secondary) were higher for patients in the dextrocardia group when compared to the propensity matched control group [Odds ratio (OR) 2.21, Confidence Interval (CI) (1.52-3.21), p <0.001]. These odds were even higher when adjusted for variables listed in methodology [OR 2.60, CI (1.67-4.06), p<0.001). (Table 2) Atrial fibrillation/flutter accounted for these increased odds of arrhythmias [OR 2.04, CI (1.24-3.35), p 0.005) in patients with dextrocardia as there was no difference in the odds of other arrythmias between the two groups. (Table 2)

When looking at principal/primary diagnosis on admission, the odds of patients being admitted with arrhythmia were significantly higher in the dextrocardia group when compared to the matched cohort (Table 2). The odds were higher in the dextrocardia group even after adjustment [OR 3.70, CI (1.26-10.89), p 0.02]. Similar to any diagnosis, for primary/principal diagnosis the higher odds of arrhythmia in dextrocardia patients were influenced by the odds of atrial fibrillation/atrial flutter [OR 3.06, CI (1.02-9.18), p 0.046]. (Table 2). No significant difference was found in the length of stay between the two groups. (Table 2)

Discussion

The incidence of situs inversus has been estimated to be around 1 in 12,000 pregnancies (1 in 8000 to 1 in 25000).[1,10] Dextrocardia with or without situs inversus has been reported to cause diagnostic dilemmas with atypical presentation in acute coronary syndrome.[11] Altered anatomy seen with dextrocardia is even more of a challenge especially in patients who require interventions such as coronary catheterization, transcutaneous aortic valve replacement, ablation for arrhythmias, pacemaker/defibrillator placement.[12-22]

During embryogenesis cardiomyocytes in the caudal heart tube are the first to become electrically active and become the "pacemaker". The SA node, which develops during the fifth week, initially develops in the sinus venosus and then is incorporated into the RA. The AV node arises slightly superior to the endocardial cushions. Fibers forming the Bundle of His develop from fast-conducting ventricular myocardium while the SA and AV nodes are formed from the slow-conducting myocardium of the inflow tract and AV canal. Connective tissue grows in from the epicardium, forming the cardiac skeleton that separates conduction in the atria and ventricles.

A distinctive and essential feature of the vertebrate body is a pronounced left-right asymmetry of internal organs. The left right handedness of visceral organs is conserved among vertebrates and is regulated during embryogenesis by asymmetric signals relayed by molecules such as Shh, Nodal and activin.[23] Molecular signals emanating from the node confer distinct left/right signaling pathways that ultimately lead to activation of the transcription factor Pitx2 in the left side of embryonic organ anlagen, including the developing heart.[3] A highly controlled temporal and tissue-specific action of Pitx2 during cardiac development has been described. Pitx2 is therefore the last effector of the left/right signaling cascade transmitting positional information from the uncommitted lateral plate mesoderm to distinct organ primordia such as the heart, lung and gut, among others, leading to distinct sidedness alterations within these organs if impaired.[3]

Abnormalities in expression of Pitx2 has been directly linked to distinct congenital heart diseases including (Atrial Septa Defects, Ventricular Septa Defect, Double Outlet Right Ventricle, Right Atrial Isomerism, Transposition of Great Arteries and Tetralogy of Fallot).[3] Depletion of the asymmetric Pitx2c function has been shown to unbias the direction of heart looping, produce reversed heart looping and heart isomerisms, reversed body rotation, and reversed gut situs.[24, 25] Dextrocardia could be a result of the right-left mis-signaling and the altered looping of the congenital heart tube and thus Pitx2 may be linked to dextrocardia.

Atrial fibrillation is the most common arrhythmia in the general population, and it has been related to several risk factors, such as advanced age, male gender, hypertension, obesity, ischemic heart disease, myocardial infarction, valvular diseases and hyperthyroidism.[26] Several genome-wide association studies (GWAS) have been published reporting chromosomal loci in association with atrial fibrillation. Seminal GWAS study by Gudbjartsson et al., proposed an association between Pitx2 and atrial fibrillation, as a causative molecular link.[27] Pitx2 regulates atrial fibrillation through modulation of multiple genes and its functional role in atrial arrhythmias using distinct experimental

Table 1: Patient characteristics.

Patient characteristic	Patients with dextrocardia (n) 1255	Patients without dextrocardia (n) 1255	p-value
Demographics			
Mean Age (SD) years	56.47 (21.35)	56.47 (21.35)	1
Female (%)	49	49	1
Race (%)			
White	65.34	65.34	1
African American	17.13	17.13	1
Hispanic	13.94	13.94	1
Asian or Pacific Islander	0.8	0.8	1
Native American	-	-	-
Others	2.79	2.79	1
Insurance type (%)			
Medicare	53.78	45.42	0.06
Medicaid	16.33	21.51	0.15
Private insurance	21.51	25.9	0.24
Self-pay	3.98	3.59	0.82
No charge	-	-	-
Other	4.38	3.59	0.67
Mean Elixhauser score (SD)	3.86	3.90	0.42
Comorbidities (%)			
Hypertension	55.38	57.37	0.65
Diabetes	25.89	23.90	0.62
Hyperlipidemia	32.27	33.07	0.85
Valvular heart disease	11.16	12.35	0.70
Prior coronary artery disease/ MI	25.09	28.69	0.39
Prior PCI/CABG	9.16	9.16	1.0
Prior cardiac arrest	0.39	0.79	0.56
Chronic kidney disease	19.92	21.51	0.66
Fluid and electrolyte disorders	32.67	37.85	0.24
Chronic lung disease	33.07	30.28	0.50
Pulmonary circulation disorders	14.34	17.53	0.33
Peripheral vascular disease	9.96	9.96	1.0
Thyrotoxicosis	-	-	-
Hypothyroidism	13.15	15.54	0.46
Anemia	5.98	4.78	0.56
Coagulopathy	8.37	9.96	0.53
Obesity	14.34	15.94	0.63
Family history of CAD	3.98	5.58	0.40
Smoking status (%)	25.49	33.87	0.04
Alcohol or drug abuse	4.78	5.18	0.83
Current diagnosis or intervention (%)			
Myocardial infarction	3.59	3.98	0.82
Acute heart failure	21.91	22.31	0.92
Arrhythmia	44.62	26.69	<0.001
Arrhythmia as primary diagnosis	6.38	2.39	0.031
Cardiogenic shock	0.79	0.39	0.56
Respiratory failure	19.52	16.34	0.36
Mechanical ventilation	10.76	7.97	0.29
Acute kidney injury	21.12	21.91	0.83
Diagnostic EP study, ablation/ICD or pacemaker placement	1.19	0.39	0.31

models has been demonstrated.[3,28] (Figure 2)

Based on the available molecular and genetic evidence of association between arrhythmias, particularly Atrial fibrillation, and congenital heart diseases including dextrocardia, our study aimed to explore the evidence of the same in clinical practice. We used an inpatient national database to identify patients with dextrocardia and arrhythmias and compared this cohort with a control group to identify associations between the two. To minimize the effect of baseline characteristics on outcomes, we used propensity score-matching to assemble a matched cohort in which adults with dextrocardia versus without dextrocardia were balanced on select covariates. Arrhythmia being mentioned as any diagnosis was one of our primary outcomes. Arrhythmia documented as principal/primary diagnosis was also compared between the two groups. We found a higher prevalence and incidence of arrhythmias in patients with dextrocardia when compared to the control group. We also showed an independent and significant association between dextrocardia and hospitalization for arrhythmias, including a three-fold increase in the odds of hospitalization with a primary diagnosis of arrhythmia in patients with dextrocardia. The difference in the odds of arrhythmia was mostly due to an increase in the odds of atrial fibrillation/atrial flutter between the two groups. Patients with dextrocardia also showed a trend towards higher odds for other arrhythmias although this trend did not reach statistical significance.

Ours is the first study that investigates the clinical manifestations of molecular and embryologic associations between congenital heart disease and arrhythmias. Further studies to elucidate the same are needed and should be encouraged.

Table 2: Primary and Secondary Outcomes: The odds of arrhythmias in patients with dextrocardia when compared to a matched cohort

Outcomes	Univariable analysis OR (CI)	p-value	Multivariable analysis OR (CI)	p-value
Primary Outcome				
Arrythmia – Any diagnosis	2.21 (1.52 – 3.21)	<0.001	2.60 (1.67 – 4.06)	<0.001
Arrhythmia – Primary diagnosis	2.78 (1.05 – 7.36)	0.04	3.70 (1.26 – 10.89)	0.02
Secondary Outcomes				
Atrial fibrillation/ Atrial flutter	1.79 (1.18 – 2.71)	0.006	2.04 (1.24 – 3.35)	0.005
Supraventricular tachycardia	1.97 (0.85 – 4.6)	0.12	1.94 (0.82 – 4.56)	0.13
Ventricular tachycardia	1.51 (0.42 – 5.4)	0.53	1.22 (0.32 – 4.54)	0.77
Conduction disorder	1.25 (0.57 – 2.74)	0.58	1.39 (0.65 – 3)	0.39
Cardiac arrest	2.53 (0.48–13.45)	0.28	3.40 (0.42 – 27.29)	0.25
	Univariable analysis Coefficient	p-value	Multivariable analysis Coefficient	p-value
Length of Stay	-0.6 (-2.63 – 1.36)	0.53	-0.11 (-1.85 – 1.63)	0.9

The main limitation of our study is the lack of data on the appropriate use of the diagnostic code for Dextrocardia, which is a new code in ICD-10.

Conclusion

Dextrocardia is an uncommon condition which is often, but not always associated with situs inversus. Dextrocardia is not just an anatomical malposition of the heart in the thorax, but also seems to correlate with clinical consequences. Molecular pathways involving the misexpression of transcription factor Pitx2 have been implicated in congenital heart diseases and arrhythmias. We explored the association between one of the congenital heart diseases (dextrocardia) and prevalence as well as adjusted odds of arrhythmia in these patients. In a large inpatient population, patients with dextrocardia were more likely to have arrhythmias especially atrial fibrillation/atrial flutter than patients without dextrocardia. A trend towards increased odds of other arrythmias were also seen in patients with dextrocardia however these odds did not reach statistical significance.

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