Transposition of the great arteries: A laterality defect in the group of heterotaxy syndromes or an outflow tract malformation?

Rana S Al-Zahrani[#], Samaher H Alharbi[#], Rawan M A Tuwaijri[#], Bayan T Alzomaili[#], Alaa Althubaiti, Talat Mesud Yelbuz[1]

College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [1]Department of Cardiac Sciences, King Abdulaziz Cardiac Center, Section of Pediatric Cardiology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia

[#]All 4 first listed authors have contributed equally to this project as part of their obligatory research block during their medical school, which is a requirement for graduation

ABSTRACT

Background/ Aim : **Transposition of the great arteries (TGA) is traditionally classified as a "conotruncal heart defect", implying that TGA evolves from abnormal development of the outflow tract (OFT) of the embryonic heart. However, recently published genetic data suggest that TGA may be linked to laterality gene defects rather than OFT gene defects. The aim of our study was to clarify whether there is any statistically significant link between TGA and clinically diagnosed laterality defects (heterotaxy).**

Methods : **Retrospective cross-sectional analysis of 533 patients diagnosed with TGA at our cardiac center over a period of 13 years (2002-2015). Hospital informatics and digital data recording systems were used for collecting patients' data and all patients were reviewed to check the echocardiograms for verification of the diagnosis, type (TGA, congenitally corrected TGA (ccTGA), and levo-position of the great arteries (LGA)), complexity of TGA, and all other variables (e.g., abdominal organ arrangement, cardiac position, presence or absence of other cardiac defects).**

Results : **Of 533 TGA patients, 495 (92.9%) had the usual arrangement of the internal organs, 21 (3.9%) had mirror-imagery, 7 (1.3%) had left and 10 (1.8%) had right isomerism. 444 (83.3%) patients had TGA. The number of patients who had usual visceral arrangement in each TGA type was: 418 (94.1%) in TGA, 49 (92.4%) in ccTGA, and 28 (77.7%) in LGA. 6 (1.4%) TGA patients, 4 (11.1%) patients with LGA were found to have right isomerism, while no ccTGA patient presented with this asymmetry. 4 (0.9%) TGA patients, 1 (1.9%) ccTGA patient and 2 (5.6%) patients with LGA had left isomerism. Heterotaxy (mirror-imagery, left and right isomerism) was more associated with LGA than TGA or ccTGA with a statistically significant difference (*P* value of 0.001).**

Conclusion : **In contrast to recently published genetic data, our morphological data do not disclose a significant link between TGA and heterotaxy.**

Keywords : Heterotaxy, laterality defects, outflow tract malformation, transposition of the great arteries

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Address for correspondence: Prof. Talat Mesud Yelbuz, Department of Cardiac Sciences, King Abdulaziz Cardiac Center, Section of Pediatric Cardiology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Khashmalaan Road, P. O. Box: 22490, Mail Code: 1420, Riyadh 11426, Kingdom of Saudi Arabia. E-mail: mesudyelbuz@yahoo.de

INTRODUCTION

The term "complete transposition of the great arteries" (TGA) is traditionally used to name congenital heart defects (CHDs) that are characterized by discordant ventriculo-arterial connections. In such a situation, the morphologically right ventricle is abnormally connected to the ascending aorta while the morphologically left ventricle is abnormally connected to the pulmonary trunk. In the majority of cases, discordant ventriculo-arterial connections are associated with parallel (non-spiraling) arrangement of the arterial trunks, suggesting that the condition may have resulted from abnormal development of the outflow tract of the embryonic heart.[1,2] Parallel arrangement (non-spiraling) of the great arterial trunks, however, does not necessarily indicate the presence of TGA. For example, a few cases have been reported in which TGA occurred with normal spiraling of the arterial trunks. Furthermore, in cases of CHDs with a solitary ventricle of indeterminate morphology ("univentricular" hearts), parallel great arterial trunks cannot be connected in a discordant fashion to the ventricle since neither a morphologically right nor a morphologically left ventricle exists. Parallel arrangement (non-spiraling) of the great arterial trunks, thus, should not be named TGA but rather "malposition of the great arterial trunks". Four main types of malposition of the great arteries can be found in CHDs: (1) "Dextro (D)-malposition" in which the aortic valve is to the right of the pulmonary valve; (2) "Levo (L)-malposition" in which the aortic valve is to the left of the pulmonary valve; (3) "Anterior (A)-malposition" in which the aortic valve is anterior to the pulmonary valve, and (4) "Posterior (P)-malposition" in which the aortic valve is posterior to the pulmonary valve.

Non-syndromic cases of complete TGA principally occur in two variants: (1) in combination with normal (concordant) atrio-ventricular connections, or (2) in combination with abnormal (discordant) atrio-ventricular connections. The former variant is frequently called TGA, while the latter is called congenitally corrected TGA. In this paper, we will designate "Transposition (TGA)" as the default term for all CHDs showing discordant ventriculo-arterial connections, irrespective of the type of atrio-ventricular connections; TGA is used for the "congenitally non-corrected" variant of complete TGA, while congenitally corrected TGA is used to separate and name the "congenitally corrected" variant. In the past, the term/abbreviation D-TGA was frequently used synonymous for TGA, while levo-transposition of the great arteries (L-TGA) was used as a synonym for congenitally corrected TGA. Both terms may make sense only in the setting of usual arrangement of the internal organs (situs solitus). In the setting of mirror-imagery of the internal organs (situs inversus), however, the term L-TGA would indicate the non-corrected variant of TGA rather than the congenitally corrected variant, and the term D-TGA would indicate the congenitally corrected variant of TGA rather than the non-corrected variant. For reasons of clarity, however, we did not use these terms as they were used classically. In this study, the formerly used term "L-TGA" as a synonym for congenitally corrected TGA, is now defined only as "levo-position of the great arteries" in which the aortic valve is positioned to the left of the pulmonary valve (such as in the setting of TGA with additional complicating heart lesions or in the setting of complex heart defects with an associated TGA) and will not be used as "L-TGA" anymore.

TGA is one of the most common and severe malformations of the heart, accounting for 5% to 7% of all CHD.[3-6] It is the 2nd most frequent cyanotic CHD, but the most frequent CHD diagnosed in the neonatal period.[4] Although it is one of the most common and severe CHDs, TGA does not have a precedent in phylogeny and ontogeny, and its etiology and morphogenesis still remains largely unknown.[6,1,7] Due to the fact that TGA is usually associated with parallel (non-spiraling) great arteries, such CHDs are suspected to result from abnormal development of the outflow tract of the embryonic heart. From the patho-morphological standpoint, TGAs do not seem to represent isolated forms of CHD. They rather seem to represent one end of a morphological spectrum of CHDs primarily affecting the ventricular outflows. This spectrum includes ventricular septal defect with overriding aorta, Tetralogy of Fallot, double outlet right ventricle with TGA, and TGA. Thus, in textbooks, TGA is usually considered to be part of the so-called "conotruncal heart defect" group, which is a pathogenetic group of CHD suspected to arise from abnormal development of the outflow tract of the embryonic heart.[1,2]

However, recent studies suggest that there is probably a different etiology involved in the genesis of this heart defect. It has been speculated that TGA is a laterality defect in the group of so-called heterotaxy syndromes (mirror-imagery, asplenia/right isomerism and polysplenia/left isomerism) rather than an outflow tract defect.[1,8]

Embryonic development of the cardiac outflow tract

The heart originates from progenitor cells within the mesoderm, the so-called mesodermal precardiac cells, and when the heart starts to loop and form, the right – left axis of the embryo is already mapped.[9,10] There are three different groups of these progenitor cells: 1) "first heart field" cells, which will form the future left ventricle and the primitive atria including the appendages,[9] 2) "secondary heart field" cells, which are responsible for the formation of the outflow tract, right ventricle, atrial myocardium and inflow tract,[11] 3) "extracardiac cells", which help in the formation of the coronary

arteries of the heart and septation of the great vessels: The extracardiac cells are divided into the so-called "cardiac neural crest" cells, which are critical for correct formation of the great arteries and septation of the outflow tract. A critical step during heart development is the so-called "wedging" process during which the aorta is positioned behind the pulmonary artery through a critical counterclockwise rotation of the outflow tract, so that the aortic valve is settled (wedged) between the two atrioventricular valves.[11-15] Problems during this critical stage of outflow tract development such as the failure of migration of the secondary heart field and cardiac neural crest cells to the outflow tract result in absence or abnormal spiraling of the aorto-pulmonary septum, which in turn can lead to outflow tract defects such as Tetralogy of Fallot, double outlet right ventricle and others.[8,9,11,16] TGA is a linear non spiral development of the great arteries which is classically regarded as an outflow tract lesion within this group of outflow tract defects, too.

Definition and developmental biology of heterotaxy

The right-left body symmetry is determined in early embryological phases by various genes. Data from developmental biology have shown that the development of the visceral situs is controlled by genes and molecular left-right signals, which confer left and right identities to the lateral plate mesoderms, during the third week of human embryonic development. Any interruption in left-right signaling could result in asymmetrical development of the internal organs.

In contrary to earlier definitions used by many clinicians, in our study the term "heterotaxy" is defined as any departure from the normal arrangement of the inner organs as proposed recently by Anderson *et al.* [Figure 1].[17] In the setting of usual arrangement of the internal organs (referred to earlier as "situs solitus"), the thoraco-abdominal organs are lateralized, differing in the anatomical features of their right and left sides [Figure 1 - left-hand panel]. The second pattern, earlier usually described as "situs inversus" represents lateralized thoraco-abdominal organs in a mirror-imaged variant of the usual bodily arrangement, which is a clear departure from the normal [Figure 1 - second left-hand panel]. Two other settings within heterotaxy are characterized by visceral symmetry rather than asymmetry. These bodily arrangements are named "right isomerism" [Figure 1 - second right-hand panel] and "left isomerism" [Figure 1 - first right-hand panel]. They are characterized by the presence of bilateral right-sidedness or bilateral left-sidedness of the inner organs, respectively. Thus, in patients with right isomerism, both atrial chambers have a large and pyramid-shaped (morphologically right) atrial appendages, both lungs have three lobes (morphologically right lungs), and the abdominal situs is frequently characterized by the absence of the spleen (asplenia). In patients with left isomerism, on the other hand, both atrial chambers have small and finger-shaped (morphologically left) atrial appendages, both lungs have two lobes (morphologically left lungs), and the abdominal situs is frequently characterized by the presence of multiple spleens (polysplenia) [Figure 1 - first upper row].[17]

Genetics of transposition of the great arteries and the association with heterotaxy

Interestingly, TGA is very rarely found in genetic syndromes commonly associated with outflow tract defects (e. g. Turner, Noonan, or Down's syndrome).[18] The only genetic syndrome demonstrating a strong relation with TGA seems to be the heterotaxy syndrome.[1,19] The parallel (non-spiral) arrangement of the great arterial trunks is also present in many patients with a subtype of double outlet right ventricle (the so-called double outlet right ventricle of TGA type, consisting of dextro-position of the aorta to the right ventricle and malpositioning of the pulmonary artery with a subpulmonary interventricular communication, resulting in TGA physiology), which is associated with heterotaxy as well, here in particular with the sub-group of asplenia/right isomerism. Furthermore, although TGA with intact ventricular septum is not associated with heterotaxy, virtually all patients with heterotaxy and asplenia/right isomerism present parallel and non-spiral great arteries in the setting of TGA or double outlet right ventricle with or without pulmonary atresia.[19-29] A recent screening experiment conducted on mice showed that some mice mutants with laterality defects were the same mutants which exhibit CHD, including TGA. This experiment also demonstrated that there are mutant genes that caused TGA and atrioventricular septal defects in all the mice carrying them. Half of that group of mice showed asplenia/right isomerism (opposed to polysplenia/left isomerism), showing the association between TGA, right isomerism and atrioventricular septal defects.[30-32] Therefore, TGA might have the same etiological background with heterotaxy, as it has been speculated in previous studies based on common genes between the two, however the classical pathogenesis explanation of TGA and heterotaxy remains unclear.

The primary aim of our study is to clarify whether there is indeed any association between TGA and morphological lateralization defects (heterotaxy).

MATERIALS AND METHODS

Study area/setting

The study was conducted in King Abdulaziz Cardiac Center (KACC), a specialized cardiovascular center in

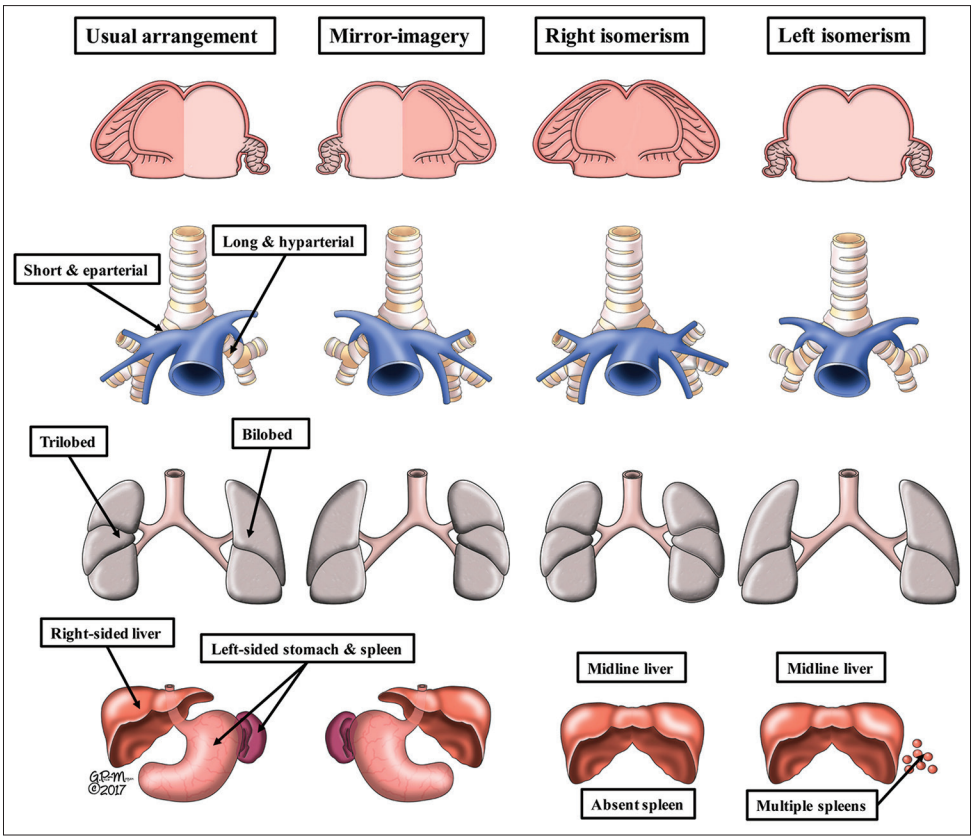

Figure 1: An illustration showing the 4 different variations of bodily organs in the lateralized (left-hand two columns) and isomeric (right-hand two columns) arrangements, including atrial appendages. The upper panels show the atrial appendages morphology, the second upper panel the bronchial morphology, and the relations of the bronchuses to the pulmonary artery feeding the lower lobes of the lungs, the third upper panel shows the pulmonary morphology, and the last lower panel shows the arrangement of the liver, stomach, and spleen. Adopted from: Anderson et al. (J Cardiovasc Dev Dis. 2018;5:11)

Riyadh, Saudi Arabia. This center has 4 Catheterization Laboratories, 4 Operating Rooms, and a total of 101 beds, 45 of these beds are Intensive care including a Medical Cardiac ICU, Cardiac Surgical ICU, Pediatric Cardiac ICU and a Coronary Care Unit.

Study objects

The study was conducted on 959 TGA patients seen in this center after applying the following inclusion and exclusion criteria on 610 patients [Figure 2]:

Inclusion criteria

- All patients registered in the database of this center who were diagnosed with TGA from 2016 to 2015.

Exclusion criteria

- Patients who didn't have echocardiograms that confirm the intracardiac anatomy and diagnosis
- Patients who were extracted from the database as TGA diagnosis but had echocardiograms that exclude TGA as the diagnosis
- Patients who had their primary lesion (TGA) repaired at other institutions, and were then transferred to this center.

Study design

This is a retrospective cross sectional study, which had the main goal of identifying the presence of any association between TGA and heterotaxy (laterality defects). All patients with TGA within the study period were analyzed through detailed chart review [Figure 2] to find out:

1) How many of the identified TGA patients also had a confirmed heterotaxy (laterality defects)?
2) How many of the TGA patients with heterotaxy belonged to the group of right isomerism?
3) How many patients with TGA and atrioventricular septal defects had right isomerism?
4) How many TGA and dextrocardia patients had usual arrangement of the internal organs (situs solitus)?

Data collection methods, instrument used, measurements

We conducted this research through chart review of all patients who presented with a TGA diagnosis to this center by reviewing in detail their suitability for the aim of our research. The main variables we looked at were:

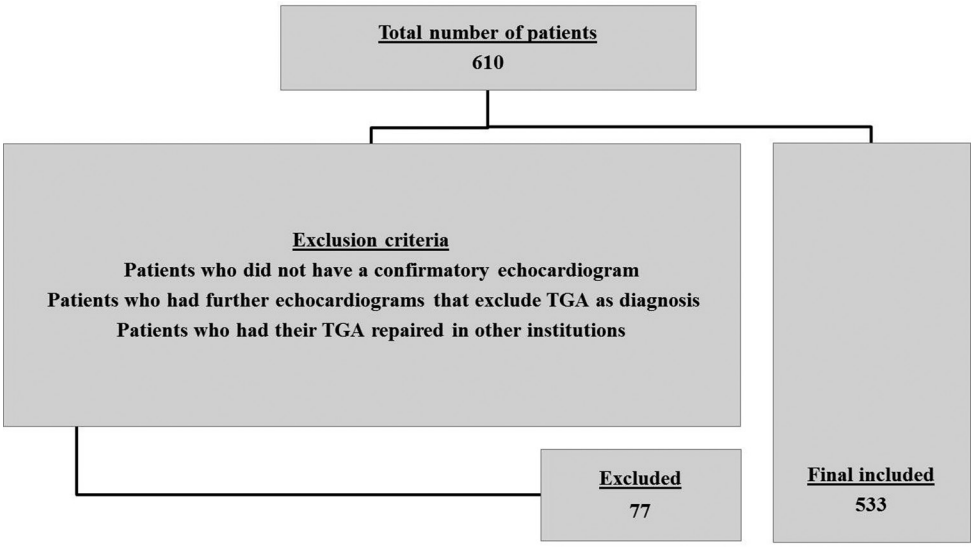

Figure 2: A flowchart showing our research methodology

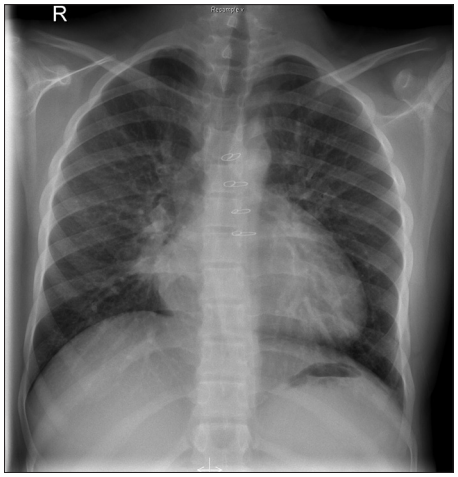

Figure 3: An inadequate chest X-ray of a transposition of the great arteries patient. The quality is not sufficient enough to identify properly the bronchial tree anatomy

1. Arrangement of the abdominal organs (usual arrangement (situs solitus), heterotaxy, including mirror-imagery (situs inversus), right and left isomerism) [Figure 1]
2. Cardiac position (levocardia, mesocardia, dextrocardia)
3. Type of TGA (TGA (discordant ventriculo-arterial connection), "congenitally corrected" TGA (discordant atrio-ventricular and ventriculo-arterial connection), "levo-position of the great arteries" (which is not "L-TGA" that is used by many as synonym for corrected TGA) in which the aortic valve is positioned to the left of the pulmonary valve (such as in the setting of TGA with additional complicating heart lesions or in the setting of complex heart defects with an associated TGA)
4. Complexity (*Simple TGA* (without complicating cardiovascular lesions), *TGA with additional complicating heart lesions*, *TGA in the setting of complex heart defects*) – the detailed definitions of which are provided in the results section
5. Interatrial septum status (intact interatrial septum, primum atrial septal defect, secundum atrial septal defect/patent foramen ovale, atrioventricular septal defect)
6. Interventricular septum status (intact interventricular septum, ventricular septal defect, atrioventricular septal defect)
7. Presence or absence of atrioventricular septal defect
8. Isomerism of the atrial appendages (usual arrangement (situs solitus), heterotaxy, including mirror-imagery (situs inversus), right and left isomerism) [Figure 1 - first upper row]
9. Aortic arch (left, right)
10. Inferior vena cava (intact, interrupted)
11. Abdominal ultrasound (done, none) [Figure 4]
12. Genetic testing (done, none).

Other data was collected as well, including demographic data such as: gender, age at diagnosis and date of birth. The main outcome variable was to find any valid association between TGA and the before mentioned variables. These associations would determine if there is a link between TGA and heterotaxy regarding the genesis of this congenital heart defect.

For TGA patients two different patient lists were generated: one ranging from 2002-2014 and another one for the year 2015. For TGA patients from 2002-2014, we extracted all the patients who were registered in the database of this center as TGA patients. The data was extracted by our clinical pediatric research technician in the center. The patient list was created using the center's form for data collection for 2002-2014 to build up a date

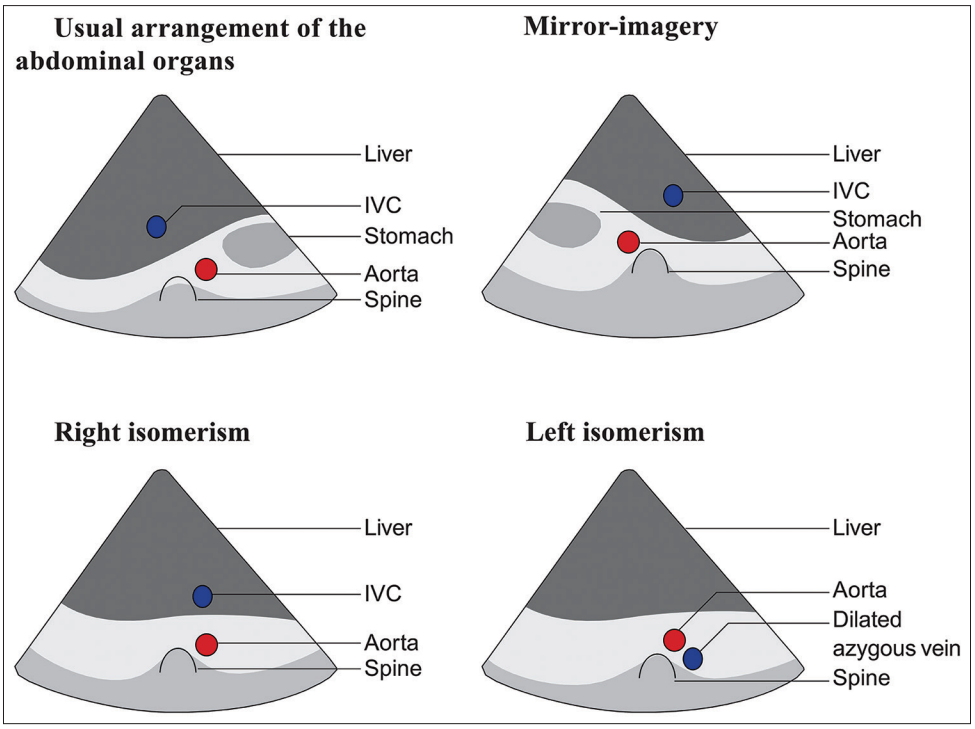

Figure 4: An illustration showing the 4 different abdominal organ arrangement variations that can be determined from echocardiograms in the abdominal transverse plane of the so-called subxiphoid (subcostal) views. IVC: Inferior vena cava. Adopted from: Echocardiography in Pediatric and Congenital Heart Disease: From Fetus to Adult. Wyman W. Lai, Luc L. Mertens, Meryl S. Cohen and Tal Geva© 2009. Page: 491

base out of the TGA patients' paper files. The data was provided to us in an Excel sheet with 498 patients. As for the year 2015, the TGA patient list was not finalized yet in the center's database by the time it was included. Thus, we created our own 2015 patient list by collecting them from 3 different sources which were: (1) 2015 pediatric cardiology discussion list (in-patient list), (2) pediatric cardiology OR list, and (3) pediatric cardiology patient-referral list. The total number of patients was 112. Then a data collection sheet was created in Excel with all the defined variables to be used in the process of data revision and rechecking. To verify the information on the database, the data was divided evenly between four medical students (the co-investigators).

The following hospital informatics and digital data recording systems were used to this end: (1) *Xcelera* with echocardiograms and reports for the main diagnosis, intracardiac anatomy, and arrangement of the abdominal organs (visceral situs); (2) *Quadramed* to check the abdominal x-ray, ultrasound, genetic test, and for further information on demographics (date of birth (DOB), age at diagnosis, gender). Xcelera (Xcelera R4.1L14.1.1.1133-2013) is the integrated multi-modality image management system for cardiovascular information at KACC. Quadramed (Quadramed 5.4.0164) is the administrative database system in this center. However, not all the data was available for review in the hospital informatics and digital data recording systems, especially the data of patients in the earlier years of the cardiac center, thus those patients were reviewed manually by checking the paper record files in the Department of Medical Records. After the process of data review by the investigators, an experienced senior pediatric cardiologist (the primary supervisor of this project as the principle investigator)-with at least one of the investigators-reviewed all the patients of the unified Master Excel sheet file by checking their echocardiograms one by one.

The best method for diagnosing heterotaxy would have been by utilizing the chest X-rays to identify the bronchial tree anatomy [Figure 1 - second upper row]. In the present retrospective study, this was not applicable due to the low quality of the available chest x-rays [Figure 3]. Therefore, we decided to determine the arrangement of the abdominal organs on the basis of the echocardiograms in the abdominal transverse plane [so-called subxiphoid/subcostal views, Figure 4]. The definitions that were used to determine the sidedness were: usual arrangement (situs solitus) is when the aorta and inferior caval vein lie apart, on opposite sides of the spine, with the aorta on the left. Mirror-imagery is the mirror-imaged arrangement with the aorta on the right and the inferior caval vein on the left. Right isomerism is when the aorta and inferior caval vein are on the same side of the spine, with the vein slightly anterior. Left isomerism is when the aorta is in the midline and the azygos vein is located in a posterolateral position.

In addition, the data was reviewed 1) to verify the diagnosis and all other variables, 2) to fill the missing data, and 3) to exclude the patients who did not meet the inclusion criteria. The final number of included patients after applying the exclusion criteria and the revision process was 533 TGA patients.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics for Windows version 22.0 (IBMCorp, Armonk, NY, USA). Descriptive statistics are presented as the means standard deviations for numerical variables and as frequencies with percentages for categorical variables. The Chi-squared test or Fisher exact test was used to compare differences in categorical variables between the groups. An independent samples *t*-test was used to compare continuous data. A P value < 0.05 was considered statistically significant.

Ethical considerations

This research was approved by the ethical research board within the Institutional Review Board (IRB) at the center's medical research center with the IRB research protocol number SP15/016. There was no need for a consent form since our data collection method consisted mainly of a chart review. Patients' confidentiality was maintained at all levels as only the PI and co-investigators had access to the data and were given permission collect it. In addition, the data collected was kept in a secure place, using computerized methods in five specific password-protected computers, and by using coded serial numbers; we insured that the data did not contain any identification of the patients included in the research. None of the patients' file numbers (MRN) were sent with the data for analysis as well.

RESULTS

Study patients

Our study population consisted of all patients who were diagnosed at KACC with any type of TGA throughout the years from 2002 – 2015. The originally extracted population from the records included 610 patients, 77 of which were excluded after thorough record review per our exclusion criteria (see Materials and Methods).

Of the remaining 533 patients, 262 (49.2%) were diagnosed as having "*Simple TGA*", 57 (10.7%) were diagnosed as having *"TGA with additional complicating heart lesions*", and 214 (40.2%) were diagnosed as having *"TGA in the setting of complex heart defects*". The mean age of diagnosis was 8 months. The male to female ratio was 2 to 1 (male = 351, female = 182). Of the 533 patients in the study, 35 (6.6%) underwent genetic analysis, 32 (6.0%) of which had normal results and 3 (0.6%) had positive results, showing deletion syndromes (not documented which particular syndrome was found). 2 (0.4%) of the patients with deletion syndrome had *TGA in the setting of complex heart defects*, and 1 (0.2%) had *Simple TGA*.

Simple transposition of the great arteries

This diagnostic sub-group included all cases of TGA without additional complicating cardiovascular lesions, such as pulmonary stenosis, coarctation of the aorta, and double outlet right ventricle. Patients who had TGA with ventricular septal defects that did not affect their clinical presentation, or led to a different initial surgical approach (such as pulmonary artery banding) were included in this sub-group as well. The main characteristics of *Simple TGA* patients are shown in Table 1.

This diagnostic sub-group comprised 262 (49.2%) patients of the whole study population. Of these patients, 5 (1.9%) had dextrocardia and 1 (0.4%) had mesocardia.

The heart defects found in this group were defects in the interatrial or interventricular septum. Secundum atrial septal defect or a patent foramen ovale were diagnosed in 253 (96.6%) patients, 145 (55.3%) of which had an intact interventricular septum. On the other hand, a total of 7 (2.7%) patients had a ventricular septal defect with an intact interatrial septum, and 2 (0.8%) patients had both an intact interatrial and interventricular septum. Only 2 (0.8%) patients had an atrioventricular septal defect. The aortic arch was right-sided in 12 (4.6%) patients.

Usual arrangement of the abdominal organs was found in the vast majority of cases consisting of 259 (98.9%) patients. Mirror-imagery of the abdominal organs was found in 3 (1.1%) patients. No patient was diagnosed as having either left or right isomerism.

Transposition of the great arteries with additional complicating heart lesions

This diagnostic sub-group included all cases of TGA with additional complicating heart lesions, such as multiple ventricular septal defects, pulmonary stenosis, straddling tricuspid valve, coarctation of the aorta. The main characteristics of *TGA with additional complicating heart lesions* patients are shown in Table 1.

This diagnostic sub-group comprised 57 (10.7%) patients of the whole study population. Of these patients, 2 (3.5%) had dextrocardia and 1 (1.8%) had mesocardia. TGA was found in 55 (94.5%) patients, while congenitally corrected TGA was not found in this sub-group, and levo-position of the great arteries was found in 2 (3.5%) patients.

The complicating cardiovascular defects found in this group were: 35 (61.4%) pulmonary or sub-pulmonary stenosis; 13 (22.8%) coarctation of the aorta; 5 (8.8%) multiple "Swiss cheese" ventricular septal defects; 3 (5.3%)

Table 1: Transposition of the great arteries basic divisions according to complexity, and associated findings in each diagnostic sub-group

TGA sub-grouping	Total	Type of TGA	Cardiac apical position	Abdominal position	Atrial position	ASD/PFO	VSD	AVSD	Aortic Arch
Simple TGA	262	TGA (262)	Levocardia (256) Mesocardia (1) Dextrocardia (5)	Usual arrangement (259) Mirror-imagery (3)	Usual arrangement (260) Mirror-imagery (2)	253	115	0	Left (250) Right (12)
TGA with additional complicating heart lesions	57	TGA (55) Levo-position of the great arteries (2)	Levocardia (54) Mesocardia (1) Dextrocardia (2)	Usual arrangement (54) Mirror-imagery (2) Right isomerism (1)	Usual arrangement (54) Mirror-imagery (2) Left-isomerism (1)	50	50	1	Left (50) Right (7)
TGA in the setting of complex heart defects	214	TGA (127) Levo-position of the great arteries (34) Congenitally corrected TGA (53)	Levocardia (181) Mesocardia (9) Dextrocardia (24)	Usual arrangement (182) Mirror-imagery (16) Left isomerism (7) Right isomerism (9)	Usual arrangement (184) Mirror-imagery (12) Left isomerism (8) Right isomerism (10)	183	186	27	Left (183) Right (31)

TGA: Transposition of the great arteries, ASD: Atrial septal defect, PFO: Patent foramen ovale, VSD: Ventricular septal defect, AVSD: Atrioventricular septal defect

Table 2: Distribution of abdominal visceral arrangement in relation to the cardiac apex position in all types of transposition of the great arteries patients

Abdominal visceral arrangement	Cardiac apex position			
	Levocardia	Mesocardia	Dextrocardia	Total
Usual arrangement	476	6	13	495
Mirror-imagery	7	4	10	21
Left isomerism	3	0	4	7
Right isomerism	5	1	4	10
Total	491	11	31	533

pulmonary hypertension; 1 (1.8%) atrioventricular septal defect; 3 (5.3%) straddling tricuspid valve; 1 (1.8%) interrupted aortic arch. The aortic arch position was found to be right sided in 7 (12.3%) patients.

Usual arrangement of the abdominal organs was found in the vast majority of cases consisting of 54 (94.7%) patients. However, 2 (3.5%) patients were diagnosed to have mirror-imagery of the abdominal organs, 1 (1.8%) patient was found to have right isomerism while no patient was diagnosed with left isomerism.

Transposition of the great arteries in the setting of complex heart defects

This diagnostic sub-group included all cases of TGA found in the setting of complex cardiac anomalies (e.g., common atrium, Taussig Bing anomaly, double outlet right ventricle, etc.). In this group, TGA was not the clinically leading defect but rather an additional defect. The main characteristics of *TGA in the setting of complex heart defects* patients are shown in Table 1.

This diagnostic sub-group comprised 214 (40.2%) patients of the whole study population. Of these cases, 24 (11.2%) had dextrocardia and 9 (4.2%) had mesocardia. TGA was found in 127 (59.3%), congenitally corrected TGA was found in 53 (24.8%) patients, and levo-position of the great arteries was found in 34 (15.9%) patients.

The heart defects found in this group were: 72 (33.6%) double outlet right ventricle; 45 (21.0%) double inlet left ventricle; 38 (17.8%) Taussig Bing anomaly; 27 (12.6%) atrioventricular septal defects; 22 (10.3%) pulmonary atresia; 19 (8.9%) tricuspid atresia; 10 (4.7%) common atrium; and 4 (1.9%) mitral atresia. The aortic arch was right sided in 31 (14.5%) patients.

Usual arrangement of the abdominal organs was found in the majority of cases consisting of 182 (85.0%) patients, while 16 (7.5%) cases had mirror-imagery of the abdominal organs, 7 (3.3%) patients were found to have left isomerism while 9 (4.2%) patients were diagnosed with right isomerism.

Transposition of the great arteries and anomalies in sidedness (lateralization) of the inner organs

Among the whole study population of 533 TGA patients, 495 (92.9%) showed the usual arrangement of the abdominal organs, out of this group 418 (84.4%) had TGA, 49 (9.9%) had congenitally corrected TGA, and 28 (5.7%) had levo-position of the great arteries.

38 (7.1%) patients had heterotaxy, out of this group 26 (68.4%) had TGA, 4 (10.5%) had congenitally corrected TGA, and 8 (21.1%) had levo-position of the great arteries [for more detailed results see Tables 2 and 3].

Sub-groups of heterotaxy in all types of transposition of the great arteries

Of the 38 patients who had heterotaxy, 21 (3.9% of all cases of TGA) patients were found to have mirror-imagery, 7 (1.3% of all cases of TGA) patients had left and 10 (1.9% of all cases of TGA) patients had right isomerism. This difference in the incidence

of patients with left isomerism versus right isomerism in patients with all types of TGA was not statistically significant (*P* value of 0.452) [Table 3].

Types of transposition of the great arteries in relation to abdominal sidedness

444 (83.3%) of all TGA patients had non-corrected TGA. Of these patients, 418 (94.1%) had the usual arrangement of the abdominal organs, 26 (5.9%) patients had heterotaxy, consisting of 16 (3.6%) with mirror-imagery of the abdominal organs, 4 (0.9%) patients were found to have left isomerism while 6 (1.4%) patients were diagnosed with right isomerism. 53 (9.9%) of all TGA patients had congenitally corrected TGA, 49 (92.4%) of which had the usual arrangement of the abdominal organs, 4 (7.5%) patients had heterotaxy, consisting of 3 (5.7%) with mirror-imagery of the abdominal organs, 1 (1.9%) patient was found to have left isomerism while none were diagnosed with right isomerism. 36 (6.8%) of all TGA patients had levo-position of the great arteries, 28 (77.7%) of which had the usual arrangement of the abdominal organs, 8 (22.2%) patients had heterotaxy, consisting of 2 (5.6%) with mirror-imagery of the abdominal organs, 2 (5.6%) patients were found to have left isomerism while 4 (11.1%) patients were diagnosed with right isomerism. However, compared to TGA and congenitally corrected TGA, levo-position of the great arteries showed a stronger association with heterotaxy (26 (5.9%) patients, 4 (7.5%) patients, and 8 (22.2%) patients, respectively) with a statistically significant difference (*P* value of 0.001) [Table 3].

Atrioventricular septal defects in relation to abdominal sidedness

Atrioventricular septal defects were found in 28 (5.3%) patients with TGA, out of which 22 (78.6%) had heterotaxy, consisting of 8 (28.6%) with mirror-imagery of the abdominal organs, 5 (17.9%) patients were found to have left isomerism while 9 (32.1%) patients were diagnosed with right isomerism [Figure 5].

Arch sidedness in relation to all types of transposition of the great arteries

In TGA, the incidence of left aortic arch was 408 (91.9%) versus right aortic arch, which was 36 (8.1%); in congenitally corrected TGA, the incidence of left aortic arch was 48 (90.6%) versus right aortic arch, which was 5 (9.4%); and in levo-position of the great arteries, the incidence of left aortic arch was 27 (75.0%) versus right aortic arch, which was 9 (25.0%) [Table 3].

Heterotaxy in arch sidedness in relation to all types of transposition of the great arteries

In the left aortic arch group (a total of 483 (90.6%) patients), 13 (2.7%) patients had heterotaxy, 10 (76.9%) of which were diagnosed with TGA, 1 (7.8%) was diagnosed with congenitally corrected TGA, and 2 (15.4%) were diagnosed with levo-position of the great arteries, while in the right aortic arch group (a total of 50 (9.4%) patients), 25 (50.0%) patients had heterotaxy, 16 (64.0%) of which were diagnosed with TGA, 3 (12.0%) were diagnosed with congenitally corrected TGA, and 6 (24.0%) were diagnosed with levo-position of the great arteries [Table 4].

DISCUSSION

Although many efforts have been made in the past to uncover the etiology and pathogenesis of TGA, this kind of congenital heart defect remains a "mysterious" lesion. TGA is traditionally assigned to the patho-morphological group of "conotruncal heart defects", which includes other lesions with abnormal positioning of the great arteries, such as Tetralogy of Fallot and double outlet right ventricle. These so-called conotruncal heart defects are suspected to result from developmental defects of the outflow tract of the embryonic heart, which are etiologically linked to genetic defects affecting the development of the secondary heart field or the cardiac neural crest. Surprisingly, however, TGA is rarely found in genetic syndromes commonly linked with outflow tract defects (e.g., Turner, Noonan, or Down's syndrome).[18] Based on a review of various genetic studies, including their own projects, Unolt *et al.*[1] reported that the only genetic syndrome with a strong association to TGA is the heterotaxy syndrome, which is etiologically linked to genetic defects affecting the establishment of the left-right body axis.

Table 3: Distribution of anomalies in sidedness (lateralization) of the inner organs and aortic arch in relation to different types of transposition of the great arteries patients

	TGA (%)	Congenitally corrected TGA (%)	Levo-position of the great arteries (%)
Usual arrangement of the abdominal organs	418 (94.1)	49 (92.4)	28 (77.7)
Mirror-imagery of the abdominal organs	16 (3.6)	3 (5.7)	2 (5.6)
Left isomerism	4 (0.9)	1 (1.9)	2 (5.6)
Right isomerism	6 (1.4)	0	4 (11.1)
Left aortic arch	408 (91.9)	48 (90.6)	27 (75.0)
Right aortic arch	36 (8.1)	5 (9.4)	9 (25.0)
Total	444 (100)	53 (100)	36 (100)

TGA: Transposition of the great arteries

Table 4: The distribution of heterotaxy in left aortic arch in comparison to right aortic arch in all types of transposition of the great arteries patients

	Heterotaxy with	
	Left aortic arch (%)	Right aortic arch (%)
TGA	10 (76.9)	16 (64.0)
Congenitally corrected TGA	1 (7.7)	3 (12.0)
Levo-position of the great arteries	2 (15.4)	6 (24.0)
Total	13 (100)	25 (100)

TGA: Transposition of the great arteries

Our present study aims to clarify whether there is any statistically significant association between TGA and clinically diagnosed heterotaxy that may have escaped the attention of previous investigators. In our study population of TGA patients, the vast majority of cases was found to have the usual arrangement of the inner organs 92.9%, while only 7.1% patients had heterotaxy, consisting of 3.9% patients with mirror-imagery, 1.3% patients with left isomerism and 1.9% patients with right isomerism. Thus, our present data do not demonstrate any significant association between TGA and clinically diagnosed lateralization defects.

We should note, however, that Unolt *et al.*[1] have reported that, in a familial type of heterotaxy syndrome linked to a ZIC3 gene mutation, congenitally corrected TGA can occur in association with the usual arrangement of the inner organs (situs solitus), so that such cases of congenitally corrected TGA may be regarded as isolated phenotypic manifestations of heritable heterotaxy syndromes. In our present study, congenitally corrected TGA was found in 49 (9.9%) patients with the usual arrangement of the inner organs. If we would consider that all these congenitally corrected TGA patients had a ZIC3 gene mutation, the portion of our patients with heterotaxy would rise from 7.1% to 16.3% (see Results, section "TGA and Anomalies in Sidedness (Lateralization) of the Inner Organs"), which is a value that still does not indicate any significant association between TGA and lateralization defects. Moreover, all TGA patients who had heterotaxy (accounting only for 38 (7.1%) patients) were linked with other major cardiac anomalies; 32 were in the sub-group of *TGA in the setting of complex heart defects*, only 3 in the sub-group of *TGA with additional complicating heart lesions*, and only 3 (all of which were mirror-imagery) of them was in the sub-group of the *Simple TGA* [Table 1].

There is another striking observation in the literature with regard to TGA and isomeric hearts. Aune *et al.*[30] reported that half of the mutants with TGA and atrioventricular septal defect have right isomerism. A similar speculation was raised by Unolt *et al.*[1] by stating that TGA associated with atrioventricular septal defect has been reported in almost 100% of cases of asplenia syndrome, which is a synonym for right isomerism. On the other hand, Ying-Liu Yan *et al.*[33] reported in their study that out of 18 fetuses with right isomerism, 6 fetuses had TGA and 10 fetuses had atrioventricular septal defects; while only 4 fetuses had both TGA and atrioventricular septal defect. Further, along with the results of Ying-Liu Yan *et al.*,[33] in our study, we found that out of a total of 533 TGA patients only 28 (5.3%) patients had atrioventricular septal defect and only 9 (32.1%) of them were found to have right isomerism; which shows no significant association between TGA patients with atrioventricular septal defect and heterotaxy [Figure 5].

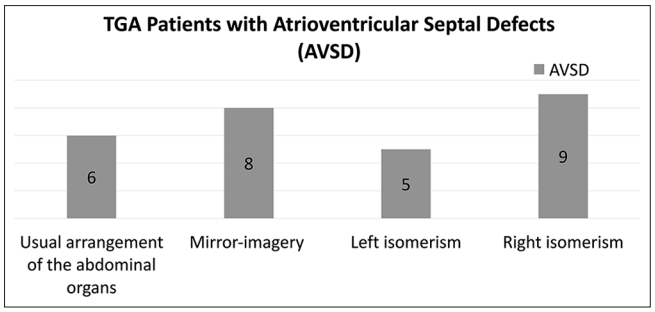

Figure 5: A bar chart showing the distribution of abdominal organ arrangements in transposition of the great arteries patients who had atrioventricular septal defect

Marino *et al.*[21] reported in their study on TGA in asplenia and polysplenia phenotypes with a total number of 36 patients with situs ambiguous (that is heterotaxy excluding mirror-imagery) a significantly higher incidence of TGA in patients with right isomerism (20/25 patients (80%)) compared to the incidence of TGA in patients with left isomerism (2/11 patients (18%)). Although in our study there was some difference in the incidence of patients with left isomerism (7 (1.3%)) versus right isomerism (10 (1.9%)) in all types of TGA, this was statistically not significant (*P* value of 0.452) to indicate that there is any association with either type of heterotaxy and TGA. However, as shown clearly in the results section, when we looked into the incidence of heterotaxy in the different types of TGA, we found interestingly that compared to TGA and congenitally corrected TGA, levo-position of the great arteries showed a stronger association with heterotaxy (26 (5.9%) patients, 4 (7.5%) patients, and 8 (22.2%) patients respectively) with a statistically significant difference (*P* value of 0.001) [Table 3].

In right aortic arch, 25 (50.0%) out of 50 patients had heterotaxy, compared to only 13 (2.7%) out of 483 patients who had left aortic arch. This means that in our TGA patients with abnormal (right-sided) lateralization of the aortic arch, the incidence of heterotaxy was 19 times higher compared to patients with the usual (left-sided) lateralization of the aortic arch. However, in right aortic arch, 24.0% of the patients had levo-position of the great arteries, but in left aortic arch there were as much as 15.4% of patients who had levo-position of the great arteries, making the presence of levo-position of the great arteries in right aortic arch only 1.6 times higher compared to levo-position of the great arteries in left aortic arch. With the previously mentioned association between heterotaxy and levo-position of the great arteries in comparison to TGA and congenitally corrected TGA with its significant *P* value of 0.001, the difference in incidence of levo-position of the great arteries in right aortic arch compared to the incidence of levo-position of the great arteries in left aortic arch was expected to be much higher, 4-10 times as high at

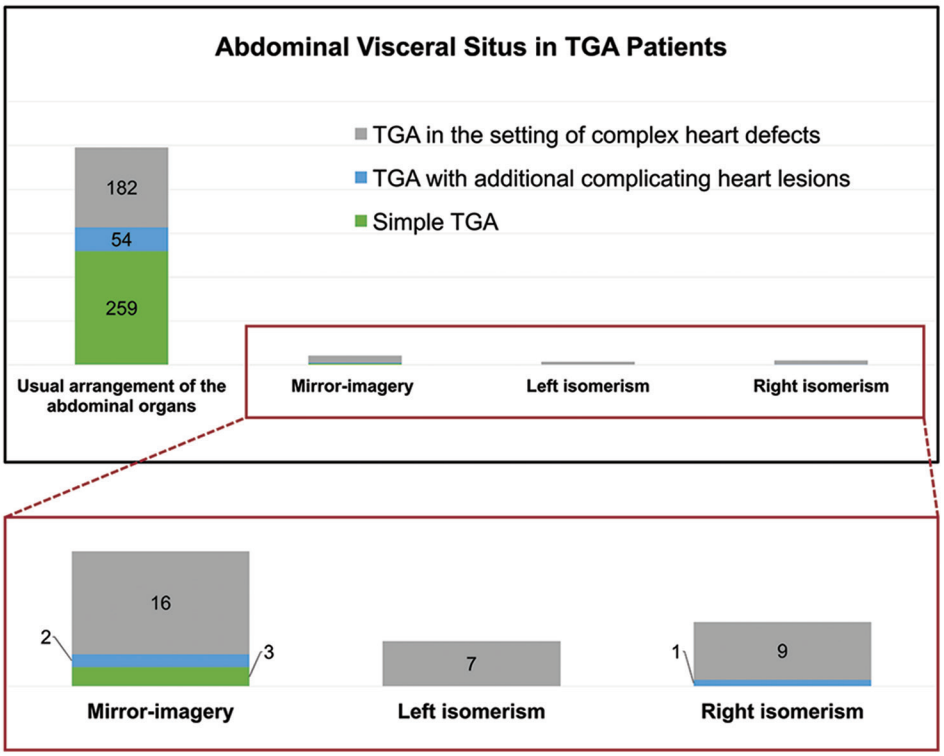

Figure 6: A bar chart showing the distribution of abdominal organ arrangements in the transposition of the great arteries sub-groups according to complexity

least, in support of the association between levo-position of the great arteries and heterotaxy [Table 3].

Given the fact that the higher association of levo-position of the great arteries and heterotaxy is seen only in patients in which the primary heart lesion is not TGA (but a complex heart defect with abnormal positioning of the great arteries in any form as an additional finding), to establish a true link is impossible. Therefore, even the association between levo-position of the great arteries and heterotaxy is under question for cofactors resulting in this link, namely the other major cardiac anomalies. This can be clearly seen when looking at all the heterotaxy patients in our population, which is a total of 38 patients (including patients with mirror-imagery as departure from normal), 32 (84.2%) of which were patients in the sub-group of *TGA in the setting of complex heart defects*, only 3 (7.9%) of which were patients in the sub-group of *TGA with additional complicating cardiovascular lesions*, and 3 (7.9%) of which were patients in the *Simple TGA* sub-group, showing that the possible association between heterotaxy and other major cardiac lesions is more likely than the association between heterotaxy and TGA [Figure 6 and Table 1].

Limitations

This study used a chart review system as the main basis for finding all the required variables. Chart review, however, is inherently limited in data collection, especially with old data before the era of digital records. Having said that, all patients with insufficient data were excluded, namely 10 patients with no echocardiograms to review, which shows that the significance of the sample size of the patient population is not affected. Some variables, including genetic testing, and abdominal imaging (x-ray/ultrasound), were not adequately present in patients' records. This led to the inability of showing any association between TGA and specific genetic abnormalities mentioned in previous papers. On the other hand, abdominal imaging did not have a major impact on defining the type of isomerism in our patient population.

Another limitation was the known variability in defining the atrial appendages morphology by echocardiograms, which led to the use of the abdominal visceral situs acquired by echocardiograms and the bronchial tree in chest x-rays to define the type of isomerism.

A more reliable method to classify the type of atrial appendages' isomerism is the chest x-ray showing the bronchial morphology, because the arrangement of the atrial appendages is usually congruent with the bronchial morphology, although this is not always the case.[17,34] Even though the arrangement of the abdominal organs acquired by echocardiograms is not the most reliable method in defining heterotaxy, the abdominal

echocardiograms were the only choice we could use in our study since in pediatric patients the actual effective radiation dose is small resulting in lower quality of chest x-rays in relation to identifying the bronchial tree anatomy.[34,35]

Future studies are needed to uncover the exact etiology and pathogenesis of TGA by overcoming existing limitations as mentioned before. A better look into bronchial tree in chest x-rays to define the atrial appendages anatomy and lateralization, and with that the type of isomerism could lead to a more specific and comprehensive analysis of TGA patients. A well-developed protocol in working up patients with laterality problems, including proper chest x-rays, abdominal ultrasounds, comprehensive echocardiograms, cilia studies, if possible, and genetic testing as well could ease the collection of robust data for better conclusive prospective studies.

CONCLUSION

Although genetic data suggest that TGA is etiologically linked to laterality defects (heterotaxy syndrome), our present morphological data do not disclose any significant association between TGA and laterality defects. With that, our data do not seem to support the hypothesis of a laterality defect-based etiology of TGA.

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Conflicts of interest

There are no conflicts of interest.

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