

Conjoined Twins: Does Cardio-Vasculogenesis Determines the Time and Type of Twinning?

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Received: August 23, 2017; Published: October 05, 2017

Abstract

Background: Fission or fusion theory for conjoined twinning has been proposed in the past, but they fail to predict the exact timing and type of twinning.

Aim: To study the cardio-vascular anatomy of conjoined twins and to study its relationship with the type and the timing of twinning.

Methods: The cardio-vascular anatomy of 3 cases of conjoined twins [epigastric heteropagus (2), dicephalous parapagus (1), thoraco-omphalopagus (1)] was studied in detail using various modalities like echocardiography, CT angiography (CTA) and autopsy findings.

Results: In the case of epigastric heteropagus twins, CTA revealed the blood supply to the parasite was arising from the left Subclavian artery. In dicephalus parapagus dibrachius dipus twins, the echocardiography and CTA revealed that the twins had a complex cardiac anatomy and 2 separate arches of Aorta but a common thoracic and abdominal Aorta. The CTA and autopsy of thoraco-omphalopagus twins showed a fused heart with a single large atrium, common Inferior Vena Cava, 2 fused ventricles and their corresponding well developed arches of Aorta. The degree of cardio-vasculogenesis was in coherence with the degree of organogenesis. The probable timing of fission/fusion could be traced to the timing of inception of the respective cardio-vasculogenesis.

Conclusion: The degree of cardio-vasculogenesis probably determines the timing of twinning and hence governs the type of twinning in conjoined twins.

Keywords: Conjoined Twins; Cardiac Morphology; Vascular Anatomy; Embryo-Pathogenesis; Timing

Abbreviations

CT: Conjoined Twins; ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; PDA: Patent Ductus Arteriosus; SVC: Superior Vena Cava; IVC: Inferior Vena Cava; CTA: Computed Tomography Angiography; LV: Left Ventricle; RV: Right Ventricle; TGA: Transposition of Great Arteries; EHT: Epigastric Heteropagus Conjoined Twins

Introduction

Conjoined twinning may be considered as a form of duplication or a doubling anomaly [1]. This may range from a simple supernumerary digit to an intestinal duplication, and finally, to the duplication of a part or whole of an individual [1-3]. Conjoined twins (CT) occur in 1 in 50,000 to 200,000 live births [4-6]. Asymmetric CT are even rare, constituting 1 - 2% of all CT [7]. Two main theories have been proposed to explain this curious phenomenon. The Fission theory believes that if the split occurs 12 days after conception, the embryos may not divide completely and may form with an anatomical connection between them [8,9]. Fusion theory believes that stem cells from

one twin adhere to like stem cells from the other twin, fusing together and developing conjoined [10-13]. However, both fail to explain the cause of such an insult and the timing of the event. Also, they don't explain the symmetric or asymmetric nature and the different types of twinning that occurs in CT. The cardiovascular morphology of 3 such cases of conjoined twins has been presented in detail and literature reviewed. The authors propose that the probable timing and type of twinning is determined at the time of inception of cardio-vasculogenesis in the embryo.

Materials and Methods

The cardio-vascular morphology of three cases of CT that included 2 symmetric and 1 asymmetric managed in the Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi between 1998 to 2017 has been discussed in detail.

Results and Discussion

Thoracopagus Conjoined Twins

The obstetrician conducted a caesarean section for an obstructed breech presentation in a 25-year-old un-booked gravida-three female who presented in labour. Interestingly, they delivered a pair of female CT joined together at the chest and the upper abdomen. The CTs were referred to our hospital for further management. They had 2 heads and necks facing each other, separate trunks fused to each other in the midline in the thoracic and the upper epigastric region, and a pair of upper and lower limbs for each. At presentation, they had respiratory distress, weak peripheral pulses, were cyanosed below mid-thigh level, a delayed capillary filling time and a saturation of 62%. They were managed supportively with oxygen by nasal cannula, intravenous fluids, antibiotics, nasogastric tube feeds but ultimately succumbed to cardiogenic shock and arrhythmias after a hospital stay of 66 days (Figure 1).

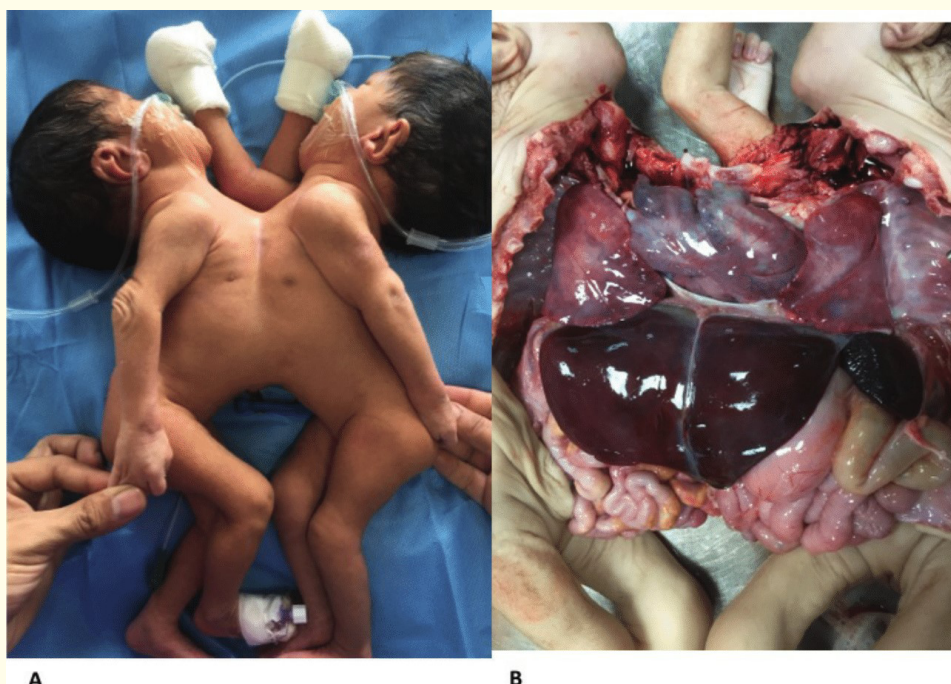


Figure 1: A-Thoraco-omphalopagus conjoined twins at presentation, B- Autopsy showing a shared common heart with 2 livers fused in midline.

Echocardiographic findings

The pediatric cardiologists reported that the twins had a complex cardiac anomaly with probably a single heart, common atria with a large Atrial Septal Defect (ASD) connected to the 4 ventricular chambers. Twin B had Ventricular Septal Defect (VSD). The arch of Aorta was visualized clearly in Twin A but not in Twin B on Echo. A tiny Patent Ductus Arteriosus (PDA) was present. Both had their own Superior Vena Cava (SVC) and Inferior Vena Cava (IVC).

CT Angiography (CTA)

Complex cardiac defects with a large shared common atrium for both babies, connected to 4 ventricles. The ventricles of both the twins were connected via VSD. Arch of Aorta arose from the left ventricle (LV) and the Pulmonary artery from the Right Ventricle (RV) (Figure 2).



Figure 2: A- Sagittal and coronal views of CT angiogram of Thoracopagus Conjoint Twins showing a single shared heart with the separate outflow and inflow tracts.

Dicephalus Dibrachius Dipus Parapagus Conjoined Twins

Another set of female CT with two heads placed side to side, a shared common trunk, two arms and two legs were referred to our hospital from a peripheral nursing home after caesarean delivery for antenatally diagnosed at 36 weeks. Their vitals were stable except for mild chest retractions seen in Twin B and oxygen saturation was 87%. They received supportive treatment and the work-up revealed the following: Skeletal system- 2 vertebral columns but single pelvis; Gastro-intestinal system- 2 livers fused in midline; Renal system- 2 normal kidneys and a single urinary bladder; Thoracic cavity- Right Twin (A) had a congenital diaphragmatic hernia with her stomach in the thoracic cavity; a shared heart, and a pair of lungs for each. Detailed cardiac evaluation is described below. The twins died after 19 days due to inoperable cardiac malformation.

Echocardiographic Findings

Complex congenital cardiac malformation with a single large common atrium; 2 ventricles with a large VSD and a very small septum; Atrio-ventricular canal defect; large septum primum ASD; Aortic regurgitation and PDA.

CT Angiographic Findings

The pulmonary artery was seen and the right Aortic origin was seen separate from the left Aortic origin. Twin B (left) had a large ASD and VSD, a hypoplastic LV, transposition of great arteries (TGA) and a moderate sized PDA. Left Aorta was not dilated and was normal in relation to the pulmonary artery. The relation of the great vessels was normal (Figure 3).

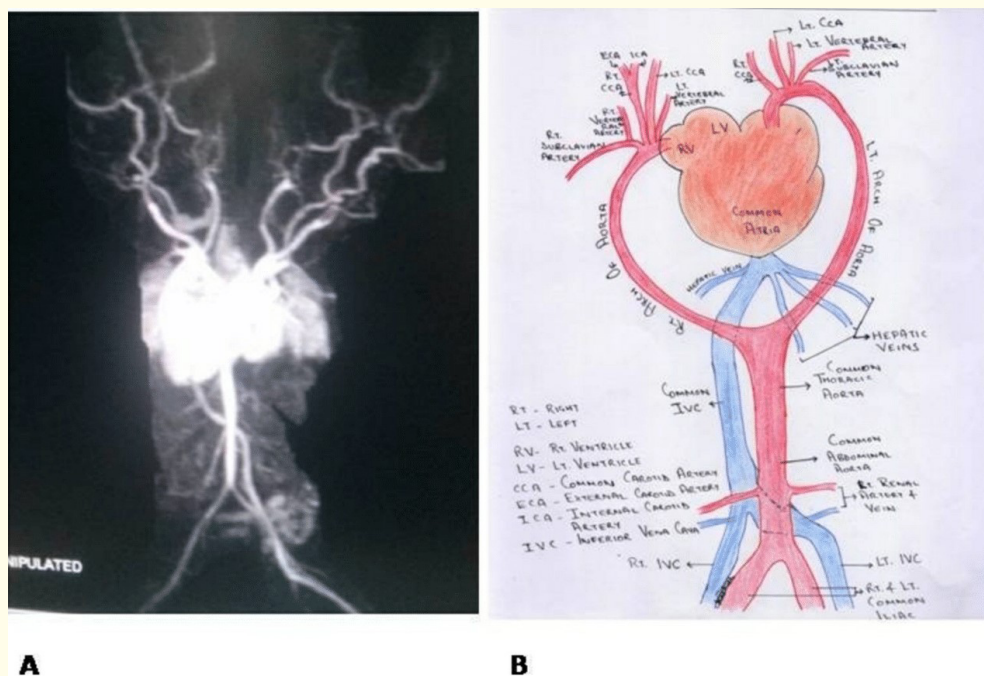


Figure 3: A-CT Angiogram of the Dicephalus Parapagus Dibrachius Dipus twins showing fused heart with 2 separate arches of Aorta. B- Diagrammatic Representation of the complex cardio-vascular anomaly.

Autopsy Findings

Single shared heart; common atrium; separate set of ventricles with Twin B having a VSD, hypoplastic LV, TGA and PDA; 2 separate Aortic arches with respective mirror-image branching; 4 hepatic veins but common IVC. Shared central pleural cavity with 2 pairs of lungs arising from separate trachea-bronchial trees, hypoplastic lungs placed medially.

Epigatric Heteropagus Conjoined Twins (EHT)

The case of EHT was successfully separated surgically. This case had no gastrointestinal or skeletal system sharing, however had a VSD and a PDA. The parasite in this case received its vascular supply from the left Subclavian artery [7].

Table 1 summarizes the findings in the 3 sets of CT.

S. no	Age (days)/ Sex	Year	Type	Bony connection	Gastro-Intestinal	Hepatobiliary connection	Diaphragmatic defect	Cardiac defect	Vascular Connection
1	66/ F	2017	Thoraco-omphalopagus	None	2 Separate	Liver fused in midline	Absent	Single large common atrium with 4 ventricles, large ASD and VSD, Anterior ventricle of twin B fused with the LV of Twin A	IVC and of Twin A pulmonary veins draining into common atria, Aorta arising from LV seen clearly in Twin A, Pulmonary artery seen to arise from RV. Tiny PDA in Twin B
2	19/ F	2014	Dicephalus, Dibrachius, Parapagus	2 parallel vertebral columns with single shared pelvis	2 Separate	2 livers fused in midline by a small connection	Present with stomach of right Twin herniated into thorax	Common atrium with ASD; 4 ventricles; left twin VSD and hypoplastic LV	2 Aortic arches; Pulmonary artery; common IVC; TGA and PDA in Twin B
3	60/ M	1998	Epigastric Heteropagus	None	None	None	None	VSD+PDA	Vascular supply from Left Subclavian artery

Table 1: Summary of Conjoined twins and their associated anomalies.

Discussion

Twinning is a natural phenomenon that can be seen in human beings, animals and plants. Levin., *et al.* [14] suggested that early in embryogenesis, either incomplete fission of the developing embryo or the development of co-dominant axes with apposition of part of the axes leads to conjunction. The conjunction of the heart is the bottleneck to survival as well as surgical separation.

McMohan and Spencer [15] reviewed the cardiac malformations in 1262 cases of CT reported between 1804 and 2001 and correlated them to the proposed site of embryonic fusion. They concluded that surgical separation was only rarely successful in twins with united hearts. Hence the cardiovascular morphology not only governs the survival but also the feasibility of surgical separation in CT. The cardiovascularogenesis is completed by the 5th - 6th week of gestation. If the detailed cardiovascular morphology of the developing fetus can be tracked antenatally, a timely decision about the pregnancy and relevant antenatal counseling can be done.

Understanding the Embryo-pathogenesis

In the middle of the 3rd week, when the embryo is no longer able to satisfy its nutritional requirements by diffusion alone, vascular system begins to develop [16]. Progenitor heart cells lie in the epiblast migrate through the primitive streak and lodge into the splanchnic layer of lateral plate mesoderm where they form endothelial heart tubes (16 to 18 days). They are specified on both sides from lateral to medial to become the atria, left ventricle, and most of the right ventricle. Patterning of these cells occurs at the same time that laterality (left-right sidedness) is being established for the entire embryo. This process and the signaling pathway it is dependent upon is essential for normal heart development. The remainder of the heart, including part of the right ventricle and outflow tract (Conus Cordis and Truncus Arteriosus), is derived from the secondary heart field (20 to 21 days). The rest of the cardiovascularogenesis is summarized in table 2 [16].

S. No	Event	Embryonal age (days)
1	Formation and position of heart tube	18 - 22
2	Fusion starting from the caudal region of the horse shoe shaped heart tube	22
3	Lengthening of the heart tube and formation of the cardiac loop	23 - 28
4	Development of sinus venosus	25 - 34
5	Formation of cardiac septa (atria; atrio-ventricular; inter ventricular)	30 - 35; 42 - 49; 49 - 55
6	Formation of aortic arches and the venous system	28 - 35
7	Formation of Inferior vena cava, Azygos vein and Superior vena cava	40 - 49

Table 2: Events in normal cardiac and vascular system development.

Cardiovasculogenesis and the phenomenon of Conjoined Twinning

The insult during normal cardio-vasculogenesis by any mechanism, mechanical or genetic, temporal or spatial, fission or fusion results in creation of CT. The timing of the insult can be determined by the degree of cardiovasculogenesis. McMohan and Spencer [15] discussed the different patterns of cardiac union which could be correlated with the site and extent of union of the trunks (and heads); ventrally CT continuum ranged from 2 shared hearts with double aortic arches, a shared single heart, a multi-ventricular heart with duplication of great vessels, inter-atrial connection between 2 hearts or 2 separate hearts. Most cases of thoracopagus, typically shared a single compound heart with supernumerary chambers with variable degree of communications and convoluted patterns of blood flow [15-18]. In our case of thoracopagus, a single heart with common atrium was connected to 4 ventricles with ASD and VSD with Pulmonary artery seen arising from the RV and the Arch of Aorta from the LV of Twin B. This probably points to a period of insult between 30-35 days during the formation of the cardiac septae.

The parapagus are united ventro-caudo-laterally with varying degrees of rostral separation. The parapagus dicephalus dibrachius have one heart in two-thirds of the cases with complex anomalies [15]. Similar to this, in our case there was a single heart with 4 ventricles and duplication of great vessels tracing the period of insult between 28 - 30 days of embryogenesis; correlating with the formation of outflow tract and the division of atria. The ventricular division and the branching of aorta may have followed a normal course thereafter. The surgical separation of such cases is next to impossible [15].

In case of parasitic CT, Donitz., *et al.* [19] first postulated the theory of vascular compromise that causes tissue of the parasitic twin to become dependent on collaterals derived from the autosite. Selective ischemic atrophy of the deprived portion of the parasite’s body followed [7,20]. The vascular pedicle derived from the autosite are frequently identified pre-operatively using CTA [14] to aid during surgical separation. The factors that cause this selective atrophy are not certain, but the oversensitivity of the brain, heart and lungs to ischemia are noted [7]. In a review on studies of heteropagus twins [20] reported between 2001 and 2011, cardiac malformation was noted in 9 autosites (23%), 3 with multiple heart defects. All 9 were associated with omphalopagus parasites [20]. VSD was the most common, accounting for one third of the defects [20]. In the EHT in our series, the vascular supply came from a branch of the left Subclavian artery and there was an associated VSD. The probable timing of insult in this case can be traced to the time of development of the left seventh intersegmental artery (35 - 40 days), which develops later into the left Subclavian artery. There may have been a concomitant insult during this period to the ongoing ventricular septal development resulting in VSD. The occurrence of a single insult at 3 weeks gestational age that resulted in asymmetric twinning as well as disruption of early heart development has been reported previously [1,21].

Conclusion

Despite increasing number of studies, the exact etiopathogenesis of conjoined twinning still needs to be unveiled. We propose that the degree of cardiovascular development of the CT could help trace the timing of insult and hence the timing of twinning during the em-

bryogenesis. Also, since the extent of cardiac union could be correlated to the site of twinning and the extent of trunk development; the cardiovascular development of the CT during antenatal diagnosis could be used to predict early, the type of twinning.

Acknowledgements

No sponsorship and financial support has been obtained for this study. The support of doctors and staff of the department of Pediatric Surgery, Neonatology, Pediatric Cardiology, Radiology, and Anaesthesia and Critical Care at All India Institute of Medical Sciences, New Delhi in the management of these challenging cases is highly appreciated. We would also like to acknowledge the efforts put in by the multidisciplinary team consisting of Professor Maya (Department of Anaesthesia), Dr. Sanjeev Kumar (Department of Cardio Radiology), Dr. Anita Saxena and Dr. R. Juneja (Department of Cardiology) who helped in the evaluation and treatment of these conjoined twins.

Conflict of Interest

Authors declare that no financial interest or any conflict of interest exists.

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Volume 5 Issue 6 October 2017

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