Congenital Heart Disease

Tech Science Press

DOI: 10.32604/chd.2022.019743

CASE REPORT

2q37.3 Deletion with Complex Heart Defects Suggesting Interruption of Early Ventricular Looping

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Received: 12 October 2021 Accepted: 20 December 2021

ABSTRACT

A maternally inherited 828 kb microdeletion of 2q37.3 manifested in a 3-week-old premature boy as left juxtaposition of the atrial appendages associated with tricuspid atresia, double outlet infundibulum, subvalvar pulmonary atresia, large secundum atrial septal defect, and right aortic arch with mirror-image branching, consistent with developmental arrest early in heart looping. To the best of our knowledge, no previous *2q37 deletion syndrome* has been reported with such a severe cardiac dysmorphology. Hence, this case adds to the cardiac phenotypes identified in *2q37 deletion syndrome*.

KEYWORDS

2q37.3 deletion; tricuspid atresia; double outlet infundibulum; juxtaposition of the atrial appendages; right aortic arch; subvalvar pulmonary atresia

1 Introduction

Despite being a rare finding, a clear association has been found between the *2q37 deletion syndrome* and cardiac malformations. Cardiac malformation occurs in up to 20% of *2q37 deletion syndrome*, also known as brachydactyly-mental retardation syndrome or Albright hereditary osteodystrophy-like syndrome. The congenital heart defects identified in this genetic condition are mostly in the form of atrial and ventricular septal defects and aortic coarctation with only one case reported to exhibit a complex anatomy. In this paper, we describe a complex cardiac phenotype in a fetus with *2q37 deletion syndrome* that suggests interruption in early ventricular looping. This case adds to the known cardiac phenotypes identified in

2q37 deletion syndrome, and offers insight into the potential role of deleted genes in cardiac development. Awareness of the spectrum of cardiac phenotypes that may be encountered in *2q37 deletion syndrome* may inform the diagnostic approach and management of patients with this rare genetic condition.

2 Case Presentation

The patient was a 3-week-old premature boy born to a healthy 42-year-old gravida 5 para 3 mother with three healthy living children. The mother was referred for urgent Cesarean section at 35-weeks' gestation due to increased fetal head circumference. The mother denied alcohol and drug exposure, but admitted tobacco use during the pregnancy. Multiple congenital anomalies were noted on the 20-week fetal ultrasound including severe hydrocephalus, spina bifida, and complex cardiac defects. Amniocentesis identified a maternally inherited 828 kb deletion of 2q37.3. At birth, the neonate was hypotonic with poor respiratory effort, an Apgar score of 3, and required supportive care in the neonatal intensive care unit. Subsequently, he was intubated, and prostaglandins were administered. Neurologic anomalies included severe congenital hydrocephalus with thin cortical mantle, hindbrain herniation, and a lumbosacral spina bifida. The initial echocardiographic diagnosis was tricuspid atresia, double outlet right ventricle (DORV) with pulmonary atresia, transposition of the great arteries (TGA), patent ductus arteriosus (PDA), large secundum atrial septal defect (ASD), large outlet ventricular septal defect (VSD), and possible single left coronary artery. At 13 days of life, the patient underwent right-sided ventriculoperitoneal shunt, balloon pulmonary valvuloplasty, and ductus arteriosus stenting with no complications. However, he acutely deteriorated after a feeding episode due to interstitial fluid accumulation in the lungs and diffuse atelectasis requiring reintubation and ventilatory support. Eventually, he was extubated but developed mottling, hypoperfusion, hypotension, and hyperventilation, considered to be most consistent with sepsis/shock. Despite maximal supportive efforts, after 90 min of unsuccessful cardiopulmonary resuscitation, he expired.

At autopsy, dysmorphic cranio facial features included macrocephaly and low-set ears. The liver was midline with a grossly dysmorphic appearing spleen and a centrally positioned heart with multiple structural anomalies (Figs. 1 and 2). The right-sided structures were underdeveloped with tricuspid atresia, subvalvar pulmonary atresia and a bicuspid and stenotic pulmonary valve, status post balloon pulmonary valvuloplasty. A well-formed left-sided left ventricle with a well-developed mitral valve was identified connecting to a small right-sided infundibular outflow chamber via a large primary foramen. The small trabecular portion, apical and inferior to the outflow, could represent a small amount of right ventricular myocardium. The great arteries arose from this infundibular outflow chamber (double outlet infundibulum), with the aorta anterior and to the right of the pulmonary artery. The aortic valve and outflow tract were unobstructed. The stent was appropriately placed within a right-sided ductus arteriosus and was patent. The right atrial appendage was juxtaposed and superior to the left atrial appendage while the right atrium was abnormally located posterior and leftward of the great arteries with a large secundum ASD (12 mm). The aortic arch was right- sided with mirror-image branching. The right coronary artery (ostium: <1 mm) arose from the posterior right facing sinus and the left coronary artery (ostium: 1.5 mm) from the posterior left facing sinus. Histology showed patchy cardiomyocyte hypertrophy with mild endocardial fibroelastosis involving the left ventricle and infundibular outflow chamber.

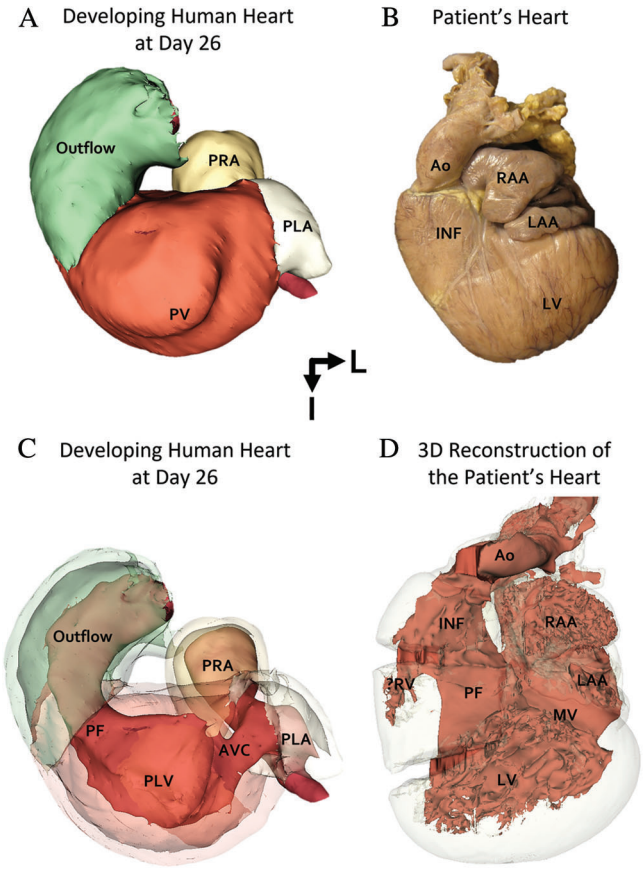

Figure 1: Comparison of Carnegie Stage (CS) 11 human embryo (~day 26) (A, C) with our patient's heart (B, D)

(A) A 3D reconstruction of a CS 11 human embryo from the Digitally Reproduced Embryonic Morphology collection (Carnegie embryo # 6344) (http://virtualhumanembryo.lsuhsc.edu/default.htm) created using 3D Slicer software (www.slicer.org). During this early looping stage, the outflow is far to the right and the primitive ventricle (PV) has descended below the inflow from which the presumptive right atrium (PRA) and presumptive left atrium (PLA) are beginning to develop. **(B)** A photograph of the anterior view of our patient's heart. Note the juxtaposed right (RAA) and left (LAA) atrial appendages. The left ventricle is oddly shaped and communicates with the infundibulum. The aorta is anterior and aligned with the infundibulum. **(C)** The same image as A with the myocardium made transparent to show the blood pool. The PRA has no connection with a ventricle but drains across the primary interatrial foramen into the PLA, which is connected to the PV by the atrioventricular canal (AVC). This resembles the formed heart with tricuspid atresia. The PV is connected to the outflow by the primitive foramen (PF) and the right ventricle has not yet developed. **(D)** A 3D reconstruction of a micro-CT scan of our patient's heart after dissection created using 3D Slicer. The myocardium has been made transparent to show the blood pool, as in C. The RAA as well as the body of the right atrium are positioned to the left of the outflow. The right atrium has no connection with the left ventricle (LV). The left atrium is connected to the LV by a mitral valve and the LV communicates with the infundibulum (INF) by the PF or outflow foramen. The small trabeculated area inferior and rightward of the INF could be a rudimentary right ventricle (RV). The anterior aorta is aligned with the infundibulum.

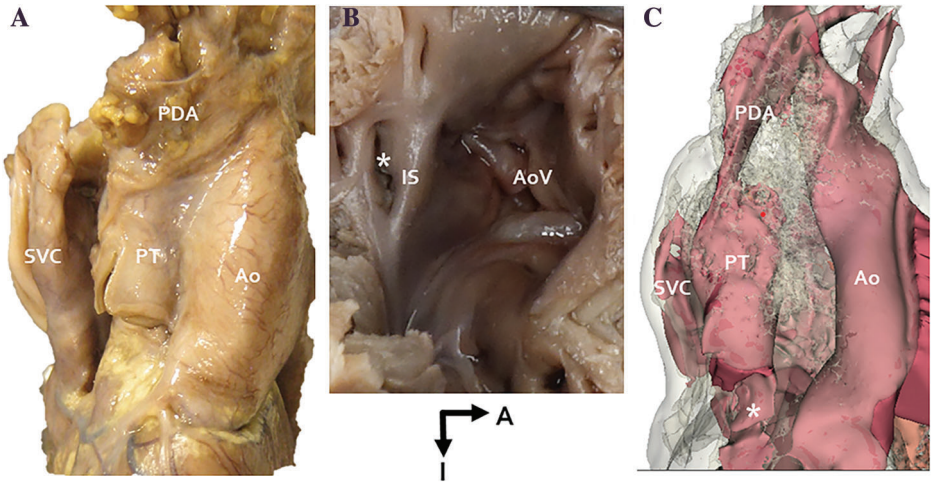

Figure 2: Views of the great arteries and infundibular outflow in our patient

(A) External view of the great arteries from the right side. The aorta (Ao) is anterior and rightward and the pulmonary trunk (PT) posterior and leftward. The superior vena cava (SVC) and right atrium are posterior and leftward of the vascular pedicle. The stented ductus (PDA) is superior. **(B)** Interior view of the infundibulum. The aortic valve (AoV) is anterior and unobstructed. The atretic pulmonary outflow (*) is posterior to the infundibular septum (IS). **(C)** A 3D reconstruction of the micro-CT with the myocardium transparent showing the blood pool of the vessels shown in A. The narrowing and atresia of the subpulmonary infundibulum is seen (*).

3 Discussion

The *2q37 deletion syndrome*, also known as *brachydactyly-mental retardation syndrome* or *Albright hereditary osteodystrophy-like syndrome*, is a rare condition reported in just over 100 patients since 1989 when the first case was described [1]. The deletion syndrome can involve more or less of the last cytogenetic band of chromosome 2 consisting of three sub-bands: 2q37.1, 2q37.2 and 2q37.3 and at least 194 genes. Only 11 of these genes have been associated so far with the *2q37*-deletion phenotype; with the most common deletion or haploinsufficiency involving the *HDAC4* gene which encodes the histone deacetylase 4 protein that acts as a transcription repressor essential for brain, muscle, and bone development and function [2]. Clinically, the syndrome has a broad phenotypic spectrum due to variability in the size and gene content of the deletions, with the most commonly associated features being brachydactyly type E (BDE) affecting the metacarpals (in about 50% of the patients), short stature, hypotonia, dysmorphic facial appearance, mild to severe intellectual impairment, developmental delay, and behavioral abnormalities [2]. In our patient, a 828,385 kb maternally inherited deletion of 2q37.3 (Arr[GRCh37](239404273-240232658)×1) was detected, including the entire *TWIST2* gene, a transcription factor that maintains cells in a preosteoblast phenotype, and the majority of the *HDAC4* gene. This interval was within the much larger region associated with the *2q37* contiguous gene deletion syndrome. *HDAC4* has been postulated to have a major role in *2q37 microdeletion syndrome* [3]. However, a patient with a *2q37* deletion, which spared the *HDAC4* gene, had similar phenotype consistent with the *2q37 deletion syndrome*, indicating other potential contributors to this deletion syndrome [4]. A familial and maternally inherited 2q37.3 deletion involving *TWIST2* and *HDAC4* genes has previously been reported in a girl and her affected mother and grandmother, all with variable severity of psychomotor and behavioral abnormalities in combination with specific facial dysmorphism but without BDE or any congenital malformations [5].

Congenital cardiac malformations occur in up to 20% of patients with *2q37 deletion syndrome* with breakpoints at any sub-band [1]. These predominantly consist of ASD, VSD, and aortic coarctation associated with terminal deletions of approximately 4500 kb [6]. Only one case with a complete terminal 2q37 deletion had more complex cardiac malformations consisting of DORV, pulmonary stenosis, PDA, VSD, and patent foramen ovale [7], somewhat similar to our patient's cardiac phenotype. Generally, patients with microdeletions are less likely to have major congenital anomalies compared to patients with cytogenetically visible deletions [1]. However, the present case demonstrates a more severe phenotype with only an 828,385 kb microdeletion of 2q37.3.

Our patient had the complex heart defects described above including left juxtaposition of the atrial appendages; a rare congenital malformation in which the right appendage is to the left of the vascular pedicle and superior to the left appendage, with both appendages maintaining their morphological features [8]. Left juxtaposition is more frequent than right juxtaposition by a ratio of about 6:1 and is usually associated with other more severe congenital heart disease, as seen in the present case, such as cardiac malposition, tricuspid valve atresia or stenosis with hypoplasia of the right ventricle, and subaortic or bilateral infundibulum with TGA or other malposition of the great arteries [8,9].

Left juxtaposition is postulated to be caused by a developmental arrest early in the looping process [10]. During the mid 4th week, Carnegie Stage 11, as the heart tube elongates, the outflow extends far to the right as the primitive ventricle descends below the inflow where the atria are starting to develop. The entire inflow is leftward of the outflow at this stage. Normally, continued elongation of the heart tube is associated with leftward movement of the outflow so that the right side of the developing common atrium comes to lie to the right of the outflow [11]. As the atrial appendages balloon out of the inflow portion of the heart tube, the right appendage is rightward, and the left appendage is leftward of the outflow. Our patient's heart strongly resembles the embryonic heart at Carnegie Stage 11 (Figs. 1 and 2), suggesting an arrest in development at about this stage. Failure of elongation of the outflow, with a rudimentary or absent right ventricle, suggest defective addition of second heart field cells to the heart tube [12]. It also closely resembles the hearts in a chick model of left juxtaposition produced by exposure to the teratogen suramin [10]. The abnormal location of the body of the right atrium behind the outflow and the conotruncal anomaly consisting of DORV, more closely resemble the chick model than the more frequently observed human phenotype with a normally positioned right atrium and TGA [8].

Most of the genes in the deleted region in this patient are not thought to be associated with heart development. The *HDAC4* gene, however, is known to be involved in repression of cardiac myocyte enhancement factor 2 (*MEF2c*) expression. *MEF2c* is necessary for addition of 2nd heart field cells to the developing outflow. Mice null for this gene fail to develop a right ventricle and have very incomplete looping [13]. However, inactivation of *HDAC4* should, if anything, result in enhanced expression of *MEF2c*. Either another gene in the deleted region is involved in cardiac development or perhaps the partial deletion of *HDAC4* in this patient resulted in a gain-of-function mutation specific for its role in regulating *MEF2c* expression. To date, this is the most complex and primitive phenotype associated with this particular syndrome.

4 Conclusion

In conclusion, due to the considerable frequency of heart defects, infants and children with a 2q37 deletion should undergo screening for cardiac defects at the time of diagnosis as the list of anomalies could range from simple to extremely complex as in this case.

Availability of Data and Materials: Not applicable.

Ethics Approval: The reporting of this case is performed in accordance with the policies of the Institutional Review Board of Boston Children's Hospital, and all identifying information has been removed. In

particular, this manuscript did not require approval by the Ethics Committee (Institutional Review Board). As such, informed consent was not required from the patient and/or their legal representative(s).

Funding Statement: The authors received no specific funding for this study.

Conflicts of Interest: The authors declare that they have no conflicts of interests to report regarding the present study.

References

1. Falk, R. E., Casas, K. A. (2007). Chromosome 2q37 deletion: Clinical and molecular aspects. *American Journal of Medical Genetics Part C (Seminar in Medical Genetics), 145C(4),* 357–371. DOI 10.1002/(ISSN)1552-4876.
2. Leroy, C., Landais, E., Briault, S., David, A., Tassy, O. et al. (2013). The 2q37-deletion syndrome: An update of the clinical spectrum including overweight, brachydactyly and behavioural features in 14 new patients. *European Journal of Human Genetics, 21(6),* 602–612. DOI 10.1038/ejhg.2012.230.
3. Williams, S. R., Aldred, M. A., Der Kaloustian, V. M., Halal, F. (2010). Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. *American Journal of Human Genetics, 87(2),* 219–228. DOI 10.1016/j.ajhg.2010.07.011.
4. Imitola, J., Khurana, D. S., Teplyuk, N. M., Zucker, M., Jethva, R. et al. (2015). A novel 2q37 microdeletion containing human neural progenitors genes including STK25 results in severe developmental delay, epilepsy, and microcephaly. *American Journal of Medical Genetics Part A, 167a(11),* 2808–2816. DOI 10.1002/ajmg.a.37268.
5. Villavicencio-Lorini, P., Klopocki, E., Trimborn, M., Koll, R., Mundlos, S. et al. (2013). Phenotypic variant of Brachydactyly-mental retardation syndrome in a family with an inherited interstitial 2q37.3 microdeletion including HDAC4. *European Journal of Human Genetics, 21(7),* 743–748. DOI 10.1038/ejhg.2012.240.
6. Casas, K. A., Mononen, T. K., Mikail, C. N., Hassed, S. J., Li, S. et al. (2004). Chromosome 2q terminal deletion: Report of 6 new patients and review of phenotype-breakpoint correlations in 66 individuals. *American Journal of Medical Genetics Part A, 130A(4),* 331–339. DOI 10.1002/(ISSN)1096-8628.
7. Wang, T. H., Johnston, K., Hsieh, C. L., Dennery, P. A. (1994). Terminal deletion of the long arm of chromosome 2 in a premature infant with karyotype: 46,XY,del(2)(q37). *American Journal of Medical Genetics, 49(4),* 399–401. DOI 10.1002/(ISSN)1096-8628.
8. van Praagh, S., O'Sullivan, J., Brili, S., van Praagh, R. (1996). Juxtaposition of the morphologically right atrial appendage in solitus and inversus atria: A study of 35 postmortem cases. *American Heart Journal, 132(2 Pt 1),* 382–390. DOI 10.1016/S0002-8703(96)90437-8.
9. Singhi, A. K., Pradhan, P., Agarwal, R., Sivakumar, K. (2016). Juxtaposed atrial appendages: A curiosity with some clinical relevance. *Annals of Pediatric Cardiology, 9(2),* 186–189. DOI 10.4103/0974-2069.173546.
10. Männer, J., Heinicke, F. (2003). A model for left juxtaposition of the atrial appendages in the chick. *Cardiology in the Young, 13(2),* 152–160. DOI 10.1017/S1047951103000295.
11. Männer, J. (2009). The anatomy of cardiac looping: A step towards the understanding of the morphogenesis of several forms of congenital cardiac malformations. *Clinical Anatomy, 22(1),* 21–35. DOI 10.1002/ca.20652.
12. Kelly, R. G. (2012). The second heart field. *Current Topics in Developmental Biology, 100,* 33–65. DOI 10.1016/B978-0-12-387786-4.00002-6.
13. Lin, Q., Schwarz, J., Bucana, C., Olson, E. N. (1997). Control of mouse cardiac morphogenesis and myogenesis by transcription factor MEF2C. *Science, 276(5317),* 1404–1407. DOI 10.1126/science.276.5317.1404.