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Monoamniotic Monochorionic Twins Discordant for Noncompaction Cardiomyopathy

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Abstract

Occasionally “identical twins” are phenotypically different, raising the question of zygosity and the issue of genetic versus environmental influences during development. We recently noted monochorionic-monoamniotic twins, one of which had an isolated cardiac abnormality, noncompaction cardiomyopathy, a condition characterized by cardiac ventricular hypertrabeculation. We examined the prenatal course and subsequent pathologic correlation since ventricular morphogenesis may depend on early muscular contraction and blood flow. The monochorionic-monoamniotic female twin pair was initially identified since one fetus presented with increased nuchal translucency. Complete heart block was later identified in the fetus with nuchal translucency who did not survive after delivery. In contrast, the unaffected twin had normal cardiac studies both prenatally and postnatally. Pathologic analysis of the affected twin demonstrated noncompaction of the left ventricle with dysplasia of the aortic and pulmonary valves. Dissection of the cardiac conduction system disclosed atrioventricular bundle fibrosis. Maternal lupus studies, amniocentesis with karyotype, and studies for 22q11.2 were normal. To test for zygosity, we performed multiple STR marker analysis and found that all markers were shared even using non-blood tissues from the affected twin. These studies demonstrate that monozygotic twins that are monochorionic monoamniotic can be discordant for cardiac noncompaction. The results suggest further investigation into the potential roles of pathologic fibrosis, contractility, and blood flow in cardiac ventricle development.

Keywords

Twins; noncompaction; heritability; cardiomyopathy; congenital heart; monozygotic; fibrosis

INTRODUCTION

It is common for monozygous twins to have identical phenotypes, yet some twins have significant discordant features [Chambers et al., 2006; Hall, 2003; Zwijnenburg et al., 2010]. Increasingly, fetal imaging detects a malformation in only one twin [Harper et al., 2012; Jo et al., 2011; Ramsey et al., 2012]. In such instances, the question of true zygosity of the twins is sometimes reexamined. Yet, in conjoined twins, indisputably monozygotic, a complex heart malformation in only one twin may rarely be present [Ursell et al., 1983]

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supporting that these monozygous twins are not always “identical.” Discordance in pathophysiologic phenotypes in monozygous twins may also be recognizable by fetal ultrasound. Thus, the colloquial expression “identical twins” is most accurate when referring to genotypic similarity.

In this report we describe monochorionic monoamniotic twins with a discordant cardiac phenotype in which one twin had no physiologic or structural heart abnormality, and the other had noncompaction cardiomyopathy. Unlike hypertrophic cardiomyopathy, for which concordance among monozygous twins has been used as a tool for defining a heritable cause [Ko et al., 1992; Maron et al., 2007; Palka et al., 2003; Reid et al., 1989], noncompaction cardiomyopathy has no clear-cut etiology and may represent a nonspecific phenotype, if not properly defined. Noncompaction cardiomyopathy is characterized by prominent, excessive ventricular trabeculations with deep intertrabecular recesses and poorly developed left ventricular papillary muscles [Burke et al., 2005; Chin et al., 1990; Maron et al., 2006; Sarma et al., 2010]. Considered to reflect a developmental abnormality of the heart, the same pathology may be seen in association with congenital cardiac malformations and is termed ventricular noncompaction. The clinical sequelae of noncompaction cardiomyopathy are variable but may include arrhythmias, thromboembolism, heart failure, and sudden cardiac death [Bhatia et al., 2011; Freedom et al., 2005]. There is evidence of genetic involvement in some cases: X-linked and autosomal dominant inheritance have been observed in familial cases, and certain genetic syndromes have been associated with noncompaction including Barth syndrome [Bleyle et al., 1997; Ichida et al., 2001], Coffin-Lowry syndrome [Martinez et al., 2011], Turner syndrome [Altenberger et al., 2009; van Heerde et al., 2003], and 1p36 deletion [Battaglia et al., 2008; Thienpont et al., 2007]. Alterations in sarcomeric genes, such as Beta-myosin heavy chain (*MYH7*) and cardiac myosin-binding protein C (*MYBPC3*), have also been documented in some familial cases [Budde et al., 2007; Probst et al., 2011]. Only in a minority of cases of noncompaction cardiomyopathy is the etiology known, making a report of discordant monozygotic twins particularly relevant. Studies of noncompaction cardiomyopathy in twins have been limited, although these may help in determining genetic and environmental contributions. In our case described below, we report discordance for noncompaction cardiomyopathy, despite proven monozygosity.

MATERIALS AND METHODS

Informed consent and DNA was obtained using protocols approved by the Committee on Human Subjects Research at the University of California San Francisco.

Genomic DNA isolation was performed using formalin-fixed tissues from the autopsy or from blood in the living twin using Puregene Blood Kit (Qiagen) with minor modifications. Briefly, fixed tissues were minced prior to incubation with cell lysis, followed by protein precipitation and DNA precipitation. Isolation from liver yielded 644ng genomic DNA/mg tissue. DNA samples were verified on agarose 2% gels and quantified using the Nanodrop1000 Spectrophotometer. For more accurate quantification and quality assessment, DNA samples were analyzed using the DNA1000 chips run on the Agilent 2100 Bioanalyzer. Zygosity of the twins was examined by genotyping highly polymorphic DNA loci using the PowerPlex short tandem repeat kit (Promega). Amplified fragments were detected using the ABI 3730xl DNA Analyzer. Data were analyzed with GeneMapper software.

CLINICAL REPORT

A 21-year-old G2P1 healthy woman was found to have monochorionic monoamniotic female twins (twins A and B) by ultrasound. There was no family history of congenital heart disease, cardiomyopathy, ventricular noncompaction, unexplained deaths, vascular conditions including thrombosis, recurrent pregnancy losses or autoimmune disorders. Imaging at 14 weeks pregnancy disclosed fetal bradycardia (<60 beats/minute) and cystic hygroma in twin B, while twin A was normal. Fetal echocardiography at 18-4/7 weeks gestation showed a ventricular heart rate of 57 beats/minute with an atrial rate that was twice as fast, indicative of complete heart block in twin B. Other findings in twin B included aortic valve stenosis, post-stenotic aortic dilation, and left ventricular thickening. Twin A had a heart rate of 149 beats/minute and normal anatomy. At 22-5/7 weeks, the ascending aorta measured 0.73 cm (Z-score = +4.77) while the aortic valve measured 0.23 cm (Z-score -3.08).

Amniocentesis showed a normal karyotype of 46,XX. FISH for chromosomes 13, 18, and 21 as well as for 22q11.2 was normal; and maternal lupus antibodies were not detected. Due to signs of fetal distress, the twins were delivered by cesarean section at 27 weeks. Twin A was born with Apgar scores 5 and 7, while twin B had bradycardia and expired shortly after delivery. A neonatal echocardiogram of female twin A was normal. Six months after birth, twin A was developing well with no evidence of health problems or cardiac anomalies. The parents were healthy and did not undergo echocardiography.

Pathology

The family consented to autopsy of twin B. This female twin weighed 730 gram (10–25%ile) and had an enlarged heart (12 gm, expected mean 5.8 ± 1.9) with normal atrial situs. There was aortic and pulmonic valve annular narrowing, both valves having three dysplastic leaflets. The left ventricular cavity was dilated and the muscular walls hypertrophied. Anteriorly and inferolaterally the endocardial surface showed numerous abnormally thick muscular trabeculae, and endocardial fibroelastosis was present. (Fig 1). The papillary muscles of the left ventricle were small and indistinct. Short-axis cross sections demonstrated left ventricular hypertrabeculation with deep intertrabecular recesses extending into the ventricular wall; anteriorly and inferolaterally, approximately 60–70% of the wall thickness was comprised of trabeculae, the rest of the myocardium being compact. Histologically, the atrioventricular conduction axis showed granulation tissue and fibrosis in the crest of the muscular ventricular septum anterior to the AV node position and extending into the AV bundle (Fig 2). No active inflammation was identified, and the etiology of the damage in this area was unclear. Twin B also had a two-vessel umbilical cord. No other organ system malformations were identified. The monochorionic monoamniotic common twin placenta was small for gestational age and exhibited a forked umbilical cord, bifurcating 1cm from the insertion site. Twin A had a three-vessel umbilical cord. On placental examination, no abnormal clots, thrombi or fibrosis were noted.

Zygosity analysis

We sought to determine whether these anatomically discordant twins were identical by performing zygosity analysis. Formalin-fixed tissues from the deceased twin B and blood from twin A were available, and these were used to isolate genomic DNA. Electrophoresis of genomic DNA samples revealed high molecular weight DNA in twin A and fragmented DNA from fixed tissues of twin B (data not shown). STR analyses were performed indicating that twin A and twin B shared 14 alleles (Table I), indicating very high confidence in monozygosity.

DISCUSSION

This is the first report of monochorionic monoamniotic twins discordant for the noncompaction cardiomyopathy. There have been three other case reports describing identical twins with noncompaction [Luckie et al., 2009; Peters et al., 2012; Vinograd et al., 2012]. However, in all three previous reports, both twins were diagnosed with noncompaction (Table II).

Discordant monozygous twins emphasize that confirmed genetic identity does not preclude a discordant cardiac phenotype. Our data strongly support monozygosity, as expected from monoamniotic monochorionic twins, and the STR analyses compared blood tissue from one twin to non-blood tissue from the other, reducing the possibility of confusion due to potential hematologic microchimerism between twins. Since these twins likely split from each other at ~7–14 days post-fertilization, it is possible that the instigating events in the cardiac phenotype may have preferentially affected one twin only after splitting. Studies suggest an estimated 10% of monozygotic twins are born with a congenital anomaly, and many mechanisms have been postulated that could lead to phenotypic discordance [Hall, 2003]. It is possible that asymmetries in physiological, environmental, or mechanical events during development may result in phenotypic discordance, including initial differences in the cells at the time of twin separation, differences in vascular flow, or differences in attachment to the placenta. It is possible that in this pair of discordant twins, initially subtle differences during development led to markedly contrasting phenotypes despite genetic identity. The difference between the number of umbilical cord vessels in twins A and B, would be consistent with one twin being disproportionately affected by a potentially development-altering event. Monozygotic twins discordant for single umbilical artery have been noted in other studies, although how this contributes to disease is unclear. In some cases the twin with congenital heart disease was observed to possess the single umbilical artery [Negishi et al., 1995] while in another case, the twin without the single umbilical artery was found to have congenital heart disease [Nakayama et al., 1998].

In our study the diagnosis of noncompaction cardiomyopathy was based on >50% of the left ventricular thickness comprised of trabecular myocardium as well as absence of well-formed papillary muscles [Burke et al., 2005]. Noncompaction is thought to reflect abnormal trabecular development in the embryonic heart. At 5 weeks of development in humans, trabeculae are present, and at 5 to 8 weeks of development, the process of trabecular remodeling and compaction occurs, as the coronary arterial circulation develops. Compaction starts at the base of the heart and continues towards the apex, which may explain why noncompaction most prominently involves the midventricle to apex of the heart [Paterick et al., 2012].

Persistence of this noncompacted muscle may be the basis for heart failure and decreased contractility. Since blood flow likely plays a role in remodeling developing heart valves in the normal embryo, the abnormal flow associated with noncompaction may well have contributed to valve dysplasia, resulting in progressive aortic and pulmonic narrowing during fetal life. Complete heart block, which can be associated with noncompaction [Freedom et al., 2005], would also decrease coordinated contractility and contribute to decreased flow through the aortic and pulmonary valves. Endocardial fibroelastosis may be a response to injury [Lurie, 2010]. The fibrosis of the AV bundle and granulation tissue seen in the cardiac conduction tissues suggest a localized insult or injury, providing further evidence for an unequal critical event. Potential contributing factors could include developmental variation in the vascular supply or in the expression of cardiac developmental genes. *SCN5A* [Papadatos et al., 2002] gene variants were reported in Japanese noncompaction patients, particularly in individuals with arrhythmia [Shan et al., 2008],

however it is important that any unifying theory for the reported twins would need to account for twin discordance in disease or penetrance. Further followup will help confirm that the co-twin remains healthy. Additional studies should strive to elucidate the cause of noncompaction and its relationship to other forms of cardiomyopathy. We conclude that monochorionic monoamniotic twins can be discordant for cardiac noncompaction despite monzygosity, and further studies should be directed at understanding the genetic and non-genetic contributions to disease predisposition.

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Figure 1. Noncompaction cardiomyopathy–gross pathology in twin B

In the short axis (panel A) the left ventricle shows excessive trabeculation in the anterior and inferiolateral regions of the free wall (arrows). At these points, the trabecular layer occupies more than 50% of the wall thickness. Viewed from the apex (panel B), the left ventricular outlet shows endocardial fibroelastosis (long arrow). Two of the 3 thick semilunar leaflets comprising the dysplastic aortic valve (short arrow) are visible.

Figure 2. Atrioventricular bundle with healing damage

At low magnification (panel A), a transverse section through the central fibrous body shows the characteristic arrowhead configuration of the atrioventricular bundle (AVB) astride the interventricular septum (IVS). The specialized muscle of the bundle, however, contains granulation tissue and fibrosis (arrows) denoting healing damage. High magnification (panel B) discloses the interface between the healing damage and the remaining viable specialized muscle. Gomori trichrome, panel A calibration bar=300 μ , panel B calibration bar=50 μ .

Table 1

Zygosity Analyses by STR Genotyping

	AMEL	CSF1PO	D13S317	D16S539	D18S51	D21S11	D3S1358	D5S818
Pos control	X Y	10 12 [‡]	11 11	11 12	15 19	30 30	14 15	11 11
Twin A (Blood)	X X	11 11	10 12	10 11	10 14	29 32.2	14 16	11 12
Twin B (Liver)	X X	11 11	10 12	10 11	10 14	29 32.2	14 16	11 12
Neg control								
	D7S820	D8S1179	FGA	Penta_D	Penta_E	TH01	TPOX	vWA
Pos control	10 11	13 13	23 24	12 12	12 13	8 9.3	8 8	17 18
Twin A (Blood)	10 12	13 14	24 26	12 14	5 10	6 6	8 8	17 17
Twin B (Liver)	10 12	13 14	24 26	12 14	n.d.	6 6	8 8	17 17
Neg control								

[‡]Numbers indicate alleles present for each marker

Comparison of Noncompaction in Twins

Table II

Study	Twin pair sex, age	Phenotype of Twin (A) ¹	Phenotype of Co-Twin (B)	Twin identity	Other abnormalities	Placenta or Membranes	Conduction system	Notes
Luckie et al. (2009) U.K.	Male twins, 20 years	LVNC ²	LVNC	identical, reported		n.d. ³	SVT ⁴ in one twin	B-thal major, transfused, iron overload
Vinograd et al. (2012) U.S.	Female twins, fetal-8 months	LVNC, tricuspid stenosis, pulmonary atresia	LVNC, mitral valve abnormality	benign CNV shared	SUA ⁵ twin B	monoamniotic		Severity of LVNC milder in twin B
Peters et al. (2012) S.Africa	Male twins, 35 years	LVNC	LVNC	identical, reported		n.d.		African descent
Current report U.S.	Female twins, fetal	LVNC, pulmonary and aortic valve abnormality	Normal	STR all identical	SUA twin A, forked umbilical cord	monoamniotic, common placenta	Heart block, fibrosis twin A	

¹ Twin A or B designations here are used for twin identification only and do not necessarily reflect which twin was born first,

² Left ventricular noncompaction,

³ No data,

⁴ Supraventricular tachycardia,

⁵ Single umbilical artery