

## “Not-so-identical” twins with trisomy 21 and perimembranous ventricular septal defects

### Trizomi 21 ve perimembranöz ventriküler septal defektleri olan tam özdeş olmayan ikizler

\*Sarosh P Batlivala, M.D., Kendra S Courtney, M.D., Makram R Ebeid, M.D.,# Aimee S Parnell, M.D.†

University of Mississippi Medical Center, School of Medicine, Jackson, MS, USA

\*#Division of Pediatric Cardiology, Blair E. Batson Hospital for Children, Jackson, MS USA

**Summary**– While trisomy 21 is a common genetic disorder in singletons, the incidence among identical twins is very rare, occurring in approximately 1–2 per 1000 twin gestations. Trisomy 21 is associated with high incidence of congenital heart defects, and commonly occurs with ventricular septal defects (VSDs). Physiologic burden of VSDs depends on prevalence of anatomic and other circulatory factors. A case of identical twins with trisomy 21 and large VSDs is described in the present report. Though genetically identical, phenotypes varied significantly. One twin was managed medically, while the other developed more significant heart failure, requiring operative repair.

**Özet**– Tekizlerde trizomi 21 sık görülen bir genetik bozukluk olmasına rağmen özdeş ikizler arasında insidansı çok düşük olup 100 ikiz gebeliğin yaklaşık 1-2'sinde görülür. Trizomi 21 yüksek insidanda doğuştan kalp defektleri ile ilişkili olup genellikle ventriküler septal defektlerle (VSD'ler) birlikte görülür. VSD'lerin fizyolojik yükü anatomik ve diğer dolaşım faktörlerinin prevalansına bağlıdır. Bu yazıda, trizomi 21'i ve geniş VSD'si olan özdeş ikizler sunuldu. İkiz olmalarına rağmen bebeklerin fenotipleri anlamlı derece farklıydı. İkiz kardeşlerden biri tıbbi tedaviyle iyileşmesine rağmen diğerinde cerrahi onarımı gerektiren daha önemli kalp yetersizliği gelişti.

Trisomy 21 is a common genetic disorder affecting approximately 1 in 650–1000 live births.<sup>[1,2]</sup> The majority of cases occur through nondisjunction, with a minority developing from unbalanced translocation.<sup>[3]</sup> Twins affected by trisomy 21 are very rare. Incidence of trisomy 21 in 1 twin of a dizygotic (i.e., “fraternal”) pregnancy is 1.2% of twin gestations, while incidence in monozygotic pregnancies is one-sixth of that.<sup>[4,5]</sup> Interestingly, a recent prevalence study noted that the adjusted relative risk of trisomy 21 per fetus was lower in multiple pregnancies, compared to single pregnancies.<sup>[6]</sup>

Congenital heart disease (CHD) is associated with trisomy 21. The majority of cardiac lesions are septal defects, particularly atrioventricular canal and ventricular septal defects (VSDs).<sup>[7]</sup> A case of monozygotic twins with trisomy 21 and CHD, in whom cardiovascular pathophysiology differed, with significant

clinical implications, despite having the same anatomic defect, is described in the present report.

#### Abbreviations:

CHD Congenital heart disease  
VSD Ventricular septal defect

#### CASE REPORT

The twins were conceived sexually (not via exogenous or *in vitro* fertilization, etc.) to a 33-year-old mother. They were born after a 35-week monozygotic, monochorionic, monoamniotic gestation. Prenatal screening was notable due to abnormal alpha-fetoprotein and human chorionic gonadotropin levels, with subsequent amniocentesis confirming trisomy 21. Selective termination was not offered, as it is not a standard of practice in the patients' state. Twin A required fewer interventions at birth. She was electively intubated to administer single dose of surfactant, then placed on high-flow nasal cannula. Twin B was intu-

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Correspondence: Dr. Sarosh P Batlivala. 2500 N. State Street, Division of Pediatric Cardiology, 39216 Jackson, United States.

Tel: 011-352-871-1448 e-mail: sbatlivala@umc.edu

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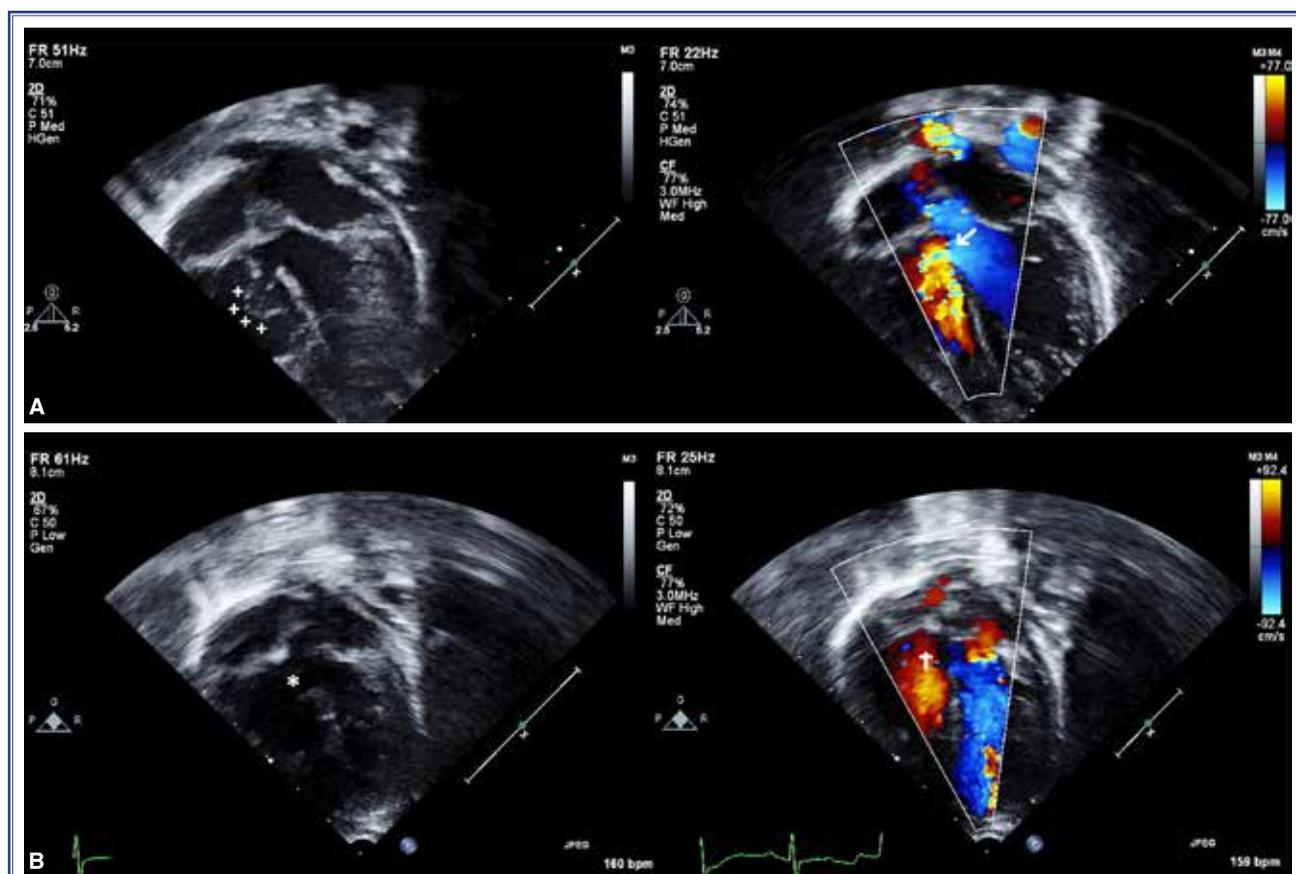
bated in delivery room due to significant respiratory distress. Single dose of surfactant was administered, but she required mechanical ventilation. Twin A did well and was weaned to air in 3 days. Twin B developed significant pulmonary hypertension requiring an additional dose of surfactant, 100% oxygen, and inhaled nitric oxide. She was weaned to high-flow nasal cannula in 4 days and to air 3 days later.

Echocardiograms were performed on both infants on first day of life. Both were diagnosed with large perimembranous VSDs, small atrial septal defects, and patent ductus arteriosus. VSD of Twin A was mildly pressure-restrictive; that of Twin B showed no evidence of restriction in neonatal intensive care unit (Figure 1). Both twins ultimately stabilized and did not require medical therapy prior to discharge at 3 weeks of age. Karyotyping confirmed 47, XX, +21, with an extra, independent copy of chromosome 21 in both twins.

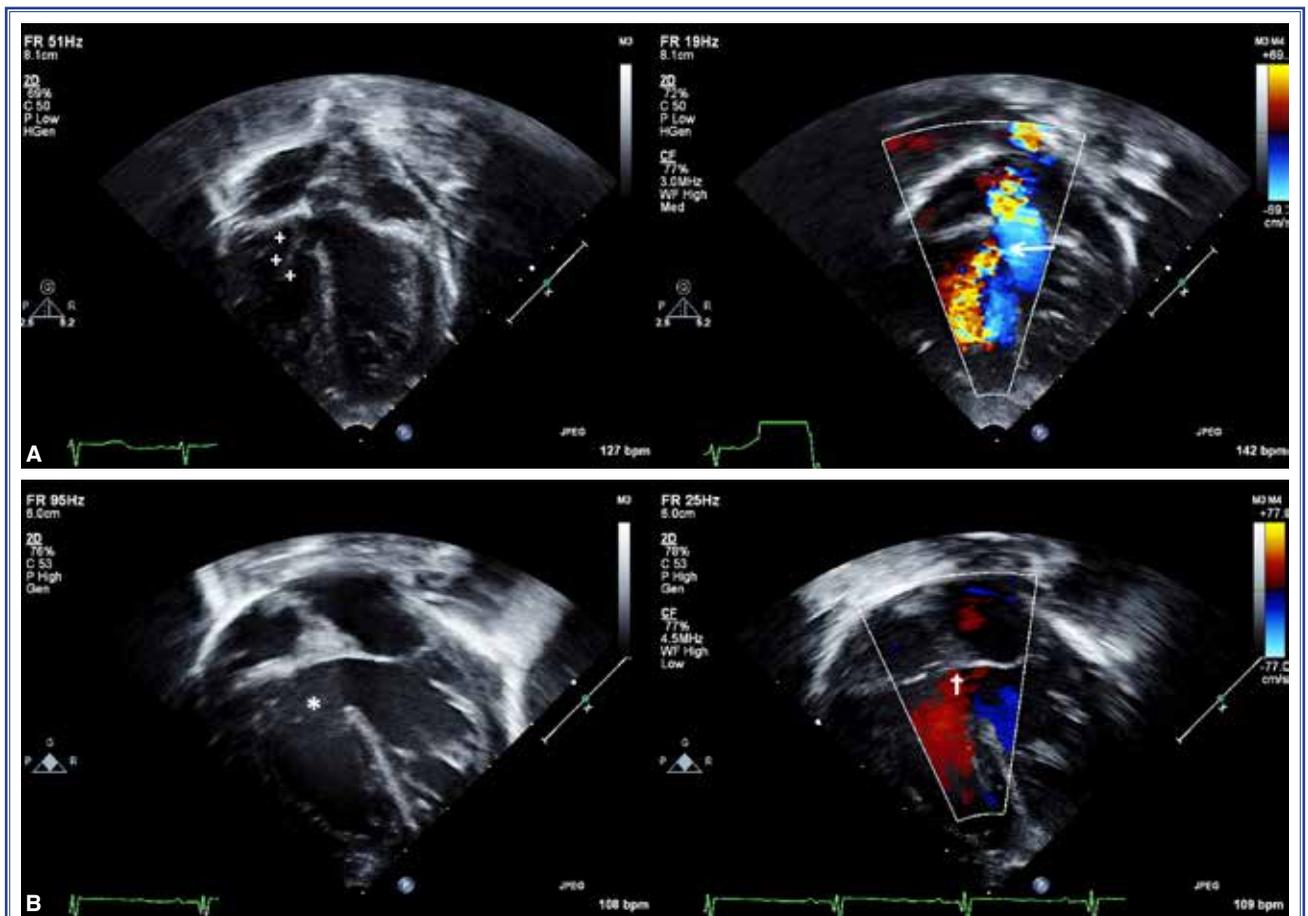
Both twins developed signs of pulmonary overcirculation by 6 weeks of age and were started on diuretic therapy with higher-calorie formula. Twin A responded well to management with single diuretic. However, Twin B continued to exhibit symptoms of overcirculation, requiring maximal doses of 2 diuretics and an angiotensin-converting-enzyme inhibitor.

Twin B presented to children's hospital in respiratory failure secondary to upper respiratory infection at 4 months of age. She required intubation and was ultimately found to have parainfluenza bronchiolitis. Though infectious symptoms resolved, she was unable to be weaned from mechanical ventilation, despite 4 attempts. VSD remained unrestrictive, and pulmonary artery band was placed after 2 weeks of hospitalization. Symptoms and oral intake improved significantly, and she was discharged 4 days after surgery.

Nine months have passed since that hospitalization; the twins were 13 months at time of submission



**Figure 1.** Transthoracic echocardiography, in apical 4-chamber orientation, of the twins' VSDs on their first day of life. **(A)** Twin A. Note that the VSD is partially covered by aneurysmal tricuspid valve tissue (++++) and is partially pressure-restrictive, with aliasing flow on color Doppler (arrow). **(B)** Twin B. Note the large VSD (\*) with unrestrictive flow on color Doppler (†).



**Figure 2.** Transthoracic echocardiography in apical 4-chamber orientation at the time of Twin B's pulmonary artery band placement. **(A)** Twin A. Note the further covering with aneurysmal tricuspid valve tissue (++++), with greater pressure restriction and aliasing flow, on color Doppler (arrow). **(B)** Twin B. Note that the VSD remains large (\*) and unrestrictive on color Doppler (+).

of the present report. VSD of Twin A was significantly pressure-restrictive, though the rate of restriction seemed to have plateaued (Figure 2); her heart failure was controlled well with twice-a-day Lasix. Twin B was improving significantly, gaining weight at 40 grams per day, and catching up with her sister. Given the positive clinical trajectory, the twins were being monitored with the intention to refer Twin B for surgical repair, while monitoring of Twin A continued.

Procedures followed were in accordance with the ethical standards of the University of Mississippi Medical Center Institutional Review Board and the Helsinki Declaration of 1975, as revised in 2000.

## DISCUSSION

In addition to the benefit of reporting a rare case in twins, these “identical” twins are notable for their

varied physiologic manifestations. This variation may suggest a multifactorial etiology in the pathogenesis of the twins' heart defects.

Atrioventricular septal defects and VSDs are the 2 most common CHDs in patients with trisomy 21.<sup>[8]</sup> Ackerman et al. used a candidate gene approach to determine whether genetic variants in certain genes known to be involved in septal development contribute to atrioventricular septal defects in trisomy 21.<sup>[9]</sup> They noted a significant excess of variants hypothesized to be deleterious in the trisomy 21 cases, with potentially causative mutations in 20% of the cases vs only 3% of the controls. Though these genes are being identified, clinical manifestations vary in regard to presence and severity of heart disease in these patients.

As Li et al. noted, roughly half of patients with trisomy 21 do not have significant heart defects, sug-

gesting that other genetic modifiers interact with dosage-sensitive genes on chromosome 21.<sup>[10]</sup> They sequenced 2 candidate genes, CRELD1 and HEY2, in a group of trisomy 21 patients with CHD and found several mutations, but at a low frequency. The group then crossed mutant forms of the modifiers into a murine model of trisomy 21 and found that crossing loss-of-function alleles of either CRELD1 or HEY2 into the trisomy model greatly increased the frequency of CHD. Their work demonstrated a basis for a threshold with additive effect of genetic modifiers.

The present case emphasizes that monozygotic identical twins may not develop identical physiology, even with similar congenital defects. Close monitoring with individualized therapies and counseling may be indicated for similar “not-so-identical” twins.

### Informed consent

For the present type of study, formal consent is not required. Written permission from the patients’ parents was obtained.

### Support

No honorarium, grant, or other form of payment/support was received.

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