Tricuspid atresia and pulmonary atresia in a child with Rubinstein-Taybi syndrome

Rohit S Loomba[1], Gabrielle Geddes[1,2]

[1]Department of Pediatrics and Children's Research Institute, [2]Human and Molecular Genetics Center, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

ABSTRACT

Rubinstein-Taybi syndrome is a well-characterized condition causing distinctive physical characteristics, intellectual disability, and multiple congenital malformations. Cardiac abnormalities are found in a third of individuals with this condition and usually consist of isolated septal defects or patent ductus arteriosus, although more complex congenital lesions have been described. We present the first reported case of tricuspid atresia and pulmonary atresia with hypoplasia of the right ventricle in the setting of Rubenstein-Taybi syndrome.

Keywords: Hypoplastic right ventricle, Rubinstein-Taybi syndrome, tricuspid atresia

INTRODUCTION

Rubinstein-Taybi syndrome (RTS) was initially described in 1963, consisting of a constellation of intellectual disability, broad fifth digits of the hands and feet, growth deficiency, and characteristic facial features.[1] It was not until nearly 30 years after its initial description that a submicroscopic 16p13.3 deletion, involving the cyclic adenosine monophosphate (cAMP) response element-binding protein-binding protein(CREBBP) gene, was found to be the underlying genetic alteration in the majority of cases.[2,3] Although the prevalence of RTS is not precisely known, RTS is estimated to affect 1 in every 300,000 people in the general population. The prevalence of RTS is higher among those who are institutionalized for mental illness with an estimated prevalence of 1 in every 300-500 people in this population.[4]

In additional to characteristic physical features and intellectual disability, those with RTS may also have mild to severe manifestations in nearly any of the other organ systems. Cardiac abnormalities are present in 24-38% of all children with RTS. These include isolated lesions such as atrial septal defects, ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, valvar pulmonic stenosis, bicuspid aortic valve, valvar aortic stenosis, vascular rings, and conduction abnormalities.[4-6] Complex congenital cardiac lesions have been infrequently described in the setting of RTS and consist of three cases of hypoplastic left heart syndrome.[6-8] We report the case of a child with RTS and tricuspid atresia type IA with a hypoplastic right ventricle. This is the first reported case of a child with RTS and tricuspid atresia with hypoplasia of the right ventricle.

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CASE REPORT

A 32-year-old G4P2212 mother was referred to our institution for a fetal echocardiogram after a routine ultrasound raised concern for multiple congenital anomalies, including cardiac defects. The fetal ultrasound demonstrated the presence of an abnormal nuchal cord, left renal agenesis, rocker bottom feet, and possible omphalocele. Fetal echocardiography demonstrated a large atrial communication with right to left shunting, dilated right atrium, tricuspid atresia with a hypoplastic right ventricle, and pulmonary atresia with a hypoplastic pulmonary trunk. Branch pulmonary arteries appeared confluent and there was a moderate sized patent ductus arteriosus with left to right flow and subsequent flow reversal in the ductus venosus. Free fetal deoxyribonucleic acid (DNA) for trisomy 13, 18, and 21 was negative and amniocentesis demonstrated a normal 46XY karyotype and normal microarray. Maternal history was unremarkable with all negative serologies

Address for correspondence: Dr. Rohit S. Loomba, Children's Hospital of Wisconsin, 9000 Wisconsin Avenue, Milwaukee, Wisconsin, 53226, United States. E-mail: rloomba@chw.org

during pregnancy. Family history was significant for a first cousin with tricuspid atresia who had undergone Fontan palliation.

The male infant was born at 36 6/7 weeks gestational age at another institution with a birth weight of 2,150 grams. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. Umbilical lines were placed and E type Prostaglandin was started before transport to our institution. The infant also required intubation due to respiratory distress before transport. Upon arrival to our institution, the infant underwent an echocardiogram, which demonstrated cardiac anatomy consistent with that noted on the fetal echocardiogram [Figures 1-3]. Of note is the absence of the right atrioventricular connection, which is the essential feature of tricuspid atresia. The pulmonary trunk was thread-like, thus, leading to an effective absence of the ventriculo-arterial connection as well. Left ventricular function was normal and the coronary arteries had normal origin and distal course. Renal ultrasound demonstrated left renal agenesis with an adequately functioning right kidney. Physical examination yielded microcephaly, low set ears with abnormal creases and posterior rotation, hypertrichosis, shawl scrotum, and micrognathia [Figure 4]. Bilateral dimpling around the umbilicus was also noted which were thought to possibly represent atypical accessory nipples. The hands bilaterally demonstrated brachydactyly, clinodactyly, broad thumbs, and hypoplastic nails [Figure 5]. The feet demonstrated webbing of the second and third toes bilaterally, broad fifth toes, and deep set hypoplastic nails. Chest radiograph also demonstrated vertebral anomalies and segmentation defects. Diagnosis of RTS was confirmed with sequencing of the CREBBP gene which revealed a previously described pathogenic sequence change of c.4444T > G which results in the amino acid change p. Tyr1482Asp.

On day of life 14, he underwent palliation for his congenital cardiac lesion with placement of a 3.0 mm Blalock-Taussig shunt and ligation of a patent ductus arteriosus. At 3 weeks of age, CREBBP sequencing demonstrated a heterozygous base pair change in exon 27, confirming a diagnosis of RTS. Because of poor oral

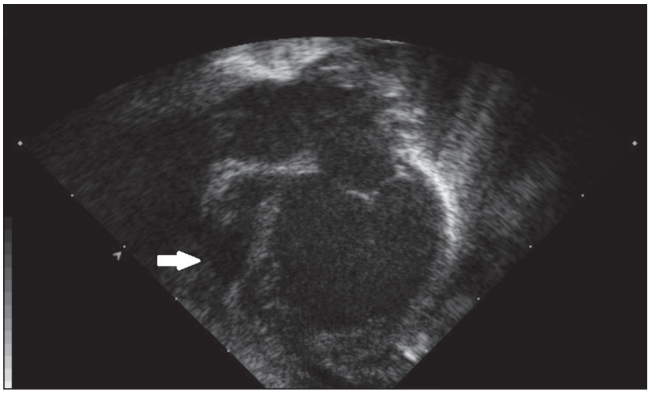

Figure 1: Echocardiography in the four-chamber view demonstrating a well-developed left ventricle, tricuspid atresia, and a hypoplastic right ventricle (white arrow)

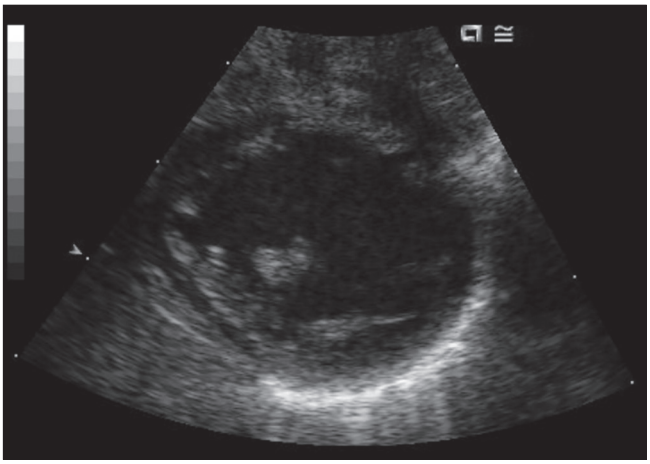

Figure 2: Echocardiography in the parasternal short axis demonstrating a well-developed left ventricle but a hypoplastic right ventricle

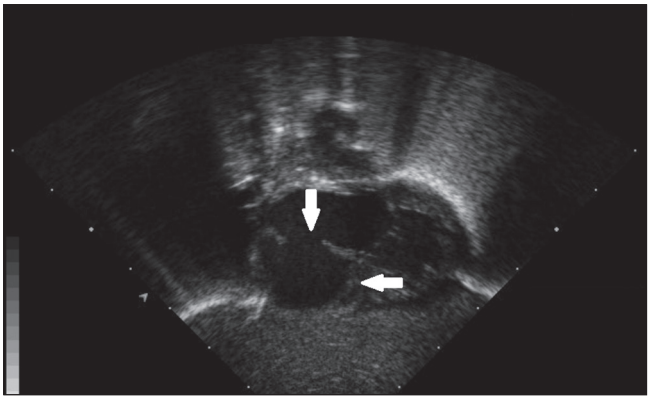

Figure 3: Echocardiography in the subcostal long-axis demonstrating an atrial septal defect (vertical arrow), tricuspid atresia (horizontal arrow), hypoplastic right ventricle, and a well-developed left ventricle

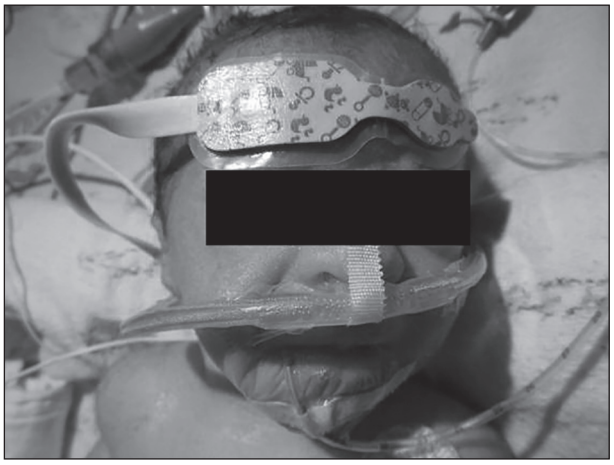

Figure 4: Image demonstrating facial features including microcephaly and micrognathia

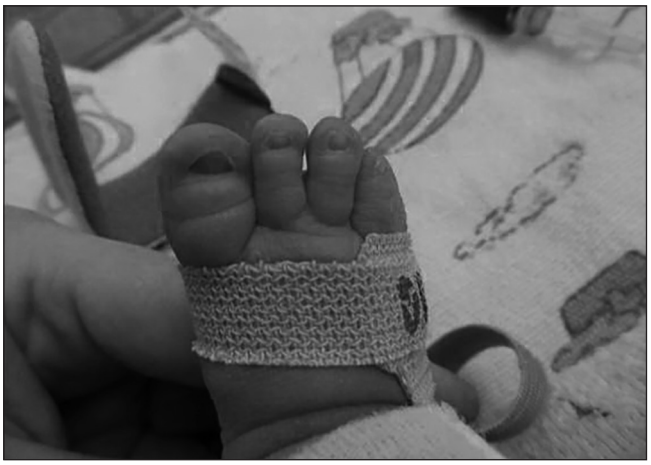

Figure 5: Image of right foot demonstrating broad fifth digit and hypoplastic nails

intake, the infant underwent gastrostomy tube placement at 8 weeks of age. The infant was discharged home at 2 months of age on ¼ liter nasal cannula.

DISCUSSION

RTS is a well-defined intellectual disability syndrome most frequently caused by a disruption of the CREBBP gene, often with a microdeletion at chromosome 16p13.3.[2] Facial abnormalities of the syndrome may include a prominent beaked nose, a low nasal septum, downward slanted palpebral fissures, colobomas, and micrognathia. Examination of the upper extremities may demonstrate broad fifth digits of the hands, abnormal palmar creases, clinodactyly, polydactyly, and hypoplastic nails. Examination of the lower extremities may demonstrate broad fifth digits of the feet and angulation of the fifth digits of the feet.[1,5]

A variety of other organ systems can demonstrate manifestations of the syndrome. Some of the most common manifestations include poor feeding and growth, renal abnormalities, increased susceptibility to keloid formation and development of hypertrophic scars, and increased susceptibility to recurrent otitis media.[9] Cardiac manifestations are also frequent and affect up to a third of all patients with RTS. While these generally include simple isolated lesions such as septal defect and patent ductus arteriosus, more complex lesions in the form of hypoplastic left heart syndrome have been documented in three patients.[6-8] The first of these cases was identified by a questionnaire sent to 292 families known to have a member diagnosed with RTS as per the RTS Parent Support Group. A total of 168 families responded to the questionnaire with 138 cases being confirmed as having RTS. One of these cases was reported as having hypoplastic left heart syndrome with mitral stenosis and aortic stenosis and was alive at a year of age.[6] The second case was that of a child noted to have RTS after birth that ultimately died at 35 days of age from complications of necrotizing enterocolitis.[8] The third case was that of child with prenatally diagnosed hypoplastic left heart syndrome who was diagnosed with RTS postnatally. The child died at 5 days of age while undergoing a Norwood procedure.[7]

We present a case of a child with RTS with congenital cardiac anomalies not previously reported with RTS. The child was born with tricuspid atresia type with pulmonary atresia and a hypoplastic right ventricle. A large atrial septal defect was present as was a moderate sized patent ductus arteriosus. Palliation for the cardiac defects was performed in the form of a Blalock-Taussig shunt. Facial features, renal abnormalities, and feeding difficulties were all consistent with abnormalities previously reported in those with RTS and sequencing of the CREBBP gene confirmed the diagnosis. While a majority of RTS is caused by a deletion at chromosome 16p13.3, this report demonstrates a case caused by a single base pair mutation that has been documented to cause a functional deficiency in a protein encoded by the gene and cause RTS.[2,3,10]

While the role of 16p13.3 deletions and their subsequent disruption of the CREBBP gene have been shown to cause RTS, its role in the development of specific abnormalities such as the cardiac defects is unclear. What is known is that the CREBBP gene is involved in the development of multiple signaling and transcription pathways and that mutation of the gene can lead to abnormal embryonic development. While the precise mechanism of complex cardiac defects such as tricuspid atresia is not completely delineated, it is very likely that gene mutations play a role, and thus the CREBBP gene may be implicated in certain cases.

CONCLUSION

RTS is an intellectual disability syndrome that can lead to several visceral defects, including cardiac abnormalities. While a majority of these are septal defects, lesions such as hypoplastic left heart syndrome and tricuspid atresia can be present and may be secondary to mutations in the CREBBP gene.

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