

Congenital second-degree heart block and total anomalous pulmonary venous return associated with microduplication of 1q32.2

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ABSTRACT

We report a term female infant with congenital heart block and total anomalous of pulmonary venous return. The results of single nucleotide polymorphism oligonucleotide microarray analysis showed an interstitial duplication of approximately 818 Kb, which involved 11 genes, including the entire LAMB3 gene which is known to associate with cardiac conduction defect. Our report adds to the collective knowledge that the cardiac conduction defect is a clinical feature of chromosome 1q32.2 duplication.

Keywords: 1q32 microduplication, congenital, congenital heart block, total anomalous pulmonary venous return

INTRODUCTION

Congenital atrioventricular block, or congenital heart block, is a rare condition. The incidence of congenital heart block in the general population varies between 1 in 15,000 and 1 in 22,000 liveborn infants.^[1,2] Total anomalous pulmonary venous return (TAPVR) is a rare congenital malformation. TAPVR occurs in approximately 4–6/100,000 live births.^[3] It accounts for 0.7%–1.5% of the cases of congenital heart disease. We report a full-term infant with prenatal diagnosis of congenital heart block and a complete TAPVR. Comparative genomic hybridization (CGH) study also showed a microduplication of the long arm of chromosome 1 (partial trisomy 1q32.2). We review the literature.

CASE REPORT

A 3200-g female infant was delivered at 38 weeks of gestation to a 32-year-old G9P5 (2 elected terminations of pregnancy and 1 ectopic pregnancy) mother by cesarean section secondary to fetal anomaly. Apgar scores were 7 and 8 at 1 and 5 min, respectively. At 28 weeks of gestation, the pregnancy was complicated by a fetal

diagnosis of atrial septal defect (ASD) of the secundum type, TAPVR, and congenital second-degree heart block with 2:1 conduction (atrial rate of 110–118 beats/min and ventricular rate of 55–58 beats/min) at 32 weeks of gestation. The four pulmonary veins were returning to the coronary sinus. A subsequent fetal echocardiogram showed additional vascular anomalies such as bilateral superior vena cava (SVC), left SVC draining into the coronary sinus, and an interrupted inferior vena cava (IVC) with a continuation of the azygos vein to the right SVC. Family history was negative for congenital anomalies. There was no *in utero* exposure to any known teratogens. Physical examination revealed a weight of 3200 g (50th centile), length of 48 cm (30th centile), and a head circumference of 34 cm (60th centile). No visible anomalies were noted. The infant was mildly cyanotic with pulse oximetric saturation values of 85%–94%. Postnatal echocardiogram confirmed the diagnosis of TAPVR draining to the coronary sinus, bilateral SVC without bridging vein, interrupted IVC with azygos vein continuing to the right SVC, and a large (4 mm) secundum type of ASD [Figure 1]. A small perimembranous

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ventricular septal defect (VSD) and a large patent ductus arteriosus (PDA) were also noted [Figure 1]. Electrocardiogram confirmed 2:1 heart block with a resting heart rate of 60 beats/min [Figure 2]. Chest X-ray showed mild cardiomegaly and pulmonary congestion. Abdominal ultrasound showed normal appearance and location of liver and spleen. The infant underwent cardiac surgery and a permanent pacemaker placement at 9 days of age. She was discharged home at 3 weeks of age. When seen at 2-month follow-up, she was doing well.

ACGH array analysis of a peripheral blood sample revealed an 818 kb duplication of the long arm of chromosome 1 – arr 1q32.2 (209,809,645 – 210,427,436) × 3 [Figure 3]. Single nucleotide polymorphism oligonucleotide microarray analysis indicated a gain of chromosome 1 from positions 209,609,645 – 210,427,436. The duplicated region contained 11 genes, seven of which are OMIM annotated and four (LAMB3, HSD11B1, IRF6, and SYT14) of which have known disease associations.

DISCUSSION

Congenital complete heart block (CHB) was first described in 1901 by Morquio, who also noted the familial occurrence and the association with Stokes-Adams attacks and death.^[4] The presence of fetal bradycardia (40–80 beats/min) as a manifestation of CHB was first noted in 1921 and is the initial sign of this disorder in many cases.^[5] The mortality rate with complete atrioventricular block in the fetus was 43% (13 out of the 15 total deaths were fetal); in the neonatal stage, it was 6%, and in children, it was none.^[6] In the presence of fetal hydrops or with endocardial fibroelastosis, the mortality was 100%. If the fetal heart rate was <55 beats/min, the majority died (9 out of 15).^[2] The degree of heart block may vary from first-degree to third-degree block, but most cases diagnosed *in utero* present with a least second-degree block or more advanced block. There is a high mortality rate, particularly in fetuses diagnosed *in utero* with hydrops, and it is approximately 20%. Of all cases with CHB, the current data show that approximately two-thirds of these patients will require a pacemaker before reaching adulthood.^[2] In 91% of affected neonates, CHB results from neonatal lupus erythematosus, a disease associated with transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antibodies. Other causes include myocarditis and various structural cardiac defects, particularly congenitally corrected transposition of the great arteries (TGA), atrioventricular discordance, or polysplenia with atrioventricular canal defect. Several hereditary disorders have also been identified.

For the infant with TAPVR to survive, an ASD or patent foramen ovale must exist to allow oxygenated blood to flow to the left side of the heart and the rest of the

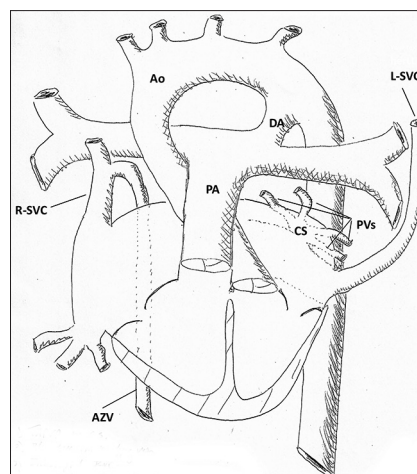


Figure 1: Diagram showed TAPVR and double SVCs. Ao: Aorta, AZV: Azygos vein, CS: Coronary sinus, DA: Ductus arteriosus, PA: Pulmonary artery, PVs: Pulmonary veins, L-SVC: Left superior vena cava, R-SVC: Right superior vena cava, TAPVR: Total anomalous pulmonary venous return

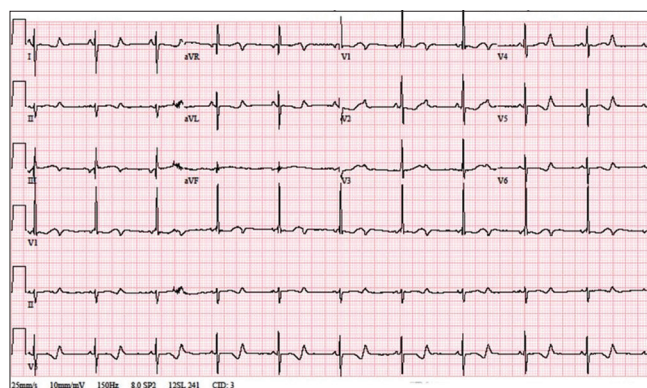


Figure 2: Electrocardiogram showing second-degree atrioventricular block in which the PR interval remains unchanged before a P wave that fails to conduct to the ventricles

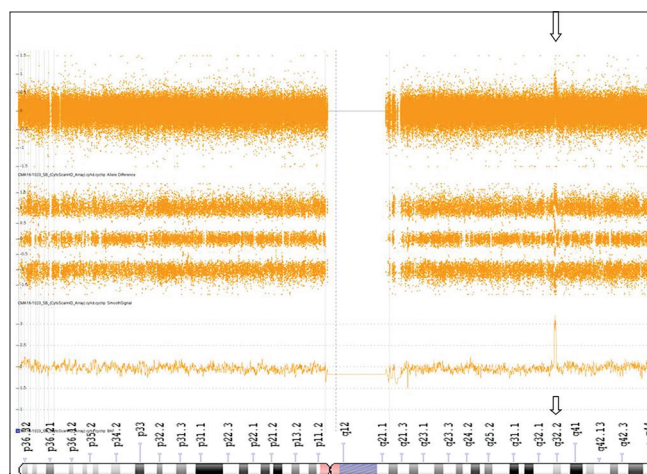


Figure 3: Single nucleotide polymorphism oligonucleotide microarray analysis using the chromosome view showed a 818 kb microduplication at chromosome band 1q32.2 (arrow)

body. TAPVR has been reported in association with asplenia/polysplenia syndrome and pulmonary atresia.^[7]

Approximately 33% of the patients with TAPVR have associated cardiac anomalies such as TGA, tetralogy of Fallot, single ventricle, tricuspid atresia, truncus arteriosus, hypoplastic left heart syndrome, and coarctation of the aorta. Although the cause of TAPVR is unknown, there are some reports of TAPVR associated with lead or pesticide exposure.^[8]

Pure duplication 1q32.2 without another chromosome aberration is rare. Most of the pure partial duplications of chromosome 1q involve microduplication of 1q32qter.^[9] Until now, about 21 cases of pure partial duplication 1q32.2 have been described.^[9-14] Major findings in patients with 1q32qter duplications include prenatal or postnatal growth retardation, microcephaly, long and overriding toes, and dysmorphic facial features such as a triangular face with a prominent forehead, midfacial hypoplasia, oral cleft, micrognathia, high palate, and low-set poorly formed ears.^[9,15] Reported cardiac defects include ASD, atrial septal aneurysm, VSD, PDA, aortic shelf, aberrant carotid artery, double right renal artery, pulmonary stenosis, and tricuspid valve dysplasia.^[9,11-13]

There are 11 genes at the chromosome 1q32.2-q32.3 that are expressed in cardiac tissues. The known cardiac conduction defect genes include *KCNH1*, *KIAA0205*, *LAMB3*, and *PPP2R5A*,^[16] and in our case, the duplicate region includes the *LAMB3* gene.

CONCLUSION

We report a novel case of congenital second-degree heart block and TAPVR associated with microduplication 1q32.2. This finding may help identify the gene implicated in cardiac conduction disorders.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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