

An Extremely Rare Case of Bonneau Syndrome with Novel Cardiac and Eye Manifestations

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Abstract

Bonneau or cardio-ducto-polysyndactyly syndrome is an extremely rare, life-threatening developmental defect, which has only been reported in eight patients previously. Here, we describe one such case of Bonneau syndrome in a newborn with additional novel manifestations. This late preterm (35 weeks of gestation) neonate born to parents of consanguineous marriage following a pregnancy complicated by polyhydramnios was symmetrically small for date at birth (<3rd centile for weight, length, and occipitofrontal circumference). She had the typical Bonneau syndrome features such as facial dysmorphism and polysyndactyly in addition to novel eye manifestations (microphthalmia, cataract, and vitreous hemorrhage) and cardiac defects such as D-transposition of the great arteries and pulmonary valve stenosis. The chromosomal study was normal (46, XX). The multiple congenital anomalies made the cardiac defects inoperable, and the patient died at the age of 16 days due to uncontrolled cardiac failure. A very high index of suspicion is required by pediatricians/neonatologists to identify this very rare syndrome based on presentation with known features.

Keywords: Bonneau syndrome, congenital heart disease, facial dysmorphism, microphthalmia, polydactyly, syndactyly

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INTRODUCTION

Bonneau or cardio-ducto-polysyndactyly syndrome is an extremely rare, life-threatening developmental defect. It was first described in 1983 in three successive children of a family with dysmorphic features including a bulbous nose, low set ears, and polysyndactyly of the fingers and toes.^[1] These features were associated with complex cyanotic congenital heart disease (CHD) as tetralogy of Fallot (ToF) and acyanotic CHD as atrioventricular septal defect (AVSD), secundum type of atrial septal defect (ASD), and ventricular septal defect (VSD).^[1] To

date, only three additional case reports, and a total of eight patients, have been described in the literature.

Bonneau syndrome has been suggested as an autosomal recessive type of inheritance. Cardiac involvement has been found in all, except one, of the reported patients,^[2] while renal cysts have only been observed in two patients.^[3,4] Ductal plate malformation in the form of atrophic biliary vesicles and liver cysts were reported in the patients of Bonneau *et al.* and Stoll and Gasser.^[1,3] Here, we report a case of a neonate with typical Bonneau syndrome features

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with additional eye manifestations and heart defects that have not been reported previously.

CASE REPORT

A Pakistani-origin newborn was admitted to our neonatal intensive care unit for multiple congenital anomalies. She was born late preterm (35 weeks of gestation) from normal vaginal delivery (Apgar scores: 7 at 1 minute and 10 at 5 minutes) to a 25-year-old gravida 2, para 1 mother. The parents had consanguineous marriage (first-degree cousins), and an unremarkable family history. The pregnancy had been complicated by polyhydramnios. Antenatal fetal ultrasound had shown intrauterine growth retardation with multiple congenital anomalies including polysyndactyly and complex cardiac malformations.

At birth, she was symmetrically small for date: birth weight was 1.6 kg (<3rd centile); birth length, 40 cm (<3rd centile); and occipitofrontal circumference, 29 cm (<3rd centile). Clinical evaluation revealed dysmorphic facial features with arched eyebrows, depressed nasal bridge, hypertelorism, low set ears with simple helix lacking any definition, and hirsutism [Figure 1]. She had microphthalmia, cataract, and vitreous hemorrhage. The thumbs appeared broad and proximally inserted, and there was cutaneous syndactyly between the second, third, and fourth digits bilaterally, and postaxial polydactyly on both hands. The big toes were broad, and there was syndactyly of the second, third, and fourth toes on both sides.

The neonate had central cyanosis with normal radial and femoral pulses and soft systolic murmur at the upper left sternal border. The pulse oximeter reading was 80% on 30% oxygen by facial mask. Electrocardiography showed normal QRS axis and right ventricular hypertrophy for age. The chest X-ray exhibited cardiomegaly with increased pulmonary vascular markings [Figure 2]. On day 2, the chromosomal study was done and found to be normal (46, XX). Plain radiological examination of the whole body (babygram) revealed normal pairs of ribs, lumbar vertebrae, and phalanges. Abdominal ultrasound was normal with no renal or liver cysts seen. The cranial ultrasound was normal. Transthoracic color Doppler echocardiography showed situs solitus, parallel great arteries with aorta originating from the structurally right ventricle, and pulmonary artery from the structurally left ventricle. These features were consistent with D-transposition of the great arteries (D-TGA). There was a large perimembranous VSD, moderate size ASD of secundum type, and large patent ductus arteriosus (PDA) all with left-to-right shunt and moderate pulmonary valve stenosis (PVS) [Figure 3a and b]. She did not require atrial septostomy (Rashkind septostomy), as there was significant

blood mixing through ASD, PDA, and VSD. She was treated medically with diuretics (furosemide 2mg/kg iv, BID) and angiotensin-converting enzyme inhibitor (captopril 0.20 mg/kg, TID). The cardiac defect was not operable, as



Figure 1: The dysmorphic features in the form of arched eyebrows, small eyes, depressed nasal bridge, hypertelorism, low set ears, and hirsutism

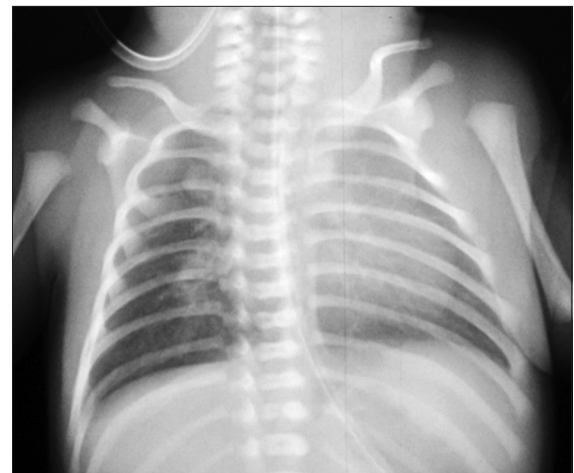


Figure 2: The chest X-ray showed cardiomegaly and increased pulmonary vascular markings

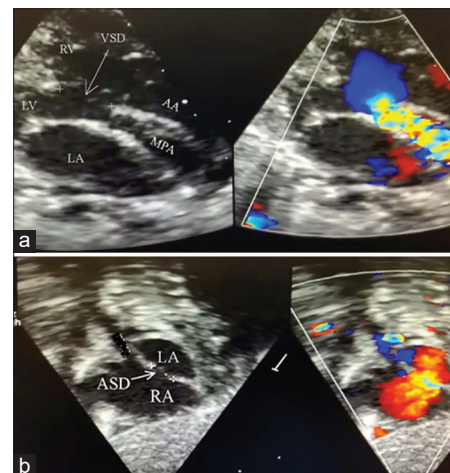


Figure 3: (a and b) Transthoracic color Doppler echocardiography showing the parallel ascending aorta (AA) and main pulmonary artery (MPA) originating from the right ventricle (RV) and left ventricle (LV), respectively. LA – Left atrium, RA – Right atrium, ASD – Atrial septal defect, VSD – Ventricular septal defect

she had multiple congenital anomalies. The baby died at the age of 16 days due to uncontrolled cardiac failure.

DISCUSSION

The authors report an extremely rare case of Bonneau syndrome; only eight cases have previously been reported.^[1-4] The neonate had typical Bonneau syndrome features in addition to findings that have not been reported previously, including eye manifestations (i.e., microphthalmia, cataract, and vitreous hemorrhage) and heart defects in the form of D-TGA and PVS. In addition, the patient had large perimembranous VSD, moderate ASD of secundum type, large PDA, as well as facial dysmorphism and polysyndactyly of the fingers and toes. All of these are typical Bonneau syndrome features [Table 1].^[1-4] The neonate reported here had no ductal plate anomalies such as cysts in the liver or kidney. Consanguinity was not described

in the first report of Bonneau's syndrome but was found to be the case in all other reports, including in the current case [Table 1].^[1-4]

Congenital heart disease was described in all Bonneau's syndrome patients except the second patient reported by Rajab, *et al.*^[2] In the previously reported cases, ToF, AVSD, and coarctation of the aorta have been reported in two, one, and one patient, respectively [Table 1].^[1,3,4] Polyhydramnios was described in all three of Bonneau's patients as well as in our patient [Table 1].^[1] Our patient was born prematurely and small for date, which has not been reported in any other patient. She had a normal karyotype (46, XX), as was also reported by Bonneau *et al.* Unfortunately, a microarray analysis was not possible because of logistical issues, and thus, although this could be an autosomal recessive disease, the same could not be confirmed. In terms of mortality, only two of the eight patients in the literature were alive by

Table 1: Literature review of the reported phenotypic features of Bonneau syndrome

Parameters	Bonneau, <i>et al.</i> ^[1]		Rajab ^[2]		Stoll and Gasser ^[3]		Olgun, <i>et al.</i> ^[4]	Current case	Total (n=9)	
	Patient number									
	1	2	3	1	2	1	2			
Consanguinity	-	-	-	+	+	+	+	+	6/9	
Polyhydramnios	+	+	+	-	-	-	-	+	4/9	
Birth weight (kg)	5.4	3.3	4.7	3.2	N	2.6	ToP	2.7	1.6	-
Gender	Male	Female	Female	Male	Male	Female	Male	Female	Female	4 male/5 female
Polydactyly	+	+	+	+	+	+	+	+	+	9/9
Syndactyly										
Fingers	+	-	+	+	+	+	+	+	+	8/9
Toes	-	+	+	+	+	+	+	+	+	8/9
Facial anomalies										
Hypertelorism	+	+	+	+	-	+	+	-	+	7/9
Epicanthus	+	-	-	-	-	+	-	-	-	2/9
Bulbous nose	+	-	-	+	-	+	-	+	+	5/9
Anteverted nose	+	-	-	-	-	-	-	+	+	3/9
Micrognathia	+	-	-	-	-	+	+	+	+	5/9
Low set ears	+	+	+	+	+	-	-	-	+	6/9
Eye anomalies										
Microphthalmia	-	-	-	-	-	-	-	-	+	1/9
Cataract	-	-	-	-	-	-	-	-	+	1/9
Vitreous hemorrhage	-	-	-	-	-	-	-	-	+	1/9
Congenital heart disease										
Cor bilocularis	-	+	+	-	-	-	-	-	-	2/9
APVR	-	-	-	-	-	+	-	-	-	1/9
AVSDs	+	-	-	-	-	-	-	-	-	1/9
VSD	+	-	-	+	-	+	+	+	+	6/9
ASD	+	-	-	+	-	+	-	+	+	5/9
PVS	-	-	-	-	-	-	-	-	+	1/9
Coarctation of aorta	-	-	-	-	-	-	-	+	-	1/9
TOF	-	-	+	-	-	-	+	-	-	2/9
D-TGA	-	-	-	-	-	-	-	-	+	1/9
Renal anomaly	-	-	-	-	-	-	+	+	-	2/9
Ductal plate anomaly (liver cyst/atrophic biliary vesicle)	-	-	+	-	-	+	+	-	-	3/9
Alive at the time of reporting	-	-	-	-	+	+	-	-	-	2/9
Death										
<i>In utero</i>	-	+	+	-	-	-	ToP	-	-	3/9
Age at death (months/day)	1 st month	-	-	5 th day	-	-	-	4 th month	1 st month	4/9

+, Present; -, Absent; APVR – Anomalous pulmonary venous return; AVSD – Atrioventricular septal defect; ASD – Atrial septal defect; TOF – Tetralogy of Fallot; PVS – Pulmonary valve stenosis; ToP – Termination of pregnancy; D-TGA – Transposition of the great arteries; VSD – Ventricular septal defect

the age of 4 years, while the others died before the age of 4 months, as was also the case with our patient [Table 1].

The rare ductal plate anomalies have been reported in two patients, although only one had a postmortem study.^[1,3,5] This anomaly in patient 3 of Bonneau's original description was atrophic biliary vesicle; however, histological examination was not performed.^[1] Liver cysts were reported in both patients of Stoll and Gasser^[3] [Table 1]. However, in our patient, the abdominal ultrasound did not show any atrophic biliary vesicles, pancreatic or renal cortical cysts.

Syndactyly and polydactyly, which are a group of inherited and clinically heterogeneous anomalies, are among the most common congenital limb malformations. They are commonly seen in Bardet–Biedl syndrome (BBS) and Smith–Lemli–Opitz syndrome (SLOS). BBS is characterized by six cardinal features: truncal obesity, intellectual impairment, renal anomalies, polydactyly, retinal degeneration, and hypogenitalism. SLOS has multiple features that vary in forms, such as wrinkled and droopy eyelids, cataracts, elongated upper lip, polysyndactyly, extra digits, micrognathia, large earlobes, cleft lip, and heart defects.^[6] However, these two syndromes were excluded from the differential diagnosis because other than postaxial polydactyly and cardiac defects, the phenotypic features of these syndromes were not present in our patient. Ellis–Van–Creveld syndrome is associated with short limbs, hypoplastic thorax due to short-ribs, dysplastic nails and teeth, as well as postaxial polydactyly. This extremely rare syndrome is associated with CHD, particularly TGA and AVSD, which affect almost 60% of the patients. However, this was excluded from the differential diagnosis because other than postaxial polydactyly and cardiac defects, the phenotypic features of this syndrome were not present in our patient.^[7]

As with most known syndromes, abnormal findings differ across cases, and it is not clear why syndromic features are manifesting at a variable rate within a given syndrome. In this case, there was no liver abnormality detected by ultrasound study, which was observed in two previously reported patients [Table 1]. This may indicate variable interactions of the developing adjacent organs, where the liver and heart development are affecting the tissues of each other, as suggested by Haworth *et al.*^[8] Their studies suggest that the Wnt pathway activation and other tissue pathway activations may play a significant role in the variable presentation of the Bonneau syndrome. In this case, the Wnt pathway activation may have suppressed the development of liver anomalies, despite the presence of congenital anomalies in the heart tissues. Future studies may shed more light on the development of congenital

anomalies in the liver and heart among Bonneau syndrome patients.

CONCLUSION

This report presents the ninth case of Bonneau syndrome in the literature. Our patient had typical Bonneau syndrome features with additional eye manifestations (microphthalmia, cataract, and vitreous hemorrhage) and heart defects in the form of D-TGA and PVS, features that have not been reported previously. A very high index of suspicion is required by pediatricians/neonatologists to identify this very rare syndrome based on presentation with known features.

Declaration of publication consent

The authors certify that they have obtained the appropriate patient consent form. The father has given his consent for his daughter's images and other clinical information to be reported in the Journal. He understands that names and initials would not be published, and due efforts will be made to conceal the identity of his daughter, but anonymity cannot be guaranteed.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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