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Neonatal myocardial infarction in Williams–Beuren syndrome

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ABSTRACT

Williams–Beuren syndrome (WBS) is a contiguous gene deletion syndrome in chromosome 7q11.23, resulting in elastin arteriopathy. Patients with WBS are at higher risk for major cardiovascular events, including sudden death due to structural congenital heart diseases and arrhythmia. Neonatal myocardial infarction is an exceedingly rare presentation of WBS. Here, we report the case of a 2-week-old infant with neonatal myocardial infarction due to severe coronary artery insufficiency. We systematically reviewed published reports of sudden death in WBS and identified an additional 19 cases. Of 10 individuals who had autopsy or direct examination of the heart during cardiotomy, 5 had evidence of myocardial ischemia or infarctions. An additional 2 patients with WBS had evidence of severe coronary insufficiency and myocardial ischemia, as determined by cardiac imaging. In agreement with prior studies, we did not find that degree of supravalvar aortic stenosis or left ventricular outflow tract obstruction were predictors of coronary artery stenosis. Additional aortic valve abnormalities, such as bicuspid aortic valve, may be better predictors of coronary stenosis.

1. Introduction

Williams-Beuren syndrome (WBS) is one of the most common conditions associated with chromosomal microdeletion and frequently includes congenital heart disease. WBS is caused by contiguous gene deletion in chromosome 7q11.23 [1]. The characteristic clinical presentation of this syndrome includes distinctive facial features, connective tissue abnormalities, intellectual disability, a specific cognitive profile, unique personality characteristics, growth and endocrine abnormalities as well as cardiovascular disease [2].

Structural cardiovascular abnormalities occur in approximately 80% of all WBS patients and are recognized in up to 93% of patients in the first year of life [3,4]. Although there are a variety of cardiovascular abnormalities identified in WBS patients, the majority consist of some form of arterial stenosis [5]. Haploinsuficiency of the elastin (*ELN*) gene has been identified as the major contributor of cardiovascular defects [6,7]. The incidence of supravalvular aortic stenosis (SVAS) has been reported to be 45% to 75%. Although SVAS can occur in isolation, it may present with pulmonary artery stenosis or aortic arch abnormalities. Coronary artery abnormalities are also often associated with congenital SVAS and may manifest as coronary ostial stenosis, diffuse coronary artery stenosis, coronary artery dilation or obstruction to coronary artery inflow by aortic valve, the sinotubular ridge or a combination of both [5].

Neonatal myocardial infarction (MI) is exceedingly rare and associated with high mortality rate ranging from 40 to 50% [8]. Although cardiovascular disease is one of the most common presentations of WBS, it is rarely associated with significant morbidity and mortality in the neonatal period. The first case of neonatal MI in WBS was reported in 1996 [9] in a one month old neonate after RSV infection. Here we describe a case in a 2-week-old infant. A review of literature on sudden death in WBS is provided in this report.

2. Clinical Report

A 14 days old female neonate was transferred to the Cardiac Intensive Care Unit due to severe left ventricular (LV) systolic dysfunction. The infant was born prematurely at 33 weeks gestational age due to preterm labor. Pregnancy was complicated by maternal active hepatitis C infection and no prenatal care. The birth weight was 2020 g, with a birth length and head circumference of 44 cm and 32 cm, respectively. The patient was administered a prostaglandin infusion and

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immediately transferred to the Neonatal Intensive Care Unit for tachypnea and heart murmur. Postnatal echocardiography performed at day of life (DOL) 14 revealed severe LV systolic dysfunction, left atrial hypertension, and a moderate discrete coarctation of the aorta, with narrowing at the isthmus (0.19 cm; *z*-score −2.88) and retrograde blood flow in the transverse aorta, although the bicuspid aortic valve was typically sized. Additional findings on echocardiogram included endocardial fibroelastosis, tiny perimembranous ventricular septal defect, and a small patent foramen ovale. Two-dimensional imaging revealed expected origins for both coronary arteries, but color flow was not demonstrated at the time of the first study. We hypothesized that reverse flow occurred in the ascending aorta because LV function was poor. Electrocardiogram (ECG) on DOL 14 confirmed sinus rhythm with first degree atrioventricular block and biventricular hypertrophy with strain, with no evidence of ischemic injury. We performed cardiac catheterization and coronary angiography on DOL 15 to better define the coarctation hemodynamics and coronary artery anatomy. A mild-to-moderate coarctation of the isthmus was present without a posterior shelf and with a large patent ductus arteriosus. LV systolic and diastolic functions were abnormal, with a LV filling pressure of 25 mm Hg. Because of the presence of endocardial fibroelastosis, this finding was unsurprising. Aortic root injection and selective left coronary artery injection showed a diminutive left coronary artery, typical branching, arborization, and blush phase (Fig. 1).

The patient was administered epinephrine, calcium chloride, milrinone, and sodium nitroprusside infusions for inotropic support and afterload reduction. She also required continuous positive-pressure ventilatory support on admission and was eventually weaned to room air after several days. On DOL 16, she experienced an episode of nonsustained ventricular tachycardia with persistent desaturations. She received a septic work-up and was administered empiric parenteral antibiotics.

Serial echocardiography was performed throughout admission and demonstrated relatively improved LV systolic function but continued moderate-to-severe depression, with persistent hypokinesis at the posterior, inferior, and lateral walls of the LV (Table 1). However, the flow in the ascending aorta became prograde without aortic valve stenosis. Because of failure of improvement, the patient received surgical repair of the coarctation and direct investigation of coronary artery anatomy on DOL 25. The patient's family was informed that the dysfunction may be irreversible and the need for extracorporeal membrane oxygenation support was probable if a discreet coronary stenosis amenable to surgical repair could not be identified, rather than a diffusely small coronary system secondary to diffusely thickened walls. During cardiotomy, the heart was noted to be edematous and injected, and we observed a severely thickened ascending aorta and ventricular walls. A specific stenosis of the left coronary artery was not present, but it was very small throughout its course with no increase in size. Passage of a 0.5-mm coronary probe into the ostia was possible, but it could not be advanced further. The ostium was opened past the aortic wall so that a 1.5-mm probe could be passed, but the coronary artery remained diminutive, and the 0.5-mm probe was not able to pass. Extensive neovascularization was evident around the coronary arteries. The left lateral and anterior cardiac walls appeared infarcted with visible fibrosis and calcification. Upon separation from cardiopulmonary bypass, the patient experienced hypotension refractory to medical therapy and severe LV systolic dysfunction. She was placed on venoarterial extracorporal membrane oxygenation for hemodynamic support. A follow-up ECG showed sinus rhythm, possible right atrial enlargement, biventricular hypertrophy, and a nonspecific ST-T wave abnormality. Echocardiography after surgery demonstrated severely diminished LV systolic functions. Despite aggressive medical management, ventricular function did not improve, and she remained critically ill. The family elected to withdraw mechanical support. She was not considered a good candidate for transplantation because of her reduced body weight (2.1 kg) and young age (35 weeks corrected gestational age).

Because of the cardiac and vascular morphologic findings, an underlying connective tissue disorder was suspected. A genetics team was consulted before death to assist in diagnosis. An accurate dysmorphology examination was challenging to perform because of generalized edema and the presence of medical apparatuses. Several mild facial dysmorphic features were noted, including broad forehead, periorbital fullness, bilateral epicanthal folds, broad nasal bridge, and short nose with anteverted nasal tip. A 3-generation family history was remarkable for a paternal grandfather with a history of heart attack at 12 years of age; however, further details of his condition are unknown. Both parents denied history of cardiac diseases, developmental delay, or intellectual disabilities. SNP microarray analysis detected an interstitial 1.9-Mb deletion from the long arm of chromosome 7q11.23, which included the Williams–Beuren syndrome (WBS) critical region. The parents were given counseling on the diagnosis of WBS and offered parental testing.

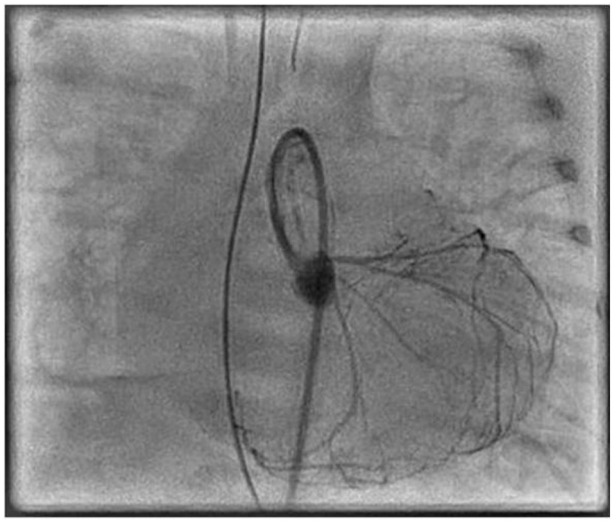

Fig. 1. Selective left coronary artery injection showing a definitive left coronary artery off the aorta. The left system appears diffusely small but with normal branching and arborization.

3. Discussion

We present this case to raise awareness among clinicians of the possibility of neonatal myocardial infarction as symptom component of the arteriopathy in WBS. Although cardiovascular diseases are well-known complications in WBS, major cardiac events in the neonatal period are rarely reported. This is most likely underestimated because of difficulties in the clinical diagnoses of both myocardial infarction and WBS in neonates. The diagnosis of myocardial infarction and subsequent cardiac failure in newborns is usually delayed because of nonspecific symptoms, such as tachycardia, respiratory distress, feeding intolerance, and irritability.

In the present case, the infant presented with acute cardiac failure. The etiology of acute cardiac failure in a newborn is known to include underlying structural congenital heart defects, congenital arteriovenous malformations, prenatal and neonatal myocarditis, cardiomyopathy (inherited, metabolic, toxic), persistent arrhythmia, and myocardial infarction. In this case, the patient had a bicuspid aortic valve and discrete coarctation of the aorta. However, LV outflow tract obstruction was not particularly evident via echocardiography and cardiac catheterization (mean gradient, 8–10 mm Hg). Diagnosis of myocardial infarction was not indicated by ECG alone; however, ischemic injury was suspected when the patient experienced global LV hypokinesis. This was eventually confirmed after open cardiac surgery.

In addition to the challenges in diagnosing the etiology of cardiac

Table 1
Echocardiogram findings of a neonatal patient with Williams–Beuren syndrome.

DOL	LVEF	Coarctation	PDA	VSD	PFO/ASD	RV	Other
14	25%	Moderate discrete; isthmus 0.19 cm ($z = -2.88$); retrograde flow transverse aorta	Large, R:L	Tiny, L:R	L:R, gradient 15 mm Hg	Normal function; trivial TR	EFE; BAV; coronary arteries normal 2D, no flow; left arch normal branching; mild MR
15	Severe	Moderate discrete	NA	NA	L:R, gradient 11 mm Hg	Normal function; trivial TR	EFE; BAV; hypokinesis post, inferior, lateral walls; LCA normal 2D and color, RCA not eval; mild MR
16	40%	Moderate discrete; isthmus 0.3 cm ($z = -1.77$)	Moderate	NA	L:R, gradient 8–10 mm Hg	Normal function; trivial TR	EFE; hypokinesis posterior, inferior, lateral walls of LV; mild MR
17	37%	Discrete juxtaductal; antegrade flow transverse aorta	NA	NA	L:R, gradient 9–12 mm Hg	Normal function; trivial TR	EFE; mild MR
18	Moderate	Discrete juxtaductal; isthmus 0.24 cm ($z = -2.47$); antegrade flow transverse aorta	Large, unrestrictive flow, R:L in systole, L:R in diastole	NA	L:R, gradient 11 mm Hg	Normal function; trivial TR	EFE; BAV; mild MR
19	NA	NA	NA	NA	NA	NA	LCA and RCA origins normal by 2D and color; LCA seen past bifurcation; no obvious narrowing, color flow seen in both LCA and RCA
20	42%	NA	NA	NA	NA	Normal function	LCA origin normal by 2D and color, with turbulent flow in origin; hypokinesis lateral wall of LV
22	41%	Severe discrete	Large; R:L in systole, L:R in diastole		L:R, with high gradient	Normal function; trivial TR	EFE "more conspicuous;" akinesis anterior, anterolateral, inferolateral walls of LV
25	Moderate	NA	NA		L:R, gradient 14 mm Hg	NA	TEE, S/P LCA unroofing and ostial revision; hypokinesis posterior, inferior, and lateral walls of LV
25	Severe	NA	NA	NA	NA	NA	Limited epicardial echo showing severe dysfunction, patient progressed to ECMO
27	13%	NA	NA	NA	NA	NA	Akinesis apex, free wall, and midventricular septum of LV; patient on ECMO

BAV bicuspid aortic valve, *DOL* day of life, *ECMO* extracorporeal membrane oxygenation, *EFE* endocardial fibroelastosis, *LCA* left coronary artery, *L:R* left to right, *LV* left ventricle, *LVEF* left ventricular ejection fraction (% or degree of dysfunction), *MR* mitral regurgitation, *NA* not assessed or not reported, *PDA* patent ductus arteriosus, *PFO/ASD* patent foramen ovale/atrial septal defect, *RCA* right coronary artery, *R:L* right to left, *RV* right ventricle, *TR* tricuspid regurgitation, *VSD* ventricular septal defect.

Table 2
Sudden death in Williams–Beuren syndrome.

Case	Reference	*ELN* deletion	Age of death	Perioperative/ periprocedural	Clinical data					Autopsy findings	
					LVOTO	RVOTO	ECG findings	ECHO	Cardiac catheterization	MI	Other findings
1	[a]	Yes	4 weeks	No	−	−	Biventricular hypertrophy, nonspecific ST-T wave changes	BAV, discrete coarctation, hypokinesis of the posterior, inferior and lateral wall, EF 20%	Mild-to-moderate coarctation of the isthmus, normal right coronary, left coronary not visualized	Yes	Myocardial hypertrophy, lateral wall infarction with fibrosis and calcification, left coronary ostium stenosis with stenosis of left coronary artery
2	[26]	Yes	6 years	No	ND	ND	Complete AV block, ST depression in lead I, II, III, aVL, aVF, and V2-V5	Myocardial hypokinesis on the lateral and inferior walls, EF 16%	Left coronary cusp abnormally adherent to aortic wall, moderate stenosis of left coronary main trunk	Yes	Myocardial hypertrophy and interstitial fibrosis in the subendocardium, with the absence of marked lymphoid infiltration and myocardial degeneration
3	[17]	ND	21 years	No	ND	ND	ND	ND	ND	Yes	Cardiomegaly, marked biventricular hypertrophy due to myocardial hypertrophy, pulmonary valve stenosis, dysplastic mitral valve, coronary ostium stenosis, SVAS
4	[27]	ND	2 years	Yes	+	−	ST depression in lateral chest leads	Mild SVAS, reduced ventricular function	Mild SVAS, abnormal origin of left coronary with severe stenosis (> 90%) from mid portion of left main stem extending into the branches	ND	NP
5	[12]	Yes	2 years	Yes	+ + +	−	RVH	Mild SVAS	ND	ND	NP
6	[18]	ND	36 years	No	−	−	Sinus tachycardia, left bundle branch block	Impaired LV function with global hypokinesia	Depressed ventricular function, normal coronary arteries, no evidence of SVAS relapse	ND	NP
7	[28]	ND	5 years	Yes	+ + +	−	No ST-T wave changes	Worsening SVAS, mild LV hypertrophy, normal coronary arteries, normal LV function	ND	ND	Biventricular hypertrophy with SVAS and post-stenotic dilation, elastic thickening in the main pulmonary artery
8	[19]	ND	17 years	No	ND	ND	ND	ND	ND	No	Mild cardiomegaly with LV hypertrophy, SVAS, and severe narrowing of the ascending aorta
9	[20]	Yes	17 months	Yes	ND	ND	ND	BAV, LV hypertrophy	Severe SVAS	No	Mild cardiomegaly with LV hypertrophy, SVAS, aortic valve stenosis with post-stenosis dilation, coronary artery stenosis
10	[29]	Yes	18 months	Yes	ND	ND	ND	ND	ND	No	Cardiomegaly, myocardial hypertrophy, mild SVAS and aortic valve stenosis
11	[30]	Yes	6 years	No	−	−	Bi-atrial enlargement and inferolateral ST depression	Severe LV dilation, severe LV dysfunction, EF 30%, mild hypoplastic of ascending aorta	Mildly hypoplastic aorta without significant stenosis, left coronary artery ostium stenosis	ND	NP
12	[11]	ND	15 years	No	−	−	Normal	SVAS, mild mitral regurgitation	Mild SVAS, mild pulmonary artery stenosis, mild mitral regurgitation	ND	NP
13	[11]	ND	16 years	No	+ +	−	Normal	ND	Moderate SVAS/AS, mild pulmonary artery stenosis	ND	NP
14	[11]	ND	29 years	No	+ + +	−	LV hypertrophy	ND	Severe SVAS	Yes	SVAS, severe LV hypertrophy, left coronary artery stenosis
15	[11]	ND	4 years	No	+ + +	+ + +	Normal	Mild SVAS	Mild SVAS, severe pulmonary artery stenosis	No	Severe pulmonary stenosis, severe RV hypertrophy, severe SVAS, severe LV hypertrophy, no coronary stenosis
16	[14]	ND	6 years	Yes	+ + +	ND	ND	Severe SVAS	Severe SVAS, stenosis of main and right pulmonary artery	ND	NP
17	[14]	ND	3 years	Yes	+ + +	+	LV hypertrophy	Severe SVAS, mild pulmonary artery stenosis, mild mitral regurgitation, LV hypertrophy, global LV hypokinesis	Severe SVAS, mild pulmonary branch artery stenosis	ND	NP
18	[21]	Yes	21 years	No	+	ND	ND	ND	Mild SVAS at 12 years old	ND	NP

(*continued on next page*)

Table 2 (*continued*)

Case	Reference	*ELN* deletion	Age of death	Perioperative/ periprocedural	Clinical data			ECHO	Cardiac catheterization	Autopsy findings	
					LVOTO	RVOTO	ECG findings			MI	Other findings
19	[22]	ND	27 years	No	+ + +	+	ND	Severe SVAS, LV hypertrophy, hypoplasia of ascending aorta	ND	Yes	Cardiomegaly with biventricular hypertrophy, diffuse narrowing of ascending aorta with thickened wall, mild pulmonary artery stenosis, moderate stenosis of coronary artery due to atherosclerosis

BAV bicuspid aortic valve, *ECG* electrocardiogram, *ECHO* echocardiogram, *EF* ejection fraction, *ELN* elastin, *LV* left ventricular, *LVOTO* left ventricular outflow tract obstruction, *MI* myocardial infarction or ischemia, *ND* not determined, *NL* normal, *NP* not performed, *RVOTO* right ventricular outflow tract obstruction, *SVAS* supravalvar aortic stenosis. − Negative, + mild (mean gradient, 25 mm Hg), + + moderate (mean gradient, 25–40 mm Hg), + + + severe (mean gradient > 40 mm Hg). Classification based on the 2014 AHA/ACC guideline for the treatment of patients with valvular heart disease.

[a] Present case.

failure in newborns, a high level of suspicion is required for WBS diagnoses. WBS is typically suspected after the diagnosis of characteristic structural heart diseases, such as supravalvar aortic stenosis or peripheral pulmonary artery stenosis. A clinical diagnostic scoring system for WBS was developed in 1994 to assist clinicians [10]. This guideline, however, heavily emphasizes the clinical findings of dysmorphology examinations and longitudinal observations of medical and neurocognitive profiles of suspected individuals, which could be challenging in the neonatal period. A clinical dysmorphology examination in the present case was also challenging because of generalized body edema and the presence of medical apparatuses.

The risk of sudden death in individuals with WBS appears to be 25- to 100-fold higher than in an age-matched healthy population [11]. Most cases of cardiovascular events in patients with WBS reportedly occur in periprocedural and perianesthetic settings [12–14]. A recent multicenter analysis identified major cardiac events in 9% of patients with WBS undergoing cardiac surgery [15]. Earlier reports suggest that 2 major anatomic abnormalities predispose individuals with WBS to sudden death, including coronary artery stenosis and severe biventricular outflow tract obstruction. The mechanisms for sudden death most likely constitute a combination of myocardial ischemia, decreased cardiac output, and arrhythmia [9]. It is now well accepted that WBS confers a higher risk for sudden cardiovascular collapse during anesthesia, and guidelines for risk stratification and perioperative management of WBS have been developed [16]. However, despite these precautions, sudden death in individuals with WBS occurring outside of perioperative or periprocedural settings is frequently reported [9,11,17–23]. Guidelines for the surveillance of myocardial ischemia in patients with WBS have not been established.

The etiology of acute cardiac failure in the present case was severe myocardial infarction due to left coronary artery stenosis and subsequent decreased cardiac output. The first case of sudden death in a newborn with WBS was reported by Bird et al. as part of a series [9], in which a 1-month-old infant with confirmed WBS (*ELN* deletion) presented with acute inferior myocardial infarction during a respiratory syncytial virus infection. Although an autopsy was not performed, the infant received a thorough cardiac work-up 2 weeks before the onset of symptoms. Interestingly, this infant had similar cardiac findings to those of the present case, including bicuspid aortic valve with mild stenosis, hypoplasia of the ascending aorta, and mild supravalvar aortic stenosis (SVAS). Specific imaging to evaluate coronary arteries was not performed. These findings suggest that aortic valves abnormalities may be associated with severe coronary artery abnormalities in WBS. In the remaining patients with WBS and sudden death in this series, 5 of 7 patients who received autopsies had coronary artery stenosis with myocardial infarctions.

We systematically reviewed previously published case reports and series after 1997 and identified 19 additional cases of sudden death in WBS (Table 2). Of 10 patients who had autopsies or direct examinations of the heart during cardiotomy, 5 had evidence of myocardial ischemia or infarctions. An additional 2 individuals (case 4 and 11) had evidence of severe coronary insufficiency and myocardial ischemia from cardiac imaging. Similar to that of the case reported here, we did not identify the degree of SVAS or LV outflow tract obstruction as predictors of coronary stenosis in our systematic review because 3 patients (case 1, 4 and 11) lacked marked supravalvar obstruction. In addition, 7 of 19 patients experienced sudden cardiovascular events during perioperative or periprocedural periods. This number is lower than those previously reported by Bird et al. [9] (37% vs. 58%) most likely because of a better understanding of cardiac risk and management strategies for anesthesia in patients with WBS. Latham et al. [13] performed a single center retrospective study in 2013 of 48 individuals with confirmed elastin arteriopathy and identified higher rates of cardiac arrest and complications (15%) in individuals with elastin arteriopathy undergoing anesthesia. This finding was further supported by a report by Hornik et al. [15] who identified major cardiac events in 9% of patients with WBS

undergoing cardiac surgeries.

WBS is caused by a deletion of 26 to 28 genes, including elastin, on chromosome 7. Several studies have been performed to determine modifiers of disease severity in WBS [24,25]. *NCF1*, which encodes nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) complex, is an invariably deleted gene in WBS. Kozel et al. identified *NCF1* gene copy number and the ratio of *NCF1* to its pseudogenes (*NCF1B* and *NCF1C*) as possible modifiers of vascular disease severity in WBS [24]. This study concluded that decreased *NCF1* gene copy number protected patients with WBS from vascular stiffness and hypertension. Chronic oxidative stress was suggested to directly affect the severity of vascular stiffness in WBS. In the present case, our patient had a 1.89-Mb deletion in 7q11.23, which includes *ELN*, *NCF1B*, and the first 5 exons of *NCF1* gene. This finding contrasts with those of the previous study, indicating that copy number of *NCF1* is not an exclusive variable affecting cardiovascular outcomes. Therefore, we hypothesize that additional modifier gene(s) contribute to the severity of arteriopathy in WBS, especially to the degree of coronary artery involvement. Further molecular studies or larger patient cohorts with coronary artery abnormalities are needed to provide better insight.

4. Conclusion

We describe a unique case of WBS presenting with severe coronary artery abnormalities that led to neonatal myocardial infarction. This case illustrates the challenges in diagnosis and management of acute cardiac failure and WBS during the neonatal period. Predictors of severity of coronary artery stenosis and risk for myocardial infarction have not been established for WBS. Guidelines for periprocedural risk stratification and management of WBS have been developed to reduce the risk of sudden death, but no current surveillance guidelines that specifically address the risk for myocardial infarction or coronary artery ischemia in this population are available. Previous consensus statements from the American Academy of Pediatrics for health care supervision of children with WBS are primarily intended for pediatrician and other primary care providers. A specific surveillance guideline for cardiologists caring for infants, children, and adults with WBS should be established.

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Author Contributions

HL and RJH contributed to the conception and design of the study; HL, DLSM, TDR and RJH contributed to the acquisition and analysis of the data; HL, LD, DLSM, TDR and RJH contributed to drafting, editing, and preparing the figures.

Conflict of Interest

All the authors declare no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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