Cardiovascular Abnormalities, Interventions, and Long-term Outcomes in Infantile Williams Syndrome

R. Thomas Collins, II, MD, Paige Kaplan, MBBCh, Grant W. Somes, PhD, and Jonathan J. Rome, MD

Objective To determine the prevalence of cardiovascular abnormalities (CVA) and outcomes in patients with Williams syndrome presenting before 1 year of age.

Study design A retrospective review was undertaken of consecutive patients with WS at our institution from January 1, 1980, through December 31, 2007. WS was diagnosed by an experienced medical geneticist and/or by fluorescence in situ hybridization. CVA were diagnosed with the use of echocardiography, cardiac catheterization, or computerized tomographic angiography. Freedom from intervention was determined using Kaplan-Meier analysis.

Results The study group was 129 patients with CVA. Age at presentation was 127 ± 116 days, with follow-up of 8.0 ± 7.5 years (0 to 42 years). The most common lesions were peripheral pulmonary artery stenosis (62%) and supravalvar aortic stenosis (57%). Other CVA were common. CV interventions were performed in 29%, with 58% of those before 1 year. Freedom from intervention was 85%, 73%, and 66% at 1, 5, and 25 years, respectively. Four patients died.

Conclusions CVA are the most common manifestations of infantile Williams syndrome and occur with greater frequency than previously reported. In those with CVA, interventions are common and usually occur by 5 years of age. Most of these patients do not require intervention on long-term follow-up, and overall mortality is low. *(J Pediatr 2010;156:253-8)*.

Williams syndrome (WS) is a congenital multisystem, developmental disorder resulting from the deletion of approximately 28 genes on chromosome 7q11.23, in 1 in 8000 live births.[1-3] It affects the vascular, connective tissue, and central nervous systems. WS has been associated with congenital cardiac malformations in approximately 10% of patients and symptomatic narrowing of arteries in up to 80%.[4] Supravalvar aortic stenosis (SVAS) is reported to be the most common cardiovascular abnormality (CVA), with branch peripheral pulmonary arterial stenosis (PPS) being the second most common.[5] Other CVA have been described, including intracardiac and vascular lesions such as ventricular septal defect,[6] tetralogy of Fallot,[7] mitral valve prolapse,[8] coarctation of the aorta,[9] patent ductus arteriosus,[10] and peripheral arterial abnormalities.[11] Hemizygosity at the elastin gene locus on chromosome 7q11.23 has been demonstrated to be the cause of the vascular lesions in WS.[12]

The majority of available studies describing cardiovascular abnormalities in WS are small, with sample sizes ranging from 10 to 127 subjects; recently, Pham et al[13] reported on 242 patients ranging in age from 1 day to 22.7 years, without delineation of age at presentation, who required cardiac catheterization and/or operation in 47 cardiac centers. The aims of the present study were to (1) assess the prevalence and types of CVA in patients with WS who presented before 1 year of age, and (2) characterize the outcomes and frequency of intervention in patients with CVA in this cohort.

Methods

We retrospectively reviewed the available records of all patients with the diagnosis of WS who were evaluated at the Children's Hospital of Philadelphia from January 1, 1980, through December 31, 2007. Records from August 16, 1965, to March 24, 2008, were reviewed from all patients evaluated in the Multidisciplinary Williams Syndrome Clinic and/or the division of Cardiology. The diagnosis of WS was confirmed by the clinical phenotype assessed by an experienced medical geneticist and/or by demonstrating elastin hemizygosity by fluorescence in situ hybridization. Congenital CVA were diagnosed by echocardiography, cardiac catheterization, or computed tomographic angiography. The study was approved by the hospital's institutional review board.

CVA	Cardiovascular abnormalities
CBI	Catheter-based interventions
CoA	Coarctation of the aorta
PPS	Pulmonary arterial stenosis
SVAS	Supravalvar aortic stenosis
SVPS	Supravalvar pulmonary stenosis
VSD	Ventricular septal defect
WS	Williams syndrome

From the Children's Hospital of Philadelphia, Divisions of Cardiology (R.T.C., J.J.R.) and Metabolic Diseases (P.K.), and the University of Pennsylvania School of Medicine (R.T.C., P.K., J.J.R.), Philadelphia, PA; and The University of Tennessee Health Sciences Center Department of Preventive Medicine (G.W.S.), Memphis, TN

The authors declare no conflicts of interest.

 10.1016/j.jpeds.2009.08.042

All available cardiovascular data on the identified patients including patient histories, physical characteristics, and ancillary testing including abdominal ultrasound and MRI/MRA of the brain (evaluating for Chiari I sequence and/or stroke) and renal arteries (in the setting of hypertension or inadequate renal growth) were reviewed. All patients were evaluated with echocardiograms, and, where clinically indicated, by cardiac catheterization and/or computed tomographic angiography. Cardiac catheterization data including hemodynamics, angiographic information, and catheter-based interventions (CBI) were reviewed. Surgical records were analyzed to determine anatomic measurements and interventions performed.

Cardiovascular abnormalities were defined as any anatomic or functional abnormality of the heart or vascular system. Patients with either isolated systemic hypertension or the isolated combination of systemic hypertension and trivial mitral regurgitation were not considered to have CVA. The severity of individual lesions was graded using published standards from echocardiography and/or catheterization.[14,15] When pressure gradients were available via catheterization or echocardiogram, catheter-derived gradients were determined by peak-to-peak measurements; echocardiographically derived gradients were determined by peak instantaneous measurements. When both catheter-derived and echocardiographically derived pressure gradient data were present, catheter data were used for the determination of lesion severity. Any lesion graded as trivial was not included in the statistical analysis.

Cox regression analysis was used to determine differences between severity grades within individual lesion groups. Hazard ratios for all cardiovascular interventions were calculated for lesion-specific severity groups. Multivariate regression was used to assess the effect of the presence of the 3 most common lesions on all cardiovascular interventions. Kaplan-Meier analysis was used to determine freedom from lesion-specific intervention for both PPS and SVAS, freedom from all cardiovascular interventions as a function of supravalvar pulmonary stenosis (SVPS), and freedom from all cardiovascular interventions independent of lesion type. Freedom from intervention analysis was based on lesion severity at the time of presentation. Statistical significance was considered present when the P value was less than .05.

Results

A total of 270 patients with WS were evaluated during the study period. All patients who were initially evaluated by a geneticist were subsequently evaluated by a pediatric cardiologist. One hundred thirty-nine patients had been evaluated by a pediatric cardiologist within the first year of life; the remaining 131 patients were neither evaluated by a pediatric cardiologist nor by a geneticist during the first year of life. Of the 139 patients who were evaluated within the first year of life, 93% (129/139) had CVA.

In the study cohort, 71 subjects were female and 68 were male. The average age at the time of initial evaluation by a pediatric cardiologist was 127 days (range, 1 to 365 days). There was no sex difference in the age at initial presentation. The average length of follow-up was 8.0 years (range, 0 to 42 years). The average age of diagnosis of WS was 1.9 years (range, 0.05 to 26 years).

Of CVA present, PPS, SVAS, ventricular septal defect (VSD), SVPS, and coarctation of the aorta (CoA) each had a prevalence of 18% or greater. There were no sex differences in the frequency or severity within these 5 lesions. The remaining CVA were seen less frequently and are described in **Table I**.

Peripheral pulmonary arterial stenosis was the most common lesion in this cohort, with a prevalence of 62% (80/129). Among these, 22 were severe, 13 moderate, and 45 mild. During follow-up, the grade of PPS severity diminished without treatment in 38% (30/80) of patients, with 40% (18/45) of the mild group showing complete resolution. The majority (21/30; 70%) of patients with spontaneous improvement in the severity of PPS initially had mild stenosis, though improvement to mild stenosis was seen in 3 patients with moderate PPS and 4 with severe PPS. Two patients with moderate PPS (15%) had complete resolution and 2 with moderate PPS had progression to severe PPS. As shown in **Figure 1**, the differences in freedom from PPS-specific intervention were highly significant between severity groups ($P < .0001$). The majority (88%) of patients who underwent PPS interventions did so by 5 years of age. Those patients requiring either surgical or CBIs for PPS have largely remained clinically and hemodynamically stable.

The prevalence of SVAS was 57% (74/129) in our cohort. SVAS was mild in 48 (65%), moderate in 9 (12%), or severe in 17 (23%) patients. There was spontaneous improvement in the severity grade of SVAS in 16% (12/74) of patients during follow-up. Spontaneous resolution occurred in 12%, all with mild SVAS, accounting for 19% (9/48) of the mild group. Seven patients, comprising 9% (7/74) of the group with SVAS, demonstrated progression of the severity of the SVAS during follow-up. The differences in freedom from SVAS-specific intervention were highly significant between severity groups ($P < .0001$), as shown in **Figure 2**. The vast majority of patients with SVAS (95%) who required SVAS intervention did so by 5 years of age. One patient with mild SVAS had progressive worsening in lesion severity and underwent SVAS-specific intervention. Surgery was performed much more commonly in the group of patients with SVAS than PPS; 26% of all patients with SVAS ultimately underwent surgery. The majority of those patients requiring either surgical or CBIs for SVAS have remained clinically and hemodynamically stable.

Of those patients with SVAS, 63% had some measure of concomitant PPS. The distribution of lesion severities of SVAS and PPS are described in **Table II** (available at www.jpeds.com). Interventions on SVAS, PPS, or both were performed on 34% of these patients.

VSDs were present in 21% (27/129) of the patients. The majority of these defects (22/27; 82%) were muscular and the remainder were conoventricular in location. No muscular