Congenital heart defects in Williams syndrome

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Williams syndrome (WS), also known as Williams-Beuren syndrome, is a rare genetic disorder involving multiple systems including the circulatory system. However, the etiologies of the associated congenital heart defects in WS patients have not been sufficiently elucidated and represent therapeutic challenges. The typical congenital heart defects in WS were supravalvar aortic stenosis, pulmonary stenosis (both valvular and peripheral), aortic coarctation and mitral valvar prolapse. The atypical cardiovascular anomalies include tetralogy of Fallot, atrial septal defects, aortic and mitral valvular insufficiencies, bicuspid aortic valves, ventricular septal defects, total anomalous pulmonary venous return, double chambered right ventricle, Ebstein anomaly and arterial anomalies. Deletion of the elastin gene on chromosome 7q11.23 leads to deficiency or abnormal deposition of elastin during cardiovascular development, thereby leading to widespread cardiovascular abnormalities in WS. In this article, the distribution, treatment and surgical outcomes of typical and atypical cardiac defects in WS are discussed.

Key words: aortic valve stenosis, congenital heart defects, Williams syndrome.

Williams syndrome (WS), also known as Williams-Beuren syndrome, is a rare genetic disorder characterized by infantile hypercalcemia, short stature, a varying degree of mental retardation, elfin like facial features, a friendly and outgoing personality and cardiovascular abnormalities caused by a chromosome 7 microdeletion1. The most common congenital heart defects are supravalvar aortic stenosis (SVAS), followed by supravalvar pulmonic stenosis2. In children with WS, SVAS is seen in 80% of cases; whereas about 50% of SVAS patients have WS3. Retrospective studies on larger series of WS patients revealed that peripheral pulmonary stenosis and SVAS were the two most common associated cardiovascular abnormalities (Table I).

Of those with cardiac anomalies, 34.5% had a single defect and 65.5% had multiple defects2. The mean age at diagnosis of the cardiac anomaly was 4.2 years, while the mean age at diagnosis of the syndrome was 6.2 years6. Among patients with mild or absent significant cardiac findings, the mean age at diagnosis was 7.1 years; whereas among patients with SVAS or severe cardiac symptoms, the mean age at diagnosis was 4.5 years2. However, the etiologies of the associated congenital heart defects in WS patients have not been sufficiently elucidated and thus represent therapeutic challenges. In this article, the distribution, treatment and surgical outcomes of typical and atypical cardiac defects of WS are discussed.

Etiologies

Most WS cases were sporadic, while only a few were familial. Nevertheless, both sporadic and familial cases are considered as a result of deletion of chromosome 7 (7q11.23)7. Deletion of the elastin gene on chromosome 7q11.23 leads to deficiency or abnormal deposition of elastin during cardiovascular development, leading to widespread cardiovascular abnormalities in WS8. The chromosomal region has been designated as “Williams-Beuren Syndrome chromosome region 1” (WBSCR1). Theoretically, causative genes for WS are the ELN (elastin), LIMK1 (or LIM kinase-1), and RFC2 (replication factor C, subunit 2) genes7. The LIMK1 gene is
believed to be responsible for the visual-spatial problems in WS patients. Deletion of ELN and contiguous genes, mutations within the elastin gene result in two different autosomal dominant disorders, SVAS and cutis laxa. Point mutations of elastin in exons 3, 17, 21, 25, and 26 in SVAS kindreds, deletion of the 30 end at exon 27, in one family, and a 30-kb intragenic deletion of exons 2 through 27, in an additional kindred were reported. These data proved that ELN mutations caused SVAS. Debates remain in terms of etiologies of vasculopathy in WS, on either by decrease of the synthesis of elastin, or by abnormal deposition of elastin in the arterial walls. Both were explained to be a pathway leading to thickening of the tunica media and smooth muscle cell hypertrophy. Accordingly, these changes might result in classic cardiovascular manifestations in WS; the most common of which would be SVAS, hypoplasia of the aortic arch and pulmonary artery stenosis. The pathological finding of the disorganized medial elements in the aortic tissues of WS patients with SVAS might partly interpret its developmental mechanism.

**Typical cardiac defects**

According to a clinical study by Del Pasqua et al., typical cardiac defects were present in 94 of the 113 patients (83%) and atypical defects were present in 19 patients (17%). They also reported that among typical congenital heart defects SVAS was found in 73 of 113 patients (64.6%), 58.9% (43/73) of which were an isolated SVAS. Pulmonary stenosis at the valvular level was present in 51 of 113 (45.1%) and in 18 cases, pulmonary stenosis was isolated, while aortic coarctation and mitral valvar prolapse were each found in 7 (6.2%), 3 of the lesions were in isolation.

**SVAS**

As reported by Bruno et al., SVAS was the most frequent malformation representing 71% of cases, with 56.3% (18/32) having a moderate or severe stenosis and 34.4% (11/32) having diffuse lesions. They reported that 24 surgical or catheter interventions were required in 21 of their patients. Of the 18 patients with a moderate or severe SVAS, 16 (88.9%) warranted surgical treatment, and they found that aortic reconstruction was associated with a 12.5% (2/16) mortality in SVAS patients, and recurrent SVAS developed in 7.7% (1/13) survivors. The surgical techniques for SVAS include McGoon’s single-patch repair, Doty’s pantaloan-fashion two-patch method, Brom’s three-patch technique and Myer’s autologous sliding aortoplasty.

By several comparative studies between the surgical techniques for SAVS in WS patients in terms of long-term prognosis, either by one-patch (McGoon technique), two-patch (Doty technique), or three-patch (Brom technique) aortoplasties, Fricke et al. and Cruz-Castañeda et al. revealed that the reoperation rate was the highest in those patients with McGoon repair, late results of Brom’s technique were good and Myer’s autologous sliding aortoplasty seemed to be the most promising (Table II). Kaushal et al. pointed out that the surgical indications for reoperation were residual aortic stenosis, aortic insufficiency and subvalvular stenosis. In contrast, Croti et al. demonstrated that SVAS patients receiving the Doty or Brom technique rarely required aortic reoperations, as for their low incidence of aortic regurgitation and an expanded ascending aorta without gradient as well as good ventricular performance. Moreover, Bonini et al. once introduced modified Sousa technique for the surgical repair of SVAS, but this has not been used in WS patients. In addition, SVAS in adult can also be managed with aortic valve replacement and arterioplasty of the ascending aorta, which have been performed by Valente et al. In general, the overall early mortality was very low, the late mortality ranged between 0% and 26%, and survival was 95-98% at 5 years as reported by Deo et al. They indicated that predictors of late mortality might include male gender, poor NYHA heart function, type of SVAS, concomitant anomalies, remarkable preexisting aortic stenosis, an elevated residual postoperative gradient and younger age at operation.

**Pulmonary stenosis**

It has been reported by Bruno et al. that in WS, the incidence of pulmonary stenosis at the valvular level was 11%, and they and Eronen et al. reached consensus that the incidence of pulmonary artery stenosis was around 40%. Del Pasqua et al. proposed that the major surgical or interventional indication for pulmonary stenosis in WS patients was a
mean pressure gradient of >45 mmHg. Clinical studies by different surgical teams, including Stamm et al.27, Monge et al.28 and Geggel et al.29 that the treatment of choice for pulmonary stenosis depended on the site of the lesion and the late results were fine (Fig. 1).

Coarctation of the aorta

Marks et al.30 described that coarctation repair was more commonly required in WS patients during neonatal period. The treatment of choice depended on patient’s age and the situation of the coarctation of the aorta. Other authors, like Mannarino et al.31 and Kammache et al.32 recommended that the open aortoplasty was indicated in the neonates and infants with discrete coarctation of the aorta and those patients with failed balloon dilation, but recoarctation rate was high. Arı et al.33 suggested that the subclavian flap aortoplasty technique for recoarctation after end-to-end anastomosis technique for coarctation and subsequent failed balloon dilation angioplasty should be indicated for the patients with a rapidly progressive form of aortic coarctation. Apostolopoulou et al.34 once reported an aggressive surgical procedure including resection of the isthmus, removal of the stent, and end-to-end anastomosis to treat obliterated stent was performed with success in a patient with recoarctation. Moreover, Marks et al.30 reported a composite left subclavian artery flap and allograft patch aortoplasty of the aortic arch and descending aorta was performed through a left thoracotomy under cardiopulmonary bypass and circulatory arrest was successfully performed in a 2.7-kg neonate.

Burrows7 proposed that dilations of the aortic arch and stent placement were indicated for those patients with coarctation of the aorta especially with diffuse hypoplasia of the aorta. As Apostolopoulou et al.34 illustrated that stent placement might be the treatment of choice for recoarctation in older patients; but Zanjani et al.35 indicated that, when massive neointimal proliferation was present, stent insertion became impossible. The reason of failure of end-to-end anastomosis and balloon dilation was considered by Mannarino et al.31 the consequence of an irregular elastic fiber arrangements of the aortic wall associated with the elastin mutation.

Mitral valve disorder

The incidence of mitral valve disease was reported by Scheiber et al.2 and by Bajracharya et al.36 to be 37-41% in WS patients, while the incidence of mitral valve prolapse was reported by Hallidie-Smith et al.37 to be 15%. Takagi et al.38 observed that the mitral valve prolapsed in

### Table I. Associated Cardiovascular Abnormalities of Williams Syndrome4,5

<table>
<thead>
<tr>
<th>Associated cardiovascular abnormalities</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis (supravalvular, valvular, or subvalvular)</td>
<td>61-72</td>
</tr>
<tr>
<td>Pulmonary stenosis (valvular or peripheral)</td>
<td>39-45</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>17</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>15</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>4</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>3</td>
</tr>
<tr>
<td>Hypoplasia of the aorta</td>
<td>2</td>
</tr>
</tbody>
</table>

Fig. 1. Management of the associated pulmonary stenosis.
AO: aorta; PA: pulmonary artery; PS: pulmonary stenosis; RV: right ventricle; WS: Williams syndrome.
WS might present with pure mitral regurgitation. Bruno et al.\textsuperscript{17} found that the concomitant severe SVAS in WS patients might exaggerate the mitral regurgitation. Bajracharya et al.\textsuperscript{36} recommended that mitral valve repair including chord, leaflet and annulus plasties could be the treatment of choice for mitral valve prolapse in WS patients.

Atypical cardiac defects

Pober\textsuperscript{1} indicated that intracardiac lesions are uncommon in WS patients. It is a common idea by Nakamoto et al.\textsuperscript{39}, Shimamoto et al.\textsuperscript{40} and Park et al.\textsuperscript{41} that these atypical heart defects usually warrant concurrent surgical repair. The associated defects and management were listed in Table III.

Surgical indications

It was reported by Eronen et al.\textsuperscript{26} that 61\% of the infantile WS patients required surgery or intervention. Based on a study by Del Pasqua et al.\textsuperscript{6}, the surgical indications included SVAS tended to progress, especially when the Doppler gradient was above 30 mmHg, and gradients over 50 mmHg. They also stated that cardiac catheterization with coronary angiography was necessary for demonstrating coexistence of coronary arterial anomalies and decreased coronary flow prior to surgery. Stamm et al.\textsuperscript{27} stated that aortic arch surgery could be performed safely and with excellent early and late results in children with SVAS. However, Eronen et al.\textsuperscript{26} found that aortoplasty or aortic angioplasty might cause postoperative mild to moderate aortic valve insufficiency and mild restenosis. Another postoperative concern as indicated by Gray et al.\textsuperscript{14} was the recurrent pseudoaneurysm after surgical correction of SVAS, which was considered the abnormal quality of the vascular tissue in WS patients.

Del Pasqua et al.\textsuperscript{6} revealed that balloon angioplasty could be effective, with or without the placement of stents, for WS patients with peripheral pulmonary stenosis, particularly distal stenosis. De Rubens Figueroa et al.\textsuperscript{3} reported that, in 58\% of cases, a surgical operation was required, depending on the severity of pulmonary artery stenosis. Geggel et al.\textsuperscript{29} reported that balloon dilation of peripheral pulmonary stenosis in WS were 134 dilation maneuvers during 39 procedures in 25 patients with a success rate for initial dilations of 51\%. Bruno et al.\textsuperscript{17} proposed, in cases of pulmonary artery branch stenosis, there was the possibility of stent placement. However, restenosis occurred in two children after pulmonary artery reconstruction. Patients with pulmonary artery stenosis, in the absence of other significant cardiovascular abnormalities, were often managed conservatively. Gray et al.\textsuperscript{14} indicated that, if treatment was required, balloon angioplasty could be used for discrete stenosis of the distal pulmonary arteries, but surgery was often necessary with long-segment disease or discrete stenosis in the main pulmonary artery. They also pointed out that patient with aneurysmal dilation of the main pulmonary artery might be at risk of obstruction of the coronary ostium.

Moreover, Maisuls et al.\textsuperscript{49} suggested, in WS patients, severe mitral regurgitation is indicated for surgical treatment at the ages of 8 and 11 years.

Adverse cardiac events

Scheiber et al.\textsuperscript{2} reported in an echocardiographic study that SVAS progressed with age, in spite of occasional spontaneous improvement; while De Rubens Figueroa et al.\textsuperscript{3} noted that pulmonary artery branch stenosis tended to improve spontaneously, and Monge et al.\textsuperscript{28} observed the same phenomenon, especially in those with mild to moderate other than those with severe peripheral pulmonary artery stenosis. In contrast to SVAS, pulmonary artery stenosis

| Table II. A Comparison of the Outcomes of Surgical Repair Techniques\textsuperscript{17,20,21} |
|-------------------------------|-------------------------------------------------|-------------------|-------------------|-------------------|
| Surgical technique            | Patient age (years) | Early mortality (%) | Late mortality (%) | Reoperation (%)    |
| Brom repair (three-patch)     | 5.2                 | 0                  | 0                 | 0                 |
| Doty repair (two-patch)       | 5.2                 | 0                  | 24                | 0-29              |
| McGoon (one-patch)            | 5.2                 | 0                  | ?                 | 62                |
| Myer’s autologous sliding aortoplasty | 7.6               | 7.7                | 0                 | 0                 |

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in this population often regressed or resolved with time. Wessel et al.\textsuperscript{50} reported the pressure gradient decreased spontaneously from a mean of 23 to 9.5 mmHg in 46.9% (23/49) patients with pulmonary artery stenosis over 14 years. Pober\textsuperscript{1} found that patients with WS were at an increased risk for major adverse cardiac events, and congenital cardiovascular disease was responsible for most of the morbidity associated with WS. A follow-up study by Sugayama et al.\textsuperscript{51} illustrated that major adverse cardiac events occurred after 41 out of 447 procedures (9%), including 20 deaths, 25 episodes of postoperative mechanical circulatory support, and 14 postoperative cardiac arrests. SVAS with significant pressure gradients posed sufficient risk of sudden death. Kececioglu et al.\textsuperscript{52} estimated that the risk of sudden death was 3% in a series of 104 patients with WS followed-up for 30 years. The exact mechanism of major adverse cardiac events in patients with WS was unknown. Hornik et al.\textsuperscript{53} reminded that the major adverse cardiac events were significantly more common after combined left and right outflow tract procedures than after complex left outflow tract or isolated SVAS procedures. Bird et al.\textsuperscript{54} provided with pathological evidences of coronary artery stenosis and severe biventricular outflow tract obstruction as causes of sudden death in 5 of 10 WS patients. Eronen et al.\textsuperscript{26} reported one WS patient without receiving an operation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient number</th>
<th>Atypical congenital heart defect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Pasqua et al.\textsuperscript{6}</td>
<td>19</td>
<td>Tetralogy of Fallot (n = 2), atrial septal defect (n = 4), aortic regurgitation (n = 1), mitral regurgitation (n = 1), bicuspid aortic valve (n = 2) &amp; ventricular septal defect (n = 9)</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Hanya et al.\textsuperscript{42}</td>
<td>1</td>
<td>Complete atrioventricular septal defect (n = 1)</td>
<td>Autopsied case</td>
</tr>
<tr>
<td>Nakamoto et al.\textsuperscript{39}</td>
<td>1</td>
<td>Complete atrioventricular septal defect (n = 1)</td>
<td>2-patch technique</td>
</tr>
<tr>
<td>Shimamoto et al.\textsuperscript{40}; Park et al.\textsuperscript{41}; Ferrero et al.\textsuperscript{43}</td>
<td>3</td>
<td>Total anomalous pulmonary venous return (n = 3)</td>
<td>Common pulmonary vein and left atrium anastomosis, and chordal reconstruction; repaired with the aid of hypothermic circulatory arrest</td>
</tr>
<tr>
<td>Mazumdar et al.\textsuperscript{44}</td>
<td>1</td>
<td>Double chambered right ventricle + coronary artery aneurysms (n = 1)</td>
<td>Died before surgery</td>
</tr>
<tr>
<td>Changela et al.\textsuperscript{5}</td>
<td>1</td>
<td>Ebstein anomaly</td>
<td>Follow-up with genetic counseling</td>
</tr>
<tr>
<td>Williams &amp; Cook\textsuperscript{45}</td>
<td>1</td>
<td>Ebstein anomaly and severe branch pulmonary artery stenosis</td>
<td>Palliative care treatment</td>
</tr>
<tr>
<td>Pober\textsuperscript{1}; De Rubens Figueroa et al.\textsuperscript{3}; Yau et al.\textsuperscript{4}; Nakamoto et al.\textsuperscript{39}; Lee et al.\textsuperscript{46}; Zalzstein et al.\textsuperscript{47}; Okagawa et al.\textsuperscript{48}</td>
<td>--</td>
<td>Displacement of lung arteries or coronary arteries\textsuperscript{3}; narrowing of the aorta, or the pulmonary, coronary, renal, cerebral, carotid, brachiocephalic, subclavian, mesenteric, and intracranial arteries\textsuperscript{1,3,4,39}; bilateral Moyamoya disease\textsuperscript{46}; coronary artery abnormalities\textsuperscript{47}; splenic artery stenosis\textsuperscript{47}; abdominal aortic narrowing\textsuperscript{47}; &amp; pulmonary artery sling\textsuperscript{48}</td>
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</tr>
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**Table III. Atypical Congenital Heart Defects Associated With Williams Syndrome**
died of pneumonia at the age of 4 years, and another died suddenly of heart failure at the age of 4 months due to a misdiagnosis. Myocardial infarctions and sudden death have been reported in childhood, secondary to lesions of coronary dysplasia in cases of WS, however, they were unusual. Surgical relief of either SVAS or more distal arch obstruction might substantially decrease coronary perfusion pressure, in turn, leading to coronary malperfusion. A ventricular arrhythmia generated by an ischemic myocardium was a possible mechanism to explain sudden death in these cases. Collins documented that arrhythmias might play an important role, because prolongation of the QTc interval were found in a subset of patients with WS. When patients were associated with hypertrophic obstructive cardiomyopathy or left ventricular pressure and volume overload, SVAS and mitral regurgitation occurred at greater risk as shown by Bruno et al. Additionally, risks of anesthesia included craniofacial features causing difficult ventilation and tracheal intubation, variable reaction to neuromuscular blockade, and endocrine and metabolic disorders, which led to impaired hepatic drug metabolism and poor temperature regulation as have been indicated by Del Pasqua et al. Moreover, Yuan et al.’s follow-up study revealed long-term sequelae of surgical resection, such as recurrence of SVAS, which might warrant reintervention.

Congenital heart defects are commonly seen in WS patients. A large numbers of the patients warrant surgical or interventional therapies. Of them, the surgical treatment of SVAS and coarctation of the aorta poses challenges due to the concerns of long-term outcomes in the patients, probably related to the younger age at operation. For SVAS patients, Brom three-patch technique is praised for its good postoperative results; whereas coarctation of the aorta seems to be refractory due to recoarctation after end-to-end anastomosis and frequent failures of transcatheter balloon commonly leading to aggressive aortoplasty. Care should also be taken as for the development of adverse cardiac events, in particular, in those with no surgical intervention or with no prompt diagnosis. Pathogenesis of congenital heart defects in WS needs to be further studied.
Congenital Heart Defects in Williams Syndrome


