Infracardiac total anomalous pulmonary venous return in a patient with Williams syndrome
A case report

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Abstract
Rationale: Total anomalous pulmonary venous return (TAPVR) is a rare condition, accounting for 1% of all congenital heart diseases, and an atypical cardiovascular abnormality in Williams syndrome (WS). Here, we report a rare case of WS combined with infracardiac TAPVR.

Patient concerns: A female newborn presented shortness of breath and purpura after crying at the age of 10 days.

Diagnosis: Based on clinical symptoms and laboratory and echocardiographic findings, the patient was diagnosed with infracardiac TAPVR.

Interventions: We performed infracardiac total anomalous pulmonary venous connection repair surgery.

Outcomes: The operation was successful and the patient was discharged from the hospital uneventfully after 2 months of treatment. However, we diagnosed the patient with WS in addition to infracardiac TAPVR 6 months postoperatively.

Lessons: This case demonstrates that patients with WS can have associated infracardiac TAPVR. The postoperative growth patterns and changes in the diameters of the aorta and pulmonary arteries were related closely to our early diagnosis of TAPVR associated with WS.

Abbreviations: CTA = computed tomography angiography, LA = left atrium, TAPVR = total anomalous pulmonary venous return, WS = Williams syndrome.

Keywords: cardiovascular abnormalities, infracardiac total anomalous pulmonary venous return, Williams syndrome

1. Introduction
Williams syndrome (WS), also termed Williams-Beuren syndrome, is a rare genetic multisystem disorder caused by chromosome 7q11.23 microdeletion that involves the facial features, connective tissue, and cardiovascular and central nervous systems.

WS occurs in approximately 1 in 10,000 persons. Cardiovascular abnormalities are frequently associated with WS, but WS with infracardiac total anomalous pulmonary venous return (TAPVR) has not been reported. Here, we present the case of a neonate diagnosed with intracardiac TAPVR who was found to have WS during postoperative follow-up.

2. Case presentation
At the age of 10 days, a female neonate presented shortness of breath and purpura after crying. Informed consent was obtained from the patient’s parents for the publication of photographs and hospital examination results. Physical examination revealed cyanosis of the skin on the torso and limbs. The neonate’s respiration was deep and rapid, dominated by abdominal breath. On percussion and auscultation, wet rales were detected in both lungs. The second heart sound was split, and systolic murmur could be heard in the tricuspid valve area. The neonate’s cardiac function was New York Heart Association class III. Echocardiography showed that the left and right upper and lower pulmonary veins formed a pulmonary venous confluence that drained via a large vertical vein through the middle hepatic vein to the inferior vena cava. An atrial septal defect caused blood flow from the right atrium to the left atrium (LA). The pulmonary artery was widened (inner diameter, ~1.0 cm), with pulmonary hypertension. The tricuspid valve showed mild to moderate incomplete closure. The LA was small and the left ventricle was poorly developed; by contrast, the right ventricle was hypercardiometric. The ascending aorta was
narrower than normal (inner diameter, ∼0.6 cm; Fig. 1). No abnormality of liver or kidney function was detected (alanine aminotransferase, 16 U/L; aspartate transaminase, 56 U/L; blood urea nitrogen, 2.46 mmol/L; blood calcium, 2.40 mmol/L). No obvious abnormality in the child's intelligence or growth was observed, but she was only 10 days old when she first visited the doctor.

For such patients, we perform infracardiac total anomalous pulmonary venous connection repair surgery under continuous cardiopulmonary bypass and mild hypothermia. In this case, the pulmonary venous confluence was exposed thoroughly during surgery. After ligation of the vertical vein, an incision was made on the anterior wall of the common pulmonary vein and a mirroring counter-incision was made in the LA. Then, anastomosis of the common pulmonary vein and LA via an autologous pericardial approach was used to repair the atrial septal defect. Upon the restoration of normal body temperature, the heart began to beat rhythmically.

After 2 months of treatment, echocardiography showed complete anomalous pulmonary venous drainage and no obstruction of left anterior pulmonary venous return, as well as a bidirectional LA septal shunt, poor left ventricular development, aortic thinning (inner diameter ∼0.6 cm), and no widening of the pulmonary artery (inner diameter ∼0.7 cm). Right ventricular wall hypertrophy was observed. The patient was discharged from the hospital uneventfully.

Despite the success of the operation and the absence of symptoms, echocardiography showed progressive deterioration of the peripheral pulmonary stenosis, but no change in the diameter of the ascending aorta, during routine follow-up when the patient was 7 months old. Computed tomography angiography (CTA) confirmed these findings (Fig. 2). In addition, we noted facial abnormalities, most notably an elfin appearance, at the age of 10 months. This WS-specific facial appearance features a broad forehead, periorbital fullness, a flattened nasal bridge with an upturned nose, a long philtrum, and rounded cheeks. The patient's liver and kidney function were normal, with changes in blood calcium and glucose levels within the normal ranges. We observed no significant change in intelligence or growth at the age of 10 months, but the child was too young for this observation to be definitive. We recommended chromosome microarray and Affymetrix Cytoscan 750K chip analysis, which we performed with the parents' consent; the results revealed a 1.436-Mb microdeletion on chromosome 7q11.23 (72,701,098–74,136,633), consistent with the diagnosis of WS.

3. Discussion and conclusions

About 80% of patients with WS have cardiovascular abnormalities, which manifest in the first year of life in up to 93% of these patients. The most common abnormalities are aortic valve stenosis and peripheral pulmonary artery stenosis, with incidences of about 75% and 40%, respectively. TAPVR is rare cardiovascular abnormality in patients with WS; to our knowledge, only two such cases have been reported. One case was mixed TAPVR in a male neonate in the United States, and the other case was type Ia TAPVR in a 14-year-old boy in Japan. To our knowledge, this report is the first to describe a case of infracardiac TAPVR in a patient with WS. It expands the range of cardiovascular abnormalities associated with WS.

The diagnosis of infracardiac TAPVR associated with WS is not easy in the early stage. Whereas TAPVR can be detected by echocardiography at birth, WS is diagnosed primarily through fluorescent in situ hybridization, and clinical symptoms suggestive of WS, such as an elfin facial appearance, mental retardation, and unique personality traits are not apparent in infants. WS with cardiovascular abnormalities is diagnosed at an average age of 6.2 years. In our patient, she was hospitalized due to hypoxic symptoms at the age of 10 days. At that age, the elfin facial appearance typical of WS had not become evident. In addition, TAPVR is often secondary to pulmonary hypertension; in our case, inconsistent with WS, we found no pulmonary artery...
stenosis, but rather pulmonary artery widening, during surgery. Interestingly, during the 6 months after the operation, follow-up echocardiography showed that the originally widened pulmonary artery gradually became stenotic, and the final CTA results confirmed the existence of pulmonary artery stenosis. Over time, the patient showed a WS-specific facial appearance, which prompted us to consider the possibility of WS. Although liver and kidney function tests showed no significant abnormality of the serum calcium level, which would be expected with WS, we strongly recommended genetic testing, and its results confirmed our suspicion of WS. Although WS-related cardiac abnormalities can be corrected with surgery, WS is often accompanied by multiple organ damage and mental system disorders, which gradually emerge as the patient develops. Early diagnosis enables the close monitoring of disease progress and early intervention.10

In conclusion, this report is the first to describe infracardiac TAPVR in a patient with WS, expanding the range of cardiovascular abnormalities associated with WS. It should be noted that the clinical manifestations of WS and TAPVR occur simultaneously in affected patients, and the occurrence of progressive stenosis of the aortic veins and pulmonary arteries in infants with TAPVR may aid the early diagnosis, prevention, and treatment of WS.

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Author contributions

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Figure 2. Computed tomography angiography showing pulmonary artery stenosis 6 months after surgery. LPA = left pulmonary artery, RPA = right pulmonary artery.