Supravalvular Aortic and Renal Artery Stenosis in Childhood: Is There a Common Denominator?

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Supravalvular aortic stenosis (SVAS) is a rare condition characterized by narrowing of the ascending aorta above its origin. When associated with other arterial stenoses, a connective tissue disorder is implied. Accompanied by a distinctive phenotype consisting of mental retardation, behavioral traits ("cocktail" personality) and an elfin facies are pathognomonic for the diagnosis of Williams-Beuren syndrome (WBS). We present a patient with WBS who in addition to SVAS developed renovascular hypertension secondary to bilateral renal artery stenosis.

PATIENT DESCRIPTION

This 17 year old youth with a 4 year history of hypertension was admitted for a medical procedure. He is the firstborn child of five siblings to non-consanguineous Arab parents. The pregnancy was uneventful and birth was by vaginal delivery at week 42. He has mild mental retardation necessitating attendance at a school for the mentally handicapped. The family's other four children are healthy and of normal development.

At the age of 3 years the patient underwent surgical repair of supravalvular aortic stenosis. Hypertension was first diagnosed at age 13. Plasma aldosterone concentration (PAC) was 11.4 ng/dl (< 2.3–16.0 ng/dl) and plasma renin activity 1.5 ng/ml/hr (0.2–2.8 ng/ml/hr). A renal echo Doppler examination showed both kidneys to be of normal size (10.7 cm each) and structure. The aorta was narrowed with a maximal diameter of 1.2 cm. A parvus tardus flow pattern was evident over the intra-renal arteries. Serum creatinine was 0.8 mg/dl. At this stage, the parents refused further investigation and/or interventional treatment. Blood pressure has since been controlled with enalapril 20 mg twice a day and amlodipine 5 mg four times a day although severe problems with compliance were encountered.

On physical examination, weight was 94.2 kg and height 1.50 m. Facial features showed a depressed nasal bridge, long philtrum, wide mouth with a prominent lower lip, micrognathia and strabismus. Blood pressure was 104/62 mmHg. Magnetic resonance angiography (MRA) was performed, revealing severe narrowing of the left aortic arch extending through the whole length of the descending aorta, stenosis of both pulmonary arteries more marked on the right side, and critical stenosis of both renal arteries [Figure 1]. Percutaneous angiography of the renal arteries (PTRA) was performed with dilatation and stent insertion. Currently, one month after PTRA, with no medication, blood pressure is within normal limits.

COMMENT

This patient's clinical manifestations – mild mental retardation, distinctive facial features, SVAS, peripheral pulmonary artery stenosis, and renovascular hypertension secondary to bilateral renal artery stenosis – suggest the diagnosis of Williams-Beuren syndrome. WBS is a rare genetic disorder, with an estimated prevalence of 1 in 7500–20,000 births, caused by the heterozygous deletion of ~1.6 Mb of the chromosome sub-band 7q11.23 [1]. The deleted region

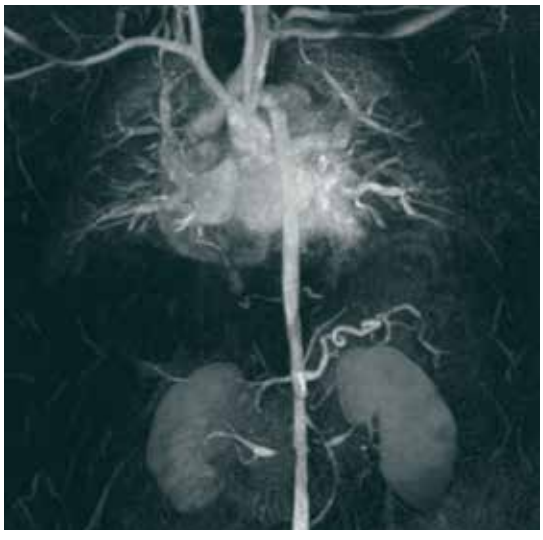

Figure 1. MRA showing severe narrowing of the left aortic arch extending throughout the descending aorta and critical stenosis of both renal arteries

includes about 28 genes, among which is the *ELN* gene encoding the protein elastin. Loss of this gene is associated with the connective tissue and cardiovascular abnormalities found in the syndrome. Reduced elastin synthesis has been shown to increase proliferation of vascular smooth muscle cells both in vivo and in organ cultures [2], leading to multiple arterial stenoses.

To establish the diagnosis of WBS, the genetic test fluorescent in situ hybridization (FISH) is used [3]. FISH test examines chromosome 7 and probes for the existence of two copies of the elastin gene. Since 98–99% of individuals with WBS lack half of 7q11.23 region of chromosome 7, the presence of only one copy of the gene is a strong indicator of the disorder.

As seen in our case, children with WBS typically have mild to moderate mental retardation. The range of mental disability can, however, vary from severe mental retardation to average intelligence. Facial dysmorphology, which is also attributed to the elastin gene haploinsufficiency, is a distinct feature of WBS. It includes a short upturned nose, flat nasal bridge, long philtrum, flat malar areas, wide mouth, full lips, dental malocclusion with widely spaced teeth, micrognatia, periorbital fullness and stellate lacy irises – an appearance named "elfin" facies. Virtually all patients with WBS exhibit some combination of the above features.

Cardiovascular disease, specifically elastin arteriopathy, is common with an overall prevalence of > 60%. The most common cardiac lesion found is SVAS but virtually any medium or large-sized artery may be affected. Hypertension develops in approximately 50% of individuals with WBS. In some, as exemplified by our patient, it is due to renal artery stenosis (RAS), while others are due to an increase in the peripheral resistance secondary to reduced elastin and increased proliferation of vascular smooth muscle [2]. Most cases are, however, considered idiopathic, perhaps caused by as yet unexplained genetic factors. Although our patient's hypertension was well controlled on treatment, non-compliance despite parental supervision proved to be an insurmountable problem. It is for this reason that PTRA with stent insertion of the renal arteries was performed which led to a successful outcome.

Notably, our patient's plasma renin activity was within normal limits. Although renovascular hypertension due to RAS is typified as high renin hypertension, a distinction must be made between unilateral and bilateral RAS. In unilateral RAS with a normally perfused and functioning contralateral kidney, renin is elevated but volume expansion is limited by the natriuresis of the contralateral kidney. In contrast, in bilateral RAS, intravascular volume increases and renin secretion decreases, a situation akin to one kidney, one-clip Goldblatt hypertension [4].

In conclusion, WBS has a wide phenotypic spectrum. It is a multisystem condition consisting of connective tissue abnormalities, multiple vascular anomalies, and a characteristic neurodevelopmental and behavioral profile. The combination of an elfin facies, mental retardation and multiple arterial stenoses, in particular SVAS, should alert the physician to its diagnosis. Diagnosis is confirmed by the FISH test showing the haploinsufficiency of the *ELN* gene.

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