Supravalvular Aortic Stenosis

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BEFORE Denie and Verheugt (1958) drew attention to the possibility of diagnosing supravalvular aortic stenosis from the characteristics of the pressure tracings across the aortic valve region, there had been only autopsy reports of 17 cases with supravalvular obstruction. Fourteen of these earlier accounts concern bands or membranes stretching across the aortic lumen and only three previous cases are strictly comparable to Denie and Verheugt's patient, in whom the obstruction was due in part to hypertrophy of the media just above the sinuses of Valsalva and in part to constriction of the aortic wall at the same level. This patient presented the usual features of valvular or subvalvular aortic stenosis and the true condition was not recognized until operation. Denie and Verheugt commented that "as surgical correction of the aortic stenosis becomes more commonplace, . . . these anomalies may well be encountered more frequently." Subsequently, Morrow et al. reported three similar cases, of which two were unsuspected until operation but one was diagnosed preoperatively by left heart catheterization. Angiocardiograms taken after retrograde left ventricular catheterization in two further cases were published by Hanson et al. and by Dotter and Gensini, and with the aid of cardiopulmonary bypass McGoon et al. and Senning have successfully relieved obstructions of this type.

Four new instances of this anomaly to which the term supravalvular aortic stenosis is becoming specifically applied are now reported. In three patients, who otherwise had the signs of valvular or subvalvular stenosis, the correct diagnosis was suggested before investigation by the close facial resemblance they bore to the fourth patient, who had been found to have supravalvular stenosis at operation. All four patients are mentally deficient and the association of supravalvular stenosis with the physical and mental characteristics here described may constitute a previously unrecognized syndrome.

Clinical Features

The patients, three female and one male, are aged 7 years (E.C.), 7 years (P.W.), 12 years (H.B.), and 11 years (J.S.). Their sexual characteristics are normal and in agreement with the leukocyte nuclear sex. Although mentally retarded they are receiving a limited education at special schools and they have sufficient understanding to have acquired normal social habits. Their intelligence quotients (Stanford-Binet) are 72, 67, 42, and 67, respectively.

Their facial resemblance, less strikingly shown in figures 1 and 2 than in real life, appears to derive largely from soft-tissue similarities, no common abnormality having been found in roentgenograms of their skulls. The faces are full, the foreheads broad, the eyes set well apart, the cheeks heavy and dependent, the mouths wide, and in some the lips are pouting. The chins, however, are pointed. Some have prominent ears and some have malocclusion of the teeth. Although there are clearly differences from face to face, the above features in varying degree combine to give the patients a similarity of appearance not easily defined but evident to their parents and the subject of comment by casual observers.

All the patients have siblings and, while they share with these siblings some family features, their own peculiarities of appearance are emphasized when they are seen in a family group (fig. 3). No other cases of congenital heart disease are known in the families. The parents were born in widely separated parts of the world, and there are no known family relationships.

The mothers were well during the pregnancies. At birth the three girls weighed only 5 lb. (E.C.), 4 lb. (P.W.), and 5 lb. (H.B.), and the boy (J.S.), although weighing 7 lb. 4 oz. at birth is said to have gained only 2 lb. in the first year. Except for H.B. they have remained below average weight for age.

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No patient gave a history of limitation by cardiac symptoms, and in none was a heart defect suspected before the discovery of a murmur during a routine examination. In each the physical findings were similar to those found in valvular or subvalvular stenosis. There was a thrusting left ventricular apex beat and, in the aortic area, a loud systolic ejection murmur that was conducted to the carotids. Neither the peripheral pulse nor the respiratory variation of splitting of the second heart sound was abnormal. In no case was there an early systolic click or an early diastolic murmur.

The electrocardiograms (fig. 4) and the appearances in the chest roentgenograms were consistent with the presence of left ventricular hypertrophy. The ascending aorta was not prominent in any instance.

Pressure gradients across the aortic valve were not obtained in one patient (E.C.) until operation for suspected valvular stenosis; in the other patients gradients were recorded either by retrograde left ventricular catheterization via the right radial artery (J.S.), or by percutaneous left ventricular puncture (P.W., H.B.). In each case continuous pressure tracings during passage of the catheter between high aorta and low left ventricle showed a rise in systolic level a short distance above the aortic valve (fig. 5). The systolic gradients across the supravalvular stenosis were 100 (E.C.), 84 (J.S.), 68 (P.W.), and 38 mm. Hg (H.B.). In one case (E.C.) there was also a systolic gradient of 68 mm. Hg across the subaortic region of the left ventricle.

Angiocardiograms were taken in two patients (P.W., H.B.) at the time of left ventricular puncture (fig. 6). In each there was a localized narrowing of the lumen of the ascending aorta. Beyond this constriction the aorta returned to a normal caliber without developing a transitional "post-stenotic" dilatation. Large coronary arteries were displayed. The coronary ostia were at different levels, the right being the higher and lying close to the constriction.

At operation on E. C. (December 10, 1959) the stenosis was found to lie immediately distal to the sinuses of Valsalva, and the right coronary artery was dilated and arose immediately below the site of constriction. The stenosis could be seen externally as a localized narrowing of the aorta, while internally the lumen was further reduced by a bulky ridge of tissue projecting circumferentially from the aortic wall. Adjacent to the right sinus this ridge lost its attachment to the aortic wall and stretched across the lumen to create a secondary slit-like orifice. The aortic valve was tricuspid, the leaflets were normal except for slight thickening at their line of attachment to the aortic wall, and no subvalvular membrane was seen. Beyond the stenosis the ascending aorta gradually widened over a distance of 2.5 cm. to reach a normal diameter as it passed beyond the pericardial reflection. The lumen of the aorta was successfully enlarged by excising the subintimal ridge and inserting a pear-shaped Teflon patch into the aortic wall at the site of the constriction. The systolic pressure gradient between high and low ascending aorta was abolished. No attempt was made to correct the subvalvular obstruction, which it was thought might be due to muscular hypertrophy and might decline with the reduction in left ventricular pressure load.

In J.S., also, the supravalvular stenosis has been successfully relieved by the insertion of a Teflon patch into the aortic wall at the site of constriction, which, as in the previous case, lay just above the origin of the dilated and tortuous right coronary artery. Although the aortic wall was thickened in the region of the constriction, the aortic lumen was not further reduced by a projecting ridge.
Discussion

The clinical findings in our four cases were indistinguishable from valvular or subvalvular stenosis and, as others have commented,\textsuperscript{1,14} it may not be possible to differentiate these three conditions on clinical grounds alone. In our cases there was no dilatation of the ascending aorta in the chest roentgenogram but, since the ascending aorta is not always prominent in valvular or subvalvular stenosis, this appearance is not diagnostic. The absence of aortic dilatation may, however, serve to distinguish between supravalvular aortic stenosis and supravalvular membrane, for in the sole reported case\textsuperscript{19} of this closely allied condition the ascending aorta was grossly dilated. In two cases of supravalvular stenosis associated aortic regurgitation was caused by tethering of the aortic cusps to the constriction ring.\textsuperscript{1,14} The presence of this complication might suggest the correct diagnosis, since significant incompetence is unusual in congenital aortic stenosis and is uncommon in subaortic stenosis when there is absence of dilatation of the ascending aorta.

Initially all our cases were believed to have aortic or subaortic stenosis and the first of the series (E.C.) was submitted to operation with this diagnosis. When the true condition was disclosed, patients with similar abnormalities of facial appearance believed to have aortic stenotic lesions were recalled for investigation and all three proved to have supravalvular aortic stenosis. The confirmation of the diagnosis in these circumstances suggests that supravalvular stenosis should be strongly suspected when mentally retarded patients with the facial features here described present the signs of a stenotic aortic lesion. In addition to the other common features all our patients had blue irises and their retinal vessels were unusually tortuous resembling those found in association with coarctation of the aortic isthmus (fig. 7).

Other physical abnormalities are present in three patients. H.B. is the most severely affected. She has prognathism, a marked thoracic kyphoscoliosis, and poor muscular coordination. When younger, she required

\textit{Figure 3}\n
The unusual appearance of E.C. (top) and H.B. (bottom) is emphasized when they are seen with their siblings.
Figure 4

Electrocardiograms and systolic pressure gradients between left ventricle and high ascending aorta. The precordial leads in E.C. and P.W. have been recorded with half standardization.

Figure 5

Pressure tracing in J.S. showing that the systolic gradient marking the site of stenosis lies above the aortic valve.

treatment for talipes, and she has recently undergone femoral herniorrhaphies. P.W. has retrognathism and both she and E.C. have incurving of the little finger on each hand. Abnormalities of physical development have been reported in other cases. Two patients have been considered to show some of the features of Marfan's syndrome. One of these, Denie and Verheugt's patient, was of short stature but had long slender fingers and toes, prognathism, and a thoracic kyphosis. There was slight mucoid degeneration of the media of the aorta at the site of the constriction and for a short distance along the coronary arter-
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The other, reported by Burry,11 had long slender limbs, characteristic facies, high arched palate, and moderate kyphoscoliosis. Cystic medionecrosis of the aorta was not found at autopsy and features suggestive of Marfan’s disease could not be found in the patient’s relatives.

Subvalvular aortic stenosis appears to be commonly associated with other lesions of the aorta. Some degree of hypoplasia of the aorta distal to the stenosis (patient J.S.) has been a frequent finding.11,14 A difference in blood pressure in the arms suggesting stenosis of the left subclavian artery was found in our patient E.C. and also in one of the cases described by Morrow and associates.14 This latter patient had constriction of the aortic isthmus and Monckeberg-Gieben’s patient13 had coarctation of the aorta. In another case operation on a patent ductus arteriosus led to the discovery of supravalvular stenosis.14 The aortic cusps have been tethered to the supravalvular stenosis in two cases,11,14 but in all reported cases the aortic valve has been tricuspid.

The degree of left ventricular hypertrophy, in the electrocardiograms of our patients correlates poorly with the systolic pressure gradient (fig. 4) but it is not known whether the cardiac indices were comparable when the gradients were recorded. In the patient J.S. the electrocardiographic abnormalities and the degree of cardiac enlargement in the chest roentgenogram seem more than what might reasonably be attributed to the measured left ventricular pressure load. This patient has a loud apical systolic murmur but neither the phonocardiogram nor the wedge pulmonary
artery pressure curve gave evidence of mitral incompetence so that the possibility of cardiomyopathy in addition to supravalvular aortic stenosis has been entertained. The left ventricular muscle in Denie and Verheugt’s patient was said to have shown an advanced stage of fibrous myocarditis, while in Burry’s case there were fibrosis of the endocardium and thinning of the myocardium toward the apex of the left ventricle, where the muscle fibers were atrophic and replaced by fibrous tissue. These patients were thought to be forms frustes of Marfan’s syndrome, and diffuse fibrosis of the left ventricular muscle has been considered a likely contributory cause of cardiac failure in one instance of this condition. On the other hand, taken together with the suspicion of a myocardial abnormality in our patient J.S., these reports raise the question whether myocardial degeneration may be another facet of a syndrome of supravalvular aortic stenosis in which the associated physical peculiarities are distinct from Marfan’s disease.

The natural history of this uncommon condition is not known. In the patient H.B. serial electrocardiograms over 9 years show slowly progressive left ventricular hypertrophy. The earliest record of this patient, however, and

an electrocardiogram of patient P.W. at 5 weeks (fig. 8), which was taken following the discovery of a cardiac murmur during a routine neonatal examination, both showed evidence of only right ventricular hypertrophy. Right ventricular hypertrophy in infancy has been reported in some cases of coarctation of the aorta and has been attributed to the effect on the neonatal circulation of a ductus arteriosus entering the aorta proximal rather than distal to the aortic constriction. Since aortic stenosis also may appear in infancy with electrocardiographic evidence of right ventricular hypertrophy, it may be that conditions causing left ventricular systolic overload alter the fetal circulation, possibly by an increase in resistance to end-diastolic left ventricular filling and or by septic hypertrophy, so as to lead to right ventricular hypertrophy.

Growth has been retarded in all our cases and the 28-year-old man described by Denie and Verheugt was only 159 cm. tall and weighed 45.5 Kg. Limitation of exercise capacity by shortness of breath has not been reported in childhood but undue fatigue on effort has been a common early complaint. Dizziness on effort had been experienced by the 10-year-old girl J.R. Denie and Verheugt’s patient was severely limited by angina and palpitation at the age of 25 years and the electrocardiogram had shown a progressive increase in left ventricular hypertrophy over the previous 6 years. The clinical course of this patient, however, may well have been affected by the presence of aortic incompetence and narrowing of the entry into the left sinuses of Valsalva. Another patient died of cardiac arrest at the age of 10 years on the morning of projected operation. Burry’s report of a patient dying at 37 years in congestive heart failure is the only other instance of natural termination of the condition.

In the supravalvular stenosis there is high pressure in the coronary arteries. It is possible that obstruction at this level may be better tolerated than obstruction at or below the aortic valve. Since myocardial oxygen consumption and the tendency to left ven-
tricular muscular hypertrophy may be expected to increase in direct proportion to the systolic pressure load, it appears reasonable to adopt criteria for surgical relief similar to those applied to the more common forms of aortic stenosis. At operation on our two patients with the higher systolic gradients (E.C., J.S.) the insertion of a Teflon patch into the aortic wall at the site of the constriction effectively relieved the supravalvular stenosis as judged by abolition of the pressure gradient. Although the long-term result of this type of operation is not yet known, it is encouraging that a year after operation the electrocardiogram in the patient with the longer follow-up shows changes suggesting a significant reduction in left ventricular hypertrophy.

Summary

Facial resemblance to a patient in whom supravalvular aortic stenosis was discovered and successfully relieved at operation has led to the correct diagnosis of supravalvular stenosis in three other patients. All four patients are mentally subnormal. The presence of supravalvular aortic stenosis in mentally retarded patients with the unusual facial features here detailed may constitute a syndrome that has not previously been described.

References

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Cardiac Hypertrophy

There are many cases of hypertrophy, and of great hypertrophy of the heart, in which during life and after death no source of increased work can be discovered. The degree of enlargement found in many hearts in which there is a valve defect, such as aortic regurgitation or mitral stenosis, is sometimes out of all proportion to the apparent increase of burden. There is still much that remains to be explained; it is clear that there must be hidden sources of increased work, or the conclusion that increased work is the cause of hypertrophy needs revision.—Sir Thomas Lewis. Diseases of the Heart. New York, The MacMillan Company, 1933, p. 106.
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