CLINICOPATHOLOGIC CORRELATIONS

A Developmental Complex Including Supravalvular Stenosis of the Aorta and Pulmonary Trunk

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SUMMARY
A developmental complex is described characterized by (1) supravalvular stenosis of the aorta and pulmonary trunk, (2) dysplasia of valves and (3) stenosis of ostia of coronary arteries and branches of the aortic arch. From the four cases described, it is evident that not all of the features of the complex need be present in a given case and, when present, some lesions are not of functional significance. The variations underly the potential for differences in the hemodynamic states of affected subjects.

Additional Indexing Words:
Peripheral pulmonary arterial stenosis
Congenital coronary ostial stenosis

A DEVELOPMENTAL complex may be described as a constellation of anomalies in which more than one structure is involved. In some subjects, each of the features of the complex may be present and of functional significance. In others, only some of the features are evident, while the others are either absent or, if present, are not hemodynamically apparent.

A particular developmental complex of current interest to us is that in which the ascending aorta and pulmonary trunk are maldeveloped. When functional expression of these changes is present, it takes the form of obstruction in these vessels. In the aorta this is termed supravalvular aortic stenosis. Additional manifestations of the complex include obstruction of branches of the aortic arch and/or the coronary arterial ostia as well as dysplasia of the semilunar and atrioventricular valves. Involvement of the semilunar valves may lead to stenosis, while the atrioventricular valves, when involved, may be incompetent.

This report is based upon observations in four patients, in each of whom autopsy findings were available to us.

Stenosis involving the ascending aorta (supravalvular aortic stenosis) may assume one of three forms, namely, (1) the membranous, (2) the hourglass and (3) the hypoplastic.¹ The latter form is characterized by diffuse involvement of this segment of the aorta with a lesion in which the wall of the aorta is thick, yielding a narrow lumen, while the external diameter of the vessel may either be normal or more narrow than normal. This type of supravalvular aortic stenosis may be associated with similar changes in the pulmonary trunk as well as in the branches of the aorta. Peripheral pulmonary arterial stenosis may also be present.

Reports of similar cases have appeared in the literature.² Beuren and associates³ described a case of diffuse arteriopathy involving the aorta and pulmonary artery as well as the carotid, coronary and renal arteries. McDonald and associates⁴ described two cases with similar findings in a mother and daughter, suggesting a syndrome of familial nature. Schmidt and associates⁵ described two cases in sisters.
In the descriptions to follow, the pathologic observations in four cases will be considered and followed by the clinical observations.

Two of the patients were female and two male. The ages at death were one month (case 1), four months (case 2), 14 months (case 3) and seven years (case 4).

Pathologic Features

The common pathologic feature was one of involvement both of the ascending aorta and of the pulmonary trunk, while changes in branches of the aortic arch and of the pulmonary trunk in the coronary arteries and cardiac valves were present in some of the cases (fig. 1).

Grossly, the wall of the ascending aorta and of the pulmonary trunk showed major thickening (fig. 2) which tended to encroach to some extent upon the lumen. In case 4, there was no obvious encroachment upon the lumen of the pulmonary trunk (fig. 2a). In case 2 the ostium of the right pulmonary artery was also distinctly narrowed (fig. 3a). In the pulmonary arterial system, the process of thickening of the pulmonary trunk tended to extend uniformly into its primary branches. The thickening gradually diminished in degree with progressive branching of the arteries and tended to disappear at the hilus (fig. 3b).

The aortic thickening was most marked in the ascending portion and became progressively less in the arch and beyond.

Histologic examination of the aorta and major pulmonary arteries showed two patterns which might alternate from segment to segment in a given case. One picture was that of a mosaic orientation of medial elements (fig. 4a and b), while the other was one of thickening of the media, appearing as though there were an excess in number of units of elastic and intervening layers (fig. 4c). In some segments with the latter change, the subintimal aspect of the media showed mild elements of the mosaic change (fig. 4d).

Branches of the aortic arch showed a strong tendency for major thickening of their walls associated with corresponding degrees of luminal narrowing, a process seen in each except case 2 (fig. 5a and b). Histologically, the dominant picture was that of medial hypertrophy and, in some segments, the mosaic change beneath the adventitia (fig. 5c and d).

Of coronary arteries, case 3 showed associated stenosis of both ostia, while in each except case 2, histologic examination showed medial thickening by virtue of muscular hypertrophy and deposits of collagen and elastic tissue in this layer (fig. 6).

It was common for valvular lesions to be associated.

In two of the cases (cases 1 and 2; fig. 2b-d), the cusps of the pulmonary valve showed dysplasia yielding major thickening to a degree that was
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The left valve. Pulmonary valve (a.) Case 1. This process results in infundibular stenosis. The latter process was also present in case 3 wherein the pulmonary valve was not involved while the pulmonary trunk showed major obstruction (fig. 2b).

In two of the cases (cases 1 and 2), each with pulmonary valvular involvement, the aortic valve was dysplastic. The process caused valvular stenosis in one of these (case 2; fig. 2a), while in the other (case 1) the changes were not sufficiently severe to cause stenosis (fig. 2c). Histologic examination of dysplastic semilunar valves showed thickening of cuspid tissue with a loose cellular type of connective tissue (fig. 7).

Lesions of the mitral valve were observed in three cases (cases 1, 2 and 4), the latter two being described by Becker and associates6 (their cases 1 and 2). The picture was one of hooding of thickened leaflets with a tendency for the occurrence of friction lesions of that part of the left

Figure 3
(a.) Case 2. The pulmonary trunk (P.T.) and pulmonary valve. The left pulmonary (L.P.) artery is open. The pulmonary valve is dysplastic and stenotic. D.A. = patent ductus. (b.) Case 3. The right pulmonary artery (R.P.A.). As the vessel proceeds distally (toward the left side of illustration), the wall becomes progressively thinner.

Figure 4
Photomicrographs, each from sections stained for elastic tissue. (a.) Case 2. Aorta. The media shows a mosaic pattern. (× 40) (b.) Case 2. Pulmonary trunk. Mosaic pattern is present in the media. (× 40) (c.) Tertiary pulmonary artery, from case 1. Medial hypertrophy. The elements are regular although the wall appears to contain more elements than normal. (× 100) (d.) Case 2. Aortic arch. The medial elements are increased in number although fairly uniformly distributed except beneath the adventitia where a mosaic pattern is present. (× 40)

Figure 5
Branches of aortic arch. (a.) Case 4. The three branches of the aortic arch viewed grossly and in cross section; each shows major thickening of the wall with luminal narrowing. The left common carotid artery (L.C.) is particularly narrowed. (b.) Case 1. The branches of the aortic arch show thickening of their walls with corresponding luminal narrowing. (c.) Case 4. Photomicrograph of left common carotid artery. Major medial thickening with corresponding luminal narrowing. (Elastic tissue stain; × 12.5) (d.) Case 1. Photomicrograph of left common carotid artery. Medial thickening with luminal narrowing present to a lesser degree than in case illustrated in c. (Elastic tissue stain; × 26)
ventricular endocardium that was related to chordae of the posterior mitral leaflet. Chordal thickening was also present (fig. 8). Histologically, fibrous thickening of leaflets and surface fibrous deposits upon chordae were observed. In two of the cases (cases 2 and 4), the lesions were highly developed and may have accounted for mitral insufficiency.

In only one of the cases (case 1) was the tricuspid valve involved and this by a minor process of dysplasia.

**Clinical Manifestations**

Each patient manifested signs of cardiac disability with dyspnea being common. Cyanosis of mild degree was present in two (cases 1 and 3). Basal systolic murmurs of ejection type were present in each case. In each of the three younger patients, the electrocardiogram showed signs of right atrial and right ventricular hypertrophy. Thoracic roentgenograms showed either a normal-sized heart or moderate cardiomegaly without prominence of the major pulmonary arterial segments. The intrapulmonary vasculature was within normal limits.

In case 4, the supravalvular aortic stenosis was treated at the age of six years by insertion of a teflon patch in the narrowest segment of the aorta, just above the aortic valve. One year later, a mycotic aneurysm at the junction of the aortic arch and the descending aorta was discovered. The child died 17 days after resection of the aortic aneurysm. Two other patients (cases 1 and 3) died during cardiac catheterization after injection of contrast material into the right ventricle and the fourth (case 2) died of pneumonia at the age of four months.

Invasive diagnostic procedures were attempted in three of the patients (cases 1, 3 and 4). In two (cases 1 and 3), sudden death occurred immediately following injection of contrast material into the right ventricle. Limited studies in each of the latter showed elevation of right ventricular pressure. In case 1, in which stenosis of the pulmonary valve and pulmonary trunk were dominant, the right ventricular pressure was 110/0-8, while the left ventricular pressure was 118/5-25. In case 3, with a normal pulmonary valve but with stenosis of the pulmonary trunk and its branches, the right ventricular systolic pressure was reported as 120 mm Hg.

More complete studies were obtained in case 4 in which the most significant obstruction was in the aorta. Measured in mm of Hg, pressures in the right ventricle and pulmonary artery were normal (RV = 30/0-8; PA = 28/12 [mean-18]) while the left ventricular pressure was 260/0-18 and aortic pressure just beyond the valve was measured at 270/94 and slightly more distally, 160/90.

Angiographic studies were available in two cases (cases 1 and 4).

In case 1, the right ventriculogram showed an adequate-sized right ventricle, localized stenosis at the level of the pulmonary valve and hypoplasia of the pulmonary arterial tree (fig. 9). During the levophase of the study, the aortic diameter was

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**Figure 6**
Photomicrograph of a coronary artery of case 4. Medial hypertrophy with elastic fibers present in thickened media. (Elastic tissue stain; × 24.)

**Figure 7**

**Figure 8**
Case 4. Mitral valve, left atrium (L.A.) and left ventricle (L.V.). Hooding of valvular leaflets associated with thickening of leaflets and of chordae. Signs of mitral insufficiency were evident in the left ventriculogram (fig. 11).

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interpreted as either normal or slightly reduced from the anticipated normal.

In case 4, the pulmonary arteriogram showed a somewhat narrowed uniform state to the pulmonary arterial tree (fig. 10a). Pathologic studies showed involvement of the pulmonary trunk but without evident stenosis. Pulmonary arterial obstruction was not confirmed by catheterization studies. The obstructed ascending aorta and branches of the aortic arch were clearly demonstrated in an angiocardiogram (fig. 10b). The latter study also showed left ventricular hypertrophy. Case 4 was one of the two cases with significant mitral valvular changes (fig. 8) and in which a left ventriculogram had been done. This showed signs of mitral insufficiency (fig. 11).

Comment

Supravalvular stenosis is recognized as a condition which may be associated with other anomalies, including obstruction of branches of the aortic arch, peripheral pulmonary stenosis and facial deformities. Except for the report of Becker and associates, valvular lesions have not been emphasized.

The cases here described appear to be part of a developmental complex in which (1) obstruction occurs in the ascending aorta, the branches of the aortic arch, and the pulmonary trunk and its branches, (2) lesions occur in the cardiac valves, and (3) coronary ostial stenosis is present. The material shows that each condition of the complex need not be present in each case. Moreover, when the various manifestations are present, some are functionally significant while others are not.

Obstruction of the aorta or pulmonary artery appeared to be the dominant condition from the clinical point of view. In each, both the ascending aorta and pulmonary trunk were involved to some extent pathologically, while only one case (case 3) showed significant obstruction of both vessels. Among the three cases in which only one of the two major arteries was obstructed, the pulmonary artery was so affected in two and the aorta in one.
Among the semilunar valves, two of the cases showed lesions in each valve. In one of these both the aortic and pulmonary valves were stenotic and, in the other, the changes were sufficient as to cause stenosis of the pulmonary valve only.

It is of interest that in one of the cases left ventricular outflow obstruction was primarily on the basis of aortic valvular stenosis rather than in the ascending aorta, even though qualitative changes of the complex described were present.

Of the atrioventricular valves, the mitral was most affected showing lesions in three cases, in two of which these were marked. From the appearance of the involved mitral valves, one might anticipate that regurgitation would have occurred and had been demonstrated in the one case.

The flavor of the case material suggests a developmental complex in which forme frustes are possible and potentially responsible for variations in hemodynamic disturbance from case to case. In this regard, one is attracted to a report on multiple valvular abnormalities as described recently by Bharati and Lev. In one of the cases of Schmidt and associates, the tricuspid valve was involved allowing regurgitation.

An example of the variation from aortic obstruction was observed in a specimen from a 5-month-old girl referred to our group by Dr. W. P. Baker. The dominant process was obstruction of the left coronary artery including its ostium, while the aorta showed minimal mosaic changes and the mitral valve was dysplastic.

References
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