Cardiovascular Abnormalities in Osteogenesis Imperfecta

By MODESTINO G. CRISCITIELLO, M.D., JAMES A. RONAN, JR., M.D., EDWIN M. M. BESTERMAN, M.D., AND WILLIAM SCHOENWETTER, M.D.

The group of diseases characterized by McKusick as generalized "heritable disorders of connective tissue" includes the Marfan syndrome, the Ehlers-Danlos syndrome, osteogenesis imperfecta, the Hurler syndrome, and pseudoxanthoma elasticum. With the exception of osteogenesis imperfecta, all of these have been known to involve significant cardiovascular abnormalities.1 The Marfan syndrome is frequently associated with dilation of the aortic root,2 sacculcation or stretching of aortic cusps, and dissection of the aorta.3-6 There have also been reports of fenestrations of aortic cusps,6,7 aneurysms of the sinus of Valsalva,8,9 dilatation and rupture of the pulmonary artery,5,6,8-10 mitral stenosis,6 mitral insufficiency,1,11,12 and mitral valve fenestration.11 Associated congenital lesions have included atrial septal defect,6,13 patent ductus arteriosus,5,9,10 and coarctation of the aorta.5-7 The Ehlers-Danlos syndrome has been associated with dissection of the aorta,1 aneurysm of a sinus of Valsalva,34 atrial septal defect,15 partial AV canal defect,16 tetralogy of Fallot,17 and mitral and tricuspid insufficiency.18 Heart disease is commonly present in the Hurler syndrome12,19 and is the cause of death in the majority of cases. Valvular deformities represent the most common form of pathology in these patients,10 the aortic and mitral valves being most frequently involved.10-21 Both endocardial and myocardial lesions are observed,19,20 and severe coronary disease is often present.12,19,21 Cardiovascular involvement in pseudoxanthoma elasticum is generally confined to the arterial network.1 Claudication in childhood,22,23 premature calcification of arterial walls,22-24 and decreased pulse-wave velocities in large arteries of the extremities25 have been noted. An aneurysm of the internal carotid artery has been reported26 and angina pectoris and hypertension occur frequently enough in association with pseudoxanthoma elasticum to consider them as significant factors in the natural history of the disease.1

In this report, the authors wish to present three patients with osteogenesis imperfecta, two of whom had dilatation of the aortic root with associated aortic insufficiency, and a third who proved to have multiple cardiac lesions.

Report of Cases

Patient 1, C.E. This 47-year-old laborer was admitted to the Georgetown University Hospital for evaluation of lightheadedness, substernal pain, palpitations, and fatigue of 3 years' duration. He had been aware of prominent pulsations in the neck for 10 years. Two months prior to his admission he had developed severe cough, dyspnea, and hemoptysis. These symptoms abated with the administration of diuretics and digitalis, and restriction of salt intake. During his youth the patient had fractured his upper extremities on four occasions by falling on the sidewalk. At the age of 27 he had developed deafness, which progressed to complete dependence upon a hearing aid.

His mother had blue sclerae, and his only brother is known to have blue sclerae, marked deformity of the spine, and a history of multiple fractures. His father died at the age of 76 of a ruptured aortic aneurysm.

He was a slender adult white man with a triangular-shaped head and prominent frontal bossing. The blood pressure was 160/30 and the pulse rate 80. The sclerae were blue, and there was arcus senilis. There was a bilateral conduction-type deafness. The carotid arterial pulsations were prominent, and there was a diastolic thrill in the aortic area. The heart was enlarged with a lifting left ventricular impulse in the sixth intercostal space 3 cm. outside the midclavicular line.

From the Department of Medicine, Georgetown University School of Medicine, Division of Cardiology, Georgetown University Hospital, Washington, D.C.
A grade-III aortic-systolic ejection murmur and a grade-IV aortic-diastolic blowing murmur were heard in the aortic area. The diastolic murmur radiated down both sides of the sternum but was more easily heard along the right sternal margin than the left. At the apex there was a grade-III pansystolic murmur and a short, mid-diastolic rumble (Austin Flint). An aortic ejection sound and a ventricular diastolic gallop were present. There were inspiratory rales at both lung bases.

The VDRL response was nonreactive. A chest x-ray (fig. 1) showed cardiomegaly due to left ventricular enlargement. No calcification could be seen in the region of the aortic valve or in the aorta. The ascending aorta appeared to be dilated. Other films revealed marked osteoporosis of the cervical, thoracic, and lumbar vertebral bodies as well as the pelvic bones. An electrocardiogram displayed left ventricular hypertrophy and digitalis effect. Because of the x-ray configuration of the aortic shadow and the presence of a diastolic murmur louder at the right sternal margin than the left, the patient was considered to have severe aortic insufficiency due to dilatation of the aortic root. There was no evidence of any of the disease states usually responsible for this type of aortic disease.

Patient 2, R.S. This 43-year-old white man was seen at the Middlesex Hospital, London, for cardiac evaluation. He had sustained eight fractures and experienced progressive loss of hearing over a 25-year period. There was a history of brittle bones, blue sclerae, and deafness in nine members of his family. The patient had been known to have heart disease since childhood.

On physical examination he was found to have a large calvarium (circumference of 24½ inches) and a small facial skeleton. The sclerae were blue and he was deaf. The blood pressure was 130/80 and the pulse rate normal. The heart was enlarged with a forceful apical lift outside the midclavicular line. A systolic pulsation was palpable in the second right intercostal space, and a loud ejection sound could be heard in the aortic area. There was a grade-III aortic diastolic murmur. The femoral pulses were normal.

The chest x-ray (fig. 1) showed cardiomegaly with some left ventricular enlargement. The ascending aorta was tortuous and accentuated to the right. Fluoroscopy revealed dilatation of the ascending aorta with greatly increased pulsations of the entire arch. The electrocardiogram showed left ventricular dominance with an axis of −16 degrees. Serologic tests were negative. Those examining the patient were not able to determine the etiology of the aortic root disease, and a diagnosis of idiopathic dilatation of the aorta, due to medial hypoplasia, with aortic incompetence, in addition to osteogenesis imperfecta, was made.

Patient 3, T.G.L. This 50-year-old World War II veteran was admitted to the Minneapolis Veterans Administration Hospital because of exertional dyspnea, angina, and episodes of syncope occurring during the previous year. Since the age of 6 years he had sustained multiple fractures involving the long bones of the extremities. He had also experienced fractures of the bones of his hands, ribs, skull, and thoracic vertebra. He had blue sclerae and at the age of 19 began to develop progressive deafness. At 19 years of age he had an episode of fever and rash which was diagnosed as erysipelas, but there was no history of rheumatic fever at any time. At the age of 34 he was hospitalized with flank pain, fever, chills, sweating, anemia, and the

Figure 1

Chest films of patients 1, 2, and 3 (from left to right). All three patients show cardiomegaly with left ventricular enlargement. There is prominence of the aortic shadow along the right heart border indicating aneurysmal dilatation of the aortic root.
murmur of aortic insufficiency. Recurrent episodes of fingertip pain suggested a diagnosis of subacute bacterial endocarditis, but all blood cultures were negative. Nevertheless, he was treated for 5 weeks with daily injections of 15 million units of penicillin, and he improved. He remained free from cardiac symptoms until the age of 40 years, when he first noted mild dyspnea on exertion. It was not until 1 year prior to admission, at the age of 49, that his symptoms became limiting.

His father and paternal grandfather had "soft bones" with a history of numerous fractures. His father had died at the age of 74 with a "leaky heart." The patient's 12-year-old son is known to have blue sclerae, is short of stature, and has sustained multiple fractures.

The patient was a short, thin white man with a triangular-shaped face and a bulging calvarium. The blood pressure was 180/200 and the pulse rate 90. The sclerae were blue. The heart was enlarged with a left ventricular lift at the apex. There were a grade-II aortic systolic ejection murmur and a grade-IV diastolic blow heard along the left sternal border. The peripheral arterial pulses were quick-rising.

A chest x-ray (fig. 1) showed enlargement of the left ventricle, and fluoroscopy demonstrated increased pulsations of the arch. An electrocardiogram showed left ventricular hypertrophy and strain with digitalis effect. The VDRL response was nonreactive. An audiogram revealed bilateral conduction deafness. X-rays of the elbows showed marked deformity of the olecranon process, and the ulna and radius of both forearms were osteoporotic and deformed. There was outward bowing of both femora and tibiae. Films of the thoracic spine revealed generalized demineralization with compression of three thoracic vertebrae. The cranium appeared widened in its transverse diameter with some overhanging of the base of the skull. Serum, calcium, and phosphate levels were normal and the alkaline phosphatase was 4.2 King-Armstrong units. Urinary acid-mucopolysaccharide excretion was 2.75 mg. per 24 hours and the urinary hydroxyproline level was 26.9 mg. per 24 hours. Both values were within normal limits.

Because of the severity of the patient's aortic insufficiency, an attempt was made at surgical correction of the valve at the Minneapolis Veterans Administration Hospital with use of perfusion-hypothermia technic. When the root of the aorta was incised, the aortic valve was found to be deformed. The left and right coronary cusps could be separately identified but there was fusion of the commissure between them. There was retraction and scarring of all three cusps. The base of the left coronary cusp was torn from its aortic attachment with an 8-mm. fibrous tag lying free in the aortic orifice. It appeared that this tag had once been the outer margin of the cusp bordering a defect in valve substance. There was a 5-by-5-mm. defect in the noncoronary cusp near its free margin. In the course of the operative procedure, the aortic cusps were excised, and three Bahnsen Teflon leaflets were sutured in place. During the postoperative period the valve seemed competent, but it was difficult to achieve hemostasis because of generalized small vessel bleeding. Subsequent hypotension, renal failure, and disturbances in rhythm led to the patient's death on the fourth postoperative day.

At autopsy, the heart weighed 690 Gm. The mitral valve was 12.5 cm. in circumference and the mitral leaflets were normal except for a globular aneurysm, 1 cm. in diameter, on the atrial side of the anterior leaflet (fig. 2). This
Microscopic studies showed an acute fibrinous pericarditis with a layer of surface fibrin varying in thickness up to several millimeters. In the underlying myocardium there were focal areas of old fibrosis and cellular infiltration, chiefly lymphocytic in type. There were also scattered areas of recent acute necrosis. No stigmata of rheumatic heart disease were noted. Sections of the aneurysm from the mitral valve (fig. 3) showed a marked decrease in fibrous connective tissue. The fact that no inflammatory change was seen in this aneurysm supported the possibility that it represented a congenital lesion. Various sections from the aorta and pulmonary artery showed the walls to be extremely thin with the elastic lamellae reduced in number so that the total elastic layer thickness was approximately two thirds of normal. Focal areas of degeneration were present between the elastic lamellae, and accumulations of acid mucopolysaccharide could also be detected. The changes in the arterial walls were consistent with the diagnosis of cystic medionecrosis (fig. 4). The aortic valve leaflets removed at surgery showed increased cellularity consistent with a healed or healing valvulitis. There was no evidence of active endocarditis. In the kidney, there were multiple cysts, probably of congenital origin, in both the medulla and cortex.

Discussion

Reports of heart disease associated with
the osteogenesis imperfecta have been very few. Hass detected heart disease in several members of a kinship having osteogenesis imperfecta, but the lesions described in his report appeared to have been rheumatic in origin. McKusick has noted two patients with osteogenesis imperfecta who appeared to have aortic regurgitation. One case of "congenital deformity of the heart" not well documented, was reported in a family of "blue sclerotics" by Voorhoeve. Kaul described abnormalities of the media, including the external elastic membrane, with segmental thinning and weakening of the walls of the brachial, renal, femoral, pulmonary, and coronary arteries in a 6-day-old male infant who died of hemorrhage from spontaneous rupture of the left renal artery. Aside from these reports there has been no well-described association of any type of cardiovascular abnormality with osteogenesis imperfecta.

The first two patients reported here had aortic insufficiency secondary to dilatation of the aortic root. Since there are many resemblances between the connective-tissue defect of osteogenesis imperfecta and that seen in the Marfan syndrome (including hyperextensibility of joints, blue sclerae, and a tendency to hernia formation), the possibility arises that the aortic defect is also common to both entities. Although attention has been directed primarily toward the skeletal abnormalities in patients with osteogenesis imperfecta, the changes involving the cornea, sclerae, skin, and ligament structures indicate that the disease process involves a generalized defect in the formation of connective tissue. The fundamental developmental difficulty in osteogenesis imperfecta relates to a failure of maturation of collagen beyond the reticulin fibril stage. According to McKusick an atypical form of fibrous connective-tissue protein is synthesized. Therefore, it appears likely that the aneurysmal dilatation of the ascending aorta observed in our first two patients may be related to defective collagen formation.

The third patient presented here differs from the first two with respect to the site of the cardiovascular lesions. He had a bicuspid aortic valve, fenestrations of the pulmonic valve, and an aneurysmal deformity of the anterior leaflet of the mitral valve. There appeared to be a tear in the left aortic cusp with the fenestration in the noncoronary cusp. Although the patient sustained an illness suggestive of bacterial endocarditis, the diagnosis was not substantiated with blood cultures, and it would appear unlikely that all of the above lesions, including involvement of both semilunar valves as well as the mitral valve, were the result of bacterial endocarditis.

The origin of the defects of the semilunar valves observed in patient three cannot be determined with certainty. The occurrence in normal hearts of small fenestrations of the semilunar valves is not unusual. Careful examination has led to the detection of this defect in as many as 82 per cent of routine postmortem studies and spontaneous rupture of aortic cusps secondary to valve fenestration has been demonstrated in a total of five cases. In our patient the aortic insufficiency may be ascribed to spontaneous rupture of fenestrations in a bicuspid valve. The history also suggests the possible involvement of healed bacterial endocarditis in the changes described in this valve. However, in view of the defect seen in the pulmonary and mitral valves and in the aorta and pulmonary artery, it is likely that the extensive destruction of the aortic valve was related to the same underlying connective-tissue defect. There have been two reports of multiple fenestrations of the aortic valve with spontaneous rupture of a cusp in patients with cystic medionecrosis of the aorta, one of whom had many other features of a generalized disorder of connective tissue.

The aneurysm of the mitral valve found in this patient had unusual features. Most mitral aneurysms are secondary to bacterial endocarditis and represent "false aneurysms," consisting of a hollow thrombotic mass, not lined with endothelium, communicating through an ulceration on the valve leaflet. This differs from the "true aneurysm" considered to be congenital in origin which contains ganulation tissue and scar covered by val-
vular endothelium. The aneurysm found in our patient is histologically of the true type and lacks those features usually characteristic of aneurysms related to bacterial endocarditis. There were no inflammatory changes, no thickening or retraction of the mitral leaflets, and no endothelialized vegetations. The aneurysm appeared to exist on an otherwise normal valve. There have been two case reports of mitral aneurysms in patients with connective-tissue disorders. One involved a 34-year-old man with an aneurysm of the ascending aorta and a ruptured aneurysm of the mitral valve. Histologic studies of the aorta and the mitral valve revealed changes characteristic of the Marfan disorder. The other case report was that of a 4-year-old girl with a typical Marfan syndrome. She, too, had an aneurysm of the ascending aorta with aortic insufficiency and severe thickening of the mitral valve. It was noted that the posterior cusp of the mitral valve “balanced out like a billowing sail.” Sections of this mitral valve showed myxomatous change with “focal accumulations of basophilic homogeneous ground substance resembling that seen in medionecrosis of the aorta.” Its appearance as a true aneurysm together with the knowledge that similar lesions have been reported in the Marfan syndrome suggested that a basic connective-tissue defect was the major factor in the formation of the mitral valve lesion in patient 3.

In the general group of patients with heritable disorders of connective tissue, many of the lesions ultimately responsible for death or disability first become apparent in adult life. In the Marfan syndrome, for example, the connective-tissue abnormality is present at birth, but in most instances the gross deformities of vascular or skeletal structures manifest themselves only after the passage of several years. Patients with osteogenesis imperfecta, the severe type, classified as osteogenesis imperfecta congenita, do not survive childhood and succumb to bone injuries in early life. It is chiefly in the group of patients with osteogenesis imperfecta tarda that one would expect to detect cardiovascular lesions including aortic aneurysms and valvular defects. The patients described in this report were 43, 47, and 50 years of age, respectively, and the symptoms related to their cardiovascular defects had been present for a decade at the longest. It is in this age range that heart disease related to hypertension, syphilis, and atherosclerosis most commonly makes its appearance. It is highly likely that lesions basically related to the underlying tissue defect of osteogenesis imperfecta have gone unrecognized and have heretofore been classified in other categories. Reports of the Marfan syndrome accumulated chiefly during the past decade have defined the important role of cardiovascular lesion in the life history of this disorder. It is our belief that a similar pattern will emerge in further study of those patients with osteogenesis imperfecta.

Summary

Three adults with osteogenesis imperfecta and associated cardiovascular lesions are reported. Two presented with aortic insufficiency due to dilatation of the aortic root for which none of the usual causes is apparent. The third patient was found to have lesions involving pulmonary, aortic, and mitral valves in addition to microscopic changes in the pulmonary artery and aorta. It is suggested that in osteogenesis imperfecta, as in other heritable disorders of connective tissue, cardiovascular defects may become apparent after the passage of time and play a dominant role in the natural history of the disease process.

Acknowledgment

The authors would like to express their thanks to Dr. William C. Manion, Chief, Cardiovascular Branch, Armed Forces Institute of Pathology, Washington, D.C., for reviewing the histologic material of patient 3.

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OSTEOGENESIS IMPERFECTA


Reports of Medical Cases, With 
a View of Illustrating the Symptoms and Cure of Diseases

By Richard Bright—1827

Case II. Elizabeth Beaver, aet. 37, was admitted November 23rd, 1825, into the Clinical ward, with swelling of the whole abdomen, attended by evident fluctuation; but depending in part on tympanitic distention. The more marked effusion was into the cellular membrane of the parietes of the abdomen, and into that of the lower extremities, which were greatly swollen; and there was considerable erythematous inflammation above the ankles. Her face and arms had likewise occasionally swollen.

She had been ill altogether about six months, her illness commencing with pain in the chest, and the increase of a cough to which she had been subject for four or five years.

Urine coagulates by heat, for the last two days scanty, passes frequently and unconsciously. Two watery dejections, much improved in character. Pulse from 108 to 120, weak. Tongue a little furred, and red at its edges.

The reports for the next three days were very nearly the same; but she gradually became weaker. The respiration increased to 32 in the minute, the pulse to 132. Vesications arose on various parts of her lower extremities, and she died on the evening of the 29th.

Sectio Cadaveris.—Nov. 30th.

The Kidneys were both of unusual size, certainly half as large again as most commonly seen; the right was the largest: on an external view they were obviously granulated with a large proportion of yellow granular matter: on taking off the proper tunic this was more distinctly seen; and on cutting in, the whole of the cortical structure seemed to be converted into a yellow substance in appearance like fat in many parts; though in other parts the change had not gone so far.

In this case we have an example of dropy with coagulable urine, connected with no other organic derangement except that which had taken place to so great an extent in the kidneys; unless indeed we take into view the small size of the heart, which appears to have been an original formation, or the result of a continued state of debility. The size of the kidneys considerably larger than usual, certainly suggested the idea that the fatty and granular substance had been the effect of the deposit of fresh matter in the interstices of the natural structure.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, pp. 10-12.
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Circulation. 1965;31:255-262
doi: 10.1161/01.CIR.31.2.255

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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