Some Unusual Features of the Marfan Syndrome

Report of Four Cases

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It is generally agreed that the Marfan syndrome is a heritable disorder of connective tissue characterized by widespread malformations affecting the musculoskeletal, cardiovascular, and ocular systems. It was first described by Marfan in 1896 under the name of dolichostenomélie. In 1902 Archard presented a case and called the syndrome arachnodactyly. Thus, the musculoskeletal malformations were initially described in this syndrome. Later, attention was drawn to the frequency of associated cardiovascular and ocular abnormalities, particularly ectopia lentis. Other malformations have also been reported such as susceptibility to respiratory infections, developmental malformations of the lung, cystic disease of the lung, and spontaneous pneumothorax. Several reviews covering different aspects of this syndrome have been published.

The purpose of this paper is to present some unusual findings in four patients with the Marfan syndrome.

Case Reports

Case 1

C. W. UH no. 652585, a 33-year-old white man, was admitted to the University of Minnesota Hospitals because of stiffness and pain in the knees and shortness of breath of 6 months' duration and progressive loss of vision due to subluxation of lenses since early childhood. Six years prior to admission he noted a hard mass in the left side of his neck close to the angle of the mandible. Three years prior to admission he noted a second mass in front of the previous one. Both masses progressively increased in size. Associated with the appearance of masses in the neck the patient noted dizzy spells lasting from a few seconds to a minute. There was no family history of ocular abnormalities or skeletal changes.

Physical examination revealed a slender young male who was comfortable at rest. The blood pressure was 102/60 mm. Hg. The height and the span were 71 3/4" and 72 1/4" respectively. Both lenses were dislocated. The vision on the right side was 20/200 and on the left side 10/400 (with glasses). The palatal arch was high. There was a mass about 3 by 2 by 3 cm. underlying the left jaw in the midcervical region laterally and a second mass, posterior to the left sternocleidomastoid muscle, which was firm and ovoid and about the same size. A moderate degree of pectus excavatum was present. The heart was not enlarged. The aortic second sound was louder than the pulmonic and there was a grade III (graded I-VI) aortic diastolic murmur, best heard along the left sternal border and the third and fourth intercostal spaces. He had typical arachnodactyly. There was some stiffness of the knees with minimal limitation in the range of motion. The hemoglobin, leukocyte count, leukocyte differential count, urinalysis, and serum proteins were normal, and the serology was negative. The electrocardiogram showed high QRS voltages compatible with left ventricular hypertrophy. Chest film showed normal heart silhouette (fig. 1). Cardiac fluoroscopy demonstrated increased pulsations of the left ventricle, ascending aorta, and aortic arch. X-rays of the neck revealed a soft tissue mass in the left side of the neck with a smooth outer contour. X-rays of the knees showed marked subchondral sclerosis with no significant decrease in the joint spaces. There was also some osteoporosis, and a loose body in the left knee. Retrograde aortogram done after injection of 50 ml. of 90 per cent hypaque through a catheter in the sinus of Valsalva area showed marked aneurysmal dilatation of the sinus of Valsalva and of the ascending aorta about the sinus of Valsalva (fig. 2). The anteroposterior diameter of the sinus area measured approximately 10 cm. There was distinct aortic regurgitation as well. The distal half of the ascending aorta and the remainder of the thoracic aorta were not remarkable. Simul-
taneous carotid angiogram showed an extensive network of small vessels, indicating a tumor mass adjacent to the left carotid bifurcation (fig. 3). Biopsy of the femoral artery was normal. On March 18, 1960, the patient was operated upon and a highly vascular, stony hard mass was removed from the bifurcation of the left carotid artery. There was a surrounding loose capsule, which was highly vascularized. A group of lymph nodes surrounded the internal carotid artery adjacent to the tumor. The histologic diagnosis was chemodenectomy (carotid body tumor) (fig. 4), and benign hyperplasia of lymph nodes.

This 33-year-old patient has typical skeletal and ocular changes of the Marfan syndrome. Although the family history is negative, disease in other members of the family cannot be excluded definitely. There are two unusual features in this case: the occurrence of marked aneurysmal dilatation of the sinus of Valsalva area undetected in routine chest x-rays, and the occurrence of a carotid body tumor in association with the Marfan syndrome.

Case 2

G. M., UH no. 949620, a 19-year-old white male student, developed spontaneous pneumothorax in November 1959. In January 1960, he noticed precordial chest pain radiating to the left jaw and down to the left ulnar region, lasting 1 to 2 hours, on two occasions, while playing hockey. He had two operations for pectus excavatum in 1950 and 1956. No cardiac abnormality was noted at that time. His parents, two brothers, and two sisters are apparently healthy. An older sister and the mother wear glasses for myopia. Physical examination revealed a slender, tall man in no distress. His height, span, heel-to-pubis and vertex-to-pubis measurements were 76 1/2, 81, 41 1/4, and 35 inches respectively. The blood pressure was 104/58 mm. Hg and equal in both arms. He had arachnodactyly, high arched palate, hammer toes, dorsal scoliosis, and partially corrected pectus excavatum. There was a grade-IV blowing diastolic murmur best heard over the aortic area and third intercostal space, left sternal border. The heart was not enlarged. Urinalysis, hemoglobin, leukocyte count, leukocyte differential count, electrocardiogram, and cardiac fluoroscopy were all within normal limits. Except for pectus excavatum and dorsal scoliosis the chest x-rays were negative (fig. 5). Retrograde aortogram on February 18 showed a large aneurysm of the sinuses of Valsalva, dilatation of the aortic ring, large aortic cusps, and minimal aortic regurgitation (fig. 6). The coronary arteries appeared normal. Biopsy of the femoral artery was normal. When seen again in 1961 he complained of tiredness and frequent sharp pains in the precordium. In addition to the diastolic murmur noticed 1 year previously, there were grade-II apical and aortic systolic murmurs. On fluoroscopy the ascending aorta appeared slightly larger. The electrocardiogram was unchanged.

This case represents the typical Marfan syndrome, with skeletal, pulmonary (pneumothorax), and aortic involvement. It is of interest that cardiac fluoroscopy and routine chest films again
failed to reveal the large aneurysm involving the intrapericardial portion of the ascending aorta.

Case 3

R. G., UH no. 958838, a 22-year-old white man, was admitted to the University of Minnesota Hospitals on June 14, 1960, because of severe congestive heart failure. The patient was slender as a child and at age 10 developed shortness of breath on exertion, and required digitalis and mercurial diuretics. He had had moderate shortness of breath until May 1960, when his symptoms began to increase gradually. He developed marked edema and bilateral pleural effusion, and required frequent mercurial injections. In February 1960, he developed severe crushing precordial chest pain aggravated by coughing but without radiation. Twelve hours after the onset of pain the patient became totally aphony for several days, with gradual return of full voice over a 2-week period. His father, brother, and sister were tall, slender persons with skeletal changes quite characteristic of the Marfan syndrome. The father had a grade-I pulmonic systolic murmur. No cardiac abnormalities were otherwise detected in the members of the family. On admission, he appeared chronically ill and in marked congestive heart failure. There was severe pectus excavatum, arachnodactyly, pes planus, bilateral subluxated lenses, and a high, narrow arched palate (fig. 7). His weight was 135½ pounds, the height 78 inches, and the span 83 inches. The blood pressure was 130/40 mm. Hg in the left arm, and 75/40 in the right arm. The pulse was regular, 108 per minute. The left carotid pulse was extremely weak; the right one was bounding. There was marked cardiomegaly, and the left subclavian artery showed aneurysmal dilatation. A left atrial gallop was prominent at the apex. In addition, there were a harsh grade-II holosystolic murmur and a palpable systolic thrill in the third intercostal space, left parasternal area, and a grade-II blowing diastolic murmur heard best in the same area. The aortic second sound was greater than the pulmonic. The liver was 1½ fingerbreadths below the right costal margin. The right radial pulse was markedly diminished. There was also a spina bifida. Urinalysis, leukocyte count, hemoglobin, blood urea nitrogen, fasting blood sugar, serum electrolytes, and carbon dioxide combining power were all within normal limits. Cardiac fluoroscopy and chest roentgenograms revealed thoracic scoliosis, marked pectus excavatum, abnormally prominent aorta with increased pulsations both in the arch and in the ascending aorta, and increased pulmonary vascularity (fig. 8). Several blood cultures were negative. In spite of treatment, the patient’s general condition rapidly deteriorated and he died on the fourth day of his hospitalization. Necropsy showed (1) dissecting aneurysm of the aorta with involvement of the carotid and subclavian arteries, (2) thrombosis of the left common carotid artery, (3) dilatation of the aortic ring, (4) severe, diffuse, cardiac dilatation involving both valve rings and cardiac chambers, (5) patent ductus arteriosus, (6) pulmonary emphysema, and (7) skeletal changes of the Marfan syndrome: high arched palate, tall, thin habitus, arachnodactyly, spina bifida, involving the ninth and tenth thoracic vertebrae, and pectus excavatum. The dissecting aneurysm starting from three intimal ruptures just distal to the aortic valve extended into the innominate, left common carotid, and left subclavian arteries and ruptured back into the aortic lumen, approximately 2 cm. distal to the origin of the left subclavian artery. There was a recent thrombus in the left common carotid artery extending up into the neck.

Microscopic examination of the left ventricular myocardium was normal. Sections from the aortic valve area, however, showed fragmentation and fatty infiltration of the myocardial fibers. The root of the aorta showed marked medinecrosis with disruption of elastic fibers. Sections from
several levels of the aorta and the renal, splenic, both carotid, both femoral, and pulmonary arteries showed similar changes.

There was capillary telangiectasia of the brain and encephalomalacia resulting from the carotid thrombosis.

In this 22-year-old man there was involvement of many systems, a patent ductus arteriosus, and one of the most common complications of the Marfan syndrome, dissecting aneurysm of the aorta. The dissection also involved the carotid and subclavian arteries. The medinecrosis was present not only in the aorta but also in the major arteries of the neck, abdomen, legs, and the pulmonary artery.

Case 4

N.D., UH no. 948650, a 27-year-old truck driver, was admitted to the University of Minnesota Hospitals on October 13, 1959, because of shortness of breath and precordial chest pain since February 1959. He was involved in a car accident in the fall of 1958, but developed no cardiovascular symptoms until February 1959. Several pre-employment examinations, as well as physical examinations in the military service when he participated in the Korean War, were all negative. His 64-year-old father has apparently had "heart trouble" since age 30, and his 58-year-old mother has had diabetes mellitus and arteriosclerotic heart disease for 9 years. One brother died of leukemia and three brothers and the patient's two children are apparently in good health and have no skeletal or ocular abnormalities. Physical examination on admission showed a slender, tall man weighing 174 pounds. His height was 78 inches and he had arachnodactyly, high arched palate, and flat feet. The blood pressure was 116/60. There were marked cardiac enlargement, grade-IV systolic and grade-III diastolic aortic murmurs, and a grade-II apical ejection murmur. The liver edge was felt two fingerbreadths below the right costal margin, and the lungs were unremarkable. The venous pressure was 19 cm. (citrate), and the arm-to-tongue circulation time was 20 seconds. Cardiac fluoroscopy revealed marked cardiac enlargement, prominent aorta (fig. 9) and increased pulsations in the arch and ascending aorta. There was left ventricular hypertrophy and strain on electrocardiography. The general condition of the patient gradually deteriorated, the heart failure progressed, and the venous pressure rose to 30 cm. Cardiac fluoroscopy done on October 26, 1959, showed massive enlargement of the heart and diminution in pulsations. A pericardial tap done on October 27, 1959, yielded 400 ml. of bloody fluid containing 3.5 Gm. of hemoglobin in 100 ml. The venous pressure dropped to 15 cm., and the patient gradually improved. A second pericardial tap done on November 12, 1959, yielded 250 ml. of thin, bloody fluid, containing .5 Gm. of hemoglobin in 100 ml. The patient improved further and was able to walk about in his room without great difficulty. He was operated upon at the Minneapolis Veterans Hospital on November 18, 1959, under hypothermia and extracorporeal circulation. There were several hundred milliliters of straw-colored fluid in the pericardial cavity. The aneurysm was sacular and located in the right lateral aspect of the ascending aorta, beginning at the aortic valve and extending to within a centimeter of the innominate artery. It measured

Figure 3
Case 1. Pathologic vessels in and around chemodectoma at the left carotid bifurcation.

Figure 4
Case 1. Medium-power view of chemodectoma.

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approximately 10 by 8 by 8 cm. The aorta was about 8 cm. in diameter at the level of the aortic ring. There were a harsh systolic thrill over the ascending aorta and moderate left ventricular hypertrophy.

After incising the aneurysm the inner lining of the aorta was seen to be smooth and glistening without evidence of luminal tear. The aortic valve appeared normal except for dilatation of the ring. The aneurysm had ruptured into the pericardial sac. The aortic wall opposite the saccular aneurysm appeared normal; therefore, the saccular portion of the ascending aorta was trimmed back to what appeared to be normal aortic wall and a wedge of sinus of Valsalva was removed from the non-coronary area to narrow the ring. The ascending aorta now appeared to be approximately normal in diameter, and there was no evidence of aortic regurgitation. Microscopically there were many areas of amudgy degeneration of the media, creating small areas of cystic medial necrosis. In one of the sections, there was a dissection of aorta between the media and adventitia, or possibly in the deep layer of the media. This area was recanalized and contained blood. The patient improved markedly after surgery. The heart size decreased, and he was discharged on December 22, 1959.

This 27-year-old man shows the complications of aortic medial necrosis in the Marfan syndrome, namely, dissecting aneurysm with rupture into the pericardial cavity and cardiac tamponade, which were treated surgically.

**Discussion**

Frequent association of cardiovascular anomalies with skeletal changes of the Marfan syndrome was first pointed out by Salle (1912) and Piper and Irvine-Jones (1926). The reported frequency of such anomalies ranges from 30 to 60 per cent. In the past, it was thought that congenital heart disease, especially interatrial septal defect, was the most common cardiovascular anomaly. Now it is agreed that dilatation of the aorta is more common. Since it involves most frequently the base of the aorta that is intrapericardially located, it may not at first be obvious radiologically. At this stage, aortic regurgitation is frequent, and cardiac fluoroscopy will usually show increased pulsations just above the right atrium. Our cases 1 and 2 demonstrate these points quite well. Both had aortic regurgitation, and routine radiologic studies failed to show the large aneurysmal dilatation of the base of the aorta. This could be demonstrated only by retrograde aortography. Although it is realized that involvement of the aortic sinuses and ring dilatation are the most frequent findings producing aortic regurgitation, ruptured aneurysm of the sinus of Valsalva, and deformities or perforations of the aortic
Figure 6
Case 2. Retrograde aortogram, posteroanterior and lateral views, showing large aneurysm involving the root of the aorta and the sinuses of Valsalva. Mild aortic regurgitation was evident on review of further films.

valve, seen in this syndrome, can produce a similar picture. Since some of these anomalies are now surgically correctable, the importance of establishing an accurate diagnosis is quite obvious. Since 1955, Steinberg and his co-workers8-10 have reported 10 cases of the Marfan syndrome in whom the diagnosis of aneurysms of the sinus of Valsalva was made during life by venous angiocardiography. Except for two patients (nos. 1 and 8) who had normal cardiac silhouettes, all the others had radiologic abnormalities indicating left ventricular enlargement or dilatation of the ascending aorta. The incidence of dilatation of the aortic ring, at autopsy, in cases of Marfan syndrome, has been reported to be about 10 per cent.11 Histologic studies of the aorta in this syndrome reveal cystic medial necrosis. The aortic involvement usually stops at the level of the innominate artery.9 The peripheral arteries are generally normal. Austin and Schaefer12 reported in 1957 the first case showing marked medial necrosis, aneurysmal dilatation, and dissection of innominate, right common carotid, and left common carotid arteries in addition to, but not as a direct result of, dissection of the aorta. Van Buchen13 reported in 1959 another case with medial necrosis of carotid, femoral, splenic, and renal arteries in addition to involvement of the ascending and descending aorta. In one of McKusick's cases (C. S., UH no. 575946) there was advanced cystic medial necrosis of the splenic artery4 and, in another case reported by Roark,14 the lesion involved the splenic, iliac, innominate, both subclavian, both common carotid, both renal, and mesenteric arteries. In our case 3 there was involvement of several arteries in the neck, abdomen, and legs in addition to that of the aorta. In cases 1 and 2, however, biopsies of the femoral artery were normal and there was no evidence of involvement of peripheral arteries.

Surgical treatment of aortic aneurysms or severe aortic regurgitation with heart failure has previously been attempted, but has gener-
ally failed. Aortic regurgitation was treated by the insertion of a Hufnagel valve in Steinberg's case 4, and two other cases with the Marfan syndrome. Since all three ended in failure, it was assumed that the aorta with its medial degeneration was probably unsuited for reparative or palliative surgery. There are several reported cases of the Marfan syndrome in which surgical treatment of the aneurysms of the aorta has been carried out. Bahnson and Nelson successfully plicated the dilated aorta and surrounded the ascending aorta with a splinting sleeve of synthetic fabric in cases with Erdheim's cystic medial necrosis. In two cases with the Marfan syndrome and aortic aneurysm the operation failed. In other cases with this syndrome, however, total replacement of the dilated aortic segments by an autograft, synthetic fabric graft, homograft, and Nylon graft has been successfully performed by Bahnson and others. In our case 4 there was marked improvement in the aortic regurgitation after operation. The association of carotid body tumor and this syndrome, as in our case 1, has not previously been reported. However, the relationship, if any, between these two conditions is not clear. There are approximately 300 reported cases of carotid body tumor.

The Marfan syndrome is a hereditary disease due to a mutant gene that produces a defect in the connective tissue. However, the nature of the basic connective tissue defect is not known. No definite abnormalities related to autosomal or sex chromosomes have been found in this syndrome. Experimentally skeletal and vascular changes quite similar to those of the Marfan syndrome have been produced in rats fed diets containing 50 per cent sweet-pea seeds. The toxic substance in sweet-pea seeds has been crystallized and identified as β-aminopropionitrile. This substance also can cause skeletal changes and dissecting aneurysm of the aorta. Biochemical studies such as the urinary excretion of hydroxyproline or the changes in the levels of serum mucoproteins or mucopolysaccharides are relatively limited and their significance is not clear. In the absence of specific tests the diagnosis is primarily clinical and relies on family history and the presence of skeletal, ocular, and cardiovascular abnormalities.

There are undoubtedly cases where all the features of the Marfan syndrome are not present; for example, aortic medionecrosis may occur without skeletal and ocular changes. These cases have been described as forms frustes of the Marfan syndrome, although their relation to Erdheim's cystic medionecrosis is still not clear. Bahnson suggests that the dilatation of the aorta in the Marfan syndrome extends into the sinuses themselves, whereas in Erdheim's cystic medionecrosis the abnormality is often localized to the ascending aorta.

To confuse the issue still further cystic

Figure 7

Case 3.
medionecrosis of the aorta has also been described in poststenotic dilatation of aortic stenosis, arterial hypertension associated with coarctation of the aorta, and in some "normal" persons. It is certainly true that Erdheim's cystic medionecrosis or formes frustes of the Marfan syndrome have not been excluded in these cases.

Summary
Four cases of the Marfan syndrome with involvement of the skeletal and cardiovascular systems are reported. In the first two cases with clinical evidence of aortic regurgitation the chest roentgenograms showed relatively normal heart silhouettes while retrograde aortograms revealed large aortic aneurysms
in the intrapericardial portion of the aorta involving the sinuses of Valsalva and the aortic ring. Case 1 had, in addition, a carotid body tumor, which was surgically removed. The remaining two cases had dissecting aneurysms of the aorta. Case 3 died and necropsy showed involvement of many systems and several arteries other than the aorta (carotid, subclavian, renal, femoral, splenic, and pulmonary arteries). Case 4 was surgically treated and showed marked improvement. Problems related to etiology, diagnosis, pathology, and treatment are discussed. It is emphasized that the existence of a large aneurysm of the intrapericardial portion of the aorta may not be detectable without aortography.

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THE MARFAN SYNDROME


Thomas Sydenham
1624–1689

Therein lies Sydenham’s historical importance, that he turned physicians’ attention in a new direction, toward particular illnesses . . . Whereas for a century investigators had been studying man in general, had been studying illness in general, had been trying with the inadequate methods and instruments of the day to solve the problems of general pathology, Sydenham proclaimed the importance of special pathology. First, he said, let us study particular diseases, let us learn how they make themselves perceptible to us in a particular patient. Let us seek to learn from experience what remedies are best in particular diseases. General conclusions can wait.—HENRY E. SIGHERST, M.D. The Great Doctors. New York, W. W. Norton & Co., Inc., 1933, p. 180.
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