Cyanotic Malformations of the Heart with Pheochromocytoma

A Report of Five Cases

By Gordon M. Folger, Jr., M.D., William C. Roberts, M.D., Ali Mehrizi, M.D.,
K. D. Shah, M.D., D. L. Glancy, M.D., Charles C. J. Carpenter, M.D.,
and John R. Esterly, M.D.

Although the occurrence of pheochromocytoma in patients with neurocutaneous defects has been reported, the occurrence of this rare tumor in patients with congenital cardiac malformations, to the best of our knowledge, has not previously been recorded. During the past 13 years, five patients with pheochromocytoma and cyanotic congenital malformations of the heart have come to our attention at The Johns Hopkins Hospital. A description of the clinical and pathologic features of these five patients forms the subject of this report.

Case Reports

Case 1

R.D. (JHH no. A 511024), a 26-year-old white man, who, although cyanotic at birth, was acyanotic during early childhood, grew and developed well and only suffered mild to moderate exertional dyspnea. At 7 years of age, cyanosis reappeared, squatting became apparent, and the dyspnea and fatigability increased. In spite of these symptoms the patient finished high school and was able to perform light farm chores. By age 18 the cyanosis had become persistent. In 1949, at the age of 26, he was referred to the Harriet Lane Home because of severe incapacity.

On examination, the blood pressure was 140/80 mm. Hg, pulse 80, respiratory rate 20, and temperature 39 C. The patient was small in stature, undernourished, and deeply cyanotic, and the digits were severely clubbed. A systolic thrill and murmur, most prominent in the third left intercostal space along the sternal border, were present.

The electrocardiogram showed right axis deviation and right ventricular hypertrophy. Chest radiogram showed a normal-sized heart and reduced pulmonary vascularity. Cardiac catheterization and venous angiography confirmed the diagnosis of tetralogy of Fallot. Oximetry revealed a resting oxygen saturation of 89 per cent, which fell to 54 per cent with exercise. The hematocrit value was 74 per cent.

A Blalock-Taussig operation was performed on September 10, 1949. Prior to operation the patient had no symptoms other than exertional dyspnea and easy fatigability. His blood pressure had ranged from 110/80 to 142/90 mm. Hg. During the operation, the blood pressure dropped abruptly when the left pulmonary artery was clamped and he became deeply cyanosed. The blood pressure gradually rose to preoperative levels after removal of the pulmonary arterial clamp and the operation was continued; the blood pressure remained satisfactory throughout the remainder of the procedure. The patient, however, did not regain consciousness and died 3 hours following completion of the procedure.

At autopsy (no. 22006), the heart weighed 480 Gm. The foramen ovale was patent but guarded by a competent valve. There was biventricular hypertrophy. The aorta was dextroposed and overriding a 3 by 2 cm-sized defect in the basal portion of the ventricular septum. Infundibular pulmonary stenosis was present; the pulmonary valve was bicuspid but of normal size. The left pulmonary artery was larger than the right. The surgical anastomosis between the left subclavian artery and the left pulmonary artery was patent. The bronchial arteries were dilated and tortuous.

A firm, encapsulated tumor, measuring 4.5 by 3.5 by 3.5 cm. was found immediately inferior to the left renal vein and just anterior to the abdominal aorta. On section, the tumor was reddish-brown, slightly friable, and contained flecks of calcium and two distinct nodules. On histologic...
Figure 1

Photomicrographs of sections of the pheochromocytomas in cases 1 to 5. Upper left, case 1. Upper right, case 2. Middle left, case 3. Middle right, case 4. Lower, case 5. Hematoxylin and eosin stains. Original magnification × 100 in cases 1, 2, and 4; × 150 in cases 3 and 5.
section (fig. 1), the tumor consisted of irregular groups of cells, varying in size and shape, resembling those characteristic of adrenal medulla. Fibrous tissue was present surrounding the chromaffin cells. The adrenal glands were intact and were in no way remarkable. The final anatomic diagnosis was tetralogy of Fallot and pheochromocytoma.

Case 2

E.H.* (JHH no. 855746), a 14-year-old girl was followed in the Cardiac Clinic of the Harriet Lane Home from 1946 until her death in 1959. Throughout this period she was markedly cyanotic and presented clinical findings compatible with transposition of the great vessels. Two years before death she began having attacks of extreme nervousness, recurrent frontal headaches, profuse sweating, insomnia, periodic vomiting, and tachycardia. The blood pressure varied from 98/70 to 150/110 mm. Hg. The arterial oxygen saturation was 77 per cent. Shortly before death a phen tolamine (Regitine) test was positive. She died during surgical exploration for a suspected brain abscess.

Autopsy (no. 29292), confirmed the diagnosis of transposition of the great vessels. A pheochromocytoma weighing 47 Gm. was present in the left adrenal gland with metastases in a regional lymph node and in the liver. Histologically (fig. 1), the tumor consisted of cells similar to those seen in case 1. They were arranged in an irregular cord-like pattern. The cells had hyperchromatic, pyknotic nuclei and eosinophilic cytoplasm. There were considerable vascularity and hemorrhage. Fetal fat was present at the periphery. The final anatomic diagnosis was transposition of the great vessels and pheochromocytoma.

Case 3

R.J. (JHH no. 423829), a 16-year-old white boy, had cyanosis and a cardiac murmur from birth. Growth and development were slow. When 18 months of age, following a convulsion, the child developed left hemiplegia. At 3 years of age he was sent from his home in Oregon to the Cardiac Clinic of the Harriet Lane Home.

Physical examination revealed a small child with clubbing of the extremities and intense cyanosis. The heart was located in the right hemithorax and was not enlarged. A grade IV/VI systolic murmur was present over the entire precordium, loudest in the fourth intercostal space to the right of the sternum. The hematocrit value was 61 per cent. The arterial oxygen saturation was 43 per cent. Chest roentgenograms showed the heart to lie in the right hemithorax. The lung fields were hypovascular. Although the patient did not appear to have a tetralogy of Fallot, he was suffering from a decrease in pulmonary blood flow. A right subclavian-to-right pulmonary artery anastomosis was performed with immediate and striking improvement.

When 13 years old (1957), during re-examination by his physician in Oregon, he was found to have hematuria, pyuria, proteinuria, and cylindruria; these findings persisted throughout the remainder of his life. Serum urea nitrogen remained normal until his terminal illness. During his last 3 years, his heart enlarged, dyspnea reappeared, and terminally he developed anasarca. The blood pressure, which had been checked on many occasions throughout his life, had always been normal (approximately 110/70 mm. Hg). He died on April 14, 1960, at age 16, in severe congestive heart failure.

At autopsy* (no. 30329) the heart was markedly enlarged (600 Gm.) and located predominantly in the right hemithorax. The right subclavian-to-right pulmonary artery anastomosis was occluded by an organized thrombus. A large oval defect was present in the lowermost portion of the atrial septum. The foramen ovale was closed. The tricuspid and mitral valves were continuous across the midline through a common atrioventricular defect. The aorta and the pulmonary artery arose from the anterior chamber, which anatomically was the right ventricle. The ascending aorta lay anterior to the pulmonary trunk. The pulmonary trunk was hypoplastic and the pulmonic valve was bicuspid and stenotic.

Both adrenal glands were partially replaced by a solid, brown-colored tumor measuring 6 by 4 by 3 cm., which connected one gland with the other by a wide bar and extended across the aorta to form a dumbbell-shaped tumor. Histologic sections (fig. 1) of the tumor disclosed that it consisted of cells of varying size and shape with uniform cytoplasm, and frequently large, pyknotic, irregular, and bizarre nuclei. Many of the cells were multinucleated. Occasional oncocytic and ganglion-like cells were present.

The kidneys were enlarged; the glomeruli were much larger than normal, slightly hypercellular, and a few were hyalinized. A number of large juxtapagglomerular bodies were seen. The renal arterioles were normal. The final anatomic diagnosis was origin of both great vessels from the right ventricle with pulmonary stenosis and pheochromocytoma.

* The authors are indebted to the Department of Pathology, Sacred Heart General Hospital, Eugene, Oregon, for sending the organs and histologic sections from this patient.

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CARDIAC MALFORMATIONS WITH PHEOCHROMOCYTOMA

Case 4 *

A.O. (JHH no. 644014), a 44-year-old man, was cyanotic from birth. He was admitted on several occasions to The Johns Hopkins Hospital with complaints of palpitation, breathlessness, weakness, and right parasternal chest pain. The diagnosis of atrial fibrillation was made, and he was successfully treated with quinidine. Later cardiac catheterization was performed and this procedure combined with intracardiac electrocardiogram was compatible with the diagnosis of Ebstein’s anomaly of the tricuspid valve.

He was subsequently seen at the Baltimore City Hospital and was diagnosed as having a pheochromocytoma. The tumor was successfully removed surgically. Histologic examination of the tumor (fig. 1) demonstrated pigment-containing cells arranged in cord-like groups resembling the pattern characteristic of the adrenal medulla. The final clinical diagnosis was Ebstein’s anomaly of the tricuspid valve and pheochromocytoma.

Case 5

J.E. (JHH no. 528646), a 20-year-old white college student, who was cyanotic at birth, squatted frequently, and fatigued easily was first seen in the Cardiac Clinic of the Harriet Lane Home at age 7 years. The hematocrit level was 77 per cent. The patient was found to have a tetralogy of Fallot, and an end-to-side right subclavian-to-right pulmonary artery anastomosis was performed with considerable improvement. During the following 3 years the hematocrit level ranged between 52 and 56 per cent and the blood pressure between 95/45 and 120/80 mm. Hg.

In 1955, at the age of 12 years the cyanosis began to increase and the exercise tolerance to diminish. The hematocrit level was 60 per cent and the blood pressure 150/90 mm. Hg. In 1958, in addition to a gradual increase in exertional dyspnea the patient developed nosebleeds, headaches, polyphagia with weight gain, polydipsia, profuse sweating, insomnia, several episodes of diaphoresis, and extreme nervousness. The blood pressure recorded at his clinic visit was 130/80 mm. Hg and the hematocrit was 75 per cent.

At 17 years of age, prior to consideration for corrective surgery, an angiocardiogram was performed, which confirmed the diagnosis of tetralogy of Fallot. During this admission in 1960 he was noted to complain bitterly of intolerance to the heat on the ward and to have unexplained episodes of sweating and irritability. His blood pressure was 170/110 mm. Hg. The possibility of a pheochromocytoma was considered. A 24-hour urine sample was positive for catecholamines (greater than 180 micrograms/24 hours). The patient, however, returned to his home in New York before the results of the test were known, and he was subsequently not seen for a period of 18 months. During this interval he had frequent episodes of headache, nervousness, epistaxis, sweating, insomnia, and diplopia. The patient was finally readmitted for study of a possible pheochromocytoma in 1962.

Physical examination revealed a temperature of 37.8 C, a pulse of 90, a respiratory rate of 20, and a blood pressure of 190/130 mm. Hg. The nailbeds were cyanotic, and clubbing was prominent. The heart was enlarged. A loud continuous murmur was present over the right hemithorax, and a grade-III/VI systolic murmur was present over the precordium, maximal along the lower left sternal border. The hematocrit value was 72 per cent.

While on the ward, the patient sweated frequently and his blood pressure was noted to vary from 140/100 to 200/150 mm. Hg. Twenty-four-hour urinary excretion of norepinephrine was 876 micrograms (normal 10 to 90 micrograms) and of epinephrine 25 micrograms (normal 5 to 40 micrograms). The diagnosis of a pheochromocytoma was thus established.

On March 15, 1962, the patient underwent laparotomy. A 2 by 1.5 cm. mass was found at the junction of the aorta and the left renal artery. The tumor was removed and histologic examination (fig. 1) revealed it to be similar to that seen in case 4. The pattern and individual cells were similar to those seen in the normal adrenal gland. Fetal fat was adherent to the fibrous tissue.

During the postoperative period, the patient’s blood pressure ranged from 120/75 to 150/100 mm. Hg. Histamine and phentolamine tests performed postoperatively were negative. Repeat 24-hour urinary excretions of norepinephrine and epinephrine were 167 and 23 micrograms, respectively.

On March 20, 1963, 1 year following removal of the pheochromocytoma, the patient returned to The Johns Hopkins Hospital for corrective cardiac surgery. Although he complained of dyspnea and fatigue on exertion, he no longer had headaches, nosebleeds, or sweats and his voracious appetite and excessive thirst had disappeared. The blood pressure now varied from 135/95 to 150/110 mm. Hg. The hematocrit value was 83 per cent. The phentolamine, histamine, and cold pressor tests were negative, and the urinary catecholamines were normal (less than 180 micrograms per 24 hours). On March 26, 1963, he underwent closure of the ventricular septal defect and removal of the hypertrophied musculature of the right ventricular infundibulum.

* This case is being reported in detail elsewhere by Dr. A. R. Christlieb et al.

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by Dr. David Sabiston. In spite of difficulty during surgery and the early postoperative period, he did well. Since operation his blood pressures have varied between 110/60 and 120/80 mm. Hg. The cyanosis disappeared rapidly and the hematocrit fell to 50 per cent.

Discussion

The association of endocrine tumors with heart disease has recently been noted by Roberts et al. These authors described five patients, ages 21 to 57 years, three with congenital cardiac malformations (total anomalous pulmonary venous connection in two and complete transposition of the great vessels in one) leading to cyanosis, and two with isolated calcific aortic stenosis of uncertain etiology. The associated endocrine tumor in three of these five patients was of adrenocortical origin (in each of the two patients with calcific aortic stenosis and in the one patient with complete transposition of the great vessels). A pituitary adenoma associated with the clinical picture of Cushing’s syndrome was present in one of the patients with anomalous pulmonary venous connection, and an islet-cell carcinoma of the pancreas was present in the other patient with this malformation. Those authors believed that the association of endocrine tumors with congenital cardiac malformations was more than coincidental.

Our observation of pheochromocytoma in five patients with cyanotic congenital cardiac malformations is indeed unusual. This tumor is rare; its reported incidence among autopsies varies from 1:400 to 1:3,000. Barbeau found 626 cases of pheochromocytoma reported up to 1957. Insley and Smallwood were able to collect 62 cases in patients under 14 years of age up to 1961. Only 21 cases of histologically proved pheochromocytoma were found among 31,227 autopsies performed at The Johns Hopkins Hospital from 1901 to 1962, and three of these (cases 1–3) are included in this report. Two of these (cases 2 and 3) represent the youngest instances of pheochromocytoma found at autopsy at this hospital.

The cause of the association between this rare endocrine tumor and cyanotic congenital malformations of the heart is obviously only speculative. Because clinical manifestations of the tumor did not appear until 12 to 41 years after birth, the pheochromocytoma in these instances does not appear to be congenital in origin. Chronic arterial hypoxemia may possibly be a factor in the production of the pheochromocytoma. Asphyxia and anoxia in the experimental animal are known to cause a striking increase in secretion of epinephrine and norepinephrine from the adrenal medulla. This is especially true of norepinephrine production. Check et al. recently found considerably elevated plasma levels of epinephrine and norepinephrine in premature infants with placental insufficiency and post-maturity. These authors related their findings to hypoxia. Propst has suggested a compensatory hyperplastic mechanism as an etiologic factor in the production of a pheochromocytoma, and recently Sherwin noted a histologic relation between adrenal medullary hyperplasia and neoplasia. Bialestock reported hyperplasia of the adrenal medulla in each of two patients who died with severe hypotension and related its occurrence to an increase in function of the adrenal medulla.

Medullary adrenal hyperplasia has also been noted by Bongiovanni et al. to occur in patients with long-standing cystic fibrosis of the pancreas. It is conceivable that persistent hypoxemia could produce adrenal medullary hyperplasia and finally an autonomously functioning medullary tumor (pheochromocytoma). Such a sequence of events would be analogous to that suggested by Albright and Reifenstein in which hypocalcemia was thought to lead to hyperplasia of the parathyroid gland and eventually to parathyroid adenoma.

Three of the five patients in this study had clinically functional pheochromocytomas (cases 2, 4, and 5). In each of these patients the tumor was diagnosed during life; in two of the three patients the tumor was successfully removed. The sign that initially led to the consideration of a pheochromocytoma was systemic hypertension. Although systemic hypertension occurs not infrequently in severely
### Table 1

**Summary of Five Cases with Pheochromocytoma**

<table>
<thead>
<tr>
<th>Patient age, race, and sex</th>
<th>Cardiac malformation</th>
<th>Signs and symptoms of pheochromocytoma</th>
<th>Highest blood pressure mm Hg</th>
<th>Highest hematocrit value, %</th>
<th>O$_2$ Sat., %</th>
<th>Diagnostic studies for pheochromocytoma</th>
<th>Diagnosis of pheochromocytoma confirmed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. R. D. 26 years WM</td>
<td>Tetralogy of Fallot</td>
<td>Hypotensive episode at time of Blalock-Taussig operation</td>
<td>142/90</td>
<td>74</td>
<td>85*</td>
<td>None</td>
<td>Autopsy</td>
</tr>
<tr>
<td>2. E. H. 14 years CF</td>
<td>Transposition of great vessels</td>
<td>Sweating, nervousness, anorexia, headaches, tachycardia, insomnia</td>
<td>150/110</td>
<td>70</td>
<td>77</td>
<td>Positive Regitine and benzodioxane</td>
<td>Autopsy</td>
</tr>
<tr>
<td>3. R. J. 16 years WM</td>
<td>Transposition of great vessels; both vessels from RV; dextrocardia; AV communis</td>
<td>None</td>
<td>110/70</td>
<td>61</td>
<td>43</td>
<td>None</td>
<td>Autopsy</td>
</tr>
<tr>
<td>4. A. O. 44 years WM</td>
<td>Ebstein's anomaly</td>
<td>Arrhythmias, palpitation, sweating, dizziness, paresthesias</td>
<td>240/150</td>
<td>66</td>
<td>90</td>
<td>Positive Regitine, norepinephrine (urine)—1390 μg, 3900 μg.</td>
<td>Surgery</td>
</tr>
<tr>
<td>5. J. E. 19 years WM</td>
<td>Tetralogy of Fallot</td>
<td>Nervousness, headaches, heat intolerance, sweating, insomnìa, epistaxis, polydipsia</td>
<td>200/150</td>
<td>83</td>
<td>80</td>
<td>Positive Regitine and benzodioxane, norepinephrine (urine)—876 μg, epinephrine (urine)—25 μg.</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

* Highest saturation at rest; lower saturation following activity.
cyanotic patients, excessive sweating and nervousness are uncommon. These findings in addition to periodic headaches, paroxysmal arrhythmias, hyperglycemia, and glucosuria offer helpful clues to the clinical recognition of a pheochromocytoma. Indeed some of these symptoms or signs were present in each of the three patients in whom the diagnosis was made clinically (table 1).

The recognition of the presence of a pheochromocytoma in these patients prior to cardiac catheterization or other operation is important in view of the occasional occurrence of sudden death in patients with pheochromocytoma during surgical procedures or during the induction of anesthesia. Although none of the five present patients manifested any difficulty attributable to the pheochromocytoma at the time of cardiac catheterization or angiography, the severe hypotensive episode during operation and the early postoperative death in one patient (case 1) may have been directly related to the associated pheochromocytoma.

Summary

The clinical and pathologic features of five patients with pheochromocytoma associated with congenital cyanotic cardiac malformations have been described. This association appears to be more than mere coincidence. Chronic hypoxemia may be a significant factor in the development of this rare endocrine tumor in such patients. The finding of systemic hypertension combined with episodes of nervousness and sweating or repeated severe headaches initially aroused suspicion of a pheochromocytoma in the three patients in which this tumor was diagnosed clinically.

Acknowledgment

The authors gratefully acknowledge the help and advice of Dr. Helen B. Taussig and Dr. Richard S. Ross in the preparation of this manuscript. We are also indebted to Dr. J. G. Wiswell for the determination of the urinary epinephrine and norepinephrine levels in case 5.

References

17. Albright, F., and Reifenstein, E. C.: The Parathyroid Glands and Metabolic Bone Dis-

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William Withering and the Foxglove

Inferences

"To prevent any improper influence, which the above recitals of the efficacy of the medicine, aided by the novelty of the subject, may have upon the minds of the younger part of my readers, in raising their expectations to too high a pitch, I beg leave to deduce a few inferences, which I apprehend the facts will fairly support.

"I. That the Digitalis will not universally act as a diuretic.

"II. That it does do so more generally than any other medicine.

"III. That it will often produce this effect after every other probable method has been fruitlessly tried.

"IV. That if this fails, there is but little chance of any other medicine succeeding.

"V. That in proper doses, and under the management now pointed out, it is mild in its operation, and gives less disturbance to the system, than squill, or almost any other active medicine.

"VI. That when dropsy is attended by palsy, unsound viscera, great debility, or other complication of disease, neither the Digitalis, nor any other diuretic can do more than obtain a truce to the urgency of the symptoms; unless by gaining time, it may afford opportunity for other medicines to combat and subdue the original disease.

"VII. That the Digitalis may be used with advantage in every species of dropsy, except the encysted.

"VIII. That it may be made subservient to the cure of diseases, unconnected with dropsy.

"IX. That it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends."—Louis H. Roddis, M.D. William Withering: The Introduction of Digitalis Into Medical Practice. New York, Paul B. Hoeber, Inc., 1936 p. 76.
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