BILATERAL PHAEOCHROMOCYTOMA IN A 6-YEAR-OLD BOY

BY

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Chromaffin cell tumours are rare in children. We have been able to find only nine cases recorded in the literature under the age of 13 years, the youngest being an infant of 18 months. Snyder and Vick (1947) review the four cases previously reported and add a further three of their own. Goldenberg, Snyder and Aranow (1947) also discuss two of these children and include an eighth case. In eight cases operative removal was attempted, and was followed in four children by complete clinical recovery. One of these successes, described by Grimson, Longino, Kernodle and O'Rear (1949), was attributed, in part to the use of adrenolytic drugs. Of the remainder, three died from post-operative collapse and one from congestive cardiac failure six weeks later; a second tumour was found at necropsy in the latter case (Linneweh, 1942). More than one tumour was present in three of these nine cases.

We are presenting this case, which was fatal, partly on account of its rarity and partly to draw attention to the problems of differentiation from pink disease (or juvenile acrodynia), problems which are, we feel, of significance not only in this case, but also in relation to the possible aetiology of pink disease.

Case Report

P.S., a boy aged 6 years, was admitted on August 11, 1948, under the care of Dr. N. M. Jacoby. For six weeks before admission he had suffered from persistent lethargy and night sweats. A single attack of vomiting occurred at the onset of his illness. His previous health had been good except for measles and whooping cough. His mother, father and sister, aged 3½ years, were all healthy.

On admission he was a thin, anxious-looking child with a sallow complexion, and weighed 38 lb. His worried expression was emphasized by widened palpebral fissures and slight exophthalmos (Fig. 1). Both hands were cold and sweating, bluish-pink, and with a very marked capillary pattern; the skin and subcutaneous tissues were thickened and showed a firm, non-pitting oedema. These changes extended about 1½ in. above the wrists. When warm, the hands became dusky pink and their appearance was indistinguishable from that seen in acrodynia. At the time of admission the mother

stated that these changes had been present since infancy, but later said that they had become more marked recently. The feet were possibly slightly pinker than normal but the changes were never convincing. The child sometimes rubbed his hands and feet, but there were no parasthesiae and despite their abnormal appearance he never complained of pain or irritation in the extremities.

There was a tachycardia of 120. Marked arterial pulsation was present in the neck; all the peripheral pulses were slapping in character. The blood pressure in the arms was 190/130 mm. Hg. A later reading of 150/130 mm. Hg in the arms was obtained, the systolic pressure in the legs being 145 mm. on that occasion. The heart was not clinically enlarged; the heart sounds were loud and forceful, and no murmurs were heard.

The abdomen was full. The liver edge was palpable two fingerbreadths below the costal margin. No other masses were felt.

There was marked hypotonia, but all reflexes were preserved throughout the course of the disease and there were no sensory changes. The ocular fundi showed arterial narrowing, but no haemorrhages or exudates were present.

Laboratory Investigations. A blood count gave: Hb. 84%; R.B.C. 5,230,000; W.B.C. 20,000 (polymorphs 55%, stabs 5%, lymphocytes 40%). The basal sedimentation rate was 40 mm. in an hour (Westergren).

The tuberculin jelly test was negative, as also was the Wassermann reaction.

Repeated examinations of the urine showed a moderate degree of albuminuria but no other abnormality. The blood urea was 22 mg. 100 ml., the urea clearance normal. An Addis count on a 12-hour specimen gave: total volume 460 ml., R.B.C. 184,000; no pus cells or casts; serum sodium level 297 mg./100 ml.; serum potassium level 25.3

FIG. 1.—P.S., aged 6 years. The typical anxious expression with some exophthalmos is shown. The pupils are dilated with atropine.

mg./100 ml. and serum chlorides 630 mg./100 ml.; serum cholesterol level 213 mg./100 ml. Repeated serum potassium estimations gave 22.7 mg./100 ml.

A radiograph of the chest showed a heart that was slightly enlarged with a suggestion of left ventricular hypertrophy. A radiograph of the long bones was normal. The skull showed no abnormality in the region of the pituitary fossa (Dr. C. H. Hodson).

An E.C.G. showed that the standard limb leads and one chest lead were normal.

While in hospital the patient retained his apprehensive expression, although he was quite cooperative and apparently fairly happy in his relations with other children and the ward staff.

He was subject to frequent attacks of profuse sweating, usually during the night. No precipitating factors were discovered, but the child was sometimes aware that an attack was imminent. He became very pale and quiet and complained of severe headache and occasionally of nausea. This was followed after an interval of 20 to 30 minutes by profuse, drenching perspiration. During attacks his blood pressure, which varied from 150/130 to 180/150, was raised to 240/156. A tachycardia of 120-140 was present at all times; there appeared to be an inconstant increase in rate during attacks, when the pulse became thready and difficult to feel. During a paroxysm multiple extrasystoles were present: it is probable that the recorded radial pulse rate was deficient.

While under observation he was very constipated. He was afebrile but continued to show a slight leucocytosis and a raised sedimentation rate of 30-40 mm. in one hour. The pinkness of the hands became more pronounced, and he developed a generalized sudaminous rash associated with marked desquamation of the hands and slight desquamation of the feet. He was seen at this time by many paediatricians who considered that he showed the classical features of pink disease.

The differential diagnosis at this stage was considered to lie between pink disease, a phaeochromocytoma and periarteritis nodosa. The sweating, rash, tachycardia, persistent hypertension and increased nervous tension, in association with the marked erythromelalgia of the hands, suggested pink disease, whereas the paroxysmal hypertensive attacks favoured a phaeochromocytoma.

Diagnostic Tests. In an attempt to confirm or disprove the presence of a phaeochromocytoma, the following further investigations were performed. Repeated attempts to induce hypertensive paroxysms by pressure in the renal angles failed. Estimation of B.M.R. (Dr. Clarke, Royal Free Hospital) gave +145%, an unsatisfactory test as the child was sweating profusely throughout. Sodium amytal, grain $\frac{1}{2}$, for three doses was given, but blood pressure was not depressed and during the third hour he developed a typical paroxysm.

The benzodioxane test (933F Fourneau) with piperidylmethyl benzodioxane was applied. The technique described by Goldenberg *et al.* (1947) was adopted. An intravenous saline drip was set up and an attempt made to stabilize the patient's blood pressure. After two hours, however, it was still 200/170, i.e. raised 10-15 mm. above the resting level. Benzodioxane,

7 mg. (933F Fourneau) was injected with an intravenous needle, but as the child screamed at the sight of the syringe the injection was given more rapidly than advocated by Goldenberg in order to minimize a psychological pressor response. A transient fall to 170 mm. systolic (i.e. lower than for four weeks previously) was obtained, but not a sustained fall such as reported by Goldenberg in his cases. This may perhaps be ascribed to the rapidity of the injection and the failure to stabilize the blood pressure at his resting level beforehand, or to excessive secretion by the tumour at this time.

Goldenberg (Goldenberg and Aranow, 1950) comments that 'standard doses of benzodioxane may be inadequate to combat the effects of such large outpourings of amines as may occur in some paroxysms of hypertension'. In retrospect there is no doubt that this test should have been repeated (Fig. 2a).

A control injection in an infant with pink disease was carried out. The reaction followed the pattern described by Goldenberg for cases of hypertension of miscellaneous origin. The technique in this case was satisfactory (Fig. 2b).

Fig. 2a.—Blood pressure recordings after injection of 933F on P.S. A transient fall only is recorded.

Fig. 2b.—Blood pressure recordings after injection of 933F on a case of pink disease with hypertension. A rise in systolic pressure is shown.

A radiograph of the abdomen and an intravenous pyelogram (Dr. C. H. Hodson) were made. Throughout this child's film series there were two small groups of persistent opacities. One lay in the region of the right twelfth rib about 3 in. from the middle line and the other at a rather lower level on the left about 2½ in. from the midline. Beyond saying that they could lie in relationship to the upper renal poles, there was nothing particular about their nature or situation.

When intravenous pyelography was carried out the pelvicalycine patterns were found to be normal and the renal outlines also appeared normal, except perhaps for a slight blunting of the upper pole of the right kidney, which could have been due to the liver. The opacities were now seen to overlie both upper poles of the kidney being slightly lower on the left side than on the right. This indefinite type of shadowing is commonly found in pheochromocytoma.

Perirenal insufflation was carried out by Mr. Swain; 260 ml. air were injected into the right perirenal space. A temporary respiratory arrest occurred, and although recovery was satisfactory, no attempt was made to insufflate the left side. The lower pole of the right kidney only was outlined.

The histamine test meal was omitted owing to the risk involved, as the naturally occurring paroxysms were very severe.

Reviewing the case at this stage it was decided that evidence in favour of the diagnosis of a pheochromocytoma was suggestive, but not strong enough to warrant exploratory laparotomy.

After four months the clinical condition was unchanged, except for the development of left ventricular hypertrophy and a loss of 2 lb. in weight. The sweating attacks were apparently less frequent, but the hypertension persisted in the range of 185/205/140.

The parents were against the performance of an exploratory laparotomy and, as no other active treatment was advised, removed him from hospital.

After three months at home, he showed little change in his condition. The hypertension persisted. The parents eventually agreed to further investigation and he was readmitted on April 27, 1949, approximately 10 months after the original onset of symptoms. He then weighed (26 lb.) and his blood pressure was 185/120 mm. Hg. No masses could be felt in the renal angles although the extreme constipation made abdominal palpation difficult.

A minute volume test to assess renal function was planned. The patient was anaesthetized satisfactorily but collapsed when urethral dilators were passed and failed to respond to resuscitation.

Necropsy. Dr. C. K. Simpson performed the necropsy. Some chronic oedema of the hands was present but there was no 'acrocyanosis' and no subungual or other petechiae.

ADRENAL GLANDS. The position of the left adrenal gland was occupied by a well-circumscribed, smooth, ovoid, yellowish-brown tumour which measured $6 \times 5 \times 4$ cm. (Fig. 3). Projecting from its upper pole were five small nodules, the largest of which was 2.0 cm. in diameter. The tumour extended downwards over the

antero-medial aspect of the kidney which, although distorted by the presence of the mass, showed no evidence of infiltration. On the cut surface the centre was brown and homogeneous whilst the more superficial part was of a softer consistency and more yellowish. A thin layer of connective tissue covered the tumour, separating it from the retroperitoneal tissue. Attached to its upper and lateral aspect were the remains of the adrenal gland, represented by a triangular piece of apparently normal adrenal cortex measuring $3.0 \times 2.5 \times 1.5$ cm., giving the impression that the tumour had arisen in the medulla and ultimately broken through the cortex.

The right adrenal gland showed a tumour measuring $3.0 \times 2.5 \times 1.5$ cm. occupying the position of the medulla and extending medially and downwards towards the hilum of the kidney. Its cut surface had a similar appearance to that of the left tumour, although there was distinct lobulation. The adrenal cortex was present in normal amount and was stretched over the greater part of the tumour. Unfortunately no biochemical assays of the tumour were made.

HEART. The heart weighed 298 g. (normal 100 g.). The left ventricle showed concentric hypertrophy and a moderate degree of dilatation. Its wall was 1.2-2.0 cm. thick. The right ventricle was slightly dilated and its wall was 0.3-0.6 cm. thick. Several small yellow patches were present on the anterior cusp of the mitral valve and definite atheroma surrounded the orifices of the right coronary artery and all the posterior intercostal arteries. The coronary arteries were normal.

The liver (1,106 g.) was pale with distinct fatty change at the periphery of the lobules. The hilar and mediastinal lymph nodes were moderately enlarged. All other organs were normal.

FIG. 3.—The left adrenal gland showing replacement by pheochromocytoma.

The cause of death was vagal inhibition during the passage of urethral dilators.

MICROSCOPY. Dr. N. France examined tissue from the tumours fixed in Zenker-formalin solution for 24

FIG. 4.—Section of tumour ($\times 59$) showing general arrangement of cells in groups.

hours followed by immersion in 2.5% potassium dichromate for seven days. Beneath a well-defined fibrous capsule occasional cells resembling those of adrenal cortex were present and these merged with the tumour itself. The tumour consisted of cells varying in size and shape, frequently with ill-defined margins. They were arranged in groups separated by loose connective tissue containing small capillaries (Fig. 4). The cells possessed round or oval, vesicular nuclei with prominent nucleoli and faintly eosinophilic cytoplasm. They were occasionally multinucleated and sometimes vacuolated (Fig. 5). Some cells contained chromaffin granules but the majority showed no reaction. Mitotic figures were scanty. The centre of the tumour was occupied by collagenous fibrous tissue in which were scattered isolated cells showing marked chromaffin staining. Despite the variation in the cells and the presence of occasional giant cells, the tumour was considered to be benign.

The muscular coats of many of the smaller arteries in the kidney were hypertrophied, and some showed fibrinoid degeneration of the intima in the absence of duplication of the internal elastic lamina. There was no evidence of glomerular damage, malignant hypertension or scar formation. Arterial changes were even

FIG. 5.—Section of the tumour. $\times 230$.

more marked in the spleen where fibrinoid degeneration was a prominent feature. The aorta showed great thickening of the intima with fatty change characteristic of established atheroma. There was considerable fatty change of the liver affecting the greater part of the lobule with moderate congestion of the central zone. All other organs of the brain were normal. No histological examination of the central nervous system was made.

Discussion

Our patient closely resembled in facial appearance and in his simulation of acrodynia the case reported by Snyder and Vick (1947) of a phaeochromocytoma in an 11-year-old boy. Vascular disturbances affecting the extremities have been noted by several authors in adults with phaeochromocytoma. Pallor and mottled cyanosis during attacks followed by flushing during the recovery phase has been described by Calkins and Howard (1947), by Ferraro and Angle (1948) and by Spalding (1947). The hands of these patients were apparently normal between the hypertensive crises, and all were subject to typical paroxysms of hypertension. Smithwick, Greer, Robertson and Wilkins (1950) stress the importance of peripheral vascular phenomena, which were present in nine out of 10 of their cases, in the differential diagnosis of phaeochromocytoma and essential hypertension. McCullagh and Engel (1942) describe a 19-year-old girl who had a persistent, glove-like distribution of erythema. It is probable that the recurrent severe anoxaemia caused by the intense arteriolar constriction caused temporary exudation of plasma into the subcutaneous tissues, producing chronic oedema in our case. Peripheral vascular changes, sometimes of a severity comparable with those seen in acrodynia, are therefore not uncommon in cases of biologically active phaeochromocytoma. The variation in the degree of peripheral vascular changes seen is possibly due to the fact that phaeochromocytoma may secrete predominately adrenaline or *nor*-adrenaline, or both, the latter having a more powerful and generalized peripheral vaso-constrictor action (von Euler, 1951).

The only other case we have found presenting a similar clinical picture was that of Anderson (1944) of acrodynia in a 9-year-old boy; this child had gross hypertension, with paroxysmal exacerbations associated with sweating. He was about to have a laparotomy performed when he suddenly developed pinkness of the extremities and a diagnosis of acrodynia was made. He recovered completely 16 months from the onset of symptoms.

Differential Diagnosis from Acrodynia. The skin changes, sweating, tachycardia and hypertension were all similar to those found in acrodynia.

Paroxysmal hypertension has not been recorded in this disease (except in Anderson's case quoted above), but this may be because the blood pressure has not been taken during sweating attacks. On studying the literature one is impressed by the very occasional blood pressure recordings actually given, possibly because the technical difficulties involved are considerable. It should be noted, however, that the absence of paroxysmal hypertension does not exclude a diagnosis of phaeochromocytoma. This point is stressed by Green (1946) in his review of the subject. Of the nine cases in the paediatric age group only four had typical attacks of paroxysmal hypertension while under observation, the remainder having sustained hypertension.

Also our child's personality did not show the typical changes of acrodynia: profound misery and irritability in infancy, and almost psychiatric changes in older children and adults. The other atypical feature was the child's age: the age limits are almost invariably between 6 months and 4 years. Wyllie and Stern (1931) mention but do not describe a case with symptoms starting at 3 weeks of age. Cases in children over 4 years are mentioned but no clinical details given by Warkany and Hubbard (1948), Blackfan and McKhann (1933) and Zahorsky (1922). A syndrome resembling pink disease has been described in adults by White (1926), and otherwise exclusively in the French literature of the Lyons school. White's cases are extremely doubtful, and the localization of all the reported cases to one area makes it probable that there is some local factor involved producing this particular clinical picture. References to some of these cases are quoted by Griffiths (1950). Similarly, an acrodynia-like syndrome can be produced experimentally in rats by a diet deficient in essential fatty acids (Kummerow, Chu and Randolph, 1948) and in man by chronic arsenical poisoning (Petren, 1921). But we have been able to find only two cases starting later than 4 years of age which appear to be clinically identical with infantile acrodynia (Anderson, 1944; Mouriquand, Dechaume, Bernheim and Weill, 1935), and therefore now feel that such a diagnosis should be made with the greatest caution, if at all.

The literature on acrodynia is marked by a paucity of clinical facts and a plethora of theories. In view of the striking simulation of acrodynia by our case we should like to draw attention to the theory, originally postulated by Kühl (1927), that the disease is due to hyperfunction of the adrenal medulla associated with hypofunction of the adrenal

cortex, and that the sharply demarcated age limits are due to its being an exaggeration of the normal physiological post-natal changes in the cortico-medullary interrelationships.

Many of the other aetiological theories are discussed by Cheek (1950), who stresses the importance of adrenocortical insufficiency in acrodynia, and by Leys (1950), who describes the disease as a diencephalopathy. We can only suggest that it may be of interest in future cases of acrodynia to look for evidence of adrenal medullary hyperactivity first by seeing if the characteristic sweating attacks are associated with hypertensive paroxysms (the use of a sphygmo-oscillometer should make this simpler than it has been in the past), and secondly perhaps by physiological experiments using the patient's serum, as suggested by Kühl (1927), or by urinary assay (von Euler, 1950), and thirdly by the use of the benzodioxane test.

Summary

A case is reported of a bilateral phaeochromocytoma in a 6-year-old boy who showed peripheral vascular changes and hypertension.

The differential diagnosis from acrodynia is discussed.

Early laparotomy in any similar future case is recommended in view of the diagnostic difficulties.

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