Bilateral adrenal medullary hyperplasia: A clinicopathological entity

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SYNOPSIS A 36-year-old white patient is described. He received treatment for hypertension and showed slightly increased excretion of 17-OHCS- and 17-ketosteroids but no increase in values for 3-methoxy-4-hydroxymandelic acid in the urine. He was admitted to hospital for a myocardial infarction, which was found to be situated in the anterior wall. During his stay in hospital a sudden increase in blood pressure occurred, together with a typical attack of perspiration, loss of consciousness, and ventricular fibrillation. The assay by 3-methoxy-4-hydroxymandelic acid now showed markedly increased amounts. A phaeochromocytoma was thought to be the most probable diagnosis, but notwithstanding therapy the patient died from cerebral lesions.

At necropsy a recent antero-septal myocardial infarction and some minor lesions were found but no tumour and notably no phaeochromocytoma, neither in the adrenals nor elsewhere. Using Dobbie's morphometric technique, as described by Munro Neville (1969), changes in the adrenals were demonstrated, which were considered to represent primary adrenal medullary hyperplasia. Criteria for the diagnosis of this syndrome are discussed. Until now it had been presumed to be present in a number of cases but never convincingly demonstrated.

Hyperfunction of endocrine glands is generally associated with either hyperplasia or neoplasia of the involved gland. Cushing's syndrome can be caused either by an adenoma or by hyperplasia of the adrenal cortex (Symington, 1969). Similarly, the question has arisen as to whether adrenal medullary hyperplasia might bring about the same symptoms as a phaeochromocytoma.

Most pathologists as well as clinicians must have dealt with the frustrating situation where a phaeochromocytoma was diagnosed clinically and endocrinologically, as well as pharmacologically, in a patient but no tumour was subsequently found at operation or at necropsy.

Attempts at proving the existence of bilateral adrenal medullary hyperplasia as a clinicopathological entity have appeared since 1933. In this article criteria for diagnosis are discussed and a case fulfilling these criteria is presented.

Case Report

A 36-year-old carpenter, who had been in good health, suffered an attack of severe abdominal

pain. The patient's mother was hypertensive, but was alive at the time aged 58 years. His father, aged 61 years, had suffered a myocardial infarction.

In December 1971 the consultant physician found hypertension, for which Aldomet therapy was instituted. Intravenous pyelography showed no lesion. In the following weeks the patient suffered from orthostatic complaints and in March 1972 he was referred to a medical outpatient department. Blood pressure then measured 200/110 mm Hg while seated, and the pulse rate of 80 per minute was regular. On physical examination the heart did not seem to be enlarged, the heart sounds were loud, and no murmurs were heard. Laboratory investigations of urine and renal function were normal, the blood showing a slightly increased cholesterol value of 323 mg/100 ml. Slightly increased 17-OHCS and 17-ketosteroids were found in the urine. The 3-methoxy-4-hydroxymandelic acid values were within normal limits. Renography showed minimally retarded excretion by the left kidney. Electrocardiograms and radiographs of the thorax showed no lesion. During one of his visits to the outpatient department the patient started complaining of retrosternal pains, which worsened and for which admission to hospital

seemed to be necessary in the near future. On 2 July 1972 he suffered at home from a severe attack of retrosternal pain, which radiated to the left arm and back, and during which he perspired profusely and became short of breath. He was immediately admitted to hospital with a diagnosis of myocardial infarction.

On investigation, a white male, still suffering from pain, was seen. The blood pressure was 180/140 mm Hg, with a regular, symmetrical pulse rate of 68 per minute. The central venous pressure was R -2. On fundoscopy, crossings and contracted arteries were seen. The heart was not enlarged on percussion and the heart sounds were not heard. There were no murmurs, but crepitating rhonchi were heard over the lungs on both sides of the back. Electrocardiographs showed signs of a large anterior wall infarction with a lateral extension, together with ventricular extrasystoles of approximately 30 per minute.

Apart from sedatives, the patient was treated with anticoagulants and an infusion of lidocaine.

The blood pressure gradually dropped and became stable at 110/90 mm Hg during the following hours. The general condition improved during the following days, but after nine days in hospital the patient suddenly suffered from an attack of perspiration and became comatose. Electrocardiography showed ventricular fibrillation, which disappeared after lignocaine therapy. Five days later the same kind of attack recurred in spite of lidocaine therapy. On the same day defibrillation was necessary 13 times and eventually normal sinus rhythm was reinstituted by means of an internal pacemaker. The patient appeared to be in deep coma and had to be connected to a respirator. The following week he became subcomatose. An electroencephalogram recorded on 28 July showed signs of a markedly diffuse derangement of the cerebral cortex. Nevertheless consciousness returned partially and on 2 August his condition improved to such an extent that he could be allowed out of bed to sit in a chair. At first this seemed successful, but after a few minutes he became comatose again, perspiring profusely, while the blood pressure showed a value of 220/160 mm Hg.

Taking into account that the blood pressure had remained about 110/80 mm Hg during the whole period of bed rest but after mobilization this rate of increase was found, together with coma and profuse perspiration, a diagnosis of phaeochromocytoma was considered.

Immediately after admission to hospital the value for 3-methoxy-4-hydroxymandelic acid in the urine was slightly increased (9.85 mg/24h; normal value 1-7 mg/24h). Immediately after the attack that

value was extremely high, 22 mg/24h. After some days normal values were again obtained, but a week later increased amounts were found. The coma subsided gradually, but the patient was now aphasic. Based upon the neurological signs brain-stem and cortical lesions were diagnosed. A urinary infection developed as a result of a prostatic abscess.

On electrocardiographic readings sinus-like ST-elevations were visible in V1-V4 recordings, suggestive of an aneurysm of the heart. Occasionally he showed a tendency for periods of ventricular tachycardia or ventricular fibrillation.

In view of the cerebral lesions further investigation was abandoned. On 26 September 1972 the patient died of ventricular fibrillation.

The final clinical diagnosis was myocardial infarction with an aneurysm of the heart, brain-stem, and cerebral cortical lesions following hypoxia, and phaeochromocytoma.

Results of the Necropsy

The following lesions and abnormalities were found: (a) myocardial infarction, anteroseptally, dating from about three months before death, with aneurysmal dilatation of the anterior left wall of the heart, containing a large parietal thrombus; (b) thrombosis of the interventricular branch of the left coronary artery; (c) cardiomegaly (weight 470 g); (d) extreme aortic sclerosis, not commensurate with the age of the patient, with thromboembolic blocking of the bifurcation and iliac arteries; (e) slight arteriosclerotic changes in the kidneys with a small infarction on the right side in the upper pole, dating from approximately the time of the myocardial infarction.

The spleen was enlarged (240 g), there was focal oedema in both lungs, acute prostatitis caused by catheterization, and friable bladder stones.

Both adrenals were enlarged, but they showed no tumour (left 9.5 g, right, 8.0 g). No phaeochromocytoma was found either in the thorax, the abdominal aorta, in the bladder wall, or in the testes. Unfortunately necropsy of the brain was not performed, so the cerebral lesions could not be evaluated. Cerebral hypoxia might have been responsible for the cerebral lesions during life.

Morphometrical Measurements

The adrenals were removed and weighed, after removing as much of the perirenal fat as possible without damaging the gland. Both glands were then divided into blocks (3-4 mm thick) which were numbered from 1 to 11 and fixed in 10% neutral formalin. A single paraffin section was cut from the

face of each block and stained with haematoxylin and eosin. In this way 22 (2×11) slides were obtained of the left and right adrenal.

Using a Reichert Visopan microscope with a magnification of 40 times, the 22 slides were screened by means of a 100-point screen for medulla compared with cortex with residual fat, the adrenal capsule, and with blood vessels in the medulla with their muscular walls and fibro-collagenous tissue. The net weight of medullary tissue in each adrenal was calculated by dividing the number of scored points, measured as medulla, by the total number of scored points and multiplying

this ratio by the adrenal weight: $M = \frac{P_m}{P_t} \cdot W \dots (1)$

The net weight of cortical tissue in each adrenal can be calculated by dividing the number of scored points, measured as cortex, by the total number of scored points and multiplying this ratio by the

adrenal weight: $C = \frac{P_c}{P_t} \cdot W \dots (2)$

The net weight of the other constituents is calculated by dividing the number of scored points, measured as such, by the total number of scored points, multiplying this ratio by the adrenal weight:

$R = \frac{P_r}{P_t} \cdot W \dots (3)$. It is clear that $P_t = P_c + P_m + P_r$.

The medullary/cortical ratio (M/C) was calculated by dividing the number of points scored as medulla

by points measured as cortex: $M/C = \frac{P_m}{P_c} \dots (4)$.

Taking into account that the mean adrenal weight varies with age, amount of stress, etc, we have accepted Symington's (1969) value for the post-mortem mean weight of a single adrenal as 6 to 6.5 g (Wm). In our institute we found a mean adrenal weight of 12.5 g (both adrenals) in 100 consecutive adrenals (Meyer and de Zwart, 1969) to be in the range 20-47 years. Quinan and Berger (1933) calculated the medullary/cortical ratio (M/C, 4) and found it to be 1:10, or 0.10. Swinyard (1940) found a ratio of 1:12.4 or 0.08 in white males. Dobbie (1968) calculated the same and found 1:5 or 0.20 in the head region, 1:8 to 1:18 (0.13 to 0.06) in the body, while the medulla disappears in the tail region. The mean ratio then amounts to 1:11.5 or 0.09. Dobbie published a case report of suspected adrenal hyperplasia, but found a normal ratio. The amount of nonmedullary/noncortical tissue, R (3), is not known but we found it to be 26.1 to 27.6% (mean 26.8%) by our calculations. We have

accepted Wm as 12.9 g, $\frac{M}{C} =$ as 0.09 (4), and R as 26.8% (3).

Results

The adrenals were sectioned and treated as described. Two facts became evident on studying the 22 slides. (1) the tails of both adrenals contained medullary tissue, which normally is never found there (fig 1); (2) in the body of the adrenals both alae contained medullary tissue; normally only one ala contains medullary tissue (fig 2); (3) histologically definite pleomorphism of the pheochromocytes was notable with the occurrence of giant cells with pale nuclei and vacuolated cytoplasm (fig 3). Munro Neville (personal communication, 1973) considers findings 1 and 2 conclusive for the lesion described; finding no. 3 merits closer evaluation, but has been described by other authors (Bialestock, 1961; Montalbano, Baronofsky, and Hall, 1962; Sherwin, 1964).

Also the amounts of medullary and cortical

Fig 1 Left adrenal (tail): (L 10): medullary hyperplasia. Note medullary tissue present.

Fig 2

Fig 2 Right adrenal: medullary hyperplasia. Note medullary tissue extending into both alae and ridge (body: R 7).

Fig 3

Fig 3 Right adrenal, body (528x): medullary hyperplasia. Phaeochromocytoma cells show pleomorphism with giant forms. Vacuolated cytoplasm is also seen.

Section	Cortex and Medulla				
	P _c	P _m	P _r	P _t	M/C
L ₁	487	127	211	825	0.26
L ₂	630	128	299	1057	0.20
L ₃	919	142	453	1514	0.16
L ₄	742	196	446	1384	0.27
L ₅	853	138	392	1383	0.16
L ₆	824	82	205	1211	0.10
L ₇	725	85	308	1118	0.12
L ₈	774	89	340	1203	0.12
L ₉	681	34	193	908	0.05
L ₁₀	681	49	255	985	0.07
L ₁₁	603	14	239	856	0.02
	7919	1084	3441	12444	0.14

Table I Results for the cross-sectional areas of cortex and medulla as measured from sections taken at 3 mm intervals throughout the left adrenal

See Methods: M = 0.83 g (8.8%), C = 6.04 g (63.6%), R = 2.63 g (27.6%), T = 9.50 g (100%).

Section	Area of Cortex and Medulla				
	P _c	P _m	P _r	P _t	M/C
R ₁	334	19	57	410	0.06
R ₂	375	23	57	455	0.06
R ₃	589	119	297	1005	0.20
R ₄	707	163	333	1203	0.23
R ₅	875	210	441	1526	0.24
R ₆	817	194	388	1399	0.26
R ₇	924	243	373	1540	0.26
R ₈	962	153	359	1474	0.16
R ₉	940	82	335	1357	0.09
R ₁₀	574	67	223	864	0.12
R ₁₁	356	22	190	468	0.09
	7353	1295	3053	11701	0.17

Table II Results for cross-sectional areas of cortex and medulla, as measured from sections taken at 3 mm intervals in right adrenal gland

See Methods: M = 0.89 g (11.1%), C = 5.03 g (62.8%), R = 2.08 g (26.1%), T = 8.00 g (100%).

Fig 4 Histograms of case discussed compared with those of normal adrenal. Superimposed on each other are the graphs of the distribution of cortical tissue (above the horizontal line) versus the extent of medullary tissue (below the horizontal line) of the adrenal in the case discussed (thick black tracings) and a normal adrenal (thin black tracings). Oblique hatching indicates the surplus of cortical tissue, solid black the surplus of medullary tissue. Note extension of medullary tissue into the tail in the case discussed. Also note displacement of medullary tissue towards body and tail in the right adrenal. Sections 1-3/4, head; 3/4-8/9, body; 8/9-11, tail.

tissue were measured by planigraphy as well as the medullary/cortical ratio. The results are shown in tables I and II and figure 4. The calculated medullary/

cortical ratio, $\frac{M}{C}$ (4), was to 0.14 or 1:7 for the left

adrenal and 0.17 or 1:6 for the right adrenal (normal 0.09 or 1:11.5 for both adrenals). Marked disturbances were found.

The amount of medulla in a normal adrenal was then calculated, ie, $M(1)$. $M:0.09$. (12.5 minus 26.8% of 12.5) and weighed 0.82 g. In our case we found 0.83 (left) plus 0.89 (right ie, 1.72 g, which is about twice the amount normally found, correlating with

the increased amount of VMA in the urine during life.

Discussion

The earliest examples of so-called hyperplasia are not convincing (Rowntree and Ball, 1933; Schwab and Denninger, 1952). Drückker, Formijne, and van der Schoot (1957) described a patient with symptoms suggestive of pheochromocytoma. Pharmacological and biochemical tests were negative yet the symptoms and signs did not abate until both adrenals were removed. Their histological illustration shows what appears to be a normal

medulla taken from the body of the adrenal gland. Sherwin (1964), in a review of phaeochromocytoma, reclassified three of his cases as hyperplasia. He noted the presence of cellular pleomorphism which he believes is a significant feature for its diagnosis, and it was apparent also in other cases (Bialestock, 1961). However, the large vacuolated cells with a faintly eosinophilic cytoplasm described in so-called medullary hyperplasia (Bialestock, 1961) can be seen in apparently normal glands. The significance of the cellular pleomorphism with giant forms merits closer consideration and evaluation.

Perhaps the most convincing example on clinical and postoperative grounds is that reported by Montalbano, Baronofsky, and Ball (1962). The signs and symptoms disappeared following removal of the left adrenal gland and a biopsy of the right. The latter was normal in appearance whereas the former weighed 8 g and was said to be hyperplastic when compared with the contralateral gland and with random samples of other glands. Although the authors state that the lesion was diffuse in its distribution, no planimetric studies were undertaken. The illustration shows only medullary tissue in the body of the adrenal gland and, as previously noted, the presence of vacuolated cells cannot be regarded as specific for hyperplasia. Despite these criticisms, the postoperative course and the subsequent return to normal as shown by various investigations on this patient are positive data not easily dismissed. On the other hand, unilateral medullary hyperplasia must be unique and the possibility that the lesion was the beginning of a tumour must be considered. Planimetric measurement which Dobbie (1968) made on a suspected case of hyperplasia of the adrenal medulla gave a normal corticomedullary ratio.

In the case under discussion we had the unique situation that typical attacks suggestive of a phaeochromocytoma were seen in a 36-year-old man, and that during life values in the urine for 3-methoxy-4-hydroxymandelic acid were markedly increased during these attacks. The patient could not be operated upon, because of the myocardial and cerebral lesions, but after his death it was possible to perform a necropsy. We were therefore able to exclude a phaeochromocytoma, either in the adrenals or elsewhere and any other chromaffin tissue in the body. Ectopic adrenal tissue has been described in the brain, but it is most improbable that it concerned medullary tissue, ontogenetically speaking.

The typical attacks which the patient showed during life, combined with the paroxysmal hypertension, indicate the action of epinephrine and/or norepinephrine in concentrations higher

than normal during these attacks. The extreme atherosclerotic changes, in general, as well as in the left coronary artery, might have been caused by the increased levels of catecholamines.

The following pathological criteria must be considered conclusive, we suggest, for the diagnosis of bilateral adrenal medullary hyperplasia: a manifold increase in medullary tissue, calculated by morphometric techniques, in this case plus 100%; the extension of medullary tissue into the tail and the two alae of the adrenals; a possibly disturbed medullary/cortical ratio, but a normal ratio has been found in one case (Dobbie, 1968). In one case abnormal ratios were found so we consider this as conclusive but normal ratios do not exclude medullary hyperplasia; increased adrenal weights are described in nearly all published cases, and as cortical and medullary hyperplasia coincided in the case under discussion increased weights may be expected.

Histological, biochemical, histochemical, and electron-microscopic data should be considered as supplementary evidence only.

Conclusion

In this paper we think we have proved the existence of a pathological lesion which we here called 'bilateral adrenal medullary hyperplasia', which may cause the signs and symptoms of a phaeochromocytoma. Till now no differentiation could be made during life between the two lesions, but when no phaeochromocytoma can be found on surgical exploration, bilateral sections of the tails of the adrenals can show whether medullary hyperplasia exists. If any medullary tissue is found in these sections (which may be frozen sections), the latter diagnosis is definitely established. Adrenals removed on this indication should be examined morphometrically. The incidence of 'bilateral adrenal medullary hyperplasia' is unknown; by analogy to what is known of the cortex, it should be more frequent than phaeochromocytoma, but this is a hypothesis.

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