PRIMARY ALDOSTERONISM DUE TO ADRENOCORTICAL ADENOMA (CONN'S SYNDROME)

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Aldosterone was first discovered by Tait *et al.* in 1952.[1] Two years later Conn[2] presented the first case of an adrenal cortical tumour secreting aldosterone (primary aldosteronism). In 1964[3] he was able to report on 145 recorded cases. Eales and Linder[4] published the first case described in South Africa in 1955.

Conn[5,6] has recently described 5 cases of the syndrome, where serum potassium has been normal, and stresses that low serum potassium is therefore not an essential feature and may only develop relatively late in the course of the condition. He has diagnosed these normo-kalaemic cases by demonstrating suppressed renin activity and has speculated that 20% of the cases of so-called essential hypertension may be due to primary aldosteronism originating in an adrenal cortical tumour, and therefore potentially curable by surgery. However, renin assay is not yet a practical laboratory procedure for routine investigation.

The case that follows has the typical features of hypokalaemic alkalosis. To our knowledge this is the second case due to an adenoma to be published from South Africa. The patient presented with recent onset of hypertension in pregnancy, simulating pre-eclamptic toxaemia. Hypertension persisted postpartum and she developed periodic paralysis and tetany. There was complete clinical and biochemical response to spironolactone. Removal of the adenoma resulted in cure.

CASE REPORT

The patient, a 39-year-old Cape Coloured mother of 6 children, had attended the antenatal clinic during all her pregnancies from 1964 to 1966. Her blood pressure had always been normal in the past and was still normal in this pregnancy on 22 February 1965. However, because of a rising blood pressure, albuminuria and oedema (Table I), labour was induced

TABLE I. RISING BLOOD PRESSURE LEVELS DURING PREGNANCY

	Blood pressure (mm.Hg)	*Proteinuria*	*Oedema*
22 February 1965	120/70	—	—
30 April 1965	130/90	+	—
27 July 1965	140/95	+	+
3 August 1965	160/100	+	++
14 August 1965	170/105	+	—

at the 38th week of pregnancy and she was delivered of a normal healthy infant on 4 August. She was discharged on the 10th postpartum day with a blood pressure of 170/105 mm.Hg and feeling well. At no stage was she given chlorothiazide or other antihypertensive therapy and, although constipated, had not taken laxatives. There was no family history of periodic paralysis.

In the sixth week after delivery (17 September 1965) she attended the outpatient department for cauterization of the cervix. While in the waiting room she experienced paraesthesiae of both hands and marked weakness of both arms, and as there was difficulty in holding her infant, someone else had to take charge of him. She made no mention of the incident to the doctor. When it came to leaving the hospital, she still had paresis of both arms and a companion had to carry her infant home. This was the first of a series of similar episodes of periodic paralysis. She experienced great difficulty in dressing and undressing the infant, and particularly in tying bows. During the next 24 hours the paresis became progressively worse. She now had difficulty in raising her arms above shoulder height and in combing her hair, and her other children had to support the infant while she fed him at the breast. In addition, paraesthesiae were now constantly present in both hands, particularly severe in the median nerve distribution. She had not experienced this before. There were also frequent and painful tetanic muscle spasms of the hands and she had to be assisted with simple household tasks. Because of these symptoms she attended the casualty department, where the disability was attributed to hysteria and tabs. A.P.Cod. prescribed. After 4 days there was complete remission with the return of power to her upper extremities.

She attended the medical outpatient department on 24 September 1965, feeling well. The blood pressure was 190/120 mm.Hg. Her history raised a suspicion of hypokalaemia and blood was taken for serum electrolyte analysis. There were further episodes of periodic paralysis between 3 and 8 October 1965, and again between 15 and 21 October 1965, with complete remission in between. During the paralytic episodes the weakness of her upper extremities was so severe that she needed spoon-feeding. There was now also paresis of the pelvic girdle and lower extremities, and once her legs buckled beneath her and she was unable to get up from the floor. She had difficulty in raising her head from the pillow and her husband improvised a firm collar from a rolled newspaper in order to prevent her head from flopping to one side. Constipation was a marked complaint, but there was no polyuria or polydipsia. Paraesthesiae of the legs and hands were a marked feature and there were frequent painful muscle spasms of the arms and hands.

On 22 October 1965, she attended the medical outpatient department for the second time in a phase of temporary remission, but she was unable to stand up when her name was called and had to be wheeled into the consulting room. The results of the previous investigations showed a serum potassium of 2·6 mEq./l., a serum sodium of 144 mEq./l. and urea 15 mg./100 ml. The electrocardiogram (Fig. 1) recorded on 24

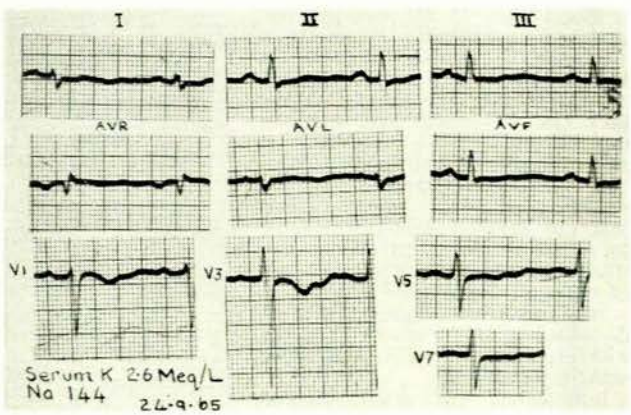

Fig. 1. Electrocardiogram showing hypokalaemia.

September 1965 showed sinus rhythm, flattening and inversion of T waves, with prominent U waves. A freshly-passed specimen of urine was alkaline and contained a small quantity of albumin. She was admitted to the Somerset Hospital.

Examination

On examination she was of average stature and her appearance was not suggestive of Cushing's syndrome (Fig. 2). There

Fig. 2. Patient's physical appearance.

was no dyspnoea, dysphagia or dysphonia. There was severe paralysis of all extremities, more marked proximally at both pelvic and shoulder girdles. She was unable to sit up or to raise her arms or legs against gravity. She could raise her head from the pillow with difficulty, but not against even slight resistance. All muscles of the extremities were hypotonic and tendon reflexes were depressed. Trousseau's sign was positive but Chvostek's was negative. Marked wasting was seen in both thenar eminences and there was marked bilateral weakness of the abductor pollicis brevis. Sensation was intact, but she had paraesthesiae in the median nerve distribution of both hands, especially the right. The blood pressure was 180/110 mm.Hg. There were no fundal changes. The heart size was normal. All pulses were palpable and no bruits were detected. The haemoglobin was 12 G/100 ml.; WBC 7,200/cu.mm.; ESR 15 mm./hr. (Westergren). The urine contained no albumin or sugar, but was alkaline and the SG was 1·010.

Special Investigations

Blood urea 36 mg./100 ml., serum sodium 150 mEq./l., potassium 1·4 mEq./l., chloride 98 mEq./l., bicarbonate 36·2 mEq./l., albumin 4·3 G/100 ml., globulin 2·5 G/100 ml., total bilirubin less than 0·5 mg./100 ml., thymol turbidity 1, zinc turbidity 6, calcium 9·8 mg./100 ml., phosphorus 3·8 mg./100 ml., magnesium 2·3 mEq./l., blood WR and Berger—negative. X-ray of the chest showed a normal cardiac shadow and clear lung fields. X-ray of the skull was normal.

The electrocardiogram showed depressed and inverted T waves with prominent U wave, in keeping with hypokalaemia.

Intravenous pyelogram showed satisfactory excretion of the dye. On both sides there were double ureters and double pelves, and a double kidney on the right side only. There was no evidence of kidney displacement. No urinary obstruction or bladder lesion was seen.

Corrected creatinine clearance 145·3 ml./min. Urine concentration test—SG did not rise above 1·014. No amino-aciduria. Urine 17-oxosteroid 4·4 mg./24 hr. Total 17-oxogenic steroid 3·45 mg./24 hr.

Glucose-tolerance test normal. Serum aldolase 11·5. Creatinine kinase 0·4 units/ml./min. The electromyogram was normal. There was prolonged terminal conduction latency of the left median nerve, probably due to carpal tunnel compression.

A selective left adrenal vein angiogram was done (Dr. T. B. Hugo-Hamman), but the adrenal vasculature was not demonstrated.

Perirenal gas insufflation was not done. The urinary potassium varied between 18·7 mEq. and 71·7 mEq./24 hrs., but a potassium balance was not done. It would appear that urinary excretion of potassium was high, in the presence of low serum potassium levels.

Progress

Her progress is illustrated graphically in Fig. 3. There was partial improvement of muscle power on the second day of admission when the serum potassium was at its lowest, viz. 1·4 mEq./l., and she had regained full power on the fourth day when the serum potassium was still only 2·6 mEq./l. On an extra supplement of potassium consisting of 8 G of Kalisol daily, the serum potassium rose to 4 mEq./l. and as high as 4·7 and 5 mEq./l. with a corresponding improvement in the electrocardiogram, but there was still metabolic alkalosis (serum bicarbonate levels ranged from 35 to 41 mEq./l.). Trousseau's sign remained positive and the blood pressure remained elevated. On withdrawing the potassium supplement, the serum potassium level again gradually sagged to 3·2 and 3·5 mEq./l. and there was a corresponding change in the electrocardiogram and an elevated serum bicarbonate, but no symptoms of hypokalaemia or alkalosis supervened.

In the next phase spironolactone (Aldactone A, 25 mg. *q.i.d.*) was given and the investigations (blood pressure, electrocardiogram, serum sodium, serum potassium

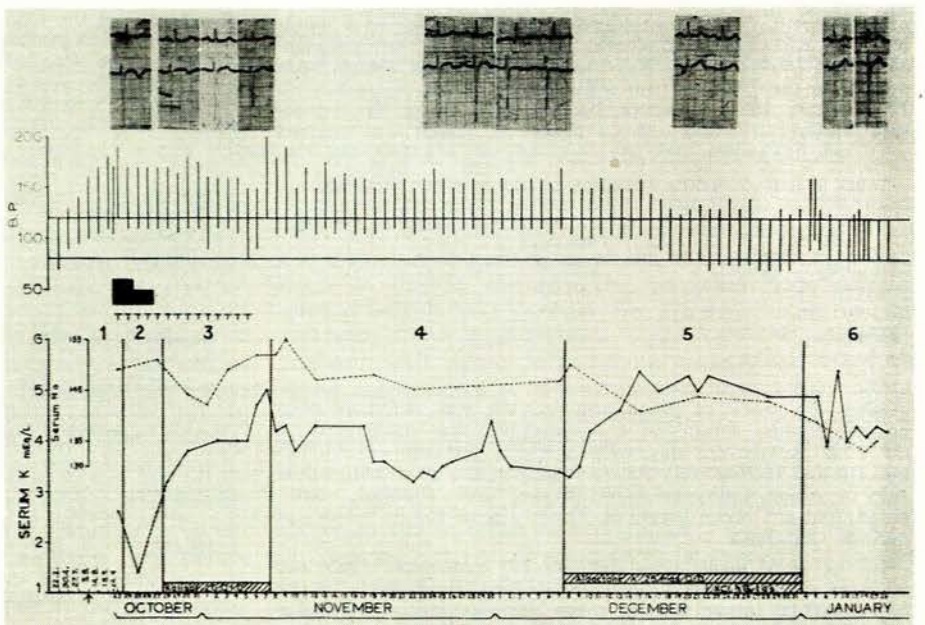

Fig. 3. Serum Na shown by dotted line, serum K shown by uninterrupted line, muscle weakness = blocked out area, Trousseau's sign = T, blood pressure is represented by vertical lines. The 6 phases are: (1) Pre-admission, (2) initial admission period, (3) supplement of Kalisol, (4) withdrawal of Kalisol, (5) Aldactone A, (6) postoperative. On 8 February 1966: serum Na 139, K 4·3, Cl 105, HCO_3 28·0 mEq./l. On 6 March 1966: serum Na 136, K 4·8, Cl 105, HCO_3 27·1 mEq./l. and blood pressure 120/80 mm.Hg.

and serum bicarbonate) returned to normal within a period of 8 days. The addition of Kalisol, 0·5 G *t.d.s.*, did not cause a further rise in serum potassium. She was maintained on spironolactone until the day before surgery. Midstream urine specimens were repeatedly cultured for the possibility of urinary tract infection, but were always sterile. The urine remained free of protein, with a low specific gravity in spite of there being no polyuria. Creatinine clearances remained repeatedly normal.

On 4 January 1966, the adrenals were explored through a transverse abdominal incision, as it is essential in this condition to have an exposure of both adrenal glands at the same time. The adrenals were normal in size. A canary yellow tumour, 1 cm. in diameter, was exposed on the posterior aspect of the right adrenal, abutting on the adrenal vein. This shelled out easily and had the colour and consistency of the yolk of a hard-boiled egg. The left adrenal had a small lipid-laden section on the surface in one area which was biopsied. The patient was given 100 mg. of hydrocortisone before surgery, but in view of the normal size of the glands no further steroid was required. Two litres of Ringer's lactate were given as a plasma volume expander, to correct any hidden contracted blood volume.

Histology (Dr. A. H. Timme): Four fragments of the right adrenal cortical adenoma are composed of large clear cells containing lipid. The latter are arranged in solid alveoli. There is slight nuclear pleomorphism, but no mitotic activity. These features are those seen in any non-functioning or functioning cortical adenoma, but are also consistent with those seen in Conn's syndrome. The rest of this adrenal gland submitted with the adenoma, is within normal limits. The wedge biopsy from the left adrenal shows definite hyperplasia of the medulla.

Postoperative Course

The precaution was taken of giving the patient intravenous saline during the immediate 24-hour postoperative period. There was an initial rise of blood pressure, but this reverted to normal on the third postoperative day, and has remained normal. When last examined on 2 August 1966, her blood pressure was 130/80 mm.Hg. At this stage she was asymptomatic except for the symptoms and signs of bilateral carpal tunnel compression of the median nerve.

DISCUSSION

This case exhibited all the typical features of an aldosterone-secreting tumour and the patient has been cured by removal of the tumour, although aldosterone assay could not be done and the results of renin assay are still pending. The results of clinical and simple biochemical investigation permitted a firm diagnosis.

The periodic paralysis, associated with the hypokalaemia, was mistaken for hysteria, presumably because organic signs of neurological disease were absent, periodicity of the weakness was not appreciated, and the entity did not come to mind.

One or several potassium estimations should be done as part of the routine investigations of 'essential' hypertension, even in the absence of periodic paralysis. We would also recommend this investigation in pre-eclamptic toxaemia as well. This case masqueraded as a pre-eclamptic toxaemia and several other cases have presented in the same way.[7,8]

One should be cautious before always attributing hypokalaemia in hypertensive patients, to thiazide therapy. Several cases of Conn's syndrome have been found among the cases of thiazide-induced hypokalaemia. It is possible that these cases are more easily potassium depleted by thiazides than other cases of hypertension and the diuretic may 'unmask' them.

Where the serum potassium is low, an elevated serum sodium and bicarbonate and a freshly voided urine that is alkaline to litmus, are additional criteria favouring the diagnosis.

Tetany, as in this case, can be a feature, although serum calcium is normal and is due to metabolic alkalosis. It may become manifest only when the potassium is replaced.

It is of interest that the patient had evidence of long-standing bilateral carpal tunnel compression of the median nerve, with marked wasting of the thenar eminences, yet she did not complain of paraesthesiae referable to this cause until the onset of the endocrine disturbance. Wasting and weakness of the thenar muscles supplied by the median nerve persist. It seems possible that a lowered serum potassium contributed to a lowered sensory threshold and aggravated the local muscle weakness, but it is well known that the carpal tunnel syndrome may become manifest in pregnancy, improve postpartum, and the lowered serum potassium may not be relevant here. Moreover, the paraesthesiae have returned subsequently.

Other causes of hypertension and hypokalaemia had to be excluded, like Cushing's syndrome, primary and secondary, to neoplasms of lung, pancreas, etc. The patient was not a chronic consumer of licorice. Secondary aldosteronism due to renal vascular disease, generally causes hyponatraemia and aciduria, and was therefore thought to be unlikely. Malignant hypertension, another cause of secondary aldosteronism, was not present.

Once the diagnosis seemed certain, the tumour had to be localized. Air insufflation might have been helpful (as in Eales' and Linder's case[4]) but these tumours are usually so small (1 - 3 cm. in diameter) that it was felt likely that the method would fail to demonstrate it. Left adrenal vein angiography has been suggested and may be a worth-while procedure.[9] Right adrenal vein angiography is not practicable.

Once the condition has been confidently diagnosed, treatment is by excision of the tumour. As in this case, surgery may have to be embarked upon without the tumour having been localized, and the search has to be extremely careful as the tumour may be quite small and they may in fact be multiple. Spironolactone, as it did in the present case, may control the electrolyte disturbance and reduce the blood pressure, and can be useful where surgery is contraindicated or necessarily delayed.[10] Such a response is not invariable, however.[5]

It is worth remembering that prolonged hypokalaemia may result in permanent renal tubular damage. Potassium supplements corrected the serum potassium in this case, but did not influence the blood pressure.

Primary aldosteronism is an eminently treatable condition. Conn reports that three-quarters of the cases have been cured dramatically and the remaining quarter much improved.

A surprise finding was medullary hyperplasia of the left adrenal gland, for which we have no explanation.

This case was previously briefly reported at a Bickersteth Medical Society clinical meeting.[11]

SUMMARY

Hypertension and albuminuria appeared in a pregnant woman simulating pre-eclamptic toxaemia. Hypertension persisted post-partum and periodic paralyses developed. Primary aldosteronism, due to an adrenocortical tumour was found to be responsible, and complete cure followed excision of the tumour.

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ADDENDUM

Results of plasma renin and aldosterone received on 20 September 1966: plasma renin (28 October 1965) 2.5 units. Repeated on 2 November 1965 after 5 days of salt-free diet and being up and walking for 4 hours: plasma renin 2.3 units (normal values 4 - 20 units)—this indicates plasma renin suppression. Plasma aldosterone (19 November 1965) 26.5 $m_{\mu}g.$/100 ml. (upper limits of normal 15).

Our thanks are due to Drs. J. J. Brown, J. I. S. Robertson and A. F. Lever of St. Mary's Hospital, London, W2, for these estimations and to Dr. G. Thatcher for so kindly arranging for them to be done. It is intended to submit further specimens of plasma now that clinical cure has been obtained.

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