PRIMARY RENINISM: HYPERTENSION, HYPERRENINAEMIA AND SECONDARY ALDOSTERONISM DUE TO JUXTAGLOMERULAR RENAL CELL TUMOURS


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SUMMARY

1. A further case of renin-secreting renal juxtaglomerular cell tumour is reported.
2. Hypertension, aldosteronism and hypokalaemia were associated with high peripheral levels of renin.
3. Renin activity was twice as high in right as in left renal vein plasma.
4. A renal juxtaglomerular cell tumour was found in the right kidney and removed, after which the biochemical abnormalities and blood pressure were promptly corrected.
5. Explants of tumour tissue in culture produced large amounts of renin.

Key words: primary reninism, hypertension, hyperreninaemia, secondary aldosteronism.

In December 1967, Robertson, Klidjian, Harding & Walters (1967) described the first case of a fascinating clinical syndrome which was believed to have been induced by a juxtaglomerular cell tumour of the kidney. Three months later a second report appeared by Kihara & Kitamura (1968) who, independently, had described an almost identical case. Each case was recognized after surgical removal of a tumour-containing kidney. The Robertson–Kihara syndrome would, therefore, be a proper designation. Since then, two similar cases have been reported (Eddy & Sanchez, 1971; Bonnin, Hodge & Lumbers, 1972), one of which (Bonnin et al., 1972) was clearly diagnosed pre-operatively. It is the only case of this kind in which significant pre-operative data on renin activity have been reported.

With the experience provided by these reports, we have been able to make a pre-operative diagnosis in such a case and to contribute additional pre-operative and post-operative observations concerning this entity. Our studies establish beyond question that the cells which make up this particular 'hemangiopericytoma' are, indeed, renin-producing juxtaglomerular cells.
and that the clinical syndrome of hypertension, hyperreninaemia and secondary aldosteronism associated with such tumours is due to the release of excessive amounts of the enzyme, renin, from the tumour.

In addition to demonstrating significantly higher levels of angiotensin I and of plasma renin activity (radioimmunoassay for angiotensin I) in renal venous blood from the tumour-containing kidney, identification of, and renin production by, the cells of the tumour have been established in the following ways. (1) In all studies in which renin activity has been measured we have employed a highly sensitive radioimmunoassay method (Cohen, Grim, Conn, Blough, Guyer, Kem & Lucas, 1971), which measures angiotensin I as the index of renin activity. Prior studies have employed the rat pressor bioassay which, theoretically, could be measuring pressor substances other than, or in addition to, those resulting from renin activity. (2) Electron-microscopic study of the tumour cells reveals that they contain a population of granules with distinctive morphology. Their structure and that of the Golgi-associated rhomboid bodies are identical with those of the granules described by Barajas (1966) and Biava & West (1966) in the epithelioid cells of the normal human juxtaglomerular complex. (3) Fluorescent antibody studies employing dog anti-human renin antibodies raised against a highly purified preparation of human renin demonstrate intense intracytoplasmic granular fluorescence of the tumour cells. (4) Explants of the tumour, grown in tissue culture, release large amounts of renin into their nutrient media and also show the same intracytoplasmic immunofluorescence as do their mother cells.

All five cases (including ours) were promptly cured on removal of the tumour. We therefore suggest that the term 'primary reninism' can now be applied appropriately to the clinical syndrome induced by renin-producing tumours and cured by their surgical removal.

Clinical profile
The following provides a brief profile of the clinical findings of the five cases (including ours) recognized to date as having had primary reninism due to juxtaglomerular cell tumours. Three have been males and two females. The age has ranged from 13 to 37 with a mean of 22.2 years. Diastolic blood pressure has ranged from 97 to 158 with a mean of 131 mmHg. Hypertension had been known to exist for from 9 months to 6 years. In all five cases diastolic blood pressure was restored to normal within 6 h and systolic blood pressure within 6 days after removal of the juxtaglomerular cell tumour. Pre-operative serum potassium levels ranged from 2.6 to 3.5 mEq/l. It is of note that, in all five cases, the initial working diagnosis was primary aldosteronism and, in two cases, adrenal surgery had also been carried out. In the three cases in which aldosterone determinations were made, the values were abnormally high pre-operatively; and in the two cases in which it was measured post-operatively it had returned to normal. In the four cases in which renal arteriography was performed the renal arterial tree was found to be normal bilaterally. In two cases a small tumour of the kidney cortex was observed during arteriography. In all five cases a complete unilateral nephrectomy was performed. All of the tumours were intrarenal, benign and ranged from 1.5 to 4 cm in diameter. In four of the five cases the renin content of the tumour was estimated to be from three times greater than normal kidney tissue to as much as 50–100 times.

Case report
An 18-year-old boy was referred to us with a tentative diagnosis of primary aldosteronism
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because he had severe hypertension (of 5 years' duration), hypokalaemia and overproduction of aldosterone. Renal arteriograms of excellent quality had shown a normal arterial tree bilaterally.

Hypertension (200/128), moderate hypokalaemia, and overproduction of aldosterone were confirmed. However, plasma renin activity, instead of being subnormal as in primary aldosteronism, was found to be excessively high in peripheral blood. This combination of findings, in the presence of normal renal arteriograms, suggested the possibility of a renin-producing tumour. Blood obtained from each renal vein disclosed that both plasma renin activity and angiotensin I (direct) were twice as high in right as in left renal venous blood. A second renal arteriogram disclosed a normal renal arterial tree bilaterally, but a suspicious 15 mm cortical lesion at the inferior pole of the right kidney. A pre-operative clinical diagnosis of a renin-secreting juxtaglomerular cell tumour was made and extensive pre- and post-operative studies were carried out.

At operation a 15 mm, brownish-grey vascular lesion within the substance of the kidney was observed on cut section. Within 3 min of its excision, small squares of the tumour were cut and immersed appropriately for electron microscopy, tissue culture and renin concentration studies. Histological impression was: juxtaglomerular cell tumour of the kidney.

Within 6 days after operation, blood pressure, serum potassium, aldosterone secretion and plasma renin activity had returned to normal. The patient continues to be normal and healthy 1 year after operation.

PRA studies

Pre-operative levels of peripheral plasma renin activity, both recumbent and upright, were abnormally high; and aldosterone excretion of 44.1 μg/day was four times our mean normal value and more than twice the upper limit of normal. PRA was measured (recumbent) on three of the first four post-operative mornings. All were grossly subnormal and were not influenced by the level of serum potassium. By the seventh, ninth and tenth post-operative days, recumbent plasma renin activity was in the normal range, as was aldosterone excretion. Three months later, aldosterone excretion remained normal, as did plasma renin activity, blood pressure and serum potassium.

Summary of special studies

1. Circadian rhythm of PRA was normal, although at each time-interval the level was supernormal.
2. Recumbency was associated with elevated levels of PRA and a further sharp elevation occurred after 2 h of upright posture (ambulation).
3. Restriction of sodium failed to elevate PRA in either position.

Thus, humoral influences increased tumour release of PRA but salt restriction did not. We interpret the latter finding to mean that the cells of the juxtaglomerular cell tumour, not being in their normal juxtaglomerular position, failed to perceive the local stimulus which normally arises at the juxtaglomerular complex during salt restriction. The normal juxtaglomerular cells of the normal juxtaglomerular complexes had been suppressed by the high levels of angiotensin II produced by the renin-producing tumour. Four months after removal of the tumour, the normal juxtaglomerular cells responded normally to sodium restriction.

Such a response, i.e. further elevation of elevated PRA by upright posture, but lack of
response to severe sodium restriction, is an alerting signal to the possibility of a renin-producing tumour; and requires that bilateral renal vein samples for PRA be done.

4. The tumour content of renin was 27 times greater than that of normal kidney tissue.
5. Explants of the tumour grew in tissue culture for 28 days and secreted large amounts of renin into their media.
6. Electron microscopy identifies the cells as juxtaglomerular cells by the distinctive morphology of their cytoplasmic granules, i.e. the granules contain electron-opaque diamond- and rhomboid-shaped crystalloid bodies identical with those seen in the juxtaglomerular cells of the normal juxtaglomerular complex.
7. Immunofluorescence studies employing dog anti-human renin antibodies disclosed intense intracytoplasmic fluorescence both in tumour slices and in the cells of the tumour grown in tissue culture.

Primary reninism is thus defined as a clinical syndrome consisting of hypertension, hyperreninaemia and secondary aldosteronism induced by a renin-producing tumour. An awareness of this syndrome by both clinicians and radiologists will result in the discovery of many more such cases of curable hypertension.

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