Correspondence

Aldosterone renin ratio in patients with resistant hypertension

Sir,
Essential hypertension resistant to treatment often warrants suitable investigations to exclude underlying secondary causes. Aldosterone renin ratio (ARR) is an effective diagnostic tool for detecting primary hyperaldosteronism among patients with presumed essential hypertension. Further confirmation of existing adrenal tumours or hyperplasia can be obtained with imaging studies such as high-resolution computed tomography (CT) scans. Appropriate timing of the laboratory tests for ARR is essential for reliability of results as posture, anti-hypertensive medications tends to interfere with the values. We present a few cases of patients with established and resistant hypertension in whom estimation of ARR was valuable as a part of their work up to ascertain a definitive diagnosis. We also present a brief review of the contemporary literature.

Case 1
A 60-year-male was being investigated for hypertension with hypokalaemia. He was treated with doxazosin, atenolol, losartan and amiloride with regular monitoring of renal function and electrolytes, which revealed a low potassium (usually <3.6 mmol/l) and raised sodium on multiple occasions. His aldosterone level was 351 pmol/l with a renin level of 0.39 µg/l.h with the ambulant ARR of 900 pmol/l per µg/l.h. Urinary cortisol was normal and an ultrasound of abdomen was normal as well but the CT scan of abdomen showed a left adrenal mass of 2 x 2 cm size that was consistent with a left adrenal adenoma.

Case 2
A 57-year-old gentleman with diabetes, hypertension and angina was noted to have persistently raised blood pressure in spite of maximal treatment with amlodipine, lisinopril, spironolactone and moxonidine. He was investigated for resistant hypertension, which revealed normal electrolytes and renal function and a urine-free cortisol level of 164 nmol/day. Further investigations revealed an aldosterone level of 746 pmol/l and renin of 0.21 µg/l.h and ARR of 3552 pmol/l per µg/l.h. A CT scan of his abdomen showed a 9-mm sized right adrenal adenoma.

Case 3
A 45-year-old gentleman was referred by the general practitioner (GP) with a suspicion of Conn’s syndrome with raised blood pressure and low potassium at the GP surgery. He was taking atenolol and clonidine at the time of presentation but had been on angiotensin-converting enzyme (ACE) inhibitors and diuretics before. His sodium level was 144 mmol/l and potassium was 3.7 mmol/l and his aldosterone levels were 385 pmol/l and the renin level was 0.05 µg/l.h with an aldosterone rennin ratio of 7700 pmol/l per µg/l.h but CT scan of his abdomen was normal with no mass in the adrenals.

Case 4
A 71-year-old lady with a past history of diabetes was referred to the endocrine clinic with resistant hypertension and increased urinary albumin/creatinine ratio. She was on amlodipine, doxazosin, losartan and moxonidine but her blood pressure remained high with low levels of potassium between 3.3 and 3.6 mmol/l on several occasion over a period of 2 years. On estimation, her renin level was <0.1 µg/l.h and the aldosterone level was 405 pmol/l with an ambulant ARR of 4050 pmol/l per µg/l.h. A CT scan of her abdomen revealed bilateral bulky adrenal glands with a homogenous enhancement suggestive of bilateral adrenal hyperplasia (BAH). She was started on spironolactone and her blood pressure was reasonably controlled.
Discussion

The above four cases demonstrate patients with resistant hypertension with established hypokalaemia being treated with multiple drugs. Further investigations for all of them confirmed an elevated ARR and an underlying adrenal pathology in three of the four patients. It has been recognized that primary hyperaldosteronism is often missed as a diagnosis in patients labelled as essential hypertensives and the frequency of diagnosis has been improved using screening methods.\(^1\) Increasing evidence indicates that the prevalence of primary aldosteronism may be up to 12% in hypertensive patients with most patients being normokalaemic.\(^2\) Screening for primary hyperaldosteronism is to be considered in patients with hypertension and hypokalaemia, resistant hypertension, adrenal incidentaloma and in cases of hypertension where we suspect secondary causes. Several reviews on primary hyperaldosteronism have recommended the use of aldosterone/renin ratio to screen patients likely to have this disease entity\(^3\)–\(^5\) and widely different cut-off levels for the ratio have been proposed ranging from 7.2 to 100.1 ng/dl per ng/ml.h (200–2774 pmol/l/µg/l.h).\(^6\)

Primary hyperaldosteronism causing resistant hypertension as in our patients could be both due to adrenal adenoma and BAH as these patients can present with similar signs and symptoms, serum chemistries, responses to medication and nodules on CT scan,\(^7\) but both these need to be distinguished as treatment of adrenal adenoma is surgical adrenalectomy and that of BAH is medication with potassium sparing diuretics.\(^8\)

ARR is now being utilized with increased effect for this purpose. ARR in conjunction with postural test shows that patients with adenoma have increased ARR whereas with BAH, ARR decreases with test.\(^9\) Similar results have been demonstrated by estimation of plasma aldosterone and cortisol after monitoring suppressibility of aldosterone by provocative tests of morning ambulation or saline infusion in sodium replete states.\(^10\) Fall in plasma aldosterone after 2 h ambulation is suggestive of adrenal adenoma and not BAH\(^11\) with a fall or no change of cortisol levels. For further clarification, clinicians are now increasingly relying on CT scan to distinguish between unilateral adenoma and bilateral hyperplasia\(^12\) as sensitivity and specificity of CT in hyperaldosteronism ranges from 48% to 58% and from 91% to 92%, respectively.\(^13\)

Anti-hypertensive’s therapy could interfere with the diagnosis of primary hyperaldosteronism in resistant hypertensives as β blockers and clonidine raise ARR.\(^14\) Conversely diuretics, ACE inhibitors, calcium channel blockers and angiotensin receptor blocker tends to reduce ARR.\(^15\) At least 3-week stoppage of medications is required for a correct wash out period for estimating ARR but it is potentially harmful to withdraw all medications,\(^16\) but the gold standard remains to estimate ARR during this washout period.

In summary, patients with resistant hypertension need investigations to rule out secondary causes. Primary aldosteronism accounts for most frequent form of secondary hypertension accounting for up to 5–10% of all hypertensive patients. Estimation of ambulant ARR is often diagnostic of primary hyperaldosteronism in such patients and confirmatory imaging studies are further helpful which may be either normal or show evidence of existing tumours or hyperplasia. ARR estimation should be appropriately timed, as interference with prescription medications is very common.

G. Das\(^1\) and P. De\(^2\)

1 Department of Diabetes and Endocrinology, Prince Charles Hospital, Waunarlwydd Road, Merthyr Tydfil Mid Glamorgan CF47 9DT, UK email: drgdas@gmail.com
2 Department of Diabetes and Endocrinology, City Hospital, Birmingham, B18 7QH, UK

References

The incidence, morbidity and mortality figures in patients with cirrhosis are all rising. An integrated diagnostic pathway from MHE to overt HE, while increased intra-astrocytic glutamine accumulation, driven by ambient hyper-ammonaemia, is probably a dominant process, neuroinflammation and neurosteroid-driven GABAergic modulation are also of importance. We would no longer consider zinc depletion to be a modern pathological dogma in describing HE and manganese deposition may reflect impaired biliary excretion of this agent, rather than be pathognomonic of HE, since studies correlate with cholestasis, rather than neuropsychiatric impairment.

We would also suggest that greater emphasis should be given to minimal hepatic encephalopathy (MHE) than was given in the review by Cash et al. Epidemiological studies have demonstrated the importance of this more recently recognized entity, with up to 50% of patients who have been diagnosed with cirrhosis estimated to have MHE. A wealth of diagnostic tests have arisen that can clearly define MHE with psychometric abnormalities and difficulties with skilled daily tasks, such as driving. The definition of these cognitive changes is likely to be of profound importance in the future. These tests include the Psychometric Hepatic Encephalopathy Score (PHES) battery (a series of ‘paper and pencil’ tests), the critical flicker frequency and the computer-based Cognitive Drug Research battery, which is available ‘on-line’, among others. We would not recommend measurement of serum ammonia in diagnosis, owing to its poor correlation with the symptoms of HE and with the levels of neuropsychiatric impairment.

Hepatologists should point out the importance of psychometric testing to non-specialists and make arrangements for this as part of a standard investigative pathway in patients with cirrhosis. However, the psychometric battery with greatest reproducibility and ease of use in clinical practice has yet to be defined in practice guidelines, since the test batteries that are used differ between countries (the PHES test being particularly popular in Germany, for example). We would caution against the late referral to specialist hepatology services suggested by Cash et al. at the stage of treatment failure by a second-line agent. We suggest that all patients with cirrhosis, irrespective of the presence of overt HE, should be managed by specialists and any decompensation leading to HE should be referred to hepatologists with links to liver transplant centres.

The incidence, morbidity and mortality figures in patients with cirrhosis are all rising. An integrated diagnostic pathway from MHE to overt HE,