Hyponatremic-Hypertensive Syndrome With Renal Ischemia
An Underrecognized Disorder

Mamta Agarwal, Kelvin L. Lynn, A. Mark Richards, M. Gary Nicholls

Abstract—Renal artery stenosis or occlusion causing the hyponatremic-hypertensive syndrome has been rarely reported. Our impression, however, was that the disorder is not uncommon. Case records from patients in one city (population 350 000) presenting between 1980 and 1997 with hypertension, hyponatremia, and evidence of renal ischemia were scrutinized. Thirty-two patients fulfilling inclusion criteria were identified. Admission supine arterial pressures were high (mean 228/124 mm Hg), but there was a vigorous fall in pressure on standing (26/12.7 mm Hg recorded in 27 patients). Mean plasma concentrations of sodium (129.7 mmol/L) and potassium (2.7 mmol/L) were low, and 24-hour urine protein excretion was elevated in 19 of 26 patients. Twenty-two of the 32 patients were female, the majority were asthenic, and all but 5 were smokers. Symptoms precipitating hospitalization were headache, clouding of consciousness, confusion, weakness, weight loss, thirst, and polyuria. Plasma renin levels, measured in 20 patients, were elevated in most cases and correlated inversely ($r=-0.63$, $P<0.01$) with the plasma sodium concentration. The hyponatremic-hypertensive syndrome in patients with renal ischemia is not rare: Rather, it is underreported. It tends to affect elderly asthenic women who smoke heavily. Stimulation of renin release from the ischemic kidney is probably central to the pathophysiology. The syndrome deserves better recognition to ensure appropriate investigations and management. (Hypertension. 1999;33:1020-1024.)

Key Words: hypertension ■ hyponatremia ■ renin-angiotensin system ■ smoking ■ aldosterone ■ renal circulation

The combination of hypertension and hyponatremia can be observed in a number of disorders including acute and chronic renal failure,1 malignant hypertension whatever the origin,2 renin-secreting tumors,3–7 and acute intermittent porphyria.8 Perhaps most commonly it is observed in patients with essential hypertension receiving diuretics, either thiazides or thiazide-potassium-sparing combinations in which elderly, asthenic women appear especially susceptible to the development of hyponatremia.9,10 Another condition that can induce both hypertension and hyponatremia is renal ischemia. The hyponatremic-hypertensive syndrome caused by renal ischemia has been reported infrequently and then usually as single-case reports. Accordingly, one might suspect it is a rare condition. Our impression that the disorder was far from uncommon prompted us to search for examples in our institution over the preceding 17-year period. We found the case records of 32 patients with the syndrome, most of whom were thin, elderly women who were smokers.

Our experience suggests that the hyponatremic-hypertensive syndrome is not rare but is underrecognized. Clinical suspicion and relatively simple investigations can lead to a correct diagnosis with exclusion of other causes of hypertension and hyponatremia listed above. If the clinical disorder and its pathophysiology are not appreciated, patients are likely to undergo inappropriate investigations and treatment.

Methods

Criteria for diagnosis of the hyponatremic-hypertensive syndrome caused by renal ischemia were as follows: (1) Hyponatremia, plasma sodium concentration below the lower limit of normal for our hospital (<136 mmol/L), (2) Hypertension, systolic blood pressure >165 mm Hg and diastolic blood pressure >95 mm Hg in the sitting or supine position in the presence or absence of antihypertensive drug treatment, (3) Renal ischemia, evidence of renal ischemia (>80% stenosis or total occlusion of a major renal artery) on selective angiography or strongly suggestive evidence of severe ischemia on captopril DTPA renography or a Doppler ultrasound study.

Exclusion criteria were evidence of renal parenchymal disease beyond the presence of proteinuria, recent use of thiazide or potassium-sparing diuretics, or a plasma creatinine >0.15 mmol/L.

All patients were attended by 1 or more of the authors in a Christchurch hospital from 1980 or later. Their case records were scrutinized for clinical, biochemical, and hormonal data.

Venous samples were drawn within 5 days of hospitalization from 20 patients, while supine or sitting, between 8 AM and noon, for measurements of plasma renin activity (PRA)11 and aldosterone12 (n=16).

Results

Thirty-two patients fulfilling the inclusion criteria for the hyponatremic-hypertensive syndrome were identified (Table). Symptoms precipitating hospitalization were headache, clouding of consciousness, or confusion in 24 patients; weakness, weight loss, thirst, and/or polyuria in 15 patients;
and recurrent ventricular tachycardia in patient 14, who had a plasma potassium of 1.7 mmol/L. A sizable minority (11 patients) complained specifically of dizziness on standing.

Twenty-two patients were women with a mean age of 65.1 years and 10 were men of mean age 57.9 years (Table). All were regular smokers except for 4 women and 1 man. Because height was rarely documented we could not calculate body mass index, but many patients were asthenic, with 9 women weighing ≤50 kg. The blood pressure on hospitalization, measured in the supine position, was very high in

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender/Age, y</th>
<th>Smoking Status, Cigarettes/d</th>
<th>Body Weight, kg</th>
<th>Supine Blood Pressure, mm Hg</th>
<th>Urine Protein, g/24 h (0–0.25g/24 h)</th>
<th>Plasma Sodium, mmol/L (136–146)</th>
<th>Plasma Potassium, mmol/L (3.5–5)</th>
<th>Plasma Creatinine, mmol/L (0.05–0.11)</th>
<th>Arteriography</th>
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<td>3.8</td>
<td>0.14</td>
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</tbody>
</table>

NR indicates not recorded; RAS, renal artery stenosis; Bil, bilateral; and Nil, non-smoker.

*Urine protein measured by dipstick.
most patients (mean 228/124 mm Hg), and many had postural hypotension (mean fall of 26/12.7 mm Hg, recorded in 27 patients). Examination of the optic fundi showed retinal hemorrhages in 4 patients and papilledema in 5 (2 of whom also had hemorrhages). No patient was in cardiac failure.

Urine protein excretion, measured formally over 24 hours in 20 patients within 5 days of hospitalization, was elevated in 19 and was probably increased in the remaining 9 patients there was evidence of bilateral ischemia (Table). None showed radiologic evidence of fibromuscular hyperplasia.

PRA, measured in 20 patients within 5 days of hospitalization while taking a variety of medications, was elevated in all but 2 patients (mean 2.7, range 1.7 to 3.9 nmol/L), and plasma creatinine concentration was above the upper limit of normal in 9 patients (Table).

Radiologic, radionuclide, or Doppler ultrasound studies indicated stenosis or occlusion of the right renal artery in 11 cases and of the left renal artery in 12 patients. In the remaining 9 patients there was evidence of bilateral ischemia (Table). None showed radiologic evidence of fibromuscular hyperplasia.

Of the 32 patients, 12 had clinical evidence of peripheral vascular disease and 15 showed ECG signs suggestive of ischemic heart disease. Management consisted of unilateral nephrectomy in 4 patients, 1 had bilateral renal endarterectomy, 6 underwent balloon angioplasty, and the remainder received antihypertensive drug therapy, usually a mixture of agents. Follow-up of the cohort has not been systematic as the syndrome develops. Barraclough partly succeeded in such an endeavor when, in 1966, he documented gross sodium, potassium, and volume depletion with the evolution of severe hypertension and hyponatremia in a patient with unilateral renal ischemia. Further, the fact that the component electrolyte and hormonal abnormalities are corrected and cumulative sodium balance increases with uninephrectomy or blockade of angiotensin II production adds weight to the thesis outlined above.

Discussion

The combination of hyponatremia and severe hypertension in patients with underlying renal ischemia has been known for many years. In 1952 for example, Bauer and Forbes reported a 42-year-old patient presenting with severe hypertension and a plasma sodium concentration between 116 and 129 mmol/L who, at postmortem examination, was found to have severe atheromatous left renal artery stenosis. Since then, other anecdotal cases have been reported, but the largest series we could find was that from McAreavey et al with 6 cases, and from Heslop and colleagues. The latter reported 4 cases, all elderly women who were heavy smokers, detected over a period of 21 months. The present series is from the same institution with a drainage population of ≈350,000 and reports 32 patients with the hyponatremic-hypertensive syndrome. The clinical and neuroendocrine features of 1 patient (No. 16, Table) have been described in detail elsewhere, and details of 5 patients have been reported previously.

As in the 4 cases of Heslop et al, which are included in the current report, the majority of patients were elderly, asthenic females. Almost all were heavy smokers and the underlying renal artery pathology was atherosclerosis. Most presented with symptoms referable to the central nervous system including headache, confusion, and polydipsia, and many had noted postural dizziness, weight loss, and polyuria. Apart from hyponatremia, which was an inclusion criterion, all but 2 patients had hypokalemia that was often severe.

As to the pathophysiology of the syndrome, the explanation provided by Atkinson et al appears plausible and is supported by our previous and current observations. With "critical" renal ischemia, renin secretion is increased, resulting in high circulating angiotensin II levels, which raise arterial pressure and stimulate aldosterone secretion from the adrenal glomerulosa. A sudden rise in arterial pressure can induce a pressure natriuresis through the normal kidney, leading to volume depletion that may result in postural hypotension, further renin release from the ischemic kidney, and heightening of the aldosterone response to angiotensin II. Potassium deficiency from hyperaldosteronism may further stimulate renin secretion and intensify the vicious circle. The hyponatremia itself is presumed to result primarily from stimulation of thirst and antidiuretic hormone (ADH) release in response to the dual stimuli of exceedingly high levels of angiotensin II and volume depletion. Direct renal actions of angiotensin II to retain water in excess of sodium may also contribute. The inverse association we observed between plasma renin and aldosterone levels on the one hand and plasma sodium on the other hand (Figure) is consistent with the above hypothesis.

Proof of this sequence of events is difficult without the aid of careful balance studies as the syndrome develops. Barraclough partly succeeded in such an endeavor when, in 1966, he documented gross sodium, potassium, and volume depletion with the evolution of severe hypertension and hyponatremia in a patient with unilateral renal ischemia. Further, the fact that the component electrolyte and hormonal abnormalities are corrected and cumulative sodium balance increases with uninephrectomy or blockade of angiotensin II production adds weight to the thesis outlined above.
Some of our patients had bilateral renovascular disease, and this has been reported previously in association with the hyponatremic-hypertensive syndrome.\textsuperscript{5,7} We presume that the stenosis was critical in one kidney, resulting in intense stimulation of renin from the juxtaglomerular apparatus, whereas perfusion pressure to the contralateral kidney remained relatively high, thereby facilitating a pressure natriuresis leading to a volume-depleted state.

Other causes of hyponatremia in hypertensive patients, beyond renal artery stenosis, include use of thiazide diuretics,\textsuperscript{9,10} renin-secreting tumors,\textsuperscript{3–7} acute intermittent porphyria,\textsuperscript{8} malignant hypertension,\textsuperscript{2} and a variety of disorders inducing acute or chronic renal failure.\textsuperscript{1} These need to be considered, along with renal ischemia, in the differential diagnosis of the hypertensive patient with hyponatremia. Of the above, malignant hypertension is the only disorder that may not, in some patients, stand as a distinct entity. Indeed it is likely that the hyponatremic-hypertensive syndrome evolves into malignant hypertension in some cases with the development of its pathological hallmark, arteriolar fibrinoid necrosis, and the clinical hallmarks papilledema and retinal exudates and hemorrhages. Of our 32 patients, 7 had papilledema and/or retinal hemorrhages and could have been categorized on clinical grounds as having malignant hypertension. In most patients, however, a clinical diagnosis of malignant hypertension was not entertained, and wide-ranging, often expensive investigations into the cause of hyponatremia had been undertaken.

As noted already, almost all of our patients were heavy smokers. Nicholson et al\textsuperscript{27} have shown an association between cigarette smoking and renal artery stenosis whether the pathology was atherosclerotic or fibromuscular renovascular disease. Furthermore, nicotine can be a potent stimulus to ADH release in humans,\textsuperscript{26} and this may have contributed to the development of hyponatremia. It is likely, therefore, that smoking was central to the pathophysiology of the hyponatremic-hypertensive syndrome in many patients, most obviously through the development of atherosclerotic renovascular disease but also by augmenting ADH secretion.

As mentioned above, the majority of our patients were elderly, thin women. In this regard it is interesting that asthenic elderly women appear to be predisposed to hyponatremia associated with thiazide diuretic therapy.\textsuperscript{9,10} We have no ready explanation for this apparent predisposition.

Proteinuria, sometimes into the nephrotic range, is well reported in patients with unilateral renal ischemia.\textsuperscript{27,28} Because angiotensin II infusion can induce proteinuria in animals, presumably through alteration of both glomerular hemodynamics and intrinsic selective properties of the glomerular membrane,\textsuperscript{29} and removal of the ischemic kidney or blockade of angiotensin II formation reduces protein excretion,\textsuperscript{28,30} we presume that sudden or intense activation of the renin-angiotensin system was central to the development of proteinuria in our patients.

The incidence of the hyponatremic-hypertensive syndrome among hypertensive patients with renal ischemia is not readily apparent from the literature, and our data provide no assistance in this regard. McAreavey and colleagues\textsuperscript{14} in Glasgow noted hyponatremia (plasma sodium <135 mmol/L) in 6 of 35 patients with renovascular hypertension. They had higher blood pressure, lower plasma potassium concentration, lower exchangeable sodium, and higher circulating levels of renin, angiotensin II, and aldosterone than patients with normal plasma sodium concentrations.\textsuperscript{14} This Glasgow experience and our own suggest that the hyponatremic-hypertensive syndrome with renal ischemia is not uncommon.

Responses to surgery, angioplasty, and drug therapy are not well documented in our cohort because follow-up was not systematic. It is our hope that this report will stimulate interest in the syndrome and lead to careful documentation of long-term follow-up information. As of now, the impression is of a high mortality rate (9 deaths) and the frequent need for multiple antihypertensive agents.

In summary, we present 32 patients with the hyponatremic-hypertensive syndrome in association with renal ischemia caused by atherosclerotic disease of the renal arteries. The majority were elderly asthenic women who smoked heavily. The pathophysiologic appears to center on intense activation of the renin-angiotensin system with angiotensin II in concert with volume depletion stimulating thirst and ADH release and enhancing aldosterone secretion, resulting in hyponatremia and hypokalemia. The syndrome deserves to be better recognized to ensure rational investigations and management.

References

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