Dissociation between the secretion and renal action of endogenous atrial natriuretic peptide in the syndrome of inappropriate antidiuresis

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Summary: A patient is described with the syndrome of inappropriate antidiuresis (SIAD) and renal sodium retention secondary to a lymphoma. The basal atrial natriuretic peptide (ANP) level and the ANP response to volume expansion were normal (age adjusted) but the natriuretic effect of ANP was attenuated by an unidentified factor. The case emphasizes the dominance of circulating volume over plasma tonicity in the regulation of ANP secretion.

Introduction

The syndrome of inappropriate antidiuresis (SIAD) occurs in association with many conditions, and continuing urinary sodium excretion despite plasma hyponatraemia is a cardinal feature of the syndrome.¹ It has been suggested that this natriuresis is mediated by atrial natriuretic peptide (ANP).² In normal man exogenous ANP inhibits osmolality-induced arginine-vasopressin (AVP) release,³ but it is unclear whether endogenous ANP produces the same effect. We have therefore studied an unusual patient with a non-Hodgkin's lymphoma and biochemical evidence of SIAD, but with urinary sodium retention, in whom we have examined the responses of ANP, AVP, and the renin/angiotensin system to hypotonic volume loading.

Case report

A 77 year old female presented with a 2-month history of malaise, left sciatic distribution pain, progressive left leg weakness, and bowel and bladder sphincter disturbance. There had been no vomiting or diarrhoea. Physical examination revealed recent weight loss, the blood pressure was 135/85 mmHg erect and supine, and the neurological signs indicated a cauda equina lesion. The cerebrospinal fluid (CSF) protein concentration was elevated at 1.44 g/l (normal <0.4 g/l) with a gamma-globulin fraction of 35% (normal 6–12%); no cells were found in the CSF. Myelo-

graphy and computed tomographic (CT) scanning of the lumbo-sacral region showed a para-spinal soft tissue mass involving the sacrum and invading the cauda equina which when biopsied was found to be a high grade B-cell non-Hodgkin's lymphoma. There was no clinical evidence of metastases and chest X-ray, abdominal ultrasound scan and isotope bone-scanning were normal.

The plasma sodium concentration was 121 mmol/l on admission, with plasma and urine osmolalities of 255 and 483 mOsmol/kg respectively. The urinary sodium concentration on two occasions was 4 mmol. The plasma urea was 4.6 mmol/l, creatinine 80 µmol/l, serum albumin concentration 37 g/l, and adrenal and thyroid function tests were normal. The patient was not thirsty, had no clinical evidence of volume depletion, nor was there any dependent oedema or signs of heart failure. Her fluid intake was therefore restricted to 1200 ml daily, and the plasma sodium concentration rose to 130 mmol/l after two days.

Water loading study

A water loading study was then performed during fasting (in preference to hypertonic saline infusion in a patient of this age) using 20 ml/kg body weight 5% dextrose given intravenously over 20 minutes followed by the previous hourly urine output replaced orally each hour during the study.⁴ Venous blood was collected into chilled heparinised tubes (or tubes containing EDTA and aprotinin for ANP estimations) and plasma immediately separated by centrifugation at 4°C. After an extraction step using methanol, acetic acid and ethanol as eluants on Sep-pac columns, ANP was measured by a radioimmunoassay employing

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Accepted: 28 June 1989

anti- α -human ANP raised in the rabbit as antibody, and ^{125} I-iodine-labelled ANP as radio-label. No correction was made for losses during the extraction process. The limit of sensitivity of this assay is 6.2 pg (1.9 fmol) per tube. Plasma renin activity, aldosterone and arginine vasopressin were also measured by radioimmunoassay. The results are shown in Table I. Forty seven percent of the total water load was excreted after 4 hours (normal >80%) and urinary osmolality fell to 121 mOsmol/kg (normal < 100 mOsmol/kg), confirming impaired urinary diluting capacity, as was also indicated by the steady fall in plasma total protein, haematocrit and osmolality. Creatinine clearance rose transiently after volume loading. The basal plasma ANP concentration was 89 pg/ml (reference range in young adults 20–60 pg/ml) and plasma ANP rose sharply after water loading. The fractional excretions of sodium and water also

rose following water loading and remained elevated after the rise in plasma ANP concentration observed at one hour had returned to the baseline level. AVP was detected in plasma at low concentrations despite the reduced plasma osmolality, the plasma AVP concentration tending to fall during the study in parallel with the falling plasma osmolality, consistent with the 'reset osmostat' variant of SIAD.¹ The cerebrospinal fluid AVP concentration was 0.6 pmol/l, also suggesting a hypophyseal rather than an ectopic origin for the continuing AVP secretion.

Progress

The patient was treated with high dose corticosteroids and local radiotherapy. There was no response either clinically or on repeat CT scanning and she ultimately died of bronchopneumonia 7 months after the onset of her symptoms. Post-mortem examination showed no tumour outside the primary site.

Table I Renal and hormonal responses to water loading

	Time from start of water load (hours)				
	0	1	2	3	4
Plasma osmolality (mOsmol/kg)	271	271	268	262	256
Plasma total protein (g/l)	61	58	58	57	56
Haematocrit (%)	33	31	30	29.5	29
Urine osmolality (mOsmol/kg)	411	235	121	131	197
Urine volume (ml)*	510	295	150	205	50
	(12 hours)				
Urine sodium (mmol)	7	12	5	4	4
Sodium excretion (μ mol/min)	4.9	59	12.5	13.7	3.3
Clearance (ml/min)					
Sodium	0.027	0.47	0.10	0.11	0.026
Free water†	−0.27	0.65	1.4	1.7	0.19
Fractional sodium excretion (%)‡	0.06	0.38	0.40	0.10	0.08
Plasma renin activity (ng AI/ml/h) (0.3–3.6)	0.7	0.5	0.5	0.6	0.6
Plasma aldosterone (pmol/l) (30–440)	170	<70	120	370	410
Plasma ANP (pg/ml) (20–60)	89	210	81	120	94
Plasma AVP (pmol/l) (lower detection limit of assay 0.2 pmol/l)	0.6	<0.3	0.4	0.3	0.4

* The patient was already catheterised because of her neurological disease. † Calculated as urine volume - osmolar clearance. ‡ Calculated as sodium clearance/creatinine clearance $\times$ 100. All hormone concentrations measured by RIA (with normal range in parentheses).

Discussion

An inappropriately elevated urinary sodium concentration, usually > 20 mmol, is regarded as essential in supporting the diagnosis of SIAD unless there is severe coexisting sodium depletion,¹ in contrast to the sodium and water retention accompanying advanced heart or liver disease which may lead to plasma hyponatraemia. Because of the decreased urinary sodium excretion in a patient who was not clinically sodium depleted we took particular care to exclude alternative diagnoses before attributing the metabolic disturbance to SIAD. The initial hyponatraemia was too severe to be attributed solely to the physiological impairment of urinary diluting capacity accompanying normal aging. Elevated plasma AVP levels are common in patients with heart failure,⁵ but there was no evidence of this either clinically or radiologically, and the normal activity of the renin-aldosterone system suggests that any cardiac dysfunction that was present subclinically was mild. Liver function tests were normal as were renal, thyroid and adrenal function, and the dietary sodium intake was approximately 50 mmol/24 hours. Physical examination indicated salt and volume repletion and the normal plasma urea, creatinine and plasma renin activity (allowing for the patient's age⁶) support the clinical findings. Finally, AVP was detected at low but significant plasma concentrations when plasma osmolality was between 256 and 271 mOsmol/kg, far below the normal osmotic threshold for AVP release. This AVP was probably of hypophyseal origin, continued release possibly occurring as a result of

afferent input produced by the irritating effect of neoplasm in the cauda equina. The plasma AVP concentration was suppressed below the detection limit of the assay only at the time when the plasma ANP concentration was at its peak, which occurred before plasma osmolality fell. It is possible that this indicates a direct inhibitory effect of endogenous ANP on AVP release but a non-osmotic baroreceptor-mediated suppression of AVP release following volume expansion cannot be excluded.

The rise in plasma ANP concentration was provoked by hypotonic volume loading and preceding any change in plasma sodium concentration or osmolality, indicating that plasma volume rather than tonicity was the major determinant of ANP secretion, as in normal subjects⁷ and in other pathological states.⁸ Plasma ANP levels are elevated in healthy elderly subjects in normal sodium balance and the levels seen in our patient are similar to those previously reported.⁹ Despite this, possibly physiological, 'up-regulation' of the ANP secretory mechanism accompanying aging, renal sodium and water excretion both at baseline and after water loading were markedly reduced when compared to normal young¹⁰ and elderly⁹ subjects exposed to the plasma ANP concentrations prevailing in this case, although fractional sodium excretion rose slightly after water loading, indicating at least some increase in the tubular rejection of sodium in association with the rise in plasma ANP.

Renal artery clamping in the dog prevents ANP-induced natriuresis¹¹ and this has been interpreted as indicating that ANP acts on the kidney via a renal haemodynamic effect rather than by a hormonal intrarenal action. An alternative explanation is that the intrarenal effects of ANP are antagonized by angiotensin II released from the clamped kidney, a mechanism that has also been suggested to explain the elevated ANP levels and sodium retention observed in patients with congestive heart failure.¹² The biochemical findings in our patient are similar to those seen in severe heart failure but neither stimulation of renal nerve

activity or the renin/aldosterone system¹³ can be implicated as the cause of the antinatriuresis in this case as plasma renin activity was normal and we observed the expected transient suppression of aldosterone secretion after volume loading.¹⁴ Vasopressin-sensitive adenylate cyclase activity (the V2 receptor) has been identified in all nephron portions distal to the hairpin turn of the loop of Henle¹⁵ but the speculation that the antinatriuretic effect in this case might have been mediated by vasopressin itself is refuted by the low plasma levels of AVP and by the observation that ANP inhibits V2-receptor mediated effects in the collecting duct.¹⁶ SIAD has been described in association with hyperprolactinaemia in man¹⁷ but the serum prolactin was normal in our patient (527 mU/l). The intrarenal mechanism attenuating the expected effects of ANP to cause sodium retention therefore remains unclear.

In conclusion, a patient is described with a lymphoma involving the cauda equina who exhibited the syndrome of inappropriate antidiuresis. Plasma atrial natriuretic peptide concentrations were normal for the patient's age and were influenced as expected by the intravascular volume rather than plasma tonicity. However, the well known renal natriuretic and diuretic actions of ANP were attenuated by an unidentified factor(s) which was not related to the renin/aldosterone system, and no alternative explanation for the patient's sodium retention was evident clinically or after detailed investigation. This combination of findings has not, to our knowledge, been reported before and suggests that an elevated urinary sodium excretion is not always an essential criterion in diagnosing SIAD.

Acknowledgements

We wish to thank Dr B. Ashworth for permission to report this case, and Professor M.R. Lee and Dr P. Baylis for their help with the hormone assays.

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